THE PCOS SOCIETY

PANDORA

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...The Newsletter of The PCOS Society of India

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THE PCOS SOCIETY

The PCOS Society of India
in collaboration with the
Breach Candy Hospital
presents

Advances in
Infertility
Management
in PCOS

Evidence, Excellence and Experience

BLOCK YOUR DATES
FOR OUR FUTURE WEBINARS

14th Aug., 2019

Adjuvant therapy

11th Sept., 2019

The Male Factor – Double Trouble!

9th Oct.,2019

Assisted Reproduction

Timings:
7.30-9.30 pm

Venue:
Auditorium, 3rd floor
Breach Candy Hospital

Register online:
http://www.pcosindia.org/

Registration Free
Link will be provided to those who register on the PCOS Society Website.

Events & Updates

Webinars on Advances in Infertility Management in PCOS

The PCOS Society of India along with **the Breach Candy Hospital** is conducting a Series of Webinars on **"Advances in Infertility Management in PCOS"** which are held at the Breach Candy Hospital Auditorium from 7.30 pm to 9.30 pm, once a month, along with a live webcast globally.

All interested are requested to register on the PCOS Society Website http://www.pcosindia.org/ in order to receive the link for the live Webinar. Each webinar is initiated by a **Welcome from Dr. Duru Shah**, the President of the PCOS Society of India, followed by an academic discussion on the latest advances on the topic of the Webinar, followed by **a Panel Discussion with multi-disciplinary experts on "Clinical issues"** related to the subject of discussion. Please check the videos on the website to watch the previous sessions.

8th May 2019, Mumbai

Topic – Ovulation Induction and Controlled Ovarian Hyperstimulation in PCOS

1. Current evidence..... **Dr. Manzer Shaikh** 15min
2. Excellence in research ..... **Dr. Sudha Tandon** 15 min
3. Experience of the Experts learn through case discussions: 1hr. 30min
   Moderator: **Dr. Sujata Kar**
   Panelists: **Dr. Jaydeep Tank, Dr. Kedar Ganla, Dr. Madhuri Patil, Dr. Shreyas Padgaonkar**

L to R: Duru Shah, Sudha Tandon, Sujata Kar, Shreyas Padgaonkar, Jaydeep Tank, Kedar Ganla, Madhuri Patil

Manzer Shaikh

Sudha Tandon

12th June 2019, Mumbai

Topic – Endometriosis in PCOS, Is it more common?

1. Current evidence on PCOS and endometriosis .....**Dr. Nagendra Sardeshpane** 15min
2. Excellence in research in PCOS and endometriosis... **Dr. Deepak Modi** 15min
3. Experience of the Experts – learn through case discussions: 1hr.30 min
   Moderator: **Dr. Kaustubh Kulkarni**
   Panelists: **Dr. Sadhana Desai, Dr. Pankaj Desai, Dr. Prakash Trivedi, Dr. Parikshit Tank**

Duru Shah

Nagendra Sardeshpane

Deepak Modi

L to R: Deepak Modi,Kaustubh Kulkarni, Duru Shah, Sadhana Desai, Pankaj Desai, Nagendra Sardeshpane, Parikshit Tank

Editorial

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Dear Friends,

We complete 4 glorious years of the PCOS Society of India in August this year. I clearly remember the day we launched it in Mumbai, with a little anxiety, when we were wondering how our Society would grow.

But I am happy to say that we have done quite well for ourselves, with truly academically oriented dedicated Patrons, Life Members and Associated Members, more than a thousand of them and still counting!

None other than Prof. Rob Norman, declared to a group of International colleagues, with whom we were in a meeting, that the PCOS Society of India is doing the maximum amount of work in the field of PCOS globally ! It was a proud moment for us and I thanked him on behalf of all of you who have made it possible. I owe my gratitude to all our experts who have offered their expertise voluntarily and helped to drive the pace of our learning exponentially! I must also thank all our Collaborators, the pharma industry, who have been the wheels which supported this endeavor. Without our experts, our industry and our pharma colleagues, we would never be able to reach out to you as we have over the past few years!

Wishing you all a wonderful monsoon month, we welcome our showers in today's world! In this beautiful weather, put your feet up, relax in an arm chair, and over a cup of "**Masala Chai**" and "**hot pakoras**" browse through "**Pandora**".

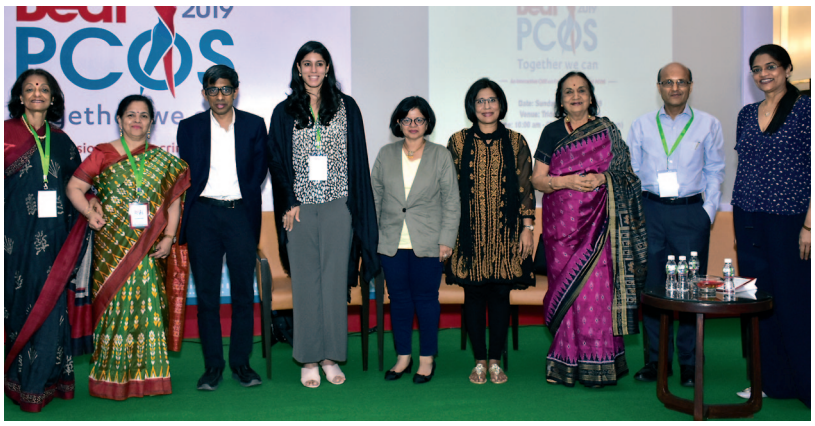
Please read inside some wonderful articles, events held over the last 4 months and events awaited! Register for the 9th-10th November meeting (page 11) the "***ISGRE Certified Course***" ***(International Society of Gynecological Reproductive Endocrinology Course)*** which will be fantastic and the "***Clinical Dilemma Day***" will be truly useful.

My sincere thanks to our guest authors, especially Prof. Joop Laven for such a detailed article, our Editorial team and Torrent for their gracious support towards this Newsletter.

Duru Shah
Founder President,
The PCOS Society

CME: Endocrine Aspects of PCOS

27th April 2019
L to R: Uday Thanawala,Reema Shah, Piya Ballani, Gulrez Tyebkhan, Aswini Bhalerao, Sandhya Saharan, Padma Ramakrishnan,Meena Malkani



30th June 2019
L to R: Duru Shah, Suchitra Pandit, Shashank Joshi, Tanya Vasunia, Sangeeta Agrawal, Gulrez Tyebkhan, Usha Saraiya, Mahesh Balsekar, Anita Soni

30th June 2019
L to R: Shashank Joshi, Tanya Vasunia, Sangeeta Agrawal, Gulrez Tyebkhan, Mahesh Balsekar

30th June 2019
Piya Ballani

30th June 2019
Duru Shah, Usha Saraiya

27th April 2019, Mumbai

TIME	TOPIC	SPEAKER
03:00-04:00 pm	Free Registration	
04:00-04:10 pm	Welcome	**Dr. Uday Thanawala**
	Session I Chairpersons: **Dr. Nita Dalal, Dr. Rakesh Pandia**	
04:10-04:40 pm	Diagnosis and Investigations of PCOS	**Dr. Piya Ballani**
04:40-05:10 pm	PCOS and Insulin Resistance	**Dr. Nikhil Bhagwat**
05:10-05:40 pm	PCOS and Gestational Diabetes	**Dr. Uday Thanawala**
05:40-06:10 pm	Tea/Coffee	
	Session II Chairpersons: **Dr. Sandhya Saharan, Dr. Padma Ramakrishnan**	
06:30-07:00 pm	PCOS & Fertility discussion Does obesity matter?	**Dr. Kedar Ganla**
07:00-08:00 pm	**Session III** Panel Discussion on "PCOS and Adolescence"	Moderator: **Dr. Sarita Bhalerao** Panelists: **Dr. Piya Ballani** **Dr. Duru Shah** **Dr. Ashwini Bhalerao** **Dr. Meena Malkani** **Dr. Gulrez Tyebkhan** **Dr. Sandhya Saharan**
08:00 pm	Closing remark followed by Dinner	

30th June 2019, Mumbai

TIME	TOPIC	SPEAKER
09:00-10:00 am	Free Registration followed by Breakfast	
10:00-10:10 am	Welcome	**Dr. Duru Shah**
	Session I Chairpersons: **Dr. Usha Saraiya, Dr. Uday Thanawala**	
10:10-10:40 am	PCOS and Pregnancy	**Dr. Anita Soni**
10:40-11:10 am	PCOS and Insulin Resistance	**Dr. Shashank Joshi**
11:10- 11:40 am	Diagnosis and Investigations	**Dr. Piya Ballani**
11:40 am-12:10 pm	Tea/Coffee	
	Session II Chairpersons: **Dr. Piya Ballani, Dr. Anita Soni**	
12:10-12:40 pm	PCOS and Fertility management Does obesity matter?	**Dr. Duru Shah**
12:40-01:40 pm	**Session III** Panel Discussion on "PCOS and Adolescence"	Moderator: **Dr. Suchitra Pandit** Panelists: **Dr. Sangeeta Agrawal** **Dr. Roshu Shetty** **Ms. Tanya Vasunia** **Dr. Mahesh Balsekar** **Dr. Shashank Joshi** **Dr. Gulrez Tyebkhan**
01:40-02:00 pm	Closing remarks followed by Lunch	

Monash Webinars on International PCOS Guidelines

PCOS Society of India – Monash University Collaboration

A series of 12 Webinars highlighting the latest **"International PCOS Guidelines"** are being held by the PCOS Society of India in collaboration with Monash University.

Each session lasts for 1 ½ hour which consists of a 30 minute talk on a subject of clinical relevance in PCOS, by an International speaker who has been involved in the making of the Guidelines. This is followed by an hour of discussion with Dr. Duru Shah or a senior expert of the PCOS Society of India from India. Questions from the online audience are received and replied during the discussion. Please do not miss these very informative sessions by registering on the PCOS website http://www.pcosindia.org/. Recording of the previous Webinars can be viewed on the PCOS Society website http://www.pcosindia.org/recorded-presentations.php

Upcoming Monash Webinars

30th July, Tuesday
What should we expect during pregnancy in PCOS? Any precautions before, during and after pregnancy?
Dr. Roger Hart
2:00 pm IST

12th August, Monday
Hyperandrogenism in PCOS
Dr. Joop Laven
2:00 pm IST

30th August, Friday
Optimizing Ovulation Induction in PCOS
Dr. Richard Legro
7:30 pm IST

Genetics of PCOS

Professor Joop S. E. Laven
MD, PhD.[1,2]
[1:] Head of Division of Reproductive Endocrinology and Infertility, Erasmus University Medical Center, Rotterdam, The Netherlands
[2:] Corresponding Author

Abstract

PCOS is the most common female endocrine disorder affecting some 5-15% of all women in their reproductive years. It is a notoriously heterogenous syndrome which runs within families. It has a high degree of heritability and is currently looked upon as being a complex genetic disorder.

Several hundreds of candidate genes have been studied however the majority of these genetic variants have not been replicated in sufficiently large case control studies. Genetic variants in the Fibrillin gene, the Androgen receptor, FTO gene, the Insulin receptor, the FSHR gene, the TNF alpha gene and some variants in the IL-6 gene do confer a certain risk for PCOS and have been replicated in sufficiently large studies or meta-analyses.

More recently, GWAS has identified up to 20 genetic variants genes involved in neuroendocrine, metabolic and reproductive pathways. These studies also provided evidence for shared biologic pathways between PCOS and a number of metabolic disorders, menopause, depression and male-pattern balding and a putative male phenotype. There is not much of overlap between GWAS findings and most functional molecular studies. However, most of the identified SNPs seem to play a role in a pathway responsible for trafficking and recycling of large protein transmembrane receptors. Moreover, some promising SNPs involved in gonadotropin action have been identified which do not only constitute risk factors for PCOS but also seem to influence response to ovulation induction treatment.

Last but not least evidence is accumulating that epigenetic mechanisms might as well play a role in the pathogenesis of PCOS either during fetal programming or in later life via factors as obesity and diet composition.

In conclusion genetic studies have shown that neuroendocrine, metabolic and reproductive pathways are involved in the pathogenesis of PCOS. Genetic findings are strikingly consistent between different PCOS phenotypes. There is genetic evidence for shared biologic pathways between PCOS and a number of metabolic disorders, menopause, depression and male-pattern balding, the putative male phenotype.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women characterized by ovulatory dysfunction, hyperandrogenism, and polycystic ovarian morphology (PCOM)[1]. The diagnosis is made according to the so-called 2003 Rotterdam consensus criteria.The prevalence varies between 5 and 20% depending on which population is assessed. The incidence is generally lower in unselected population based samples compared to hospital referred patients[2]. The PCOS phenotype might change with increasing age or changes in body mass[3]. The syndrome is also associated with other distressing phenomena such as depression, negative self-esteem and metabolic dysfunction characterized by insulin resistance and compensatory hyperinsulinaemia. PCOS increases the risk for type 2 diabetes mellitus, gestational diabetes and other pregnancy-related complications. Women with PCOS also more often have hypertension. Finally, if left untreated, due to unopposed estrogen exposure women with PCOS are at an increased risk to develop endometrial cancer[1].

Heritability

PCOS seems to run within families and although 50% of all sisters were unaffected only 25% had a similar phenotype compared to the proband whereas the remaining 25% suffered from hyperandrogenemia per se[4]. In subsequent studies it was shown that brothers of women with PCOS have dyslipidemia as well as evidence for insulin resistance similar to that of their proband sisters with PCOS[5]. More recently evidence emerged indicating clustering of metabolic syndrome, hypertension, and dyslipidemia in mothers, fathers, sisters, and brothers of women with PCOS[6].

Twin studies revealed similar results indicating a familial component in PCOS is due to genetic factors.The resemblance in monozygotic twin sisters for PCOS was about twice as large as in dizygotic twin pairs indicating a high degree of heritability[7].

Candidate gene studies

In PCOS candidate genes have been studies that were involved in the biosynthesis and trafficking of androgens, genes related to metabolic aspects of PCOS and genes correlated with inflammatory cytokines. Currently more than 200 studies have been reporting on single nucleotide polymorphisms (SNPs) in genes involved in these pathways. Numerous studies have been reporting on other SNPs in genes that are associated with either the risk of having PCOS or one of its characteristic features, However the majority of these studies are small and lack proper replication studies and should therefore be interpreted with caution[1].

A potential association of the D19S884 marker in the fibrillin gene with PCOS in Chinese Han women was found. A meta-analysis identified that allele 8 may increase a woman's susceptibility to PCOS[8]. Genes involved in androgen metabolism have been studied extensively. Two SNPs in the promotor region of the genes encoding for CYP17A1 and CYP11A1 were associated with serum androgen levels in a subset of Indian women[9]. However, a recent meta-analysis failed to verify this relationship[10]. The androgen receptor (AR) has also been studied in relation to PCOS susceptibility and the associated hyperandrogenism. However, a recent meta-analysis including 1536 PCOS patients and 1807 controls revealed that the lengths of CAG repeats in the AR contributed to hyperandrogenism in PCOS[11].

In a recent meta-analysis including 12 studies only one single nucleotide polymorphism (rs9939609) in the Fat Mass and Obesity associated (FTO) gene did significantly increase the risk of PCOS in women. However, two other SNP's (rs8050136 and rs1421085)were associated with PCOS only in a recessive model[12]. Given the increased risk for type 2 diabetes and the insulin resistance frequently encountered in women with PCOS into account the insulin receptor (INSR) gene also has been studied frequently. In a recent meta-analysis a total of 20 case-control studies including 23,845 controls and 17,460 PCOS cases were analyzed and only 17 SNPs were found to be associated with PCOS. Further subgroup stratification by ethnicity and weight did not lead to discovery of significant correlation. Only one other SNP e.g. rs2059807 was associated with PCOS. The current meta-analysis suggests no significant correlation between both SNPs rs1799817/rs2059806 and the susceptibility for PCOS[13]. Insulin receptor substrates (IRSs)although significantly associated with PCOS in Japanese and Greek populations a recent meta-analysis of 11 studies did not reveal a significant association between IRS 1 SNPs and the risk to develop PCOS [14]. A recent meta-analysis revealed no significant association between INS VNTR polymorphisms and the risk of PCOS in the overall population[15].

There are several FSH receptor polymorphisms located inthe FSHR gene. The two most common are the Thr307Ala and Asn680Ser polymorphisms. A total of 11 studies were included in a recentmeta-analysis. The Asn680Ser variant is significantly associated with treatment outcome and pregnancy rates in ovulation induction. No significant associations were found between Thr307Ala and PCOS[16].

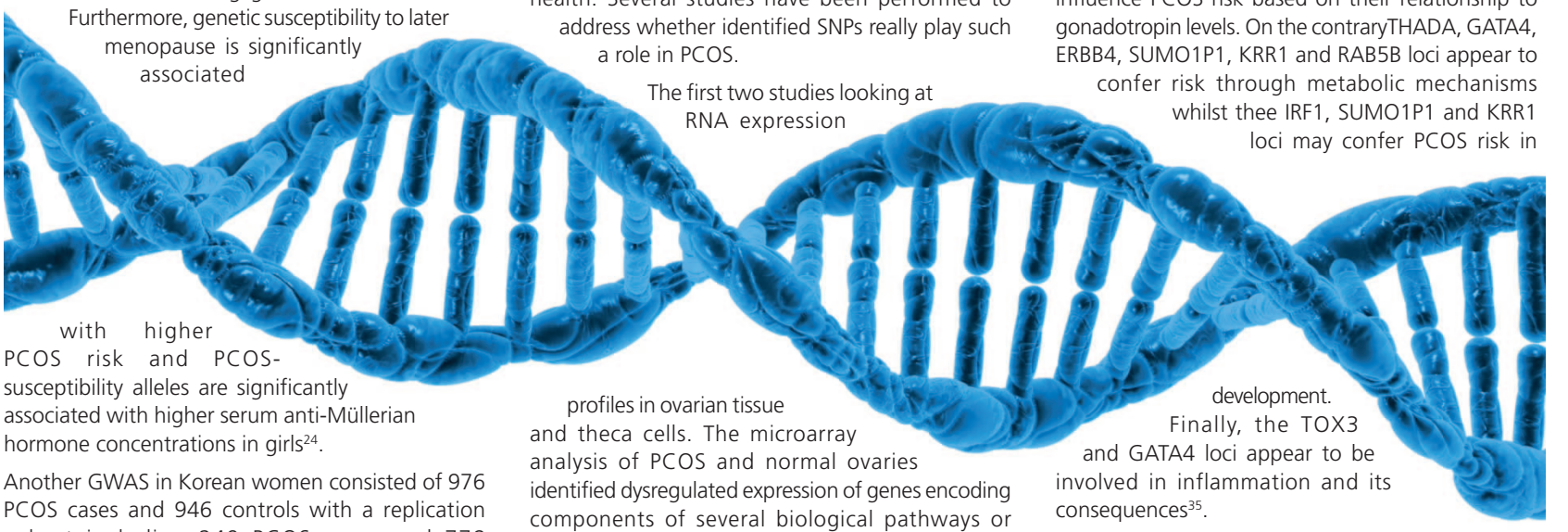
More recently based on the fact that AMH serum levels are increased in women with PCOS SNP's in the AMH gene as well as in the AMH Type II Receptor (AMHR2) gene have been studied. Neither SNP's in the AMH gene nor those in the AMHR2 did confer a heightened risk for PCOS[17]. The results of a meta-analysis,including 13 studies, assessing the role of different TNF alpha SNPs and PCOS susceptibility suggests a positive associations between oneTNF-alphaSNP (1031 T>C and IL-6 -174G>C) and the risk of PCOS. However, no associations were detected betweenanother 9 SNPs in the TNF alpha gene and the risk for PCOS[18]. Another meta-analysis including a total of 14 studies investigated the association of SNPs in the interleukins IL-6 and IL-1beta and did not find a significant relationship with the susceptibility for PCOS[19,20].

Genome Wide Association Studies (GWAS)

The first GWAS in PCOS was performed by a group based at Shandong University in China. The discovery set included 744 PCOS cases and 895 controls and subsequent replications involved two independent large cohorts of Han Chinese women with PCOS and controls. Three genome wide significant loci were identified showing strong associations with PCOS located at chromosome 2 (2p16.3 and 2p21) and chromosome 9 (9q33.3)[21]. In a second GWAS published one year later they identified 9 new loci that significantly associated with PCOS. The PCOS associated signals showed evidence of enrichment for candidate genes related to insulin signaling, gonadotropic hormone function and type 2 diabetes. Other candidate genes were related to calcium signaling and endocytosis[22].

A few years later a study in American women from European descent was published identifying two new

loci reach mapping to chromosome 8 (8p23.1) and chromosome 11 (11p14.1), and a known locus on chromosome 9 (chr 9q22.32) previously found in Chinese GWAS. The SNP on chromosome 11 in the region of the follicle-stimulating hormone B polypeptide (FSHB) gene was strongly associated with the former PCOS NIH diagnosis as well as with luteinizing hormone levels[23]. In the same year a large European collaboration produced another GWAS on PCOS. Six signals for PCOS in or near known genes (ERBB4/HER4, YAP1, THADA, FSHB, RAD50 and KRR1) were identified. Mendelian randomization analyses indicate causal roles in PCOS etiology for higher BMI, higher insulin resistance and lower serum sex hormone binding globulin concentrations. Furthermore, genetic susceptibility to later menopause is significantly associated with higher PCOS risk and PCOS-susceptibility alleles are significantly associated with higher serum anti-Müllerian hormone concentrations in girls[24].



Another GWAS in Korean women consisted of 976 PCOS cases and 946 controls with a replication cohort including 249 PCOS cases and 778 controls.One novel locus with genome-wide significance and seven moderately associated loci for PCOS were identified. The strongest association was on chromosome 8 (8q24.2). The latter signal was located upstream of the KHDRBS3 gene, which is associated with telomerase activity, and could drive PCOS and related phenotypes[25].

Another GWAS compared patients with PCOS with women from infertile couples due to tubal occlusion or male factor infertility genes identified were the known THADA,DENND1A and a new locus in the TOX3 gene[26].

A recent meta-analysis cross-ethnic effects of the through GWAS identified genetic variants showed that overall for 12 of 17 genetic variants mapping to the Chinese PCOS loci similar effect sizes and identical directions in PCOS patients from Northern European ancestry, indicating a common genetic risk profile for PCOS across populations. Therefore, it is expected that large GWAS in PCOS patients from Northern European ancestry will partly identify similar loci as the GWAS in Chinese PCOS patients[27].

Indeed, in the most recent study in over 10,000 cases of PCOS and over 100,000 controls of European ancestry identified only 3 novel loci (near the PLGRKT, ZBTB16 and MAPRE1genes) and replicated 11 previously reported loci (see Figure 1). Strikingly this study showed that the genetic architecture was similar between PCOS diagnosed by self-report and PCOS diagnosed by NIH or non-NIH Rotterdam criteria across common variants at 13 loci. Identified variants were associated with hyperandrogenism, gonadotropin regulation and testosterone levels in affected women. Moreover, linkage disequilibrium score regression analysis revealed genetic correlations with obesity, fasting insulin, type 2 diabetes, lipid levels and coronary artery disease, indicating shared genetic architecture between metabolic traits and PCOS. Finally, Mendelian randomization analyses suggested that all loci associated with body mass index, fasting insulin, menopause timing, depression and male-pattern balding play a causal role in PCOS[28].

Functional studies

The ultimate proof that SNPs in or near genes are involved in the pathogenesis of PCOS is at the end of the day derived from functional studies showing that gene products really influence phenotypical features, response to treatment and long term health. Several studies have been performed to address whether identified SNPs really play such a role in PCOS.

The first two studies looking at RNA expression profiles in ovarian tissue and theca cells. The microarray analysis of PCOS and normal ovaries identified dysregulated expression of genes encoding components of several biological pathways or systems such as Wnt signaling, extracellular matrix components, and immunological factors. Analyses of whole ovarian tissue mounts and those only harboring theca cells were surprisingly similar[29, 30]. Surprisingly there is not much of overlap between the expression array findings and the risk loci discovered through GWAS. Of interest is that most of the identified dysregulated genes were also involved in oxidative stress, lipid metabolism, and insulin signaling. This might implicate that these genes may be involved in follicular growth arrest as well as in the metabolic disorders associated with PCOS[31].

A more recent studydemonstrated that a splice variant (DENND1A.V2) derived from the DENND1Agene identified in all GWAS up till now plays a functional role in controlling theca cell steroidogenesis. This particular study showed that overexpression of DENND1A.V2 is sufficient to convert normal theca cells into a PCOS biochemical phenotype characterized by increased CYP17A1 and CYP11A1 gene expression and augmented androgen and progestin production. Moreover, suppression of DENND1A.V2 function pushes PCOS theca cells towardsa normal phenotype, non PCOS phenotype in terms of steroidogenic enzyme gene expression and steroid production[32]. The same group reviewed the functional roles of strong PCOS candidate loci focusing on FSHR, LHCGR, INSR and DENND1A. They proposed that these candidate genes comprise a hierarchical signaling network by which DENND1A, LHCGR, INSR, RAB5B, adapter proteins, and associated downstream signaling cascades converge to regulate theca cell androgen biosynthesis. Moreover, other genetic variants identified in earlier GWAS like YAP1, RAB5B, C9orf3, TOX3, HMGA2 genes also fit into this model as well[33]. Indeed, in a Chinese study it was shown that applying a recessive model certain THADA variants were associated with increased serum luteinizing hormone (LH) as well as increased testosterone levels in subjects with PCOS[34].

A very recent study looking at expression levels of several of the GWAS identified genetic variants in adipose tissue biopsies. Subsequently these women were treated with metformin for some time. A variant in the THADA locus was associated with response to metformin and metformin was a predicted upstream regulator at the same locus. Moreover, the FSHB locus was associated with serum LH levels. Hence, FSHB, FHSR and LHR loci may influence PCOS risk based on their relationship to gonadotropin levels. On the contraryTHADA, GATA4, ERBB4, SUMO1P1, KRR1 and RAB5B loci appear to confer risk through metabolic mechanisms whilst thee IRF1, SUMO1P1 and KRR1 loci may confer PCOS risk in development. Finally, the TOX3 and GATA4 loci appear to be involved in inflammation and its consequences[35].

Several other PCOS risk loci have promising functional candidate genes mapped to signals at 2p16.3 (LHCGR, FSHR) and 11p14.1 (FSHB). Data on the role of FSHR polymorphisms in PCOS are conflicting. In largeChinese studies FSHR polymorphisms are not associated with either PCOS risk or with PCOStreatment outcome whereas in Caucasians these polymorphisms seemto influence the risk of having PCOS. Moreover, these latter studies also showed that somepolymorphisms might affect some clinical features of PCOS as well as treatment outcome. Although most research has focused on the role of FSHR polymorphisms there seems to bealso some evidence showing that single nucleotide polymorphisms (SNPs) in the LHCG-Ras well as those in FSH-B gene might also alter the phenotype of PCOS[36].

Anti-Müllerian hormone (AMH) serum levels are increased in most women with PCOS. Moreover, there seems to be a genetic predisposition for this phenomenon because fathers as well as brothers form women with PCOS also have higher levels of AMH[37]. Although earlier studies were not able to show that genetic variants in the AMH and AMH type II receptor gene were associated with PCOS susceptibility. However, the latter study did reveal that the AMH Ile(49)Ser polymorphism contributes to the severity of the PCOS phenotype [38]. Interestingly, a recent report identified 24 rare genetic variants in a case control study. Eighteen of these variants were specific for PCOS patients and nearly all of them were associated with decreased AMH signaling. This might increase androgen biosynthesis due to decreased AMH-mediated inhibition of CYP17 activity[39].

Similarly, reduced methylation in the LHCGR locus and increased methylation in the INSR locus have been described in detail suggesting that local genetic variation plays an important role in gene regulation. For instance non-obese PCOS women possess significant alterations in LH receptor expression resulting in increased androgen secretion from the ovary[40, 41]. Moreover, in obese women with PCOS the insulin receptor is underexpressedin metabolic tissues and overexpressed in the ovary, resulting in peripheral insulin resistance and excess ovarian androgen production. These studies provide a genetic and molecular basis for the reported clinical heterogeneity of PCOS[41].

Conclusions

PCOS is a complex genetic disorder which runs within families of affected women and it has a high degree of heritability. Several hundreds of candidate genes have been studied however the majority of these genetic variants have not been replicated in sufficiently large case control studies. Genetic variants in the Fibrillin gene, the Androgen receptor,FTO gene, the Insulin receptor, the FSHR gene, the TNF alpha gene and some variants in the IL-6 gene do confer a certain risk for PCOS and have been replicated in sufficiently large studies or meta-analyses. More recently, GWAS has identified up to 20 genetic variants genes involved in neuroendocrine, metabolic and reproductive pathways. These studies also provided evidence for shared biologic pathways between PCOS and a number of metabolic disorders, menopause, depression and male-pattern balding, a putative male phenotype. There is not much of overlap between GWAS findings and most functional molecular studies. However, most of the identified SNPs seem to play a role in a pathway responsible for trafficking and recycling of large protein transmembrane receptors. Moreover, some promising SNPs involved in gonadotropin action have been identified which do not only constitute risk factors for PCOS but also seem to influence response to ovulation induction treatment.

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Prevention of OHSS in PCOS

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Ovarian hyperstimulation syndrome (OHSS) is a preventable, iatrogenic multi-organ disorderassociated with ovarian stimulation in PCOS. In most cases it is self-limiting, although can occasionally be life threatening. Moderate-to-severe OHSS occurs in approximately 1%-5% of cycles[1]. The traditional description of the syndrome generally includes a spectrum of findings ranging from mild, moderate to severe and critical category[2]. Severe and critical OHSS can lead to serious complications, including pleural effusion, acute renal insufficiency, and venous thromboembolism.

Prevention of OHSS

- Although complete prevention of OHSS is still notpossible, risk stratification and subsequent tailor-made treatmentwill reduce the incidence of OHSS considerably. It mainly involves identification of patients at risk and prediction of development of OHSS, and in cases of OHSS supportive therapy to prevent complications.
- **Risk factors for OHSS[3]**:
  There is fair evidence that young women (<35 yrs age), lower BMI, PCOS, AFC>24, elevated AMH values (>3.4 ng/ml), High dose gonadotropin stimulation, GnRH agonist protocol, peak estradiol levels (>3,500 pg/ml), high number of oocytes retrieved (>25 follicles), hCG for trigger or luteal support, Previous OHSS, Multiple pregnancy are associated with an increased risk of OHSS.
- **Prediction:** Ultrasound monitoring of ovarian stimulation response and estradiol monitoring (E2) are the best predictors of high risk for developing OHSS.

Preventive strategies

Metformin therapy for Polycystic Ovary Syndrome (PCOS) is a safe and effective insulin sensitizing agent whichreduces the risk of OHSS by inhibiting the secretion of vasoactive amines. A recentmetanalysis[4] has shown that metformin reduces therisk of OHSS by 63%. A daily dose of 500-1500 mg, 3-4 months prior to the ovarian stimulation is recommended.

GnRH antagonist protocol with agonist trigger:A recent Cochrane review[5] of 2016 showed that antagonist protocols are associated with a reduced risk of OHSS without a significant difference in the live birth rate when compared with agonist cycles (2.7% vs 12%). With antagonist protocol GnRH agonist trigger can be given instead of hCG trigger to further reduce the chance of OHSS to less than 0.2%[6]. But we cannot do fresh embryo transfer with agonist trigger as endometrial receptivity will be reduced, we have to freeze all and transfer on later date.

Individualized Controlled Ovarian Stimulation (iCOS) and AMH-based FSH dosing algorithm: iCOS protocols adjusting the dose and durationof gonadotropins for at-risk patientsanda new concept of AMH-algorithm can be used to select the starting dose of FSH which allows appropriate stimulation with low risk of OHSS[7].

Coasting: It is a strategy where the administration of gonadotropins is withheld along with hCG for a few days until the levels of serum oestrogen have declined to acceptable levels.

The duration ofdelay is usually 3- 4 days without affecting oocyte quality, while cycle cancellation should be considered when controlled drift period is > 4 days. A Cochrane review[8] has shown no evidence of benefit in the use of coasting to prevent OHSS.

Freezing of Embryos: This technique involves cryopreservationof all oocytes/ embryos following oocyte retrieval and transfer at a later date in a non-stimulated cycle. This will not reduce the incidence of early-onset OHSS but will reduce late onset OHSS[9].

Avoidance of hCG for luteal phase support: Progesterone, when used instead ofhCG, has shown to halve the risk of OHSS[10].

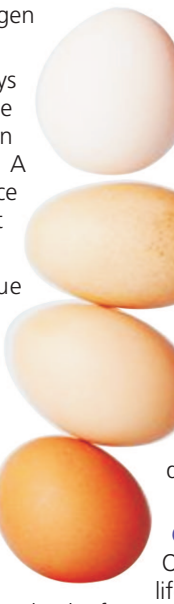
Cycle cancellation: A guaranteed method of eliminating OHSS is cycle cancellation and the withholding of hCG administration. There is an associated financial and emotional burden for the patient with this preventive strategy.

VEGF Antagonists: dopamine agonists act by inactivating VEGF receptor 2 and preventing the increase in vascular permeability. Cabergoline 0.5 mg is taken daily from the day of hCG injection and continued for 10 days. There is a moderate amount of evidence to show that dopamine agonists reduce the incidence but not the severity of OHSS, with similar pregnancy rate with routine use[11]. Other dopamine agonists like Pergolide, Quinagolide, Talipexole hydrochloride etc and VEGF inhibitor (Bivacizumab) when used for the treatment or prevention of OHSS needs titration of their dosages and more studies are needed to prove their efficacy in clinical practice.

Albumin and Hydroxyethylstarch (HES): It has been postulated that administration of 25% albumin at the time of oocyte retrieval may help to reduce the incidence of OHSS by binding to, and deactivating, vasoactive mediators. A Cochrane review found only limited evidence of benefit and hence the routine use is not recommended. HES 6% is a safe alternative to albumin and a Cochrane meta-analysis[12] suggested significant decrease in the incidence of severe OHSS. Further research is needed before its routine use.

Calcium gluconate: There is fair evidence that calcium lowers OHSS risk. Studies have investigated whether an IV calcium infusion (10 mL of 10% calcium gluconate in 200 mL normal saline) on the day of oocyte retrieval and days 1, 2, and 3 after oocyte retrieval can decrease OHSS risk[13].

In Vitro Maturation (IVM) following retrieval of immature oocytes is a safe alternative, but it is not widely used as the pregnancy and implantation rates are not as high as with IVF treatment. However due to the recent advancements in cryopreservation techniques there has been an improvement in the clinical outcomes[14].



IV Fluid and electrolyte imbalance management: In order to prevent multi system organ failure and to ensuretissue and organ perfusion, adequate intravascular volume mustbe maintained. By strict monitoring of electrolytes and haematocrit values and correcting the deficit reduces the progression and complications of OHSS.

Paracentesis is an important treatment option in severe OHSS. Ultrasound guided paracentesiseither via thetransvaginalor transabdominalroute hasshown to reduce the duration of hospital stay. Paracentesis reduces intra-abdominal pressure and improves organ perfusion. Thoracocentesis is considered after careful assessment of the degree of respiratory compromise.

Thromboprophylaxis:Women with severe OHSS are at increased risk of thromboembolism[15].

Thromboprophylaxis includes mobilisation, avoidance of dehydration, use of full-length graduated compressing stockings and administration of low molecular weight heparin. Use of intermittent pneumatic compression devices should be considered for patients confined to bed.

Conclusion

OHSS can result in significant morbidity and even life threatening complications in severe forms. With proper identification of patients at risk, and monitoring the patients, we can decrease the incidence and progress of severity of OHSS effectively with available preventive strategies.

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Association Between Polycystic Ovarian Syndrome and the Risk of Preeclampsia

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Director, Evidence-based guideline in PCOS project.

Introduction

Polycystic ovary syndrome (PCOS) is a common heterogeneous endocrine disorder characterized by irregular menses, hyperandrogenism, and polycystic ovaries. Its prevalence varies from 8-13%. In India the prevalence is 3.7 to 22.5%[1]. According to Rotterdam diagnostic criteria PCOS is diagniosed when two of three criterias are fulfilled, i.e oligo or anovulation, clinical and or biochemical hyperandrogenism, polycystic ovaries on ultrasound after exclusion of related disorders. Insulin resistance is recognized as a key feature of PCOS[2]. PCOS is more than just a reproductive disorder, and is currently considered a syndrome with metabolic consequences that could affect women's health during different stages of reproductive and post-reproductive life. As a consequence of anovulation, fertility treatment is often necessary to achieve a pregnancy. PCOS is a primary risk factor for adverse pregnancy outcomes. Data suggests that patients with polycystic ovary syndrome (PCOS) are at increased risk of developing preeclampsia; however several studies have failed to find an association between the two. The precise mechanism that links PCOS to preeclampsia remains unknown, although aberrant placental growth may play a role. In addition, many PCOS patients ultimately conceive through assisted reproductive technology, a process that has been independently associated with preeclampsia[3]. Women with PCOS have multiple factors that may lead to an elevated risk of pregnancy, including a high prevalence of Impaired glucose tolerancee-a clear risk factor for gestational diabetes-and Metabolic syndrome with hypertension, which increases the risk for pre-eclampsia and placental abruption.

Pathophysiology

Women with PCOS present a 3-4-fold increased risk of developing pre-eclampsia (PE) during pregnancy as reported by a retrospective metaanalysis by Boomsma et al., 2006; Kjerulff et al., 2011; Qin et al, 2013 [4,5,6]. The pathophysiological explanation is debated, as several characteristics of the PCOS population, including obesity and the use of assisted reproductive techniques, are potential confounding factors. Maternal metabolic, inflammatory, or hormonal profiles leading to infertility could increase the risk of adverse pregnancy outcome. Hyperandrogenism might influence the risk of pregnancy complications, as shown from clinical data on the most frequent causes of the hyperandrogenic state during pregnancy (i.e. pregnancy luteoma and hyperreactio luteinalis; in pregnant women with PCOS androgens levels are high and raise significantly through pregnancy.

In PCOS, hyperandrogenism is closely related to the incidence and extension of microscopic alterations in early trophoblast invasion and placentation. In women with PCOS and preeclampsia serum testesterone levels are increased and concentration of sex hormone binding globulin decreases, thus the excessive free testosterone induces a state of synthetic and vascular hyperactivity. The alterations in endovascular trophoblast invasion and placentation may be the result of a suboptimal

implantation process due to the direct effect of androgens on the endometrium and/or to a specific tissue susceptibility.

An abnormal pattern of low-grade chronic inflammation in combination with a subclinical impairment of vascular structure and function could result in a hypoxic state with abnormalities of physiological changes and remodelling of spiral vessels, with subsequent reduced depth of endovascular trophoblast and abnormal placentation[7]. These abnormalities of the utero-placental circulation have been confirmed by Doppler velocimetry in pregnant women with PCOS[8].

Management

Since almost all observational findings showed a lower risk of obstetric and neonatal adverse outcomes in normal weight women, losing weight before conception up to an optimal body weight is suggested (American College of Obstetricians and Gynecologists, 2013). Women should be screened and treated for hypertension and diabetes prior to attempting conception. Pregnant women with PCOD may become a high risk pregnancy at any time. Hence proper antenatal care is mandatory to prevent and treat the complications. Medical interventions that improve insulin sensitivity appear to have positive impact on both early and late pregnancy complications in women with PCOS. Data regarding the potential effect of metformin on the prevention of PIH and/or PE are scarce. Metformin administration during pregnancy reduced uterine artery impedance between12 and 19 weeks of gestation[9]. Thus, its administration in the early phases of pregnancy might influence the trophoblastic invasion of the maternal deciduas allowing a successful placentation with consequent improvement of the pregnancy outcomes. Moreover, at present, clinical data seem to show a limited effect of metformin in preventing PIH and PE[10].

Conclusion

There are various studies with contrasting results regarding association between PCOS and preeclampsia as pre-existing conditions like obesity and interventions like assisted reproductive techniques are independent risk factors for preeclampsia thus confounding the effect of PCOS on preeclampsia. However low progesterone and high androgen level have an adverse effect on trophoblast invasion and may contribute to preeclamptis agents, hence it may be prudent to start low dose aspirin and insulin sensitisers like metformin in prevention of preeclampsia and further morbidity. Preeclampsia and PCOS both have are independent risk factors for metabolic syndrome and cardiovascular diseases in future and require evaluation.

Suggested Reading

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ISGRE COURSE

International Society of Gynecological Reproductive Endocrinology Course

Saturday 9th- Sunday 10th
November 2019

Taj Santacruz, Mumbai

ISGRE COURSE CERTIFIED BY ISGE

Day 1 – Saturday 9th November, 2019

09.30 a.m.	Registration	
10.00-11.30 am	**SESSION I – Brain & Metabolism**	
10.00-10.30 am	*The Brain Phenotype in PCOS – Clinical implications*	**Sarah Berga**
10.30-10.45 am	Discussion	
10.45-11.15 am	*PCOS as a Metabolic and Neuroendocrine disease*	**Alessandro Genazzani**
11.15-11.30 am	Discussion	
11.30 am-12.00 noon	**TEA / COFFEE BREAK**	
12.00 noon-1.30 pm	**Session II – Adolescent PCOS**	
12.00-12.30 noon	*Metabolic impairment of Adolescent PCOS: new integrative therapeutic strategies*	**Andrea Genazzani**
12.30-12.45 pm	Discussion	
12.45-1.15 pm	*Risk factors for the Development of Adolescent PCOS*	**Charles Sultan**
01.15-01.30 pm	Discussion	
01.30-02.30 pm	**LUNCH**	
02.30-04.00 pm	**Session III – Clinical Phenotypes in Adolescence**	
02.30-03.00 pm	*Variable Clinical expression of Adolescent PCOS*	**Charles Sultan**
03.00-03.15 pm	Discussion	
03.15-03.45 pm	*Thyroid, Adrenal and Prolactin impairments and abnormal Ovarian Function*	**Alessandro Genazzani**
03.45-04.00 pm	Discussion	
04.00-04.30 pm	**TEA / COFFEE BREAK**	
04.30-05.30 pm	**Session IV – Adolescent PCOS – Impact on Fertility, Pregnancy, Menopause and Ageing**	
04.30-05.00 pm	*A critical Appraisal of infertility Treatment for PCOS*	**Sarah Berga**
05.00-05.15 pm	Discussion	
05.15-05.45 pm	*PCOS impairments and co-morbidities: impact on Pregnancy, Menopause and Ageing*	**Andrea Genazzani**
05.45-06.00 pm	Discussion	
06.00 pm	Close of ISGRE Course	
07.30 pm	**Evening Entertainment**	
08.30 pm	**COCKTAILS AND DINNER**	

Day 2 – Sunday 10th November, 2019

Clinical Dilemmas and Expert opinions – Get all your queries answered on Adolescent PCOS

09.00-10.30 am	**Session I – Cosmetic Issues**
09.00-09.10 am	***Capsule* – *Is skin the newly-discovered Endocrine Organ?***
09.15-10.30 am	**Clinical Dilemmas: Expert Opinions** ■ *How can I differentiate between acne of puberty and PCOS? How should I manage such acne?* ■ *How best can I diagnose and manage hirsutism in an adolescent PCOS?* ■ *Should I be concerned if my little girl starts pubic hair at 7 years of age?* ■ *What kind of Pigmentation should I look for? How should I treat?* ■ *What kind of alopecia is due to hormonal dysfunction?* ■ *Which investigations should I do for hyperandrogenemia?*
10.30-11.30 am	**Session II – Abnormal Uterine Bleeding (AUB)**
10.30-10.40 am	***Capsule* – *The Pathophysiology of AUB in PCOS***
10.45-11.30 pm	**Clinical Dilemmas: Expert Opinion** *How should we manage?* ■ *Heavy periods* ■ *Erratic periods* ■ *No periods* ■ *Continuous periods*
11.30 am-12.00 noon	**TEA / COFFEE**
12.00 noon-01.30 pm	**Session III – Obesity in adolescent PCOS**
12.00 noon-12.10 pm	***Capsule* – *Obesity: Is it the cause or result of PCOS?***
12.15-01.30 pm	**Clinical Dilemmas – Expert Opinion** ■ *Should we worry if a child is obese?* ■ *How early can we start Metformin? How much can we safely administer?* ■ *When should I suspect hypothyroidism? Is it more common in PCOS?* ■ *What kind of diet should we recommend?* ■ *What kind of exercise should we recommend?*
01.30-02.30 pm	**LUNCH**
02.30-04.00 pm	**Session IV**
02.30-02.40 pm	***Capsule* – *Adjuvants in PCOS***
02.45-04.00 pm	**Clinical Dilemmas** ■ *Are Inositols useful? If yes, dose and duration?* ■ *Does Vitamin D3 play a role in PCOS?* ■ *Should Vitamin B12 be given to all PCOS women?*
04.00 pm	**Closing Session**
04.15-05.00 pm	**TEA / COFFEE**

MEET OUR INTERNATIONAL FACULTY

Prof. Andrea Genazzani
Italy

- President, International Society of Gynecological Endocrinology (ISGE)
- President, European Society of Gynecology (ESG)
- Editor-in-Chief, Gynecological Endocrinology
- Author of more than 836 papers in peer reviewed journals and Editor of more than 45 books

Prof. Alessandro Genazzani
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- Member, Editorial Board and Reviewer of 6 peer reviewed journals
- Research areas: Neuro endocrine control of reproduction, Hypothalamic dysfunction, PCOS, Obesity, Hyperinsulinism, Peri and postmenopausal dysfunction

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- Professor and Chairman, Department of Obstetrics and Gynecology, Associate Dean Women's Health Research, Wake Forest University School of Medicine, USA.
- President, Society for Gynecological Investigation

Prof. Charles Sultan
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- Professor and Faculty of Medicine, Head of Department of Hormonology, Head of Paed Endocrine Unit, Montpellier University, France
- Editorial Board Member, J. Clin Endocrine Metab 2014-2018
- Andrea Prader Prize Awardee, the highest recognition in Pediatric Endocrinology – 2011
- President, French Society of Pediatric and Adolescent Gynecology – 2008-2010

Registration form Inclosed with this issue or Please log on to http://www.pcosindia.org

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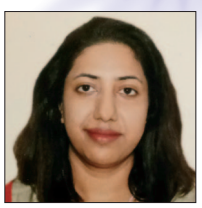
Dr. Indumathi Muthuswamy

Dr. Pankaj D. Desai



Ritu Petkar Palve

Sankalp Singh

Seema Tripathi Pandey