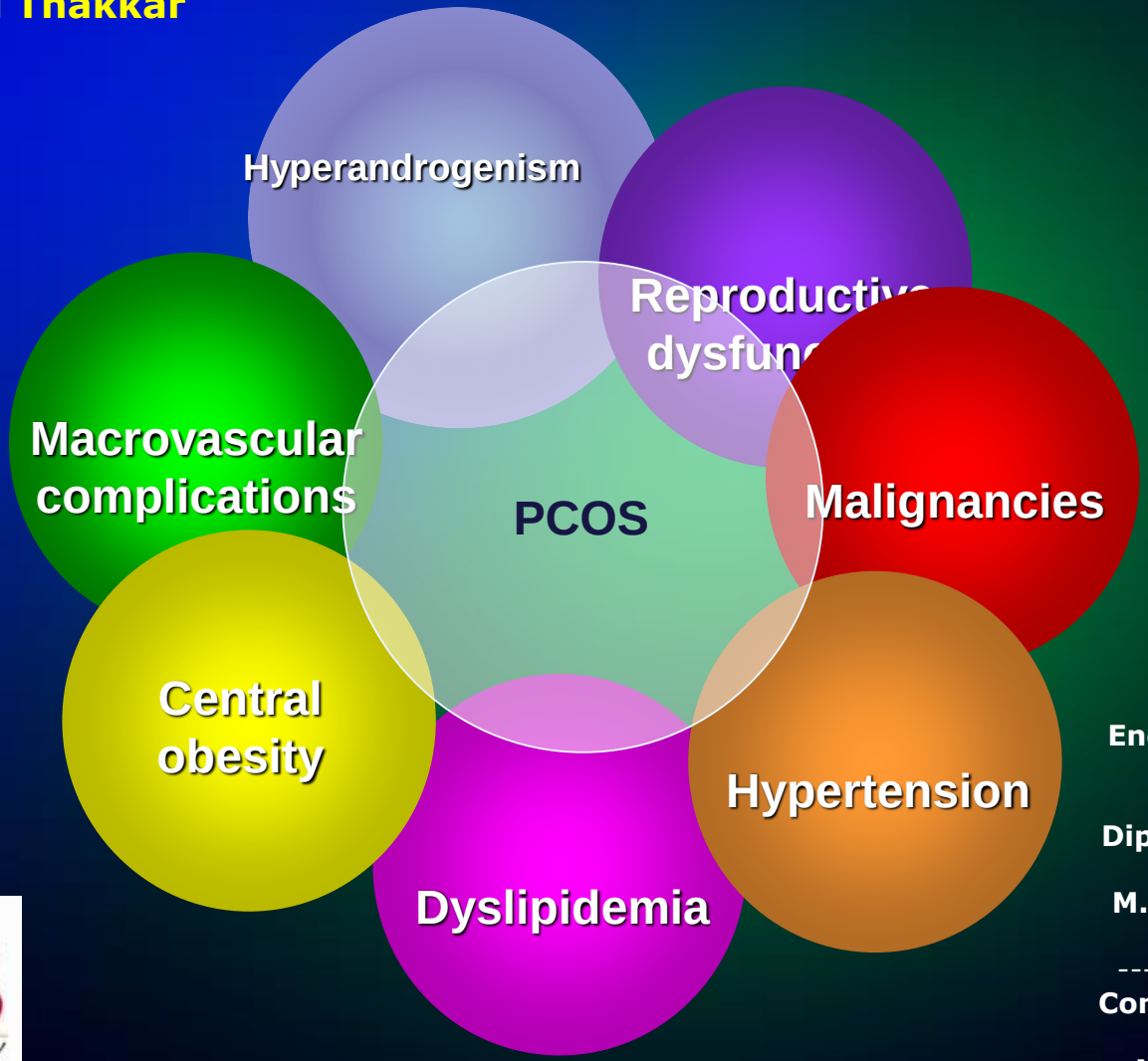
PCOS – Long Term Consequences
Need For a Preventive Strategy

Dr. Piya Ballani Thakkar



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THE PCOS SOCIETY

PCOS

- PCOS is a heterogeneous disorder linked with disturbances of reproductive, endocrine and metabolic function.
- It is characterized by hyperandrogenism, ovulatory dysfunction, polycystic ovarian morphology, and insulin resistance.
- The disorder appears to be an ancient complex genetic trait
- Multifactorial and Polygenic
- Recognized as one of the most common endocrine abnormalities of humans, with global prevalences 5%-15%

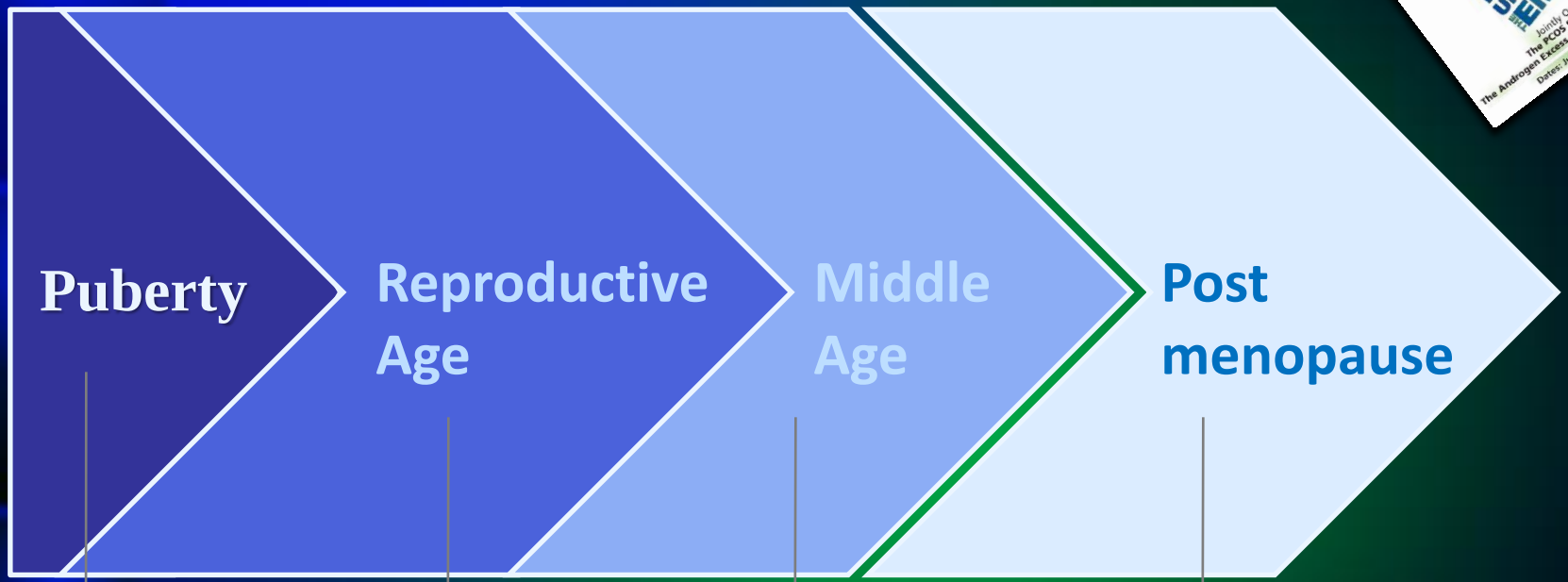
PCOS Indian Scenario

- Studies conducted on Indian PCOS women suggested that abnormalities of the insulin receptor are more common in Indian women with PCOS compared to white women with PCOS.
- Adolescent obesity and PCOS individually and together have emerged as important public health issues in India.
- There is an urgent need to organize preventive strategy to the oncoming epidemics of obesity and obesity associated PCOS in India.

1. Ramanand SJ et al, Indian J Endocrinol Metab. 2013 Jan-Feb; 17(1): 138–145
2. Joshi b t al,Indian J Endocrinol Metab. 2014 May-Jun; 18(3): 317–324.

PCOS Continuum

IR is Underlying problem at each stage



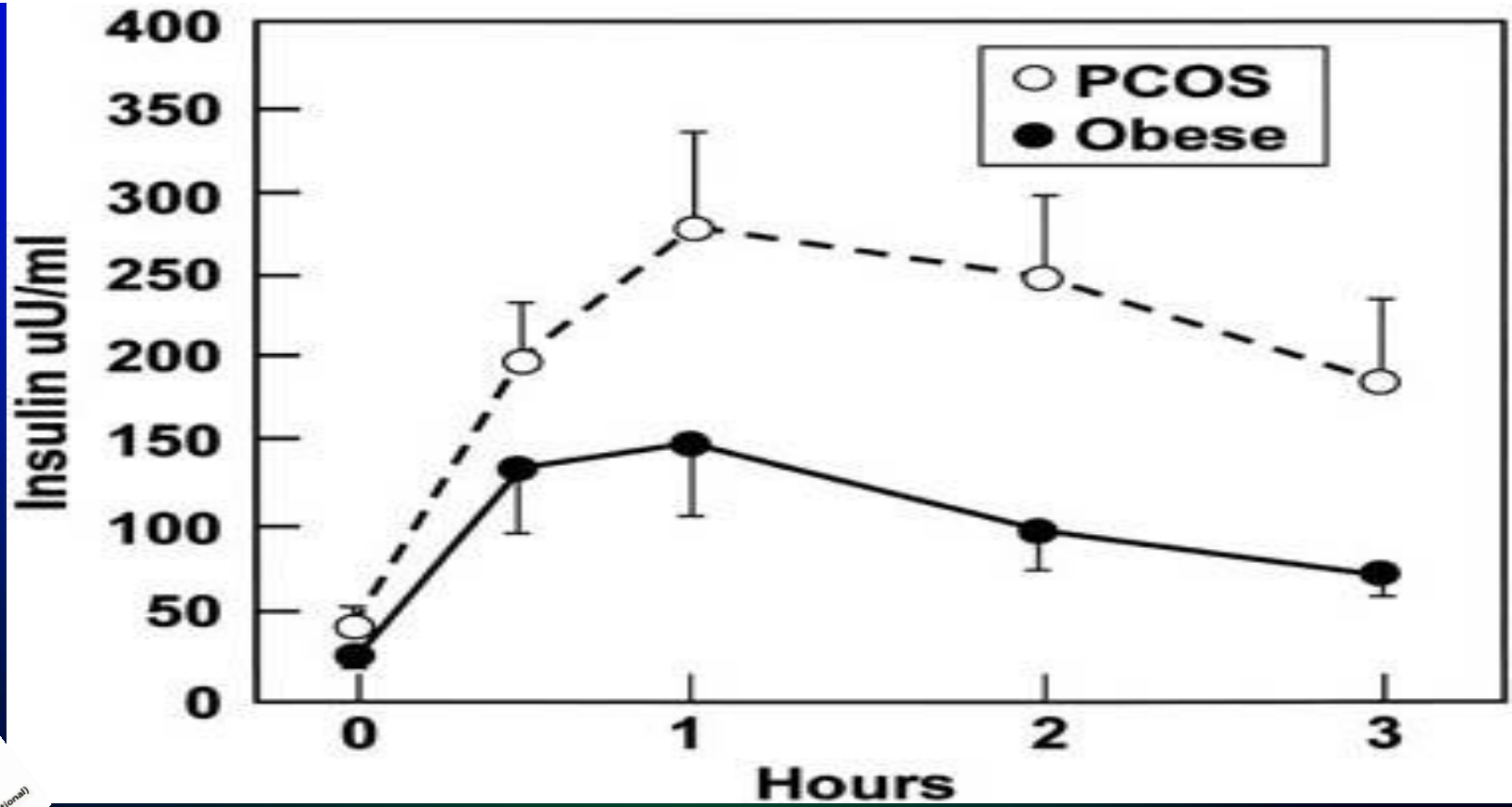
- **Puberty**
  - Irregular periods
  - Acne
  - Hirsuitism
  - Obesity
- **Reproductive Age**
  - Infertility
  - GDM
- **Middle Age**
  - Increased risk of developing T2 DM, CVD & other Metabolic disorders
- **Post menopause**
  - Metabolic disorders
  - Cancer
  - CVD

INSULIN RESISTANCE IN PCOS

INTRINSIC / EXTRINSIC

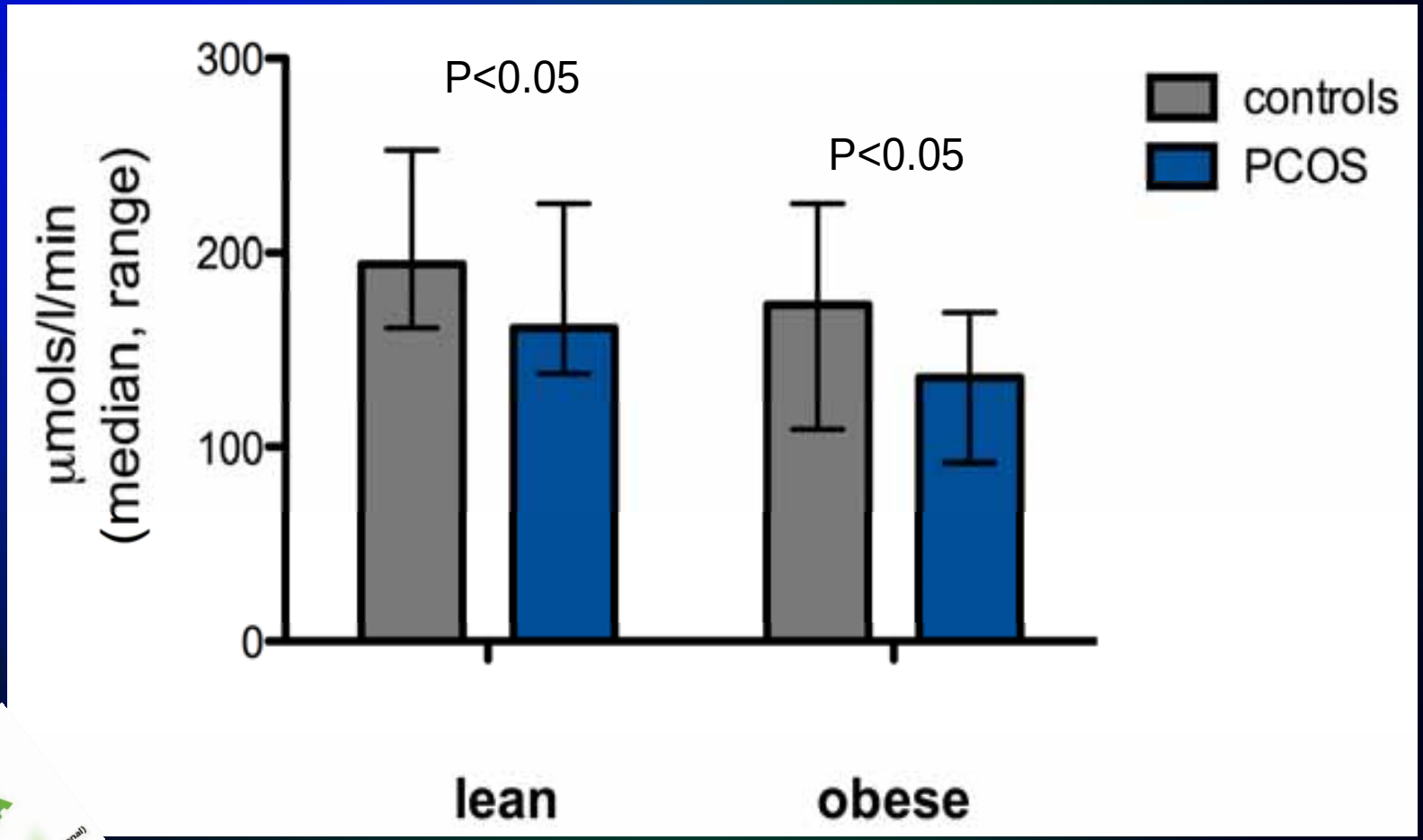
- **INSULIN RESISTANCE IS INTRINSIC TO PCOS**
- **IT PLAYS A CENTRAL ROLE IN THE PATHOGENESIS OF PCOS AS INSULIN-INDUCED HYPERANDROGENAEMIA IS THE UNDERLYING BIOCHEMICAL ABNORMALITY IN PCOS**
- **IT IS INDEPENDENT OF OBESITY (30% OF PCOS WOMEN ARE NOT OBESE)**
- **OBESITY WHEN PRESENT (de novo OR AS A RESULT OF INTRINSIC IR) IS AN EXTRINSIC CAUSE OF IR IN PCOS.**
- **PCOS is an IR Syndrome,**
- a gender-specific form of Metabolic Syndrome,
- hence also called “Syndrome XX”

Insulin levels in PCOS



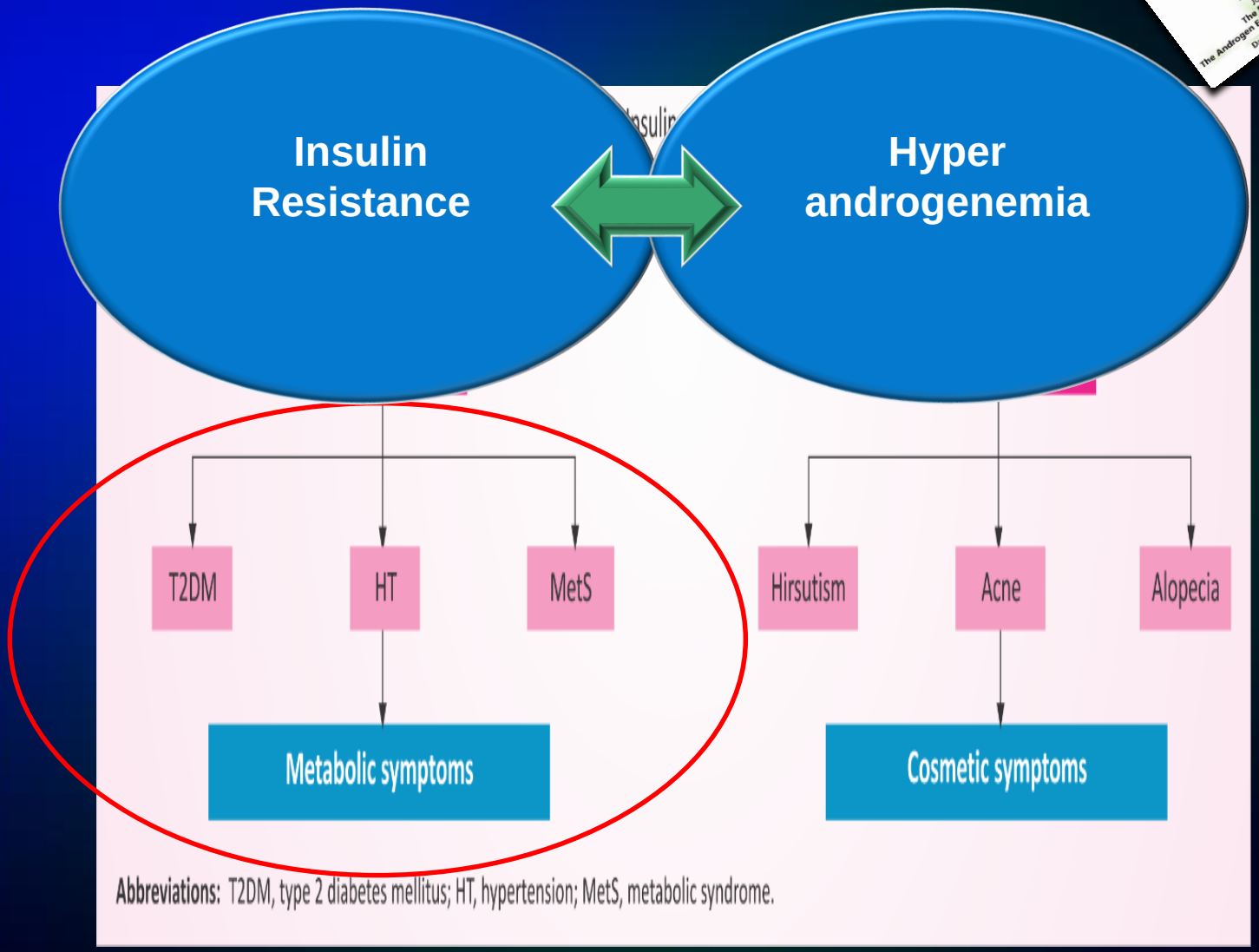
Dunaif

Insulin sensitivity is reduced in lean and obese women with PCOS



Robinson et al, Clin Endocrinol 1992 36 537

Twins


Insulin Resistance
Hyper androgenemia
T2DM
HT
MetS
Hirsutism
Acne
Alopecia
Metabolic symptoms
Cosmetic symptoms
Abbreviations: T2DM, type 2 diabetes mellitus; HT, hypertension; MetS, metabolic syndrome.

TISSUE SPECIFIC EFFECTS OF INSULIN RESISTANCE IN PCOS

INSULIN RESISTANT

- **MUSCLE**
  - ↓ Glucose Uptake
    - IGT
    - DM
- **ADIPOSE**
  - ↑ Lipolysis
    - DYSLIPIDAEMIA

INSULIN SENSITIVE

- **OVARY**
  - ↑ ANDROGEN PRODUCTION
- **ADRENAL**
  - ↑ ANDROGEN PRODUCTION
- **LIVER**
  - ↓ SHBG PRODUCTION
- **PILO – SEBACEOUS UNIT**
  - PROLI - FERATION

PCOS- Beginning of Long Term Non-Communicable Diseases

- **Increased risk of developing Type 2 Diabetes and Gestational diabetes**
- Low HDL and high triglycerides
- Sleep apnea (30 fold higher)
- Nonalcoholic steatohepatitis
- Metabolic syndrome—43% of PCOS patients (2 fold higher than age-matched population)
- Elevated CRP and CV risk
- Malignancy risk (3 fold)
- Depression

Glucose Intolerance/ Diabetes in PCOS

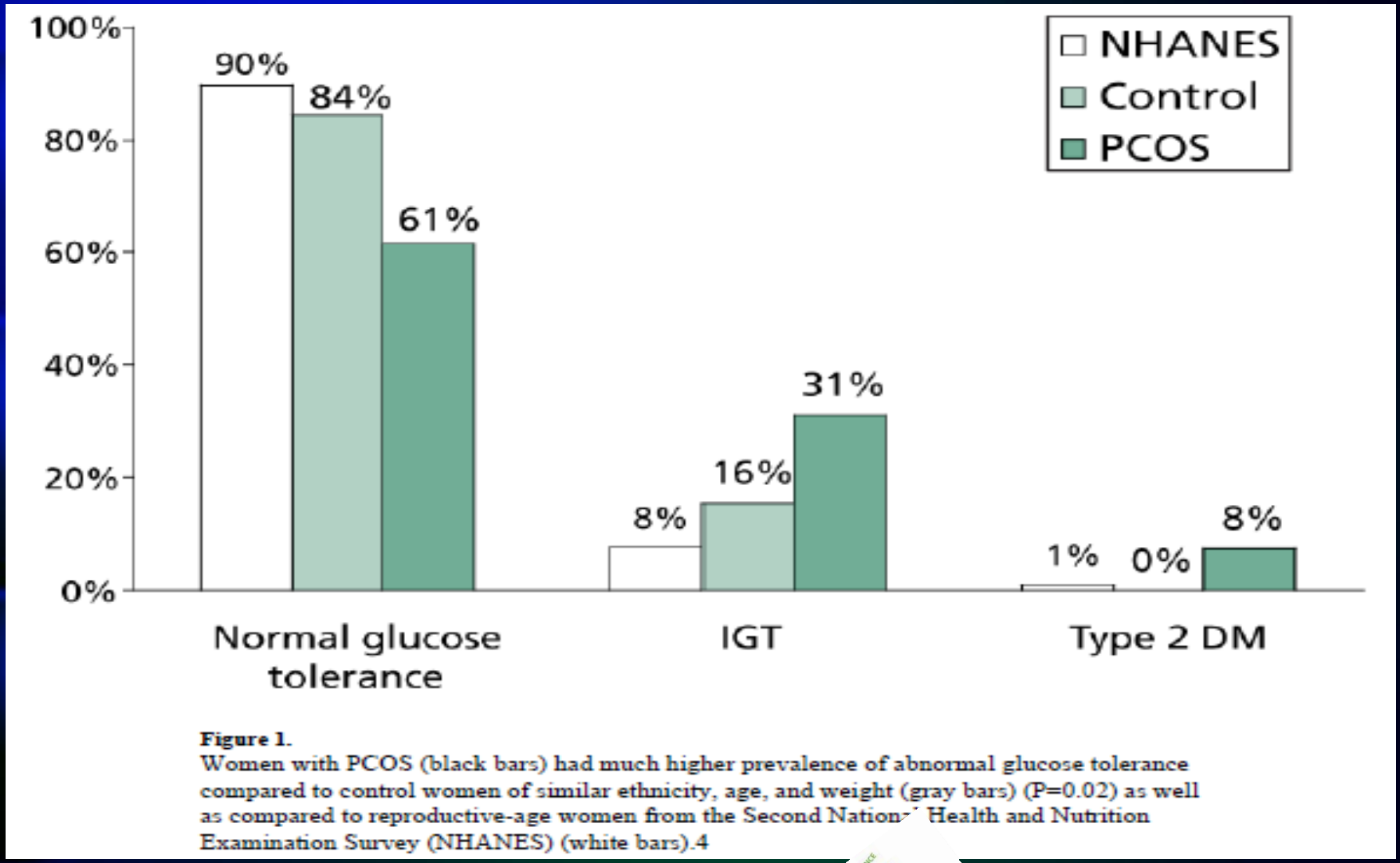


Figure 1.
Women with PCOS (black bars) had much higher prevalence of abnormal glucose tolerance compared to control women of similar ethnicity, age, and weight (gray bars) (P=0.02) as well as compared to reproductive-age women from the Second Nation[illegible] Health and Nutrition Examination Survey (NHANES) (white bars).4

Legro et al, 1999, JCEM

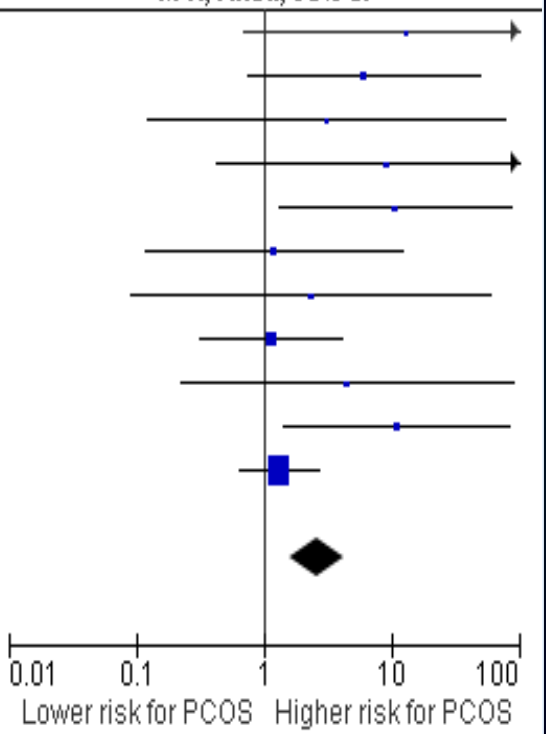
n=254

IGT - Risk in women with PCOS

Study or Subgroup	PCOS Events	PCOS Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Dos Reis 1995	7	29	0	19	1.9%	13.00 [0.70, 242.54]	1995
Rajkhowa 1996	10	72	1	39	4.6%	6.13 [0.75, 49.80]	1996
Yarali 2001	1	30	0	30	2.0%	3.10 [0.12, 79.23]	2001
Dunaif 2001	3	12	0	12	1.5%	9.21 [0.42, 200.59]	2001
Phy 2004	4	7	2	18	2.0%	10.67 [1.31, 86.93]	2004
Faloia 2004	3	50	1	20	5.5%	1.21 [0.12, 12.40]	2004
Diamanti-Kandarakis 2005	1	29	0	22	2.2%	2.37 [0.09, 60.96]	2005
Alvarez-Blasco 2006	4	32	8	72	17.8%	1.14 [0.32, 4.11]	2006
Leibel 2006	3	36	0	21	2.3%	4.49 [0.22, 91.35]	2006
Echiburu 2008	17	159	1	93	4.7%	11.01 [1.44, 84.18]	2008
Bhattacharya 2009	32	264	11	116	55.5%	1.32 [0.64, 2.71]	2009
Total (95% CI)		**720**		**462**	**100.0%**	**2.61 [1.62, 4.20]**	
Total events	85		24				

Heterogeneity: $Chi^2 = 11.69$, $df = 10$ ($P = 0.31$); $I^2 = 14\%$

Test for overall effect: $Z = 3.94$ ($P < 0.0001$)

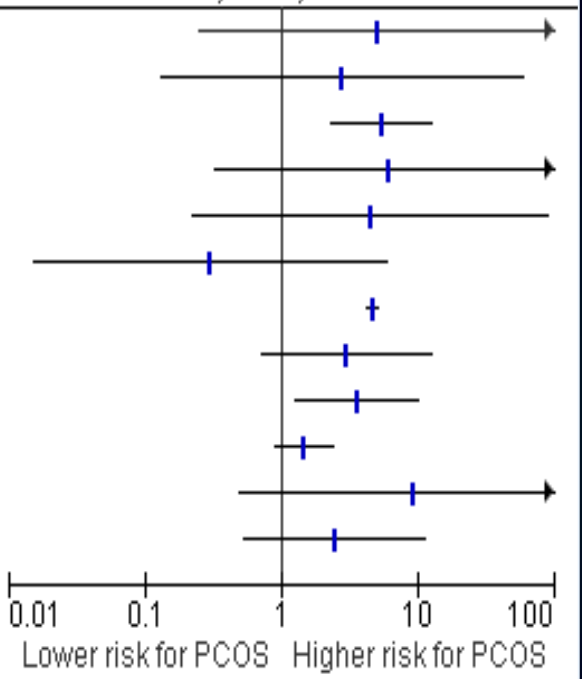


Risk of IGT in PCOS OR: 2.61 [1.62, 4.20]

Moran et al, 2010, Human Reprod Update

Type 2 Diabetes - Risk in PCOS

Study or Subgroup	PCOS Events	PCOS Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Dos Reis 1995	3	29	0	19		5.15 [0.25, 105.59]	1995
Rajkhowa 1996	2	72	0	39		2.80 [0.13, 59.82]	1996
Cibula 2000	9	28	60	752		5.46 [2.37, 12.60]	2000
Sir-Petermann 2004	4	146	0	97		6.16 [0.33, 115.68]	2004
Leibel 2006	3	36	0	21		4.49 [0.22, 91.35]	2006
Alvarez-Blasco 2006	0	32	3	72		0.31 [0.02, 6.09]	2006
Lo 2006	988	11035	1136	55175		4.68 [4.28, 5.11]	2006
Marquez 2008	6	50	3	70		3.05 [0.72, 12.82]	2008
Attuoua 2008	17	107	5	100		3.59 [1.27, 10.13]	2008
Shaw 2008	34	104	70	286		1.50 [0.92, 2.45]	2008
Moini 2009	4	273	0	276		9.23 [0.49, 172.33]	2009
Bhattacharya 2009	11	264	2	116		2.48 [0.54, 11.36]	2009



Subgroup analysis (BMI-matched studies only)

Risk of DM2 in PCOS: OR 3.66 [1.98, 6.75]

Moran et al, 2010, Human Reprod Update

PCOS and pregnancy complications

Gestational diabetes: OR 3.66 (95% CI 1.20 – 11.16)

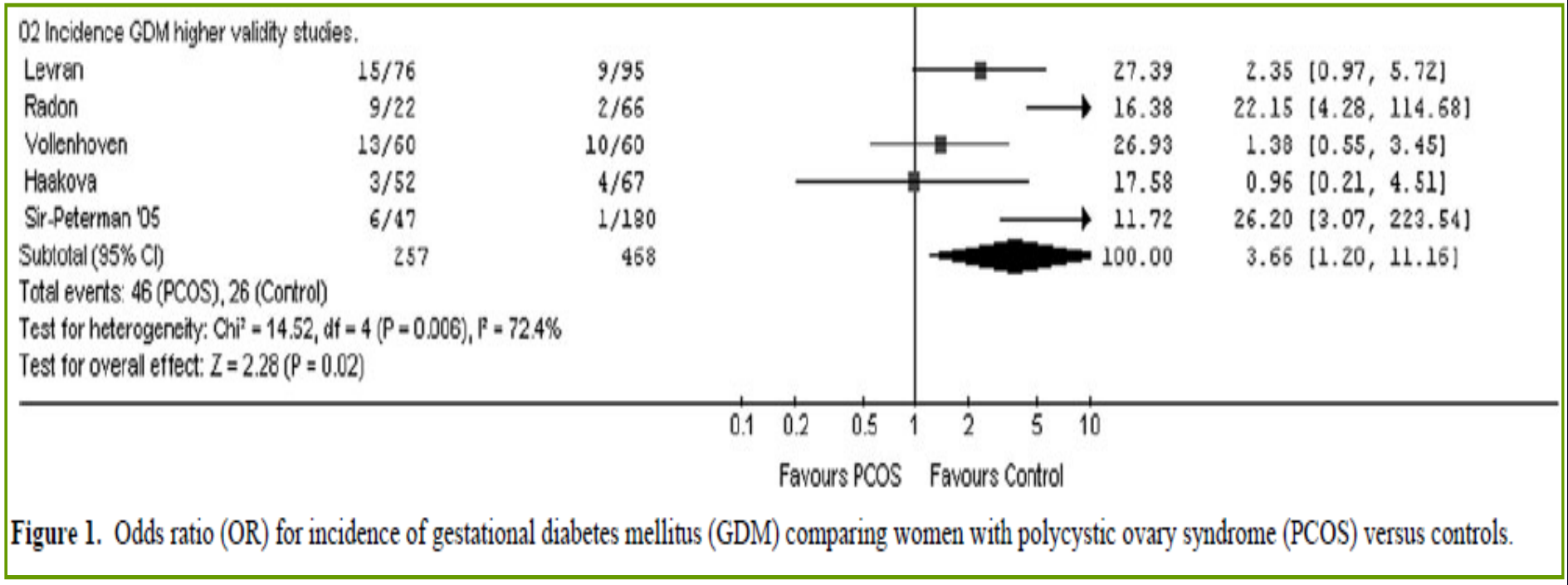


Figure 1. Odds ratio (OR) for incidence of gestational diabetes mellitus (GDM) comparing women with polycystic ovary syndrome (PCOS) versus controls.

Boomsma et al. Hum Reprod Upd 2006

Who is at risk of T2D?

PCOS (2-fold)

PCOS + obesity (3-fold)

PCOS + obesity + FH of diabetes

PCOS + obesity + GDM

PCOS + obesity + IGT

Making The Diagnosis

Supportive of insulin resistance

- "Syndrome X": 3 or more of the following criteria:
  - Waist circumference > 88 cm
  - Triglycerides > 150 mg/dl
  - HDL <50 mg/dl
  - BP > 130/85
  - Fasting glucose >110 mg/dl

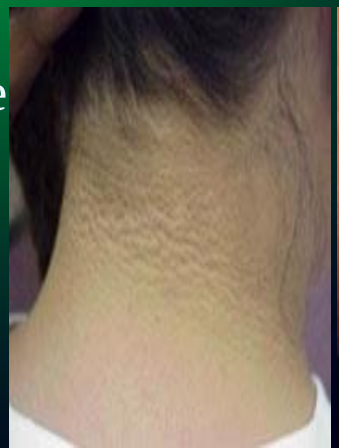
- ACOG and ADA suggest screening all women w/ PCOS for glucose intolerance, type 2 DM.

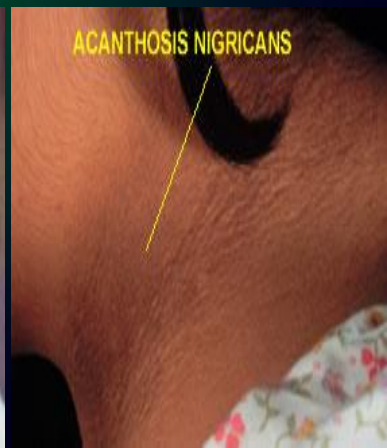
- Oral glucose tolerance test more sensitive than fasting glucose.

- No test of insulin resistance is needed to make diagnosis of PCOS or to select treatment

- Acanthosis nigricans

- Personal or family history of DM

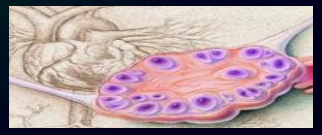




Screen and Test For Long-term Issues

- Lipids
- OGTT

- Polysomnography
- Depression Screen
- Endometrial Biopsy



Screening Recommendations for IGT in PCOS AE-PCOS Society

- All patients with PCOS, regardless of BMI, should be screened using a 2h OGTT

- Patients with normal glucose tolerance should be rescreened every 2 years or earlier if additional risk factors are identified

- Patients with IGT should be screened annually for DM

PCOS Management

- Body weight loss is associated with beneficial effects on hormones, metabolism and clinical features.

- A further clinical and endocrinological improvement can also be achieved by adding insulin-sensitizing agents and/or antiandrogens to weight reduction programmes.

International Journal of Obesity (2002) 26, 883–896

Diet

- Low in calories with limited carbohydrates,low foods, rich source fibrous and protein foods are recommended
- Dietary modification using a low calorie low glycaemic index (GI) diet could specifically reduces some of the health risks associated with PCOS such as endometrial cancer when compared to other diets
- A low GI diet contains carbohydrates that minimise changes in PPG levels and leads to a sustained reduction in hyperinsulinaemia

Egan et al. BMC Research Notes 2011, 4:53

Exercise

- Minimum 5 days a week of 30-40 min brisk walk
- Weight loss of 5-10% of the initial weight improves the endocrine actions (Ovulation,Menstrual cyclicity,fertility)[1]

1.Badaway et'al, International Journal of Women's Health 2011:3 25–35

2. Midland Fertility Services PCOS03 012007.jlaa

New Targets for Therapy in PCOS

Genetics

Aging

Drugs

Pregnancy

Life style

Central obesity

New Target for Rx

Insulin Resistance

Hyperinsulinemia

Traditional Target

Altered steroid and hormones

PCOS

- Acne
- Hirustism
- Hyperandrogenism
- Infertility

Management:

- Insulin resistance

Metformin

- Function
  - Lowers hepatic glucose production by reducing gluconeogenesis
  - Increases peripheral glucose uptake by skeletal muscle and adipose tissue
  - Reduces intestinal glucose absorption
- Outcomes
  - Estimated 31% reduction in development of type II DM over mean period 3 years
  - Taken during pregnancy, reduction in gestational diabetes and major fetal complications

- The 2013 Endocrine Society guidelines state that Metformin should be reserved for the treatment of women presenting with only menstrual irregularity because it has limited benefits in treating hyperandrogenism associated with PCOS.

- *A high prevalence of insulin resistance is noted among the Asians, and these guidelines may not hold good for this population.*

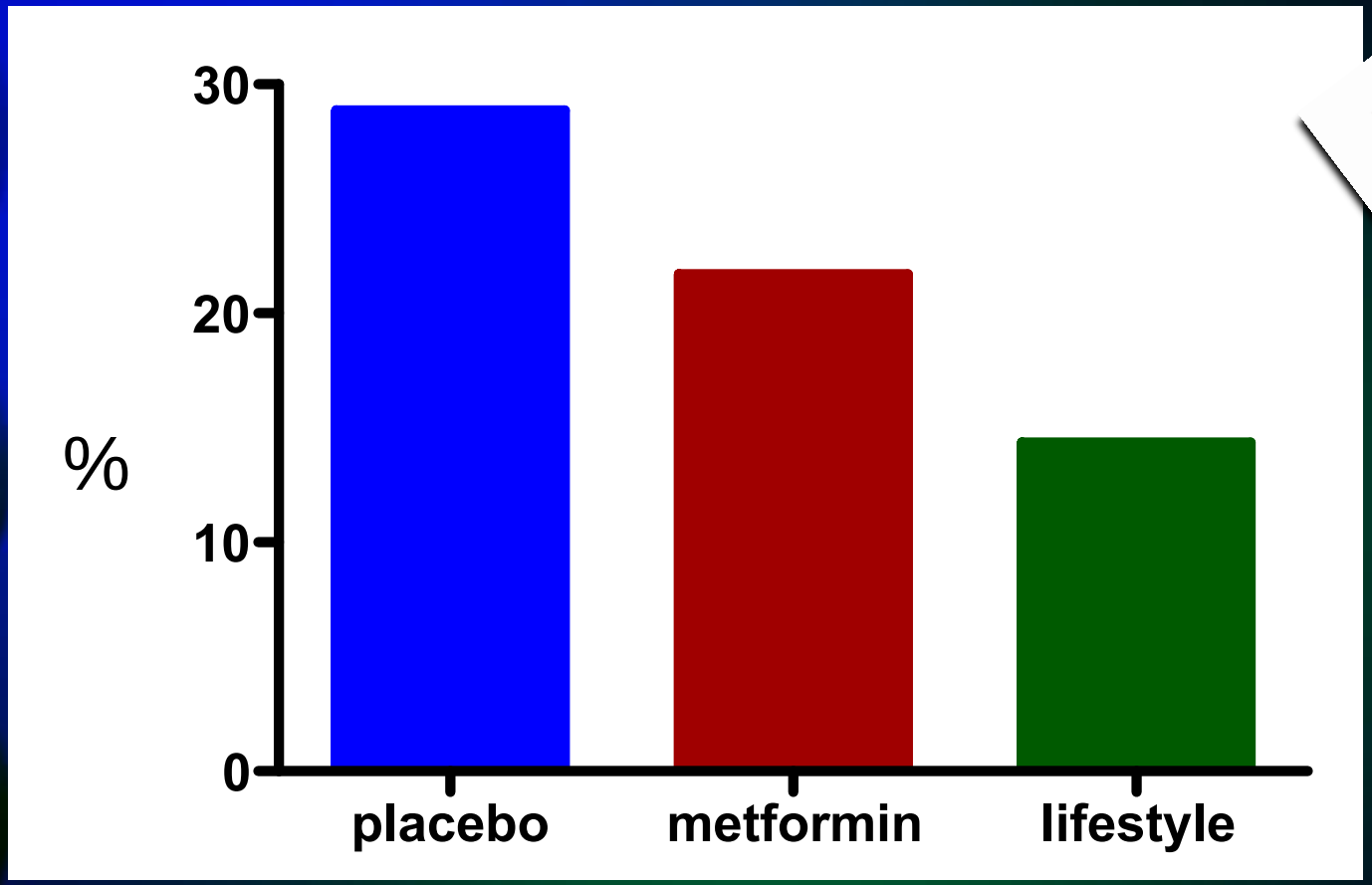
Use of metformin in PCOS in Indian population

Parameters	Baseline (Mean±SD)		6 months of therapy (Mean±SD)		
	Met	Drosp	Met	Drosp	p
BMI (kg/m^2)	27.72± 5.04	26.48± 4.56	25.61± 3.19 **	24.28± 3.98 **	0.40
Serum Testoster-one (ng/dL)	56.52± 11.70	62.23± 13.59	49.67± 13.68 **	52.57± 14.17***	0.65
Serum DHEAS (mcg/dL)	197.30± 60.35	227.16± 66.34	166.50± 43.12	195.45± 32.73*	0.22

Metformin is as effective as OC combination of ethinyl estradiol & Drospirenone in regularizing menstrual cycles, decreasing body mass index, and treating hyperandrogenism in Indian women diagnosed with PCOS

J Turk Ger Gynecol Assoc 2016; 17: 6-9

Cumulative incidence of T2D at 3 years



3234 subjects with IGT

Knowler WC *et al* Diabetes Prevention Program Research Group *N Engl J Med* 2002 346 393-403

Are Young Adult Women with Polycystic Ovary Syndrome Slipping through the Healthcare Cracks?

Anuja Dokras[1],MD, PhD, Selma Feldman Witchel[2],MD

Polycystic Ovary Syndrome

- Pediatrician
- Gynecologist
- Reproductive Endocrinologist
- High Risk OB
- Dermatologist
- Gynecologic Oncologist
- Bariatric Medicine
- Family Physician/Internist
- Medical Endocrinologist

JCEM, May 2014

Information Regarding PCOS

	North America	Europe
Satisfaction with information about PCOS		
Dissatisfied or indifferent	**606 (83.0)**	**505 (86.9)**
Satisfied	124 (17.0)	76 (13.1)
Information about lifestyle management		
Dissatisfied or indifferent	316 (43.2)	250 (43.1)
Satisfied	95 (13.0)	55 (9.5)
This information was not mentioned	320 (43.8)	275 (47.4)
Information about medical therapy		
Dissatisfied or indifferent	406 (55.7)	302 (52.2)
Satisfied	141 (19.3)	74 (12.8)
This information was not mentioned	182 (25.0)	203 (35.0)
Information on long term complications		
Dissatisfied or indifferent	299 (41.0)	225 (38.9)
Satisfied	68 (9.3)	30 (5.2)
This information was not mentioned	363 (49.7)	323 (55.9)
Emotional support and counselling after diagnosis		
Dissatisfied or indifferent	275 (37.6)	184 (31.8)
Satisfied	30 (4.1)	10 (1.7)
This information was not mentioned	426 (58.3)	384 (66.4)

Thank You

OPPORTUNITY

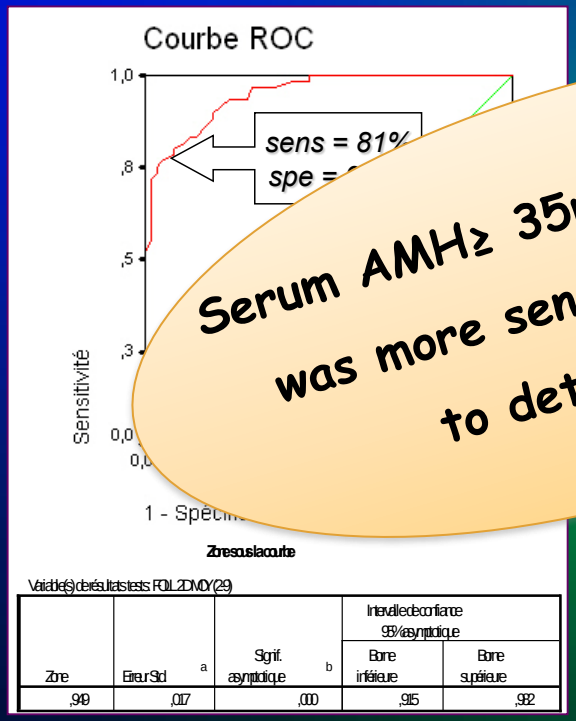
Welcome

THE PCOS SOCIETY

Let's exchange ideas

REVISITING THE CRITERIA FOR PCOM: *should we keep the follicle count or switch to AMH?*

Follicles/ovary

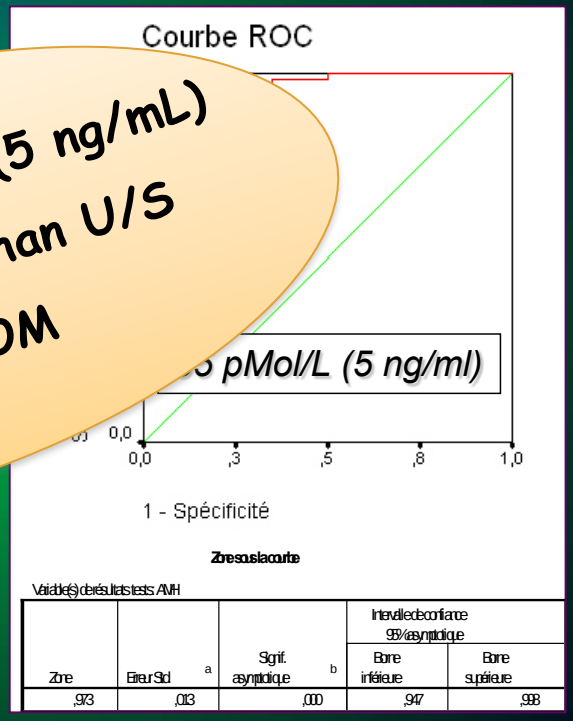


Zone sous la courbe

Variable(s) de résultats tests: FOLL2DMOY(2-9)

Zone	Erreur Std [a]	Signif. asymptotique [b]	Intervalle de confiance 95% asymptotique	
			Borne inférieure	Borne supérieure
,949	,017	,000	,915	,982

Serum AMH



Zone sous la courbe

Variable(s) de résultats tests: AMH

Zone	Erreur Std [a]	Signif. asymptotique [b]	Intervalle de confiance 95% asymptotique	
			Borne inférieure	Borne supérieure
,973	,013	,000	,947	,998

Serum AMH≥ 35pmol/L (5 ng/mL) was more sensitive than U/S to detect PCOM

Dewailly et al., Hum Reprod, 2011, 26:3123-9

WHICH CAME FIRST: HYPERINSULINAEMIA OR HYPERANDROGENAEMIA?

HYPERINSULINAEMIA IS PRIMARY CONTRIBUTING TO OVARIAN HYPERANDROGENAEMIA

EVIDENCES

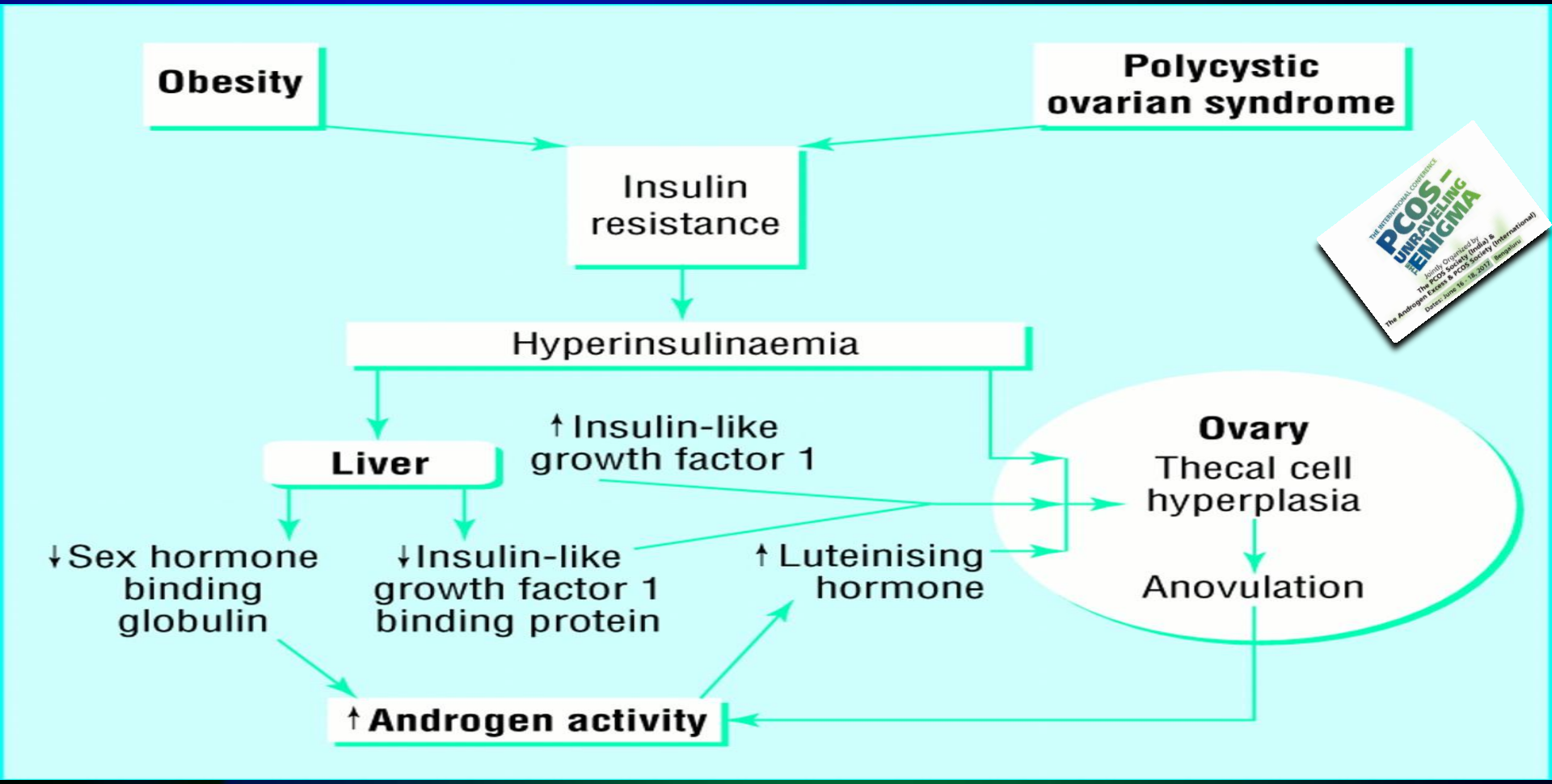
1. Pharmacologic reduction of insulin levels in PCOS women improves

2. Reduction of androgen levels by Bilateral Oophorectomy or administration of Gn RH agonist or antiandrogenic compounds in PCOS women has No effect on Insulin Resistance or Hyperinsulinaemia

Management

- Immediate/Acute issues
  - Hirsutism
  - Regulation of menses
  - Fertility issues
- Long-term issues
  - Insulin resistance
  - Cardiovascular risk
  - Obstructive sleep apnea
  - Malignancy risk

Insulin Resistance in PCOS is Independent of Obesity



- Obese women with PCOS tend to be *more* insulin resistant than normal-wt counterparts.
- *3-fold* increased incidence of metabolic syndrome in PCOS, vs general population, independent of obesity
- Obesity is an independent risk factor for glucose intolerance or DM in PCOS

Making The Diagnosis
OBESITY

- ½ patients with PCOS are obese
- 80% are hyperinsulinemic and have insulin resistance (independent of obesity)
- 2/3 of patients with PCOS who are not obese have excessive body fat and central adiposity
- Obese patients can be hirsute and/or have menstrual irregularities without having PCOS

Management: Long-Term Issues
Cardiovascular Risk

- HTN
- Dyslipidemia (↑ TG, ↓ HDL, ↑ LDL)
- Predisposition to macrovascular disease and thrombosis

- Nurses' health study: 20-60% increased risk of CAD events
- Studies of pts undergoing coronary angiography: women with significant h/o hirsutism or polycystic ovaries more likely to have CAD, and if they had it, more extensive CAD, compared to female controls.

Statins in PCOS

- Shown to decrease androgens over and above values induced by OCPs, improve hirsutism, decrease LH and LDLcholesterol, and decrease C-reactive protein and other markers of endothelial activation.

- They also prevented the hypertriglyceridemia induced by OCPs.

- Thus, statins may negate some of the adverse metabolic effects of PCOS and its treatment with OCPs.

Banaszewska B et all Clin. Endocrinol. Metab. 92, 456-461 (2007).

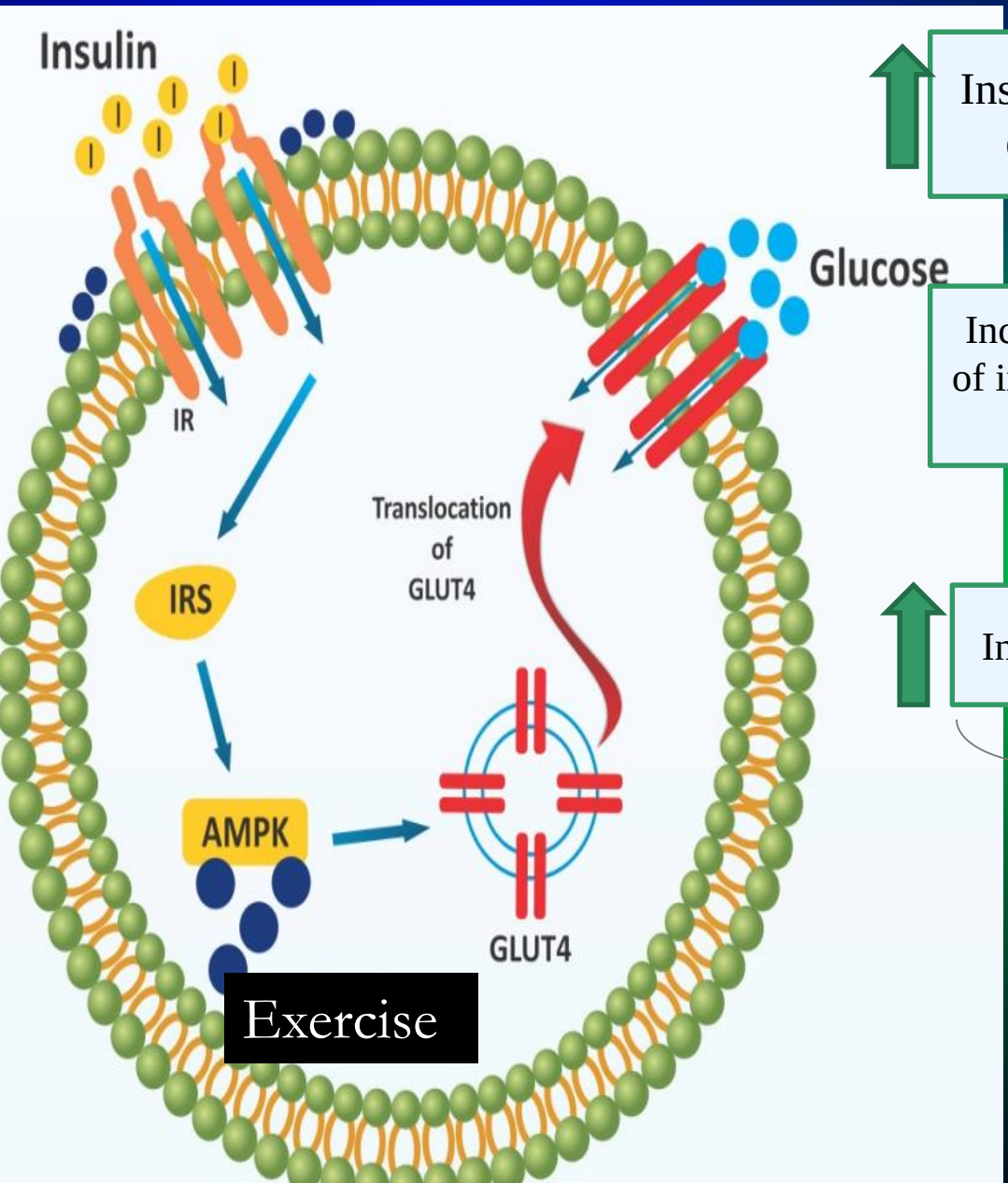
Management:
Long-Term Issues

- Obstructive Sleep Apnea
  - 30-fold increased risk of OSA, not explained by obesity alone.
  - Insulin resistance strongest predictor of OSA (not BMI, age, testosterone)
  - Consider polysomnography if at risk

Management:
Long-Term Issues

- Risk for malignancy
  - 3X increased risk endometrial carcinoma in PCOS
  - Increased risk of ovarian and breast cancer
  - Warrants regular screening, low threshold for endometrial biopsy

Lifestyle Impact on IR and PCOS



Insulin receptor expression

Intracellular AMPK activity

Increased binding of insulin to insulin receptors

Increased translocation of GLUT-4

Insulin sensitivity

Glucose Uptake

Improves Fertility outcomes and Hyperandrogenemia

Metformin mechanism of action in PCOS

- IRS (insulin-receptor substrate proteins) mRNA levels is up-regulated by Metformin
- Metformin was able to substantially enhance the insulin-stimulated translocation of Glut-4 transporters from the cytosol to the membrane.
- Net increase in Glut-4 transporters in the plasma membrane has the potential to increase glucose uptake and metabolism by granulosa cells of the insulin-resistant polycystic ovary, thereby facilitating follicle maturation.

J Clin Endocrinol Metab. 2011 Jan 5. [Epub ahead of print]

METFORMIN

- Decreases hepatic glucose production
- Reduces need for insulin secretion
- Improves insulin sensitivity (increases peripheral glucose uptake and utilization)
- Antilipolytic effect—reduces fatty acid concentrations and reduces gluconeogenesis

PCOS- Beginning of Long Term Non-Communicable Diseases

- It is not enough…….

….to only regularize her periods……

….or to treat her acne…..

…….or to manage her obesity……..

it is important for us to put a finger on what's ticking behind these symptoms.

Management:
Regulation of menses

- Lifestyle modification/weight loss
- Metformin- ie., hitting the “root cause”

  500-1000 mg bid, 6 month trial reasonable for improvement of menses
- Oral contraceptives
- Periodic progesterone withdrawal

  Medroxyprogesterone 10 mg/day x 7-10 days, every 3 months (approx 4 menses annually)

FERTILITY- Metformin

500 mg daily

Increase by 500 mg each week until:

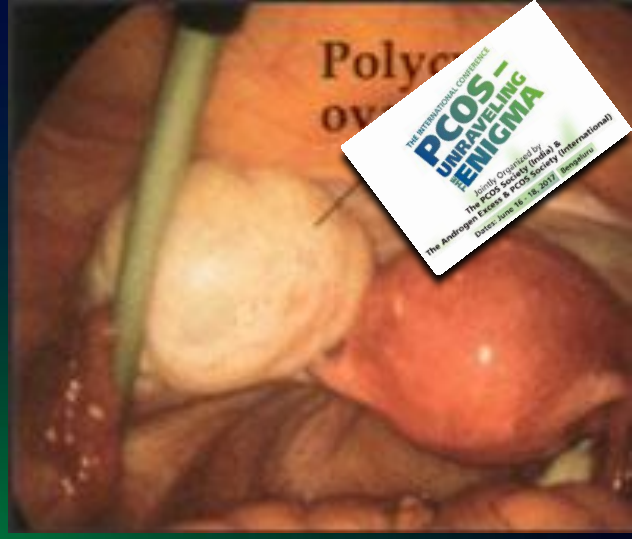
- Normal menses (Clinically significant responses not regularly observed at doses less than 1000 mg per day)
- Reached max dose (Target—1500-2550 mg per day)
- Side-effects : Diarrhea, nausea, vomiting, flatulence, indigestion, abdominal discomfort

Minimized by slow increase in dosage
Extended release formulations—fewer side-effects
Entire dose should be given with dinner

Fertility

- Weight loss—reduction in serum testosterone concentration and resumption of ovulation
- Clomiphene: 80% will ovulate, 50% will conceive
- Metformin: when added to clomid, improves ovulatory rates
- FSH injections
- Laparoscopic surgery: wedge resections, laparoscopic ovarian laser electrocautery
- IVF

Laproscopic Ovarian Drilling (LOD)- Review results



- Surgical ovarian wedge resection was the first established treatment for anovulatory PCOS patients but was largely abandoned of the risk of post-surgical adhesion formation.
- LOD is accepted second-line treatment for clomiphene citrate-resistant anovulatory infertility in PCOS.
- Value as a primary treatment for subfertile patients with anovulation and PCOS is **undetermined.**
- There **is insufficient evidence** to determine a difference in ovulation or pregnancy rates when compared to gonadotrophin therapy as a secondary treatment for clomiphene resistant women.

Cochrane Database Syst Rev. 2000;(2):CD001122.

Pregnancy Complications

- Spontaneous Abortions
  - Increased in high BMI/PCOS patients

Wang JX et al, Human Reproduction, 2001.

- Impaired Glucose Tolerance

- Gestational Diabetes

Ferhan NO et al, International Journal of Gynecology & Obstetrics, 2003.

- Hypertension

Bjercke S et al, Gynecologic and Obstetric Investigation, 2002.

- Small for Gestational Age

Weerakiet S et al, Gynecological Endocrinology, 2004.

Sir-Petermann T et al, Human Reproduction, 2005.


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 Bangalore

Thankyou

Guidelines (RCOG, May 2003)

- Evidence based guidelines for reduction of long-term PCOS consequences

- 1-Patients presenting with PCOS particularly if they are obese, should be offered measurement of fasting blood glucose and urine analysis for glycosuria. Abnormal results should be investigated by a glucose tolerance test.
- Such patients are at increased risk of developing type II diabetes (Evidence level IIb[C])

- 2- Women who have been diagnosed as having PCOS before pregnancy (eg those requiring ovulation induction for conception) should be screened for gestational diabetes in early pregnancy, with referral to a specialized obstetric diabetic service if abnormalities are detected (evidence level IIb[B])

Guidelines (RCOG, May 2003)

- 3-Measurement of fasting cholesterol, lipids and triglycerides should be offered to patients with PCOS, since early detection of abnormal levels might encourage improvement in diet and exercise (Evidence level III[C])
- 4- Olig- and amenorrhoeic women with PCOS may develop endometrial hyperplasia and later carcinoma. It is good practice to recommend treatment with progestogens to induce withdrawal bleed at least every 3-4 months (Evidence level IIa[B])

Guidelines (RCOG, May 2003)

- 5-A body of evidence has accumulated demonstrating safety and in some studies efficacy of insulin-sensitizing agents in the management of short-term complications of PCOS, particularly anovulation. Long-term use of these agents for avoidance of metabolic complications of PCOS can not as yet be recommended (Evidence level IV[B])
- 6- No clear consensus has yet emerged concerned regular screening of women with PCOS for later development of diabetes and dyslipidemia but obese women with a strong family history of cardiac disease or diabetes should be assessed regularly in a general practice or hospital outpatient setting. Local protocols should be developed and adapted as new evidence emerges (Evidence level IV[C])

Pathogenesis: Hyper-androgenism

- Symptoms of androgen excess
- Reduced sex-hormone-binding globulin (SHBG) → more free testosterone
- Insulin insensitivity
- Lipid abnormalities
- Abdominal obesity

Pathogenesis: Insulin resistanc

- Favors anovulation, androgen excess, reduced SHBG
- Metabolic syndrome
- Abdominal obesity

HYPERINSULINEMIA

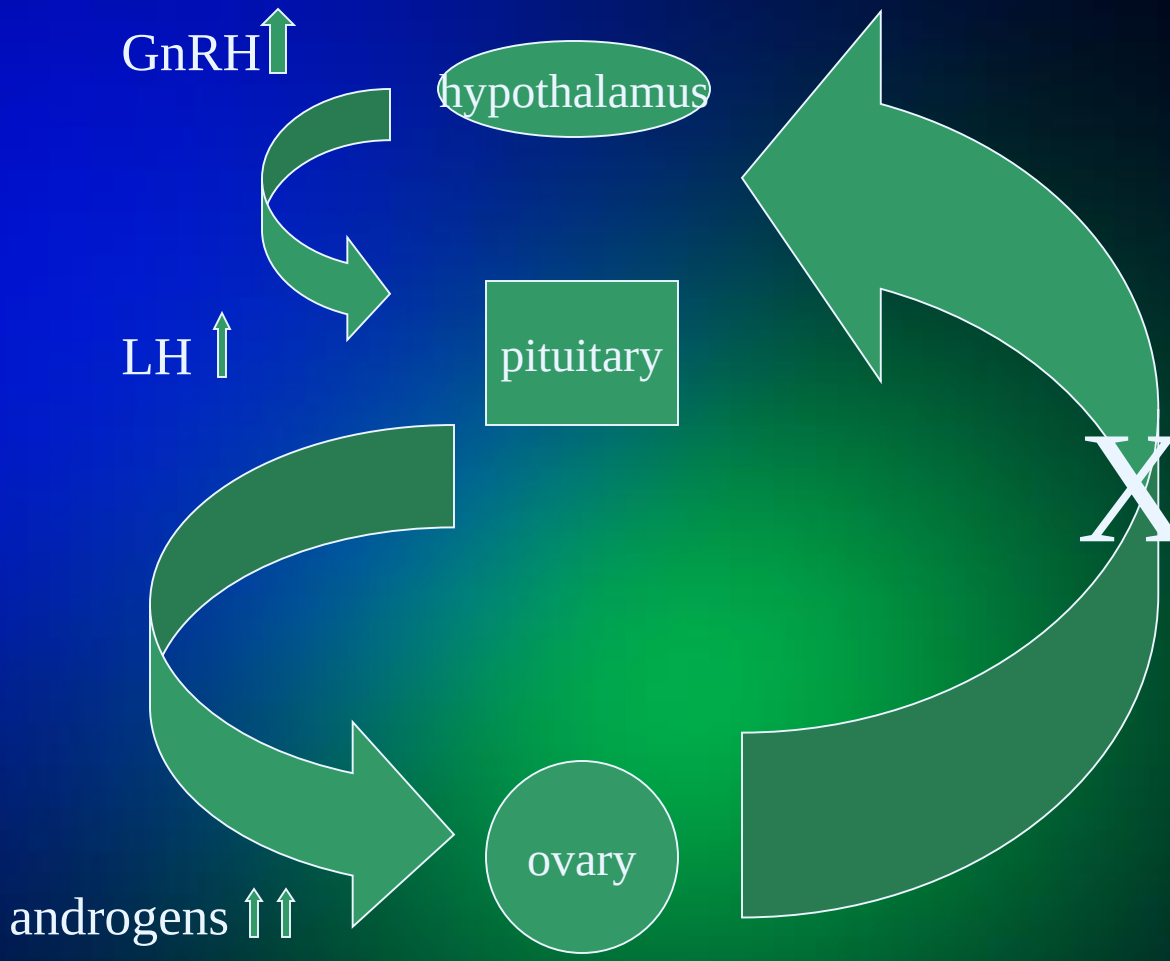
- Excess insulin production and insulin resistance
- ?? Genetic link
- Hyperandrogenism vs. hyperinsulinemia
  - Which came first?
  - Good question without Good answers

Diagnosis

1. Hyperandrogenism
   - Laboratory features
     - Elevated total testosterone
       - Most values in PCOS <150 ng/dl (if >200 ng/dl, consider ovarian or adrenal tumor)
       - Free testosterone assays may not be reliable
     - DHEA-S
       - Most normal or slightly high in PCOS
       - If >800 mcg/dl, consider adrenal tumor
     - LH/FSH ratio
       - Levels vary over menstrual cycle, released in pulsatile fashion, affected by OCPs
       - LH/FSH ratio >2 has *little diagnostic sensitivity and <u>need not be documented</u>*

TREATMENT—no fertility desir

- Monophasic antiandrogenic OCP
  - ON 1/35 (norethindrone)
  - Orthocyclen (norgestimate)
  - Desogen or Orthocept (desogestrel)
  - Yasmin


GnRH
hypothalamus
LH
pituitary
X
Androgens block inhibitory effect of progesterone
ovary
androgens

INFERTILITY

- Intermittent ovulation or anovulation

- Inherent ovarian disorder—studies show reduced rates of conception despite therapy with Clomiphene

Other issues
Role of epilepsy?

- Increased incidence of reproductive disorders in patients with epilepsy

- Pts on valproic acid may have higher levels of insulin, testosterone, and TG

New things on the horizon…

- Somatostatin analogs
  - Function
    - Blunts LH response to GnRH
    - Decreases GH secretion by pituitary
    - Inhibits pancreatic insulin release
  - Outcomes: limited studies
    - 7 d administration octreotide in PCOS women → decreased fasting and glucose-stimulated insulin levels
    - Reduced LH, androgen, IGF-1 levels
    - Short half-life (80-110 min) requiring multiple injections
    - Extended release octreotide (octreotide-LAR)- inject IM Q28 days- results in improvement in GH, insulin, IGF-1, hirsutism
    - Not approved yet

Ghrelin and PCOS

- Dysregulation of ghrelin levels may lead to physiological problems including obesity and polycystic ovary syndrome (PCOS).
- A study was done to compare ghrelin levels in women with and without PCOS.
- Serum ghrelin levels (pre- and post-prandial) were compared between 30 Saudi women suffering from PCOS and 30 healthy controls.

No relationship between circulating ghrelin levels and the abnormal hormonal pattern of the PCOS were observed.

Eur J Obstet Gynecol Reprod Biol. 2011 Jan 6. [Epub ahead of print]

Classifications of evidence lev

- Ia: Evidence obtained from meta-analysis of randomized controlled trials
- Ib: Evidence obtained from at least one randomized controlled trial
- IIa: Evidence obtained from at least one well-designed controlled study without randomization
- IIb: Evidence obtained from at least one other type of well-designed quasi-experimental study
- III: Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
- IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grades of Recommendations

- A- Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
- B- Requires the availability of well controlled clinical studies but no randomized clinical trials on the topic of recommendations (Evidence levels IIa, IIb, III)
- C- Requires evidence obtained from expert committee reports or opinions and/ or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

Abnormal Pituitary Function—Altered Negative Feedback Loop

- Increased GnRH from hypothalamus
- Excessive LH secretion relative to FSH by pituitary gland
- LH stimulates ovarian thecal cells ➡ androgen production
- Ineffective suppression of the LH pulse frequency by estradiol and progesterone
- Androgen excess increases LH by blocking the hypothalamic inhibitory feedback of progesterone

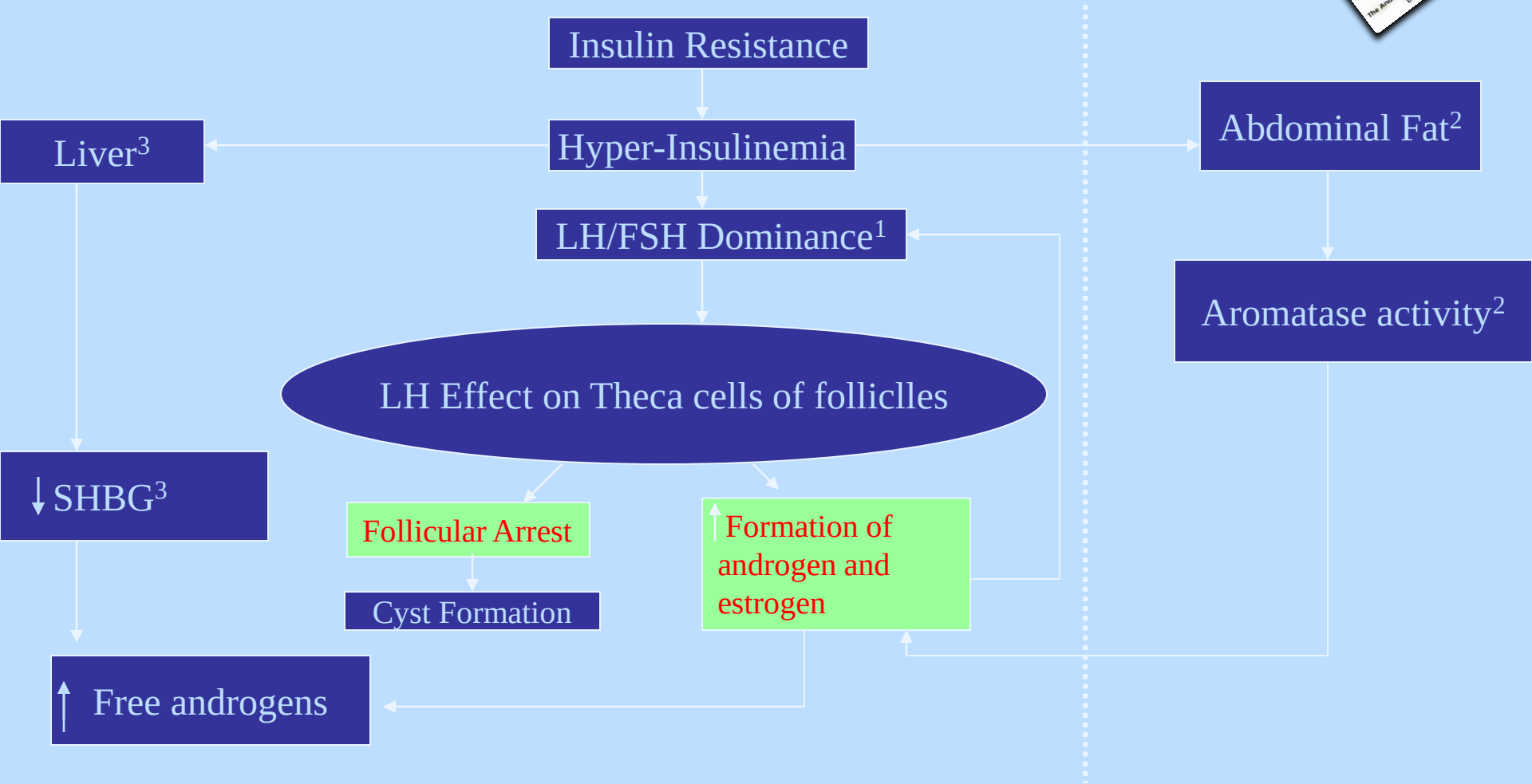
Rotterdam Criteria (2 out of 3)

- Menstrual irregularity
  due to anovulation oligo-ovulation
- Evidence of clinical or biochemical hyperandrogenism
- Polycystic ovaries by USG
  - presence of 12 or more follicles in each ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume

SIDE EFFECTS

- Lactic acidosis—rare
  - Avoid in CHF, renal insufficiency, sepsis
  - Discontinue for procedures using contrast (withhold X 48 hours)
  - Temporarily suspend for all surgical procedures that involve fluid restriction
  - Cimetidine causes increased metformin levels

PCOS: Patho-physiology



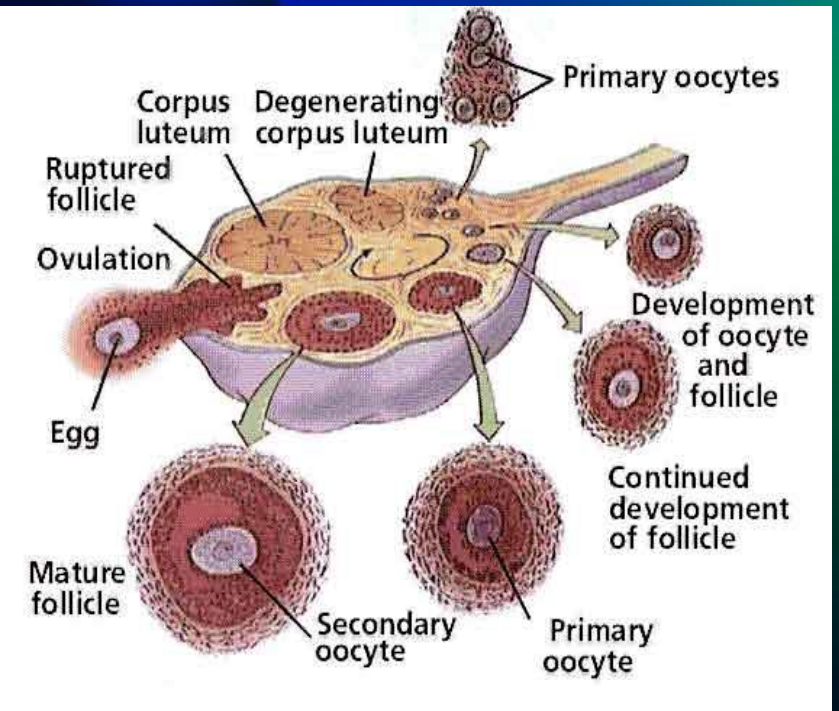
1. J.M Weiss, S. Polack et. al. Arch Gynecol Obstet (2003) 269:45–50
2. Kumar Cotran Robbins: Basic Pathology 6th ed. / Saunders 1996
3. Puget M, Crave J.C. et. al. The Journal of Steroid Biochemistry and Molecular Biology; Vol 40. Issues 4-6; 841-849

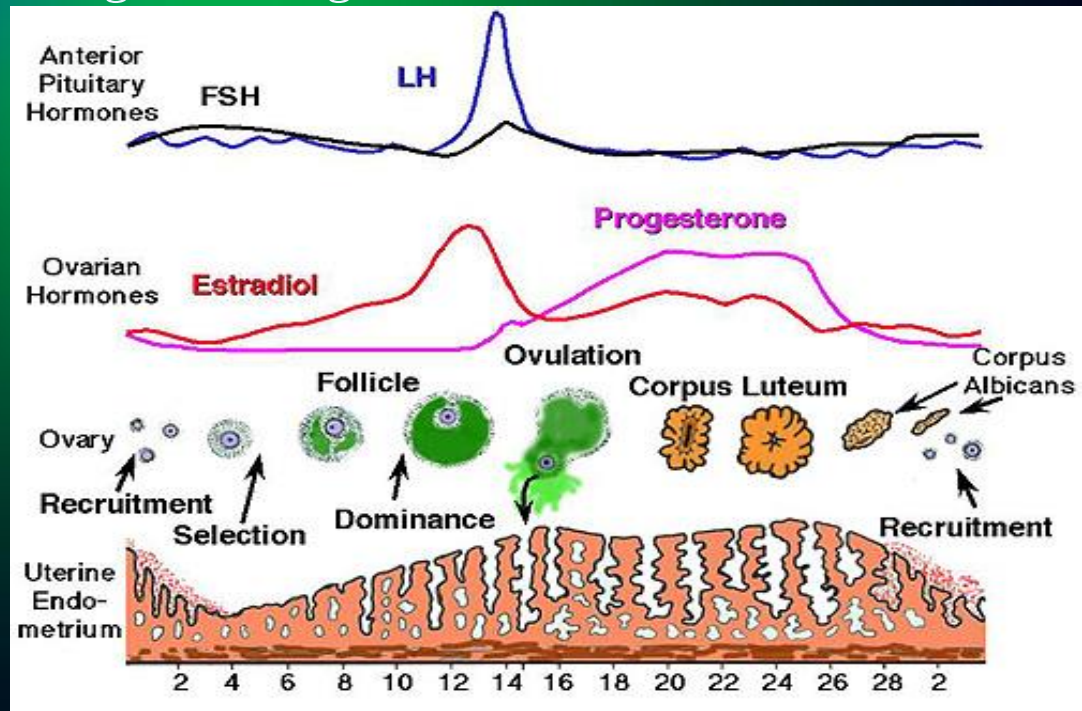
Abnormal steroidogenenesis

- Intraovarian androgen excess results in excessive growth of small ovarian
- Excess androgen causes thecal and stromal hyperplasia

- Follicular maturation is inhibited
- Reduction in ovulatory events leads to deficient progesterone secretion

- Chronic estrogen stimulation of the endometrium with no progesterone for differentiation—intermittent breakthrough bleeding or DUB





PCOS-

More Than A Reproductive Issue

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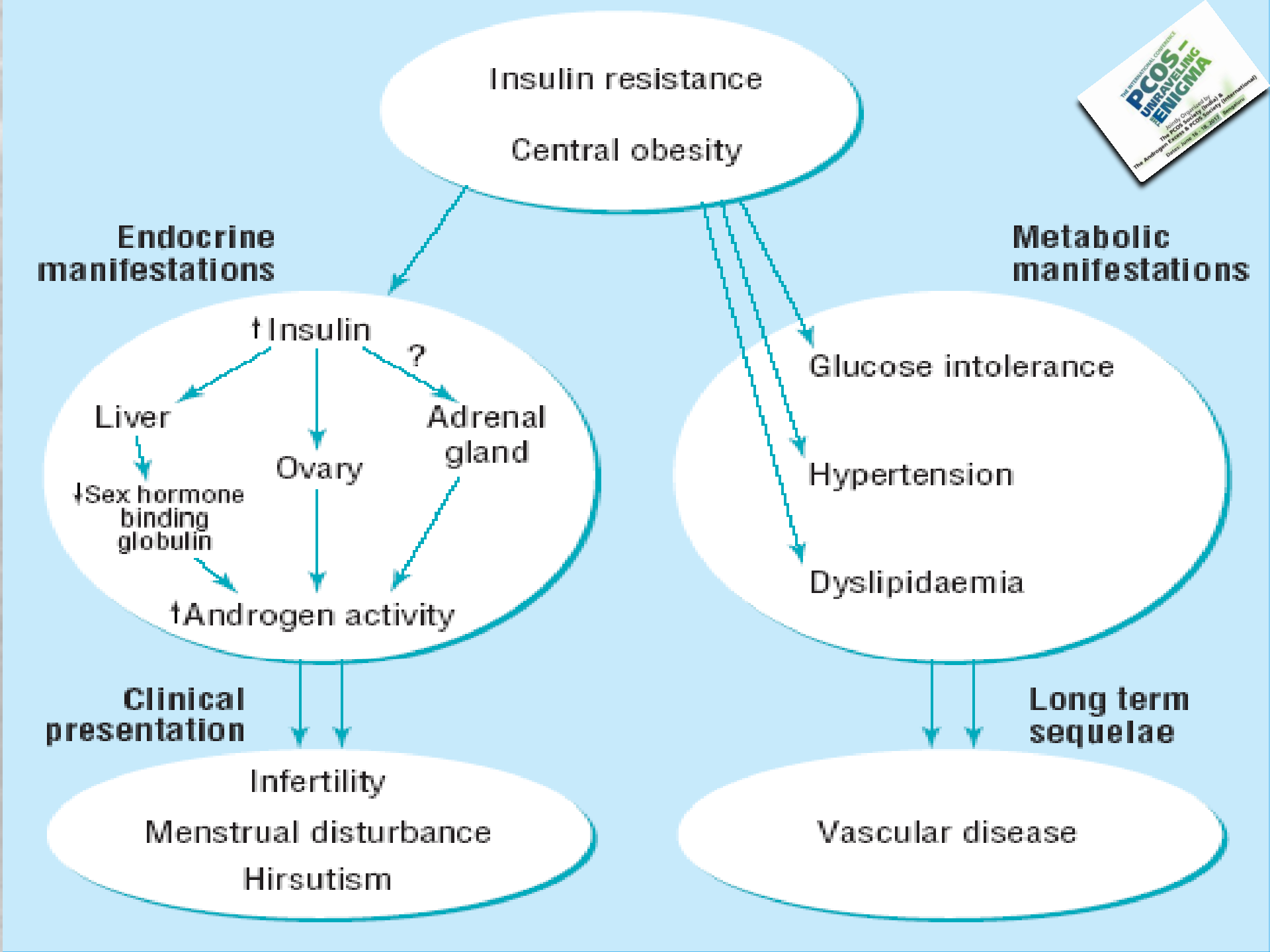
Insulin resistance
Central obesity
Endocrine manifestations
Metabolic manifestations
↑Insulin
?
Liver
Ovary
Adrenal gland
↓Sex hormone binding globulin
↑Androgen activity
Glucose intolerance
Hypertension
Dyslipidaemia
Clinical presentation
Long term sequelae
Infertility
Menstrual disturbance
Hirsutism
Vascular disease

Conclusion

- ✓ Treatment of IGT is required
- ✓ LSM as a medication Must
- ✓ LSM may not be possible for everyone
- ✓ LSM may not work for everyone
- ✓ Medication is required
- ✓ Ideal not available
- ✓ Metformin, etc are adjuvant
- ✓ Lifestyle is the best preventive vaccine