

An Overview of Research Programmes on PCOS at NIRRH

Dr. Smita Mahale

Director

Institute for Research in Reproductive Health
(Indian Council of Medical Research)

Mumbai

June 16-18, 2017

Bengaluru

NIRRH Mandate

Reproductive Health

Research

Services

Human Resource
Development

Basic

Clinical

Operational
&
Socio behavioural

Polycystic Ovary Syndrome

- Multifactorial, multigenic disorder of unknown etiology

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

- rates: 10% (Europe) 10% (USA) 10% (India) 10% (Global) incidence

- Long term health complications:

- Abnormal infertility

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 | Bengaluru

Dates: June 16 - 18, 2017 | Bengaluru

Dates: June 16 - 18, 2017 | Bengaluru

Dyslipidemia

Cardio Vascular Disorders

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

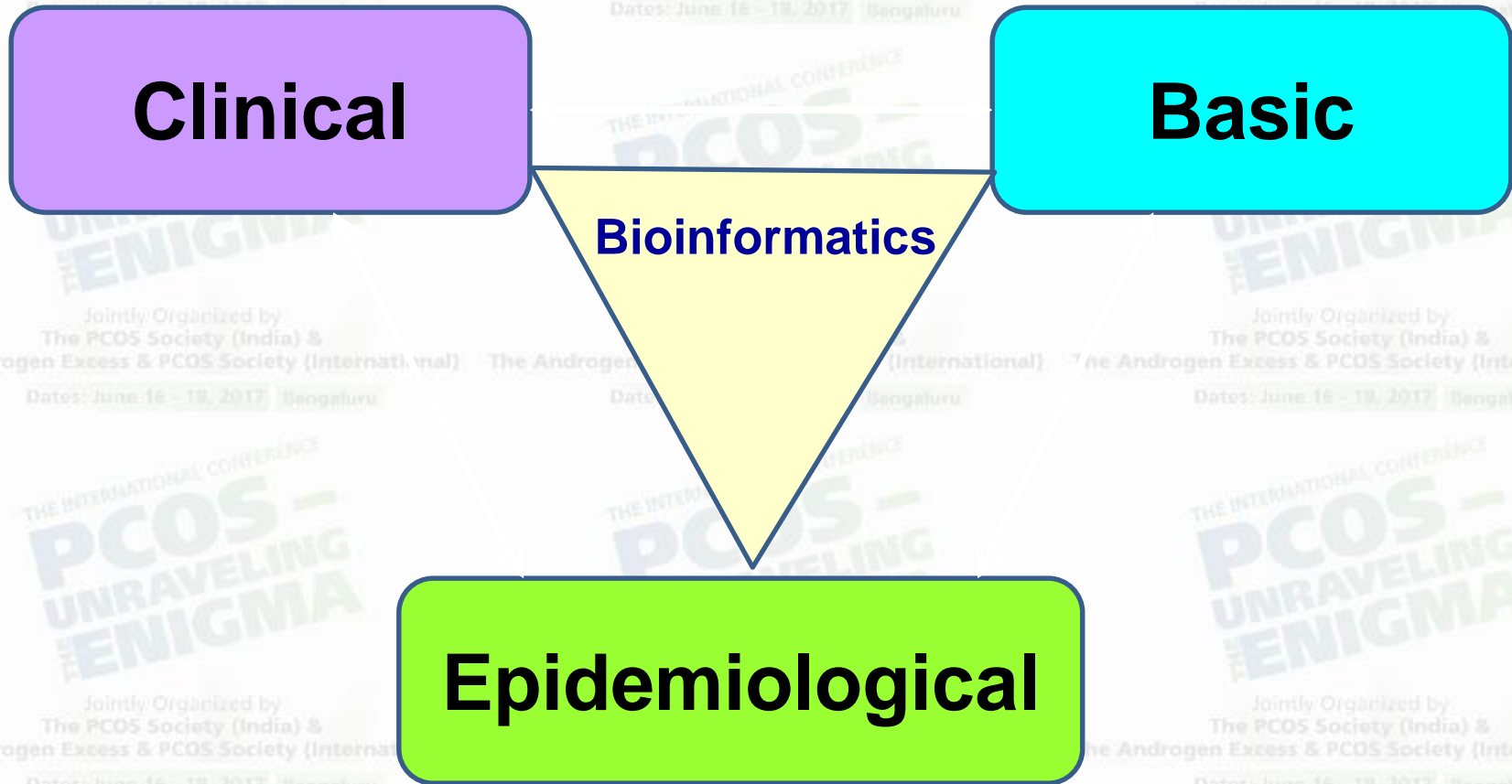
Dates: June 16 - 18, 2017 | Bengaluru

Dates: June 16 - 18, 2017 | Bengaluru

Dates: June 16 - 18, 2017 | Bengaluru

Endometrial cancer

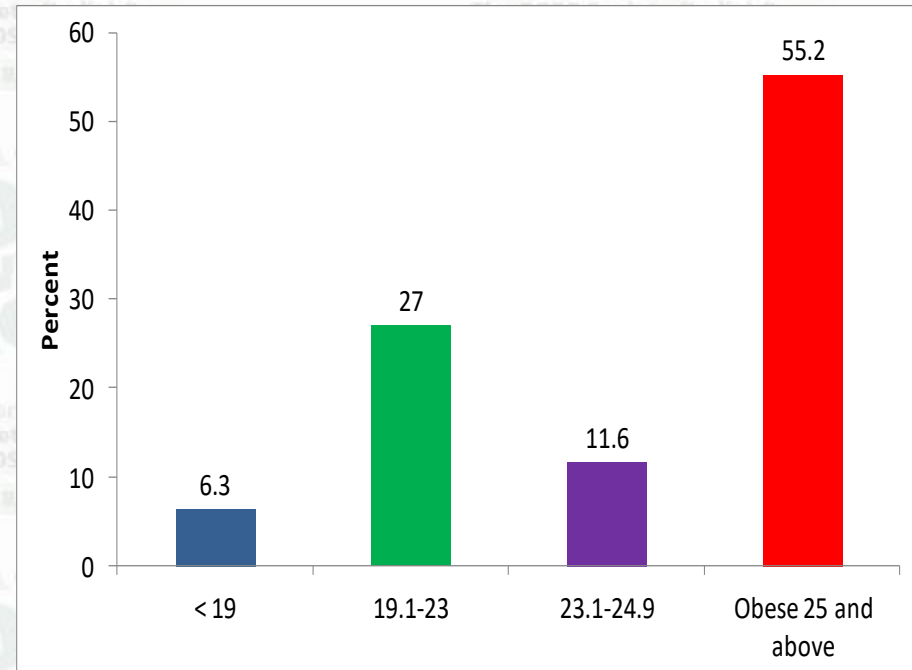
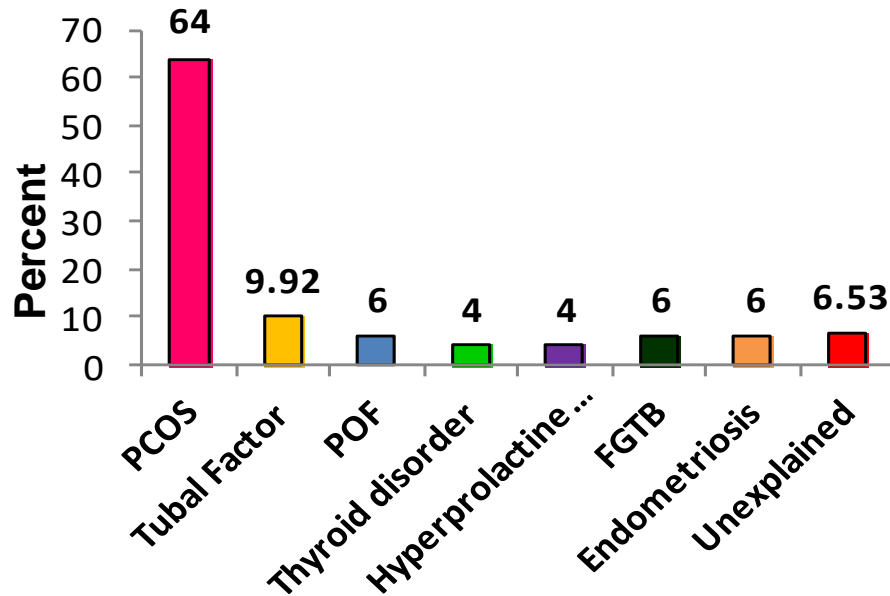
PCOS: Research at NIRRH



NIRRH Infertility Clinic Data

Female factors (n=383)

BMI (n= 98)



64% of the infertile women studies showed symptoms of PCOS

Community Based Study of PCOS: Prevalence among Adolescents and Young Girls in Mumbai

Systematic, multistage random sampling method

Jointly Organized by
The Androgen Excess & PCOS Society (International) The Androgen Excess & PCOS Society (International) The Androgen Excess & PCOS Society (International)

Jointly Organized by
The PCOS Society (India) & The Androgen Excess & PCOS Society (International) The PCOS Society (India) & The Androgen Excess & PCOS Society (International) The PCOS Society (India) & The Androgen Excess & PCOS Society (International)

Age 15-20 years (health post area) Age 12-17 years (school) Date: June 16-18, 2017

A sample size of 900 was calculated assuming a prevalence of 10% and precision of 2% at 95% confidence level

Considering a non-response rate of 10%, the total was estimated to be about 1000 girls

Eligible girls in selected study area: 10,600 (census)

Jointly Organized by
The PCOS Society (India) & The Androgen Excess & PCOS Society (International) The PCOS Society (India) & The Androgen Excess & PCOS Society (International) The PCOS Society (India) & The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru Dates: June 16 - 18, 2017 Bengaluru Dates: June 16 - 18, 2017 Bengaluru

Every 10th household approached

1st girl at household after informed consent

Medical examination at health post

Blood collection on 3rd to 7th day of normal cycle

Use of minimal-collective activity

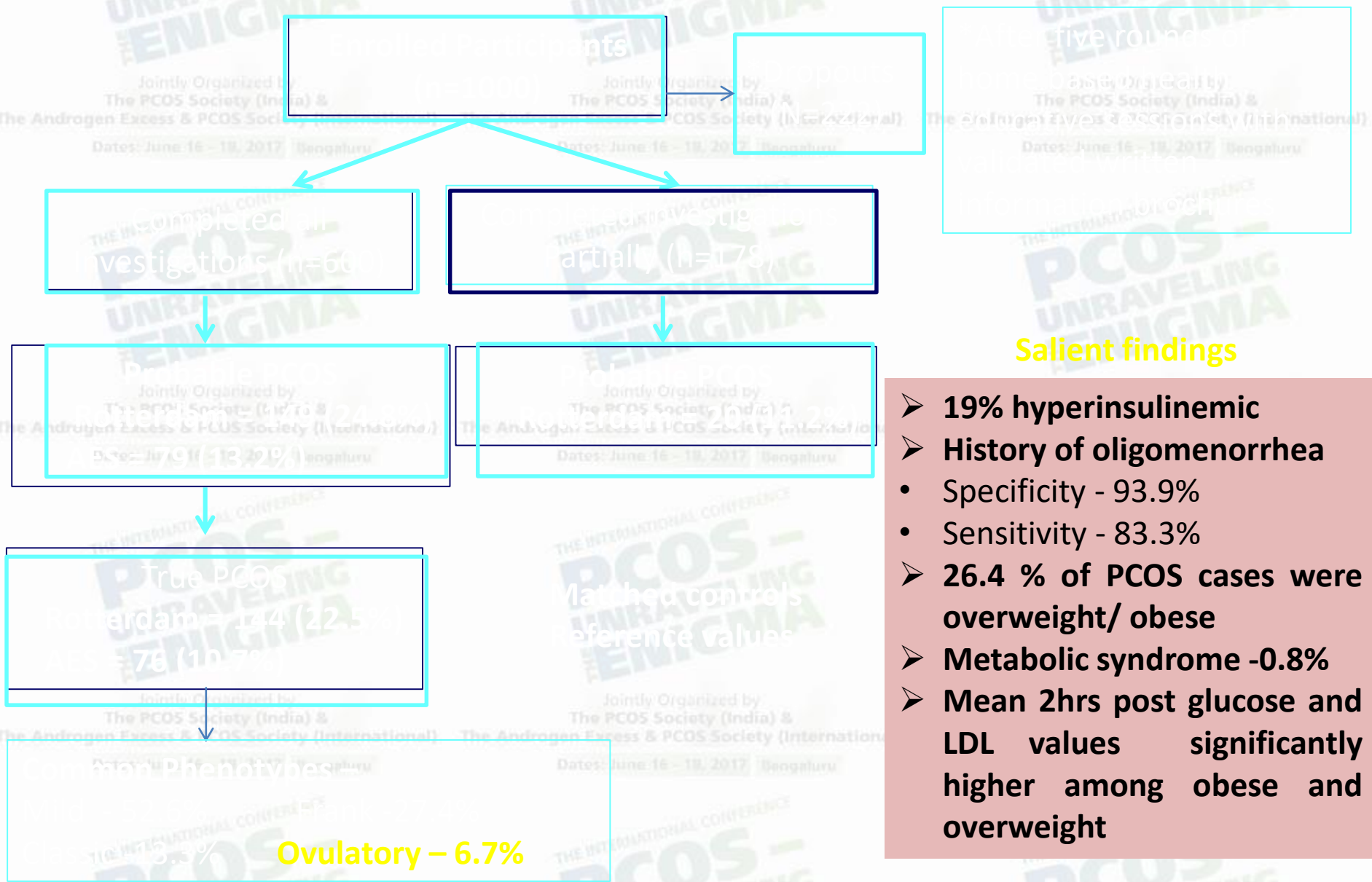
Jointly Organized by
The PCOS Society (India) & The Androgen Excess & PCOS Society (International) The PCOS Society (India) & The Androgen Excess & PCOS Society (International) The PCOS Society (India) & The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru Dates: June 16 - 18, 2017 Bengaluru Dates: June 16 - 18, 2017 Bengaluru

Controls - 1000

Joshi et al., IJEM 2014

Prevalence of PCOS among Adolescents and Young Girls in Mumbai



Five rounds of
 The International Conference
 PCOS - UNRAVELING THE ENIGMA
 Jointly Organized by
 The PCOS Society (India) &
 The Androgen Excess & PCOS Society (International)
 Dates: June 16 - 18, 2017 Bengaluru

Salient findings

- **19% hyperinsulinemic**
- **History of oligomenorrhea**
 - Specificity - 93.9%
 - Sensitivity - 83.3%
- **26.4 % of PCOS cases were overweight/ obese**
- **Metabolic syndrome -0.8%**
- **Mean 2hrs post glucose and LDL values significantly higher among obese and overweight**

Outreach Activities for the Society

THE INTERNATIONAL CONFERENCE
PCOS - UNRAVELING THE ENIGMA

THE INTERNATIONAL CONFERENCE
PCOS - UNRAVELING THE ENIGMA

THE INTERNATIONAL CONFERENCE
PCOS - UNRAVELING THE ENIGMA

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)
Local Schools
Dates: June 16 - 18, 2017 | Bengaluru

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)
Local Schools
Dates: June 16 - 18, 2017 | Bengaluru

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)
Local Schools
Dates: June 16 - 18, 2017 | Bengaluru

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)
Parents Teachers Association
Mumbai Municipal Corporation
Age Friendly Health
General Practitioners
Dates: June 16 - 18, 2017 | Bengaluru

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)
Parents Teachers Association
Mumbai Municipal Corporation
Age Friendly Health
General Practitioners
Dates: June 16 - 18, 2017 | Bengaluru

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)
Support groups
Dates: June 16 - 18, 2017 | Bengaluru

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)
Support groups
Dates: June 16 - 18, 2017 | Bengaluru

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)
Support groups
Dates: June 16 - 18, 2017 | Bengaluru



Basic Research on PCOS: (Genomics and Proteomics)

Genetics

Candidate Gene Approach

INSR, PPARG, PON1, INSL3

Polymorphisms in above candidate genes influence PCOS susceptibility and its associated metabolic and androgen traits

Proteomics

Quantitative proteomic analysis of follicular fluid

Several dysregulated processes identified may contribute to PCOS pathophysiology

Epigenetics

Global and candidate gene methylation profiles

Tissue specific epigenetic susceptibility loci are associated with PCOS

Angiogenesis

Angiogenesis in follicle of women with PCOS

Expression of angiogenic markers and angiogenic capacity of Granulosa cells and FF

Genetic Studies in PCOS

- PCOS is a complex Multigenic Disorder where gene and environmental factors interact with each other to produce PCOS phenotype
- The mode of inheritance remains unclear
- Candidate gene association studies look for differences in the frequency of genetic variants between disease cases and healthy controls
- Investigated the association of candidate genes related to insulin resistance, oxidative stress and steroidogenesis with PCOS in a population of Indian women

Genes

INSR

PPAR γ

PON1

INSL3

Candidate Gene Studies in PCOS

- Genetic pathogenic mechanism of PCOS may differ between lean and obese women
- In PCOS research, sub grouping of study participants according to phenotype is important
- Such studies would help to develop predictive genetic predisposition profiles for early identification and therapeutic intervention for women at risk of PCOS development

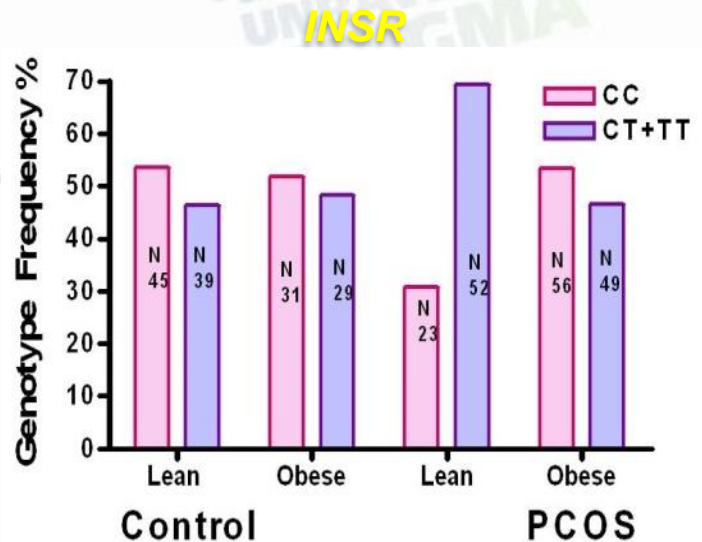
Lean vs Obese PCOS: Biochemical and Molecular Differences

Metabolic and Hormonal Profiles

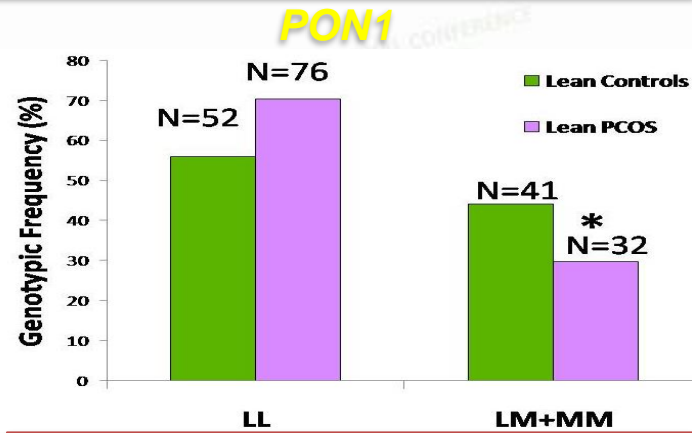
Variables	Lean PCOS (n=136)	Obese PCOS (n=199)
HOMA-IR	2.57 ± 1.58	4.28 ± 2.58*
SHBG	1.38 ± 0.86	1.38 ± 0.86
Testosterone		
TG (mg/dl)	80.51 ± 39.49	107.59 ± 46.32 *
ApoB:ApoA-1	0.64 ± 0.28	0.75 ± 0.29 *

Lean and obese PCOS women are biochemically and genetically distinct

Genotype Association



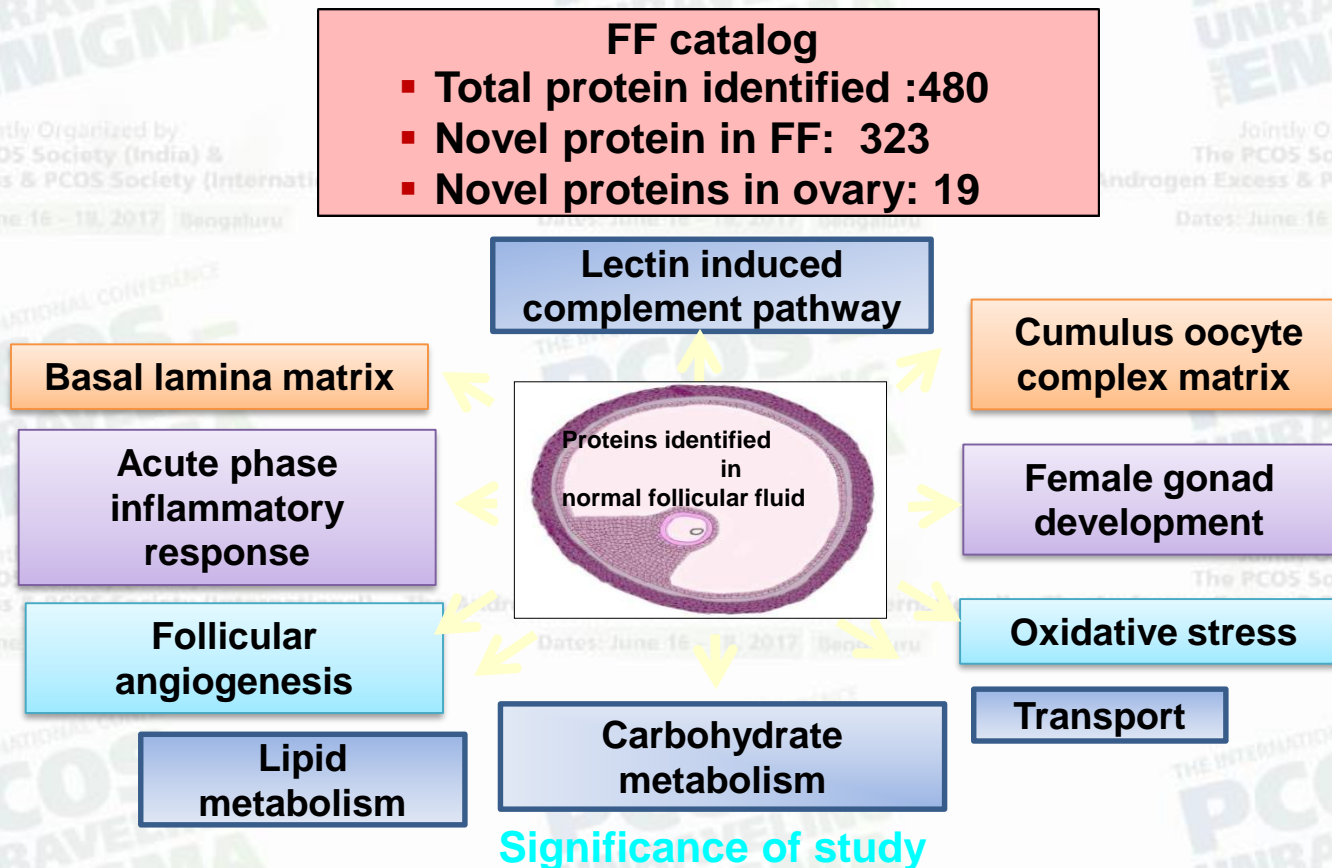
CT+TT genotype associated with lean PCOS



L55M showed association with lean PCOS

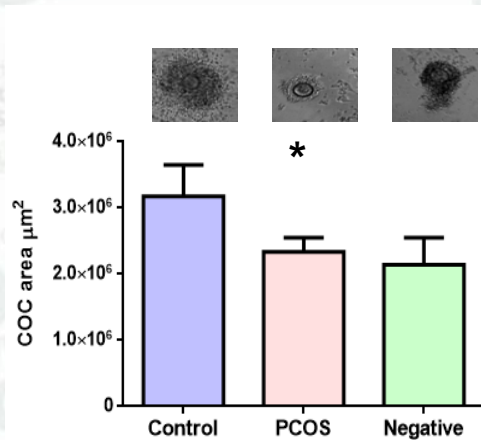
Follicular Fluid Proteomics: from Physiology to Pathophysiology of PCOS

Follicular fluid: a useful alternative for ovarian tissue

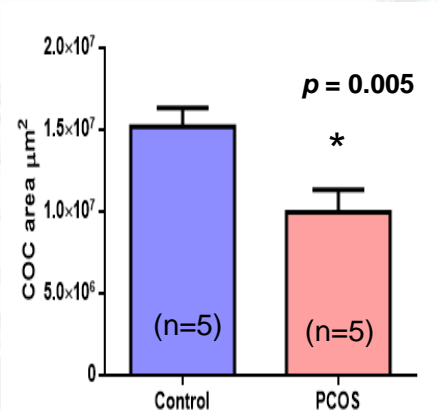


- Better understanding of the ovarian pathophysiology of PCOS
- Reference proteome for screening of suitable biomarkers for oocyte quality, IVF out come
- Suggests alteration of COC matrix functioning, follicular angiogenesis and compromised oocyte development in PCOS

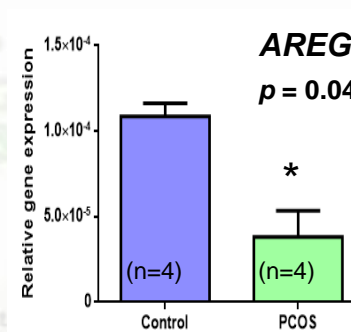
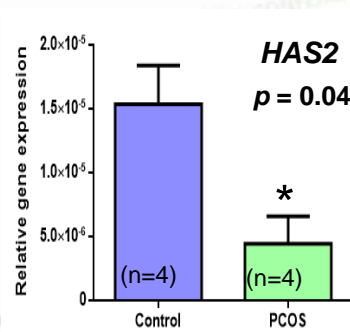
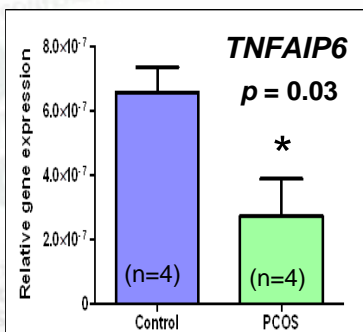
Structural and Functional Alteration of COC Matrix in PCOS



Follicular fluid from PCOS had less capacity to support murine COC expansion than control



COCs from women with PCOS were smaller than control



Expansion and mucification related genes (TNFAIP6, HAS2), growth factor AREG were significantly reduced in granulosa cells from PCOS

Understanding Follicular Angiogenesis in PCOS

Angiogenesis is essential for follicle development, oocyte growth and corpus luteum formation

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)
Dates: June 16 – 18, 2017 | Bengaluru

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)
Dates: June 16 – 18, 2017 | Bengaluru

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)
Dates: June 16 – 18, 2017 | Bengaluru

development of follicle vasculature

Proteomics study has revealed differential expression of several angiogenic proteins in FF in PCOS (*Ambekar et al 2015*)

Expression of angiogenic markers in GCs and FF of women with PCOS
Interests to be investigated

Sample collection

FF and GCs were collected from women undergoing IVF

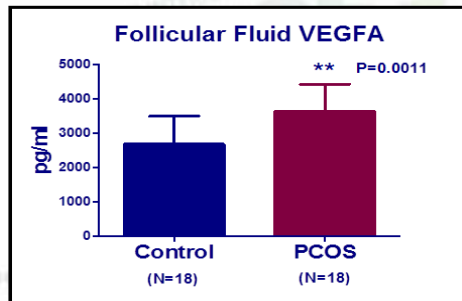
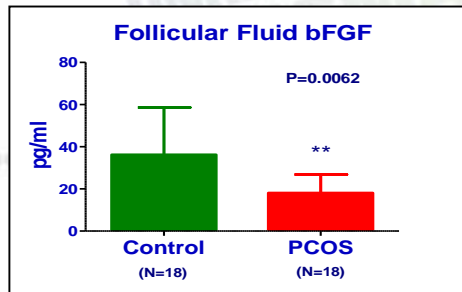
➤ **Control Women:** Healthy, regularly menstruating women of reproductive age, due to male factor infertility

➤ **Women with PCOS:** Women with PCOS undergoing IVF. Diagnosis is based on Rotterdam criteria (2003)

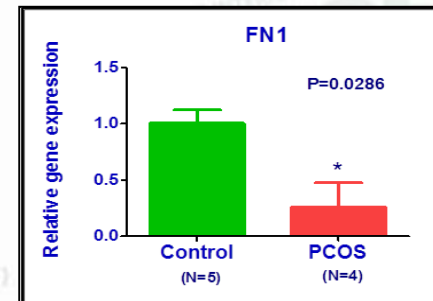
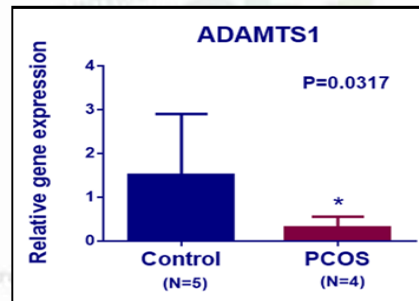
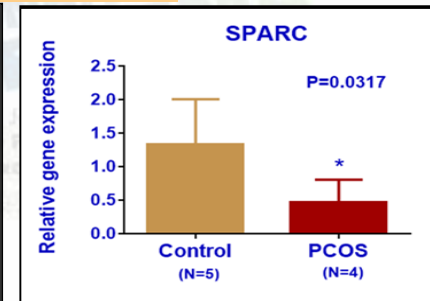
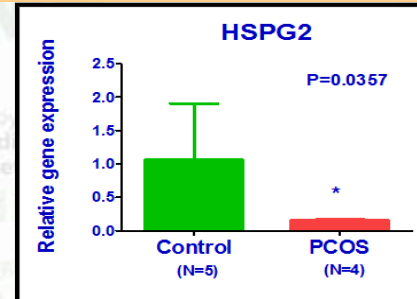
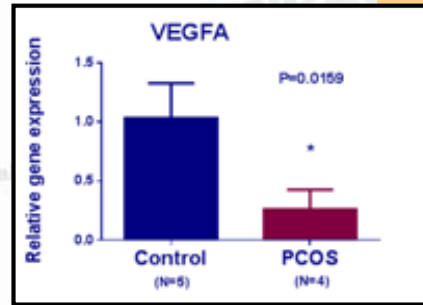
Understanding Follicular Angiogenesis in PCOS

- Angiogenesis is required for follicle development and subsequent corpus luteum (CL) formation
- Proteomics study revealed differential expression of several angiogenic proteins in follicular fluid (FF) in PCOS (Ambekar et al, JCEM 2015)
- Comparison of angiogenic markers in mural granulosa cells (MGCs) and FF of women with PCOS

Follicular Fluid Levels



Gene Expression in MGCs



Decreased concentration of bFGF in FF along with down regulation of ECM related genes involved in angiogenesis in MGCs suggests impairment of follicular angiogenesis in PCOS

Environmental Factors and PCOS

Endocrine Disruptors:

Estrogens are found in reusable plastic containers, food and beverage can liners, thermal receipt papers, baby bottles, detergents, soaps, cosmetics, dental sealants etc.

Phthalates are used in polycarbonate plastics, baby and infant products, medical devices and the enteric coating of some medications.



Dates: June 16 - 18, 2017 | Bengaluru

Dates: June 16 - 18, 2017 | Bengaluru

Dates: June 16 - 18, 2017 | Bengaluru

Dates: June 16 - 18, 2017 | Bengaluru

Dates: June 16 - 18, 2017 | Bengaluru

Dates: June 16 - 18, 2017 | Bengaluru

Dates: June 16 - 18, 2017 | Bengaluru

Dates: June 16 - 18, 2017 | Bengaluru

Dates: June 16 - 18, 2017 | Bengaluru



Plasma Levels of Endocrine Disrupting Chemicals

Jointly Organized by

The PCOS Society (India) & The Androgen Excess & PCOS Society (International)

Dates: June 16 – 18, 2017 | Bengaluru

Endocrine Disruptor

Jointly Organized by

The PCOS Society (India) & The Androgen Excess & PCOS Society (International)

Dates: June 16 – 18, 2017 | Bengaluru

Fertile Women (ng/ml)

Jointly Organized by

The PCOS Society (India) & The Androgen Excess & PCOS Society (International)

Dates: June 16 – 18, 2017 | Bengaluru

PCOS (ng/ml)

BPA	2.64	5.80
MMP	22.49	7.65
MBzP	5.72	25.71
MEHP	1.01	1.01
MEHHP	1.71	8.76

Methodology: Gas Chromatography-Mass Spectrometry (GC/MS) for

Jointly Organized by

The PCOS Society (India) & The Androgen Excess & PCOS Society (International)

Dates: June 16 – 18, 2017 | Bengaluru

Jointly Organized by

The PCOS Society (India) & The Androgen Excess & PCOS Society (International)

Dates: June 16 – 18, 2017 | Bengaluru

Jointly Organized by

The PCOS Society (India) & The Androgen Excess & PCOS Society (International)

Dates: June 16 – 18, 2017 | Bengaluru

(Advanced Instrumentation Centres at: Rula College, Mumbai & G. N. Khalsa College, Mumbai)

Basic Research: Future Perspectives

- Genome wide association study (GWAS) to identify susceptibility loci and associations of genetic variants across the genome in Indian women with PCOS

- Assessment of follicular fluid proteins as potential biomarkers for oocyte quality prediction

- Need to establish differential cytoplasmic complex between $\text{P}450_{\text{C}17\alpha}$ and $\text{P}450_{\text{C}17\beta}$

- Role of endocrine disruptors in the pathogenesis of PCOS

Bioinformatics Approach

PCOSKB: A Knowledge Base on
Polycystic Ovary Syndrome

<http://www.pcoskb.bicnirrh.res.in/>



PCOSKB

KnowledgeBase on Polycystic Ovary Syndrome

[Home](#)[Search](#) ▼[Browse](#) ▼[Tools](#) ▼[Help](#)[Analysis](#)

Polycystic ovary syndrome (PCOS) is a very common endocrine disorder reported in women worldwide and is one of the major causes of female subfertility/infertility. Numerous genes, SNPs and diseases are known to be associated with PCOS.

PCOSKB is a manually curated knowledgebase on PCOS. PCOS-related information available through scientific literature is cross-linked with molecular, biochemical and clinical databases. Information on associated genes, SNPs, diseases, gene ontologies and pathways along with supporting reference literature is collated and integrated in PCOSKB. PCOSKB will be useful for scientists and clinicians. The database currently holds information on 241 genes associated with PCOS.

Citation:

Joseph S, Barai RS, Bhujbalrao R, Idicula-Thomas S. PCOSKB: A KnowledgeBase on genes, diseases, ontology terms and biochemical pathways associated with PolyCystic Ovary Syndrome. *Nucl. Acids Res.* (2015) doi: 10.1093/nar/gkv1146. Epub 2015 Nov 17

[Statistics](#)[About BIC](#)[Feedback](#)[Links](#)[Contact Us](#)

Information Present in PCOSKB

Section	Information present	Cross-references to public databases
Gene information	Gene symbol, gene name, chromosomal location, gene summary	NCBI Gene, nucleotide databases, Ensembl database
SNP information	SNP accession, upstream and downstream sequence information, literature reference	NCBI SNP database, PubMed database
Gene Ontology	Ontology category, name, evidence and references	GO database, PubMed database
Protein information	Protein name, accession, domain information, pathway information, interacting proteins	NCBI protein database, InterPro, Pfam, KEGG, STRING, MINT, UniProt, PDB
Associated diseases	Associated diseases and their references	PubMed database
References	PubMed reference, gene symbols, accession, chromosome, polymorphism, mutation, diagnostic criteria, definition, conclusion of the study	PubMed database

PCOSKB: Browse Genes

Home

Search

Browse

Tools

Help

Analysis

Genes

SNPs

Associated Diseases

Pathways

Ontology terms

Genes

Show 10

Search

Search by alphabet All

1 to 10 of 241 Genes

Gene Symbol	Aliases	Name	Chromosomal Location	
ABCA1	ABC-1, ABC1, CERP, HDLDT1, TGD	ATP-binding cassette, sub-family A (ABC1), member 1	9q31	Details...
ACE	ACE1, CD143, DCP, DCP1, ICH, MVCD3	Angiotensin I converting enzyme	17q23.3	Details...
ACVR1	ACTRIA, ACVRLK2, ALK2, FOP, SKR1, TSRI, ACVR1	Activin A receptor, type I	2q23-q24	Details...
ADIPOQ	ACDC, ACRP30, ADIPQL1, ADPN, APM-1, APM1, GBP28	Adiponectin, C1Q and collagen domain containing	3q27	Details...
ADIPOR1	ACDCR1, CGI-45, CGI45, PAQR1, TESBP1A	Adiponectin receptor 1	1q32.1	Details...
ADIPOR2	ACDCR2, PAQR2	Adiponectin receptor 2	12p13	Details...
ADM	AM, PAMP	Adrenomedullin	11p15.4	Details...
ADRB2	ADRB2R, ADRBR, B2AR, BAR, BETA2AR	Adrenoceptor beta 2, surface	5q31-q32	Details...

PCOSKB: Browse Associated Diseases



PCOSKB

KnowledgeBase on Polycystic Ovary Syndrome



Home Search Browse Tools Help Analysis

Genes

SNPs

Associated Diseases

Pathways

Ontology terms

Associated Diseases

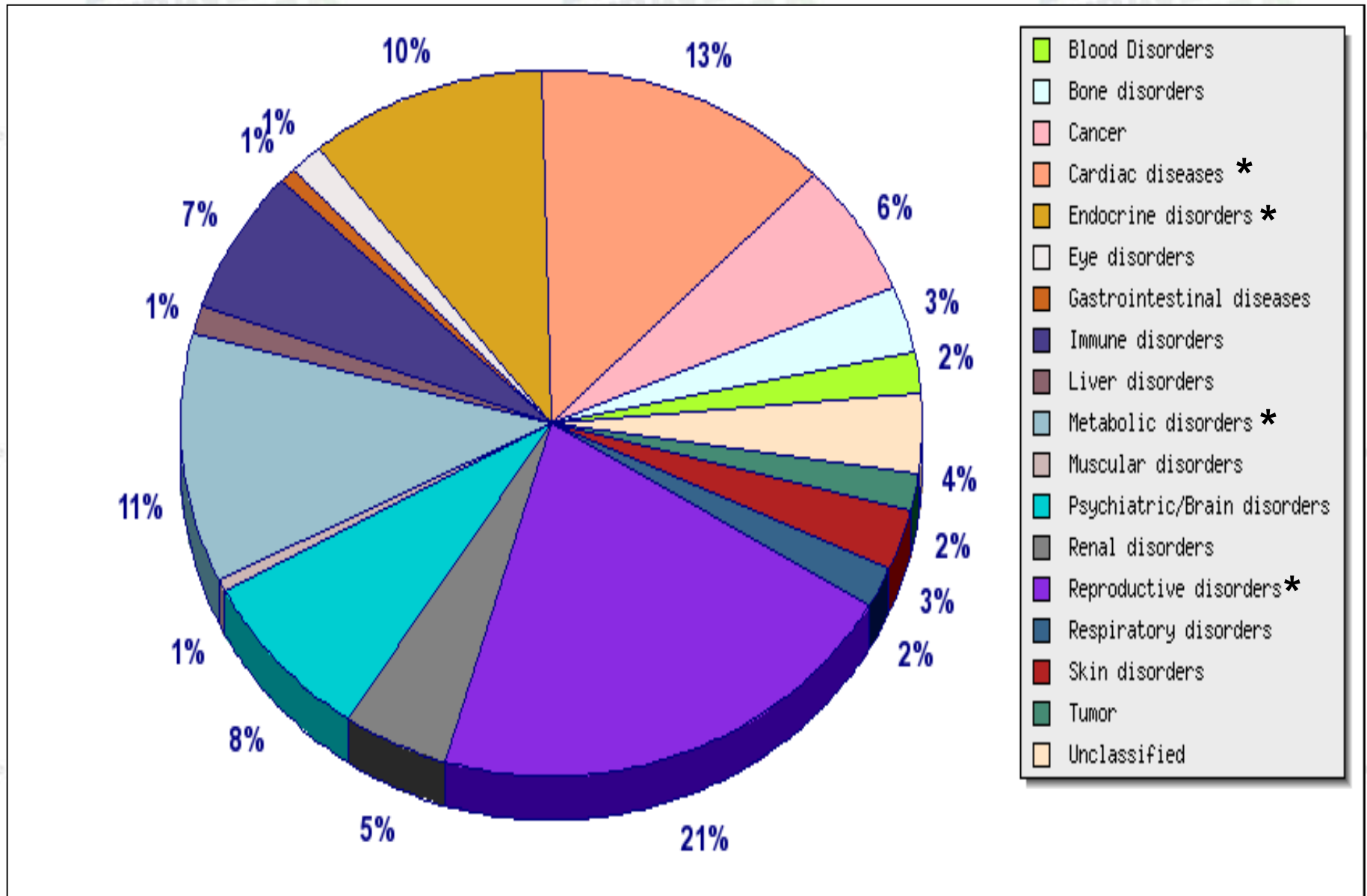
Search

Search by alphabet All

1 to 10 of 500 Diseases

Disease	Gene (G)	References
46 XY disorder of sex development	NR3C1	19246354
Abnormal endometrial function	PNPLA2	3188971
Abnormal follicular development	ESR1	12466349
Abnormal folliculogenesis	IGF2R	22951915
Abnormal glucose tolerance	CHI3L1	22583189
Abortion	LIF	16640878, 11930689
Acantholysis	IL1A	12930304, 17624241, 10082594
Acanthosis nigricans	CYP21A2	16052863

Diseases Associated with PCOS Candidate Genes



Need of the Hour



Multidisciplinary approach to address PCOS

Expert Group Meeting (Dec 2015) for Initiating Multidisciplinary PCOS Clinic at NIRRH



Team composition, Case Record Form and Logistics finalised



NIRRH Multidisciplinary PCOS Clinic Team

Mentors

Dr. Rama Vaidya

Dr. Smita Mahale

Dr. Sanjay Chauhan

NIRRH Core Team

Dr. Anushree D Patil
Gynaecologist

Dr. Beena Joshi
Public Health Specialist

Dr. Srabani Mukherjee
Basic Scientist

Dr. Rahul Gajbhiye
Basic scientist &
Public health specialist

Dr. Suchitra Surve
Paediatrician

Dr. Shahina Begum
Statistical Expert

Dr. Susan Thomas
Bioinformatics

Social Workers

Staff Nurses

Mrs Pratibha Kokate **Mrs Bhagyashree Kanje**
Mr Irrana Mashal

Mrs. Ruhi Pednekar **Mrs Sunita Kale**
Mrs Shobha Bange **Mrs Rachana Dalvi**

Mr. Ram Barai
Bioinformatics

Mr. Prashant Tapse
Computer Programmer

Mr. Vaibhav Shinde
Photographer

Clinic Staff

Multidisciplinary Team

Dr. Sukhpreet Patel
Infertility Specialist

Dr. Vidya Kharkar
Dermatologist (KEMH)

Dr. Ajita Nayak
Psychiatrist (KEMH)

Dr. Satish Pathak
Yoga Expert
Kaivalyadham Inst

Mrs Shobha Udipi
Nutritionist

Mrs Veena Yardi
Nutritionist
Nirmala Niketan

Multidisciplinary Model of Care for PCOS

Objectives:

- To address a complete set of medical problems that come in the way of women suffering from PCOS including psychological issues
- To develop a database of clinical, biochemical and ultrasound parameters of patients with PCOS in different age groups
- To develop simple management algorithms
- To develop a cohort for research on PCOS

Inauguration of NIRRH Multidisciplinary PCOS Clinic

Secretary, Department of Health Research and Director General ICMR
Dr. Soumya Swaminathan inaugurated the clinic on 30th April 2016



Yoga in Management of PCOS

Asanas Beneficial in PCOS

Pranayama

The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 | Bengaluru

Jointly Organized by

The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017

Meditation

Padmasana (Butterfly pose)

Sun Salutation (Surya)

Namaskar

Bhujangasana (Cobra pose)

Jointly Organized by

The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 | Bengaluru

Jointly Organized by

The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017

Dhanurasana (Bow pose)

Urdhva Dhanurasana (Superman pose)

Supta Badhakonasana

Bharangasana

Chakrasana (moving)

Jointly Organized by

The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017

Jointly Organized by

The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017

Shavasana (Corpse pose)

Padmasana



ICMR Multicenter Task Force Study

Evaluation of prevalence, regional phenotypic variation, comorbidities, risk factors and the variations in response to different therapeutic modalities among Indian women with PCOS

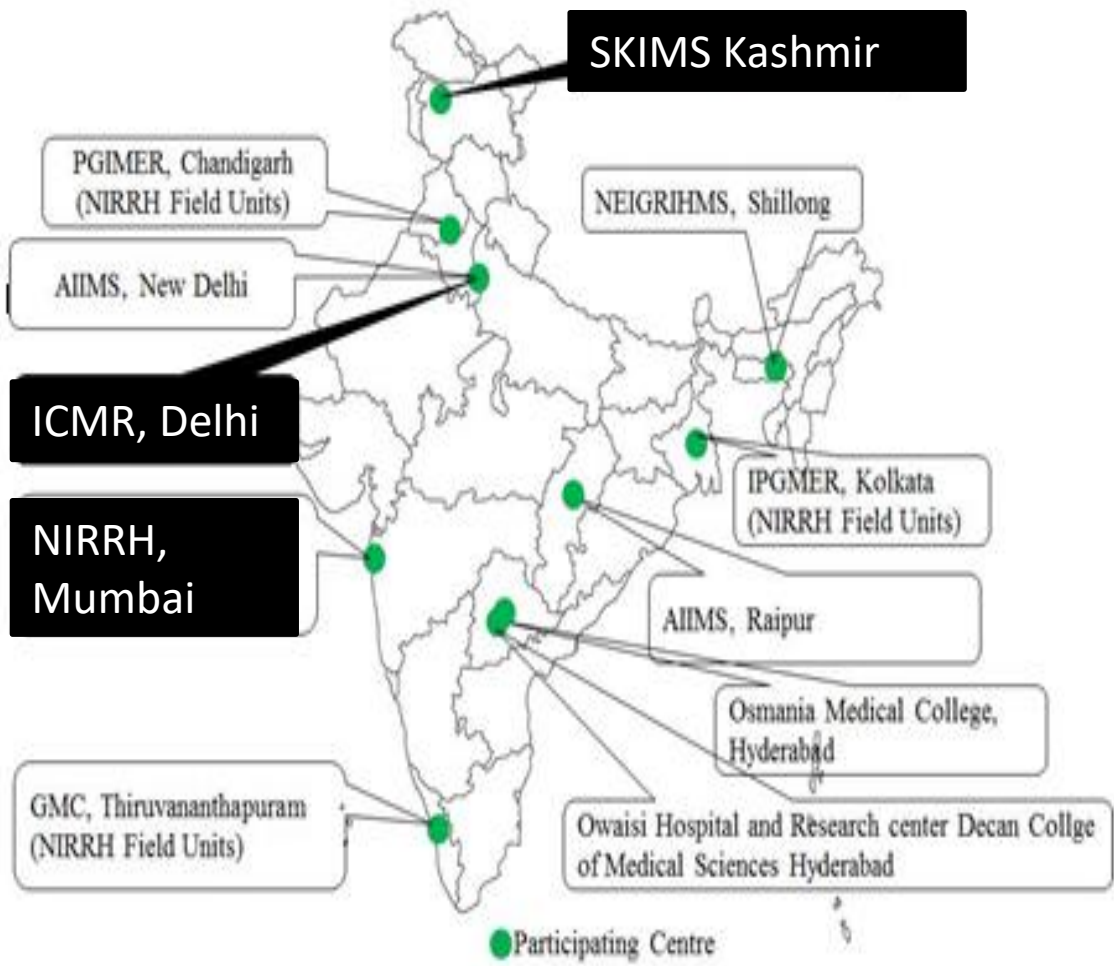
OBJECTIVES

Estimate regional prevalence of PCOS in different zones of the country

Estimate the burden of comorbidities

Assess knowledge and management practices

Study 9 States – 9000 women



**If you want to go fast, go alone.
If you want to go far, go together.**

— African Proverb



ABHIYAN PCOS

A Consortium for Healthy Womanhood

- Kasturba Health Society
Medical Research Center
- ICMR - National Institute for
Research in Reproductive Health
- Tata Institute of Social Sciences
- The PCOS Society of India

Thank You All