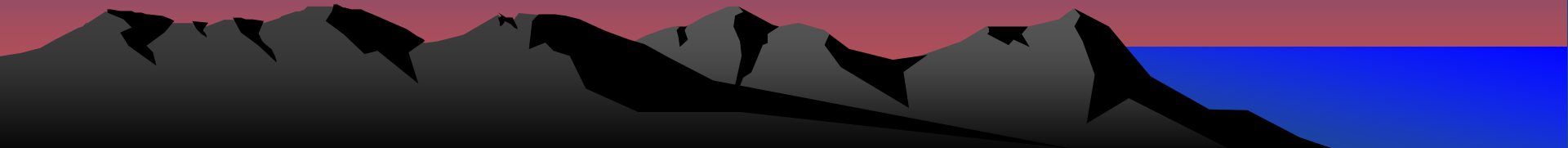


# Polycystic Ovary Syndrome

Sidika E. Karakas, M.D

Professor and Chief

Division of Endocrinology, Diabetes and  
Metabolism



# PCOS

- Affects 1 out of 16 women
  - 8% of AA; 5% of White
- Most common cause of anovulatory infertility
- Increases risks for
  - Type 2 DM
  - Gestational DM
  - Endometrial cancer
  - Cardiovascular disease

# Clinical Definition

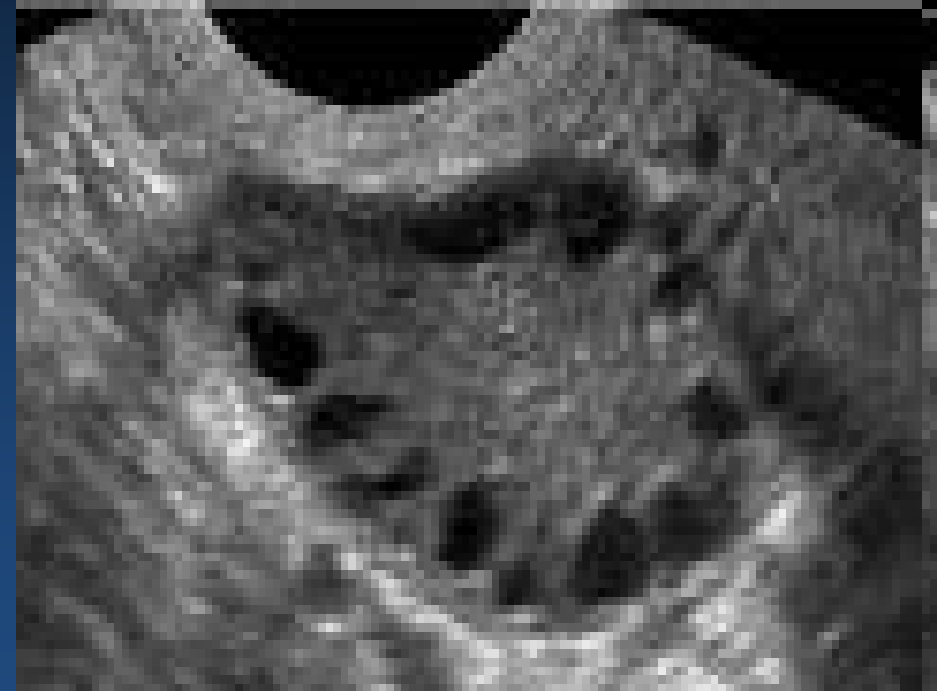
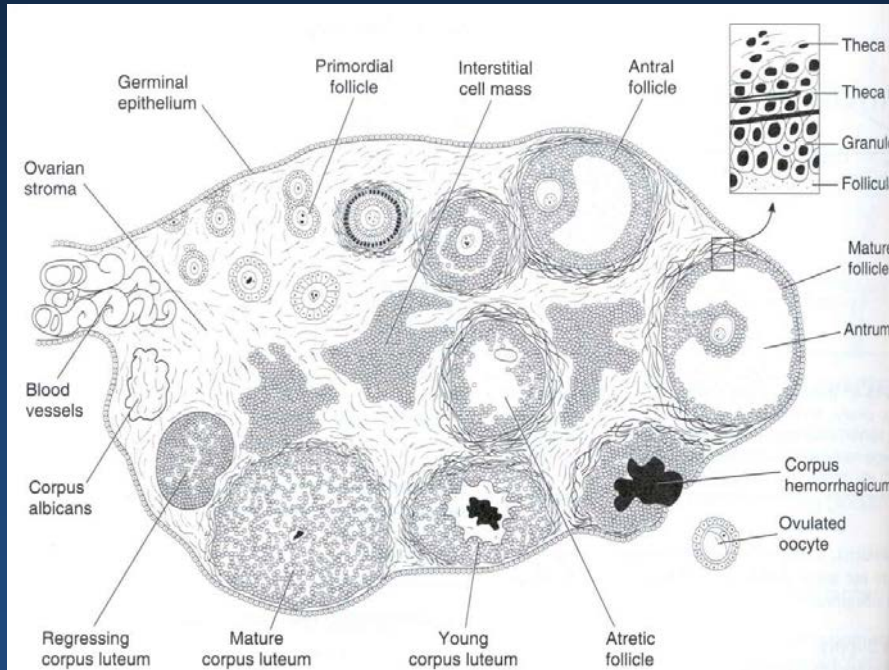
- Oligomenorrhea (< 6 periods/y)  
/Amenorrhea (no periods > 6 mo)
- Clinical and/or biochemical signs of hyperandrogenism
- Exclusion of other etiologies  
(congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome)
- Polycystic ovaries (Rotterdam Criterion)

# PCOS—Two Sided Coin



Ovarian Dysfunction

# Ovarian Dysfunction



- ovarian volume  $\geq 10$  ml
- $\geq 12$  follicles
- each 2–9 mm
- subjective appearance of PCO cannot be substituted

# Anti-Mullerian Hormone (AMH)

- Glycoprotein
- Produced by granulosa cells of primary, pre-antral and early antral follicles
- NOT by larger or atretic follicles
- Indicator of ovarian reserve
  - $>5$  ng/ml ---PCOS
  - $< 0.8$  ng/ml ---Menopause
  - $> 1.3$  ng/ml---Successful IVF

# PCOS—Two Sided Coin



Insulin Resistance

# Most PCOS patients are insulin resistant

## Presentation of Insulin Resistance



Blood Sugar: 80

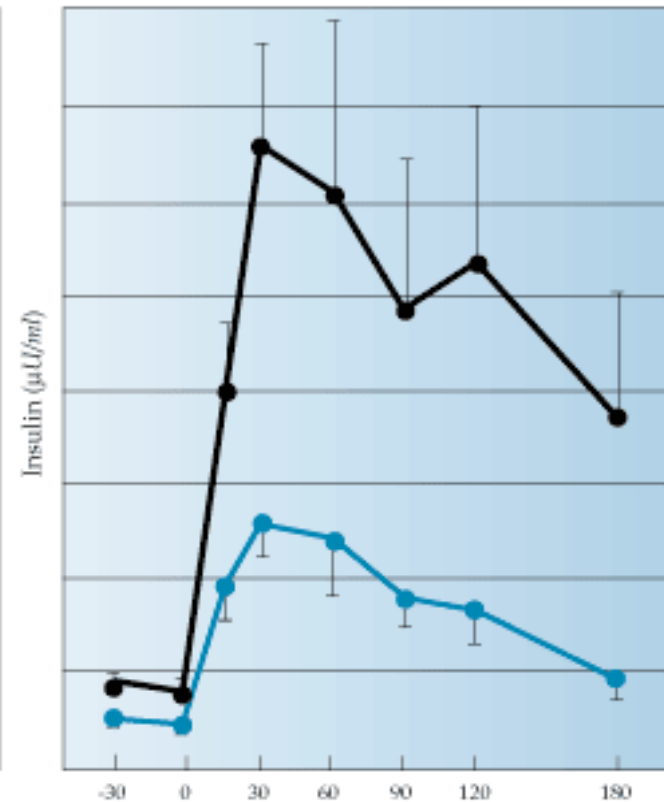
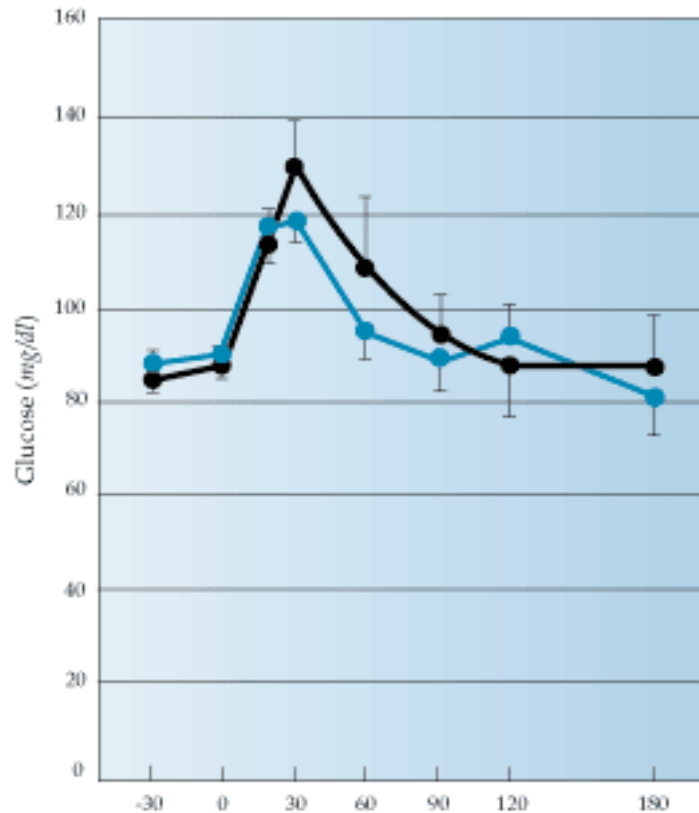
80

Insulin: 10

30



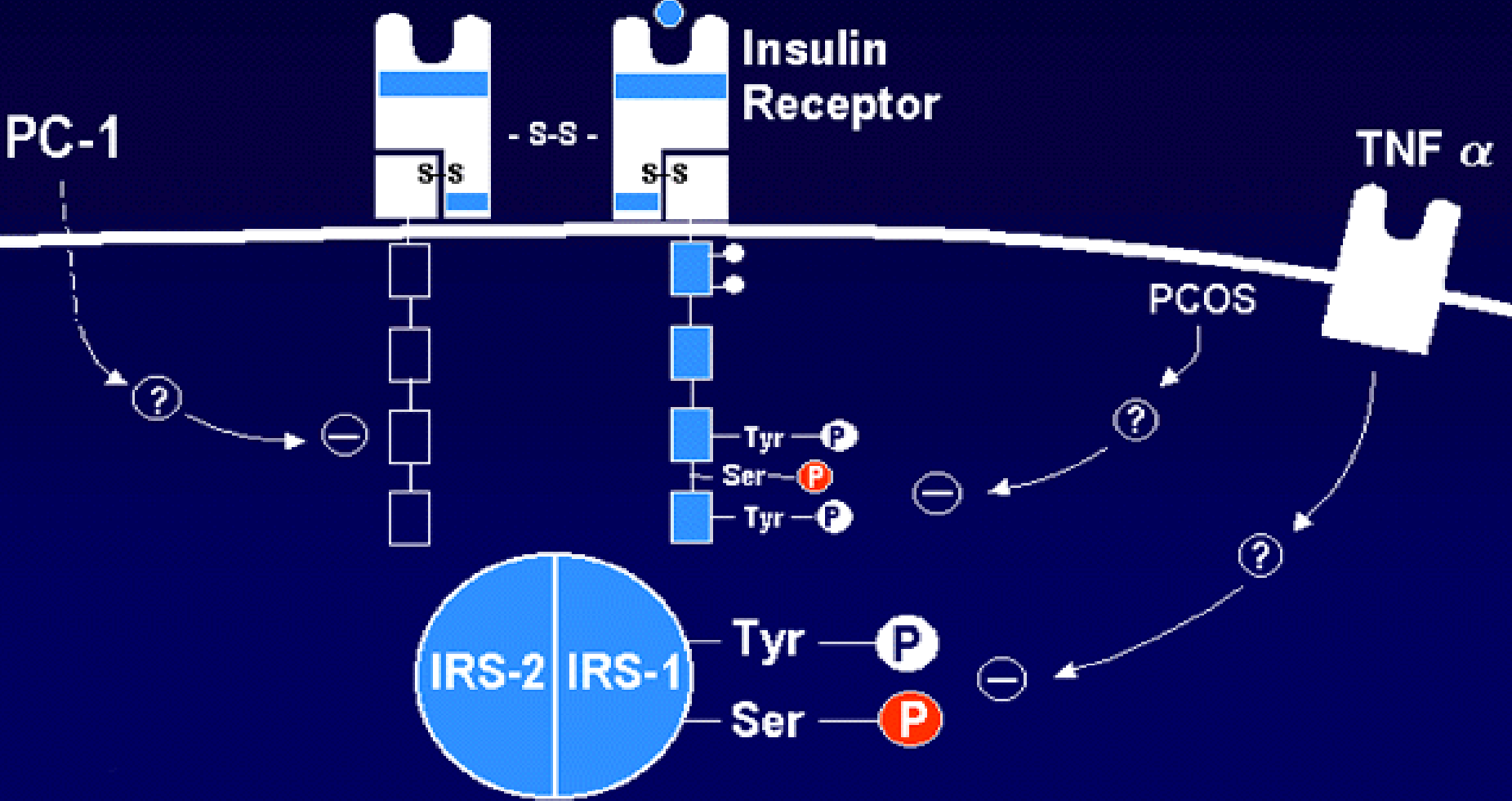
# OGTT in PCOS



—●— PCO    —●— Normal

—●— PCO    —●— Normal

# Pathogenesis of Insulin Resistance



# Insulin Resistance / Obesity



Hyperinsulinemia



↓ SHBG



↑ Free-T



↓ IGFBP

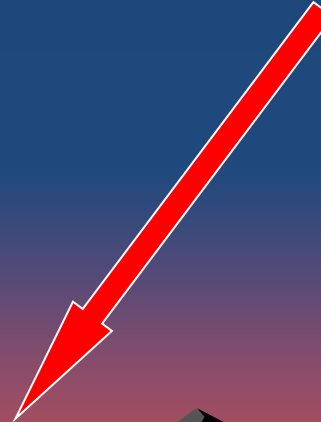
↑ IGF



↑ Ovarian Stroma

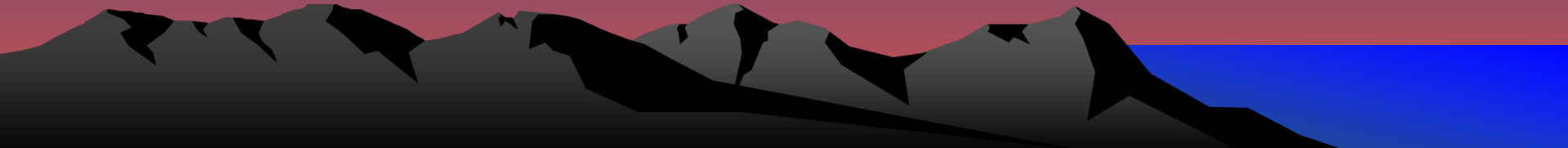


↑ Ovarian Androgen



HIRSUTISM

# Clinical Findings of PCOS



# Gestational DM

Miscarriages

Cardiovascular Disease

Infertility

Hirsutism

Type 2 DM

Weight gain

Acanthosis nigricans

Oligomenorrhea

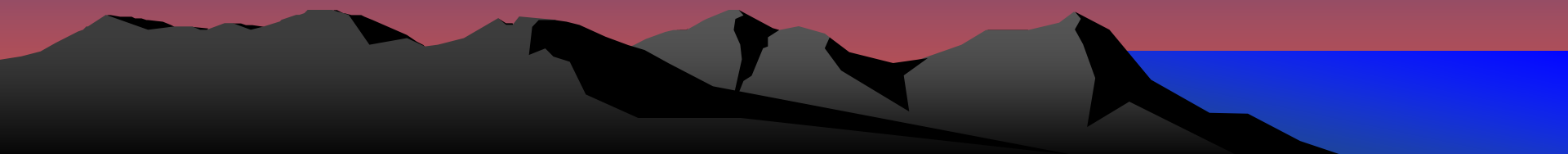
Age

10

20

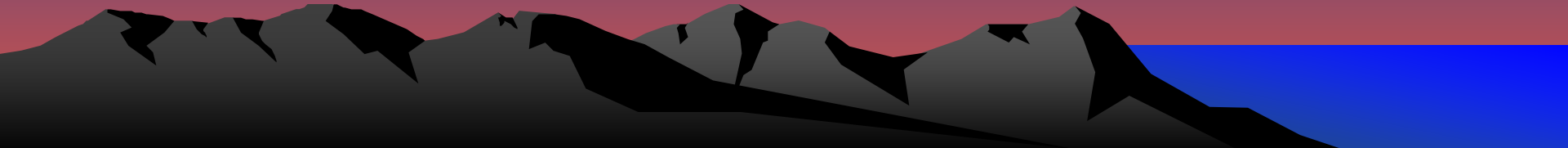
30

40



# Menstrual cycles are a vital sign

*Andrea Dunaif, MD.*



# Clinical Findings of PCOS



# Laboratory Testing for PCOS

- Confirm hyperandrogenemia
  - Bioavailable testosterone
- Differential diagnosis of hyperandrogenemia
  - DHEAS, 17OHP
- Differential diagnosis of amenorrhea
  - Prolactin, FSH, AMH
- Diagnosis of metabolic abnormalities
  - Insulin resistance
  - Hyperlipidemia



# Necessary and Sufficient

- Bioavailable testosterone
- DHEAS
- 17OHP
- Prolactin
- FSH
- AMH

# Why Bioavailable Testosterone?



- Free testosterone 2%
- SHBG bound 44%
- Albumin bound 50%
- Bioavailable -- calculated from SHBG & albumin

# Why Bioavailable Testosterone?

	<b>Reference Range</b>	<b>Patient 1</b>	<b>Patient 2</b>
<b>Total-T</b>	<b>11-56 ng/dl</b>	<b>50</b>	<b>48</b>
<b>SHBG</b>	<b>30-135 nmol/l</b>	<b>25</b>	<b>186</b>
<b>Bioavail-T</b>	<b>4.1-22.6 ng/dl</b>	<b>26.0</b>	<b>5.8</b>
<b>Free-T</b>	<b>1.3-9.2 pg/ml</b>	<b>10</b>	<b>2.3</b>

# Oral Glucose Tolerance Test?

	1	2	3	4	5...
	09/23/08 0814	03/24/08 0940	03/04/08 1025	03/04/08 0955	03/04/08 0925
<b>CHEMISTRY PANELS</b>					
FASTING	YES				
CHOLESTEROL	105 *				
TRIGLYCERIDE	98				
LDL CHOLESTEROL...	38				
HDL CHOLESTEROL	47				
NON-HDL CHOLEST...	58 *				
TOTAL CHOLESTER...	2.2				
GLUCOSE FASTING...	104				
GLUCOSE, 1 HOUR					150 *
GLUCOSE, 90 MINUTE				139 *	
GLUCOSE, 2 HOUR			129 * ▲		

17 yo AA woman, 240 lb

# OGTT: Only with INSULIN

	1	2	3	4	5...
	09/23/08 0814	03/24/08 0940	03/04/08 1025	03/04/08 0955	03/04/08 0925
<b>CHEMISTRY PANELS</b>					
FASTING	YES				
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TOTAL CHOLESTER...	2.2				
GLUCOSE FASTING...	104				
GLUCOSE,1 HOUR					150 *
GLUCOSE, 90 MINUTE				139 *	
GLUCOSE,2 HOUR			129 * ▲		
IRON TOTAL		19 ▼			
TRANSFERRIN		273			
TOTAL IRON BIND...		379			
IRON PERCENT SA...		5.0 ▼			
FERRITIN		17			
<b>MISC. CHEMISTRY</b>					
HEMOGLOBIN A1C	5.8 *				
hsCRP	26.0 *				
INSULIN	76.9 ▲		637.0 ▲	582.8 ▲	498.2 ▲

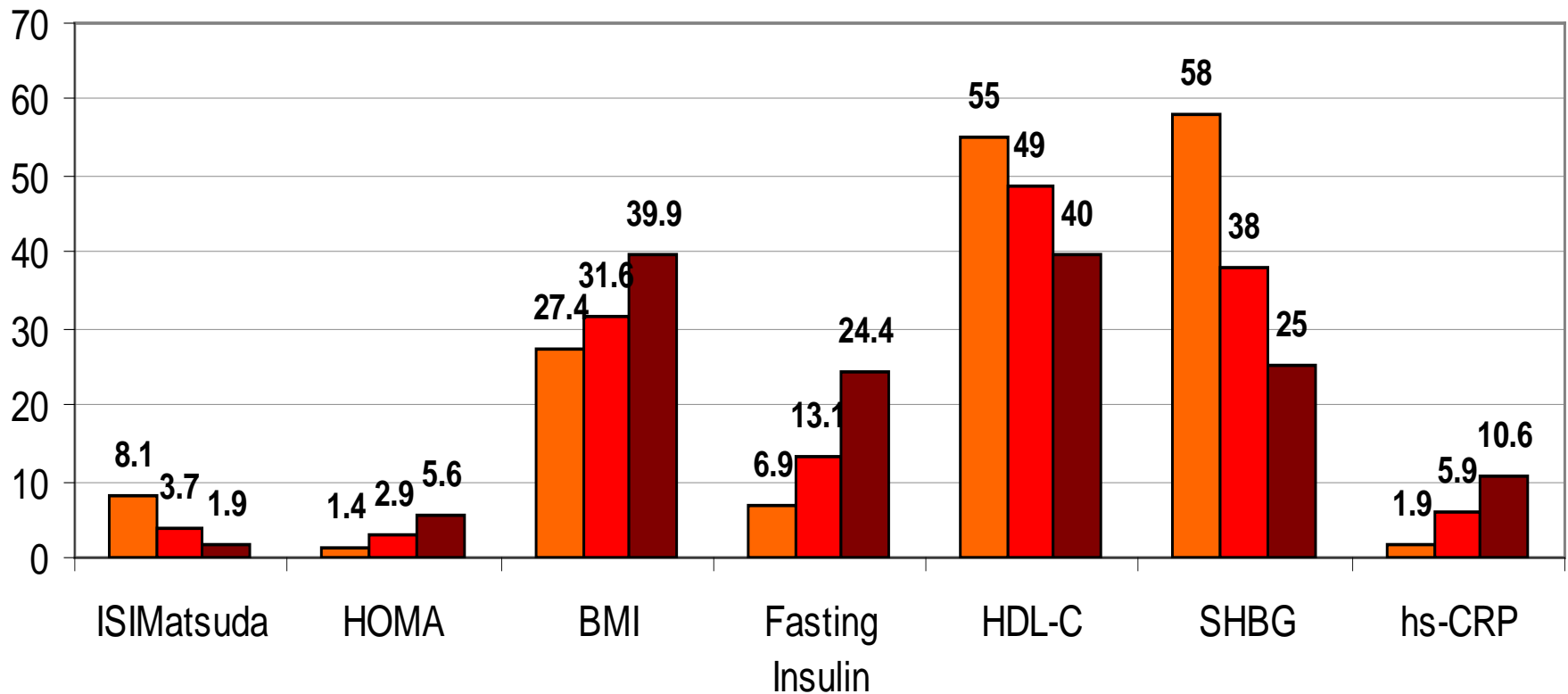
# Is HgBA1 > 5.7% Useful in PCOS?

	HgBA1 < 5.7 (n = 25)	HgBA1 >5.7 (n = 23)	P value
Age (years)	31.1 ± 1.1	35.1 ± 1.1	0.039
Fasting glucose (mg/dl)	91.5 ± 0.9	99.6 ± 2.3	0.028
Adiponectin (ng/ml)	12.4 ± 0.9	8.8 ± 0.7	0.023
<u>FS-IVGTT</u>			
SI	4.2 ± 0.6	2.0 ± 0.2	0.020
DI	1901 ± 217	1014 ± 82	0.011
<u>CVD risk factors</u>			
Triglyceride (mg/dl)	92.6 ± 4.4	125.3 ± 9.5	0.018
hs-CRP (ng/ml)	2.1 ± 0.1	4.76 ± 0.5	0.003
FABP4 (ng/ml)	34.8 ± 2.9	58.5 ± 4.9	0.021

# Almost half of the PCOS patients have Metabolic Syndrome

Risk Factor	Ehrmann ( n= 368)	Glueck (n=138)
Waist > 88 cm	80%	98%
TG > 150 mg/dL	32%	56%
HDL-C < 50 mg/dL	66%	95%
BP > 130/85 mmHg	21%	70%
Fasting glucose > 110 mg/dL	5%	11%
<b>≥ 3 Risk Factors</b>	<b>33.4%</b>	<b>46%</b>

# Clues for Insulin Resistance in PCOS Women with NORMAL Glucose Tolerance





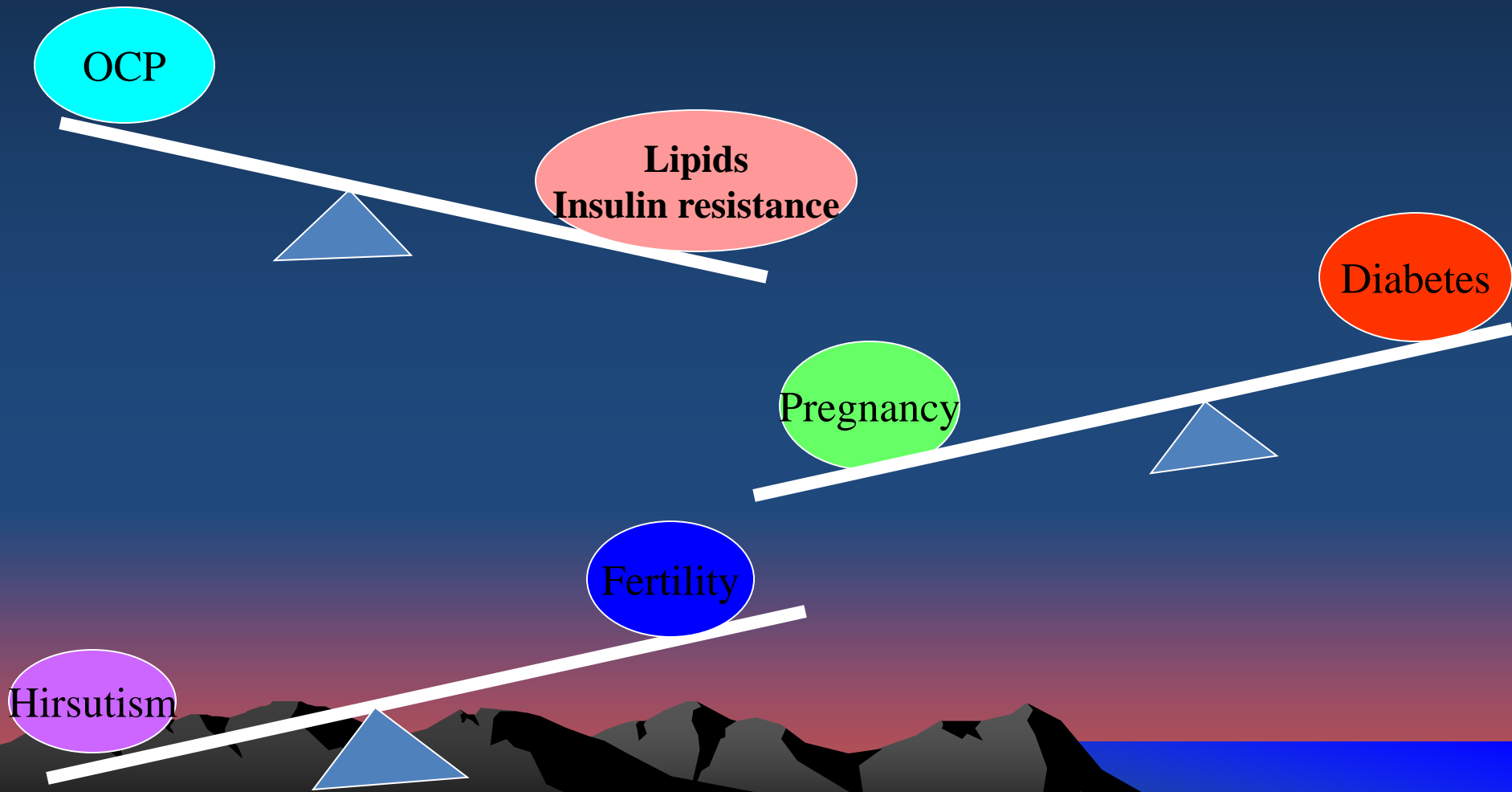
# Acanthosis and Skin Tags



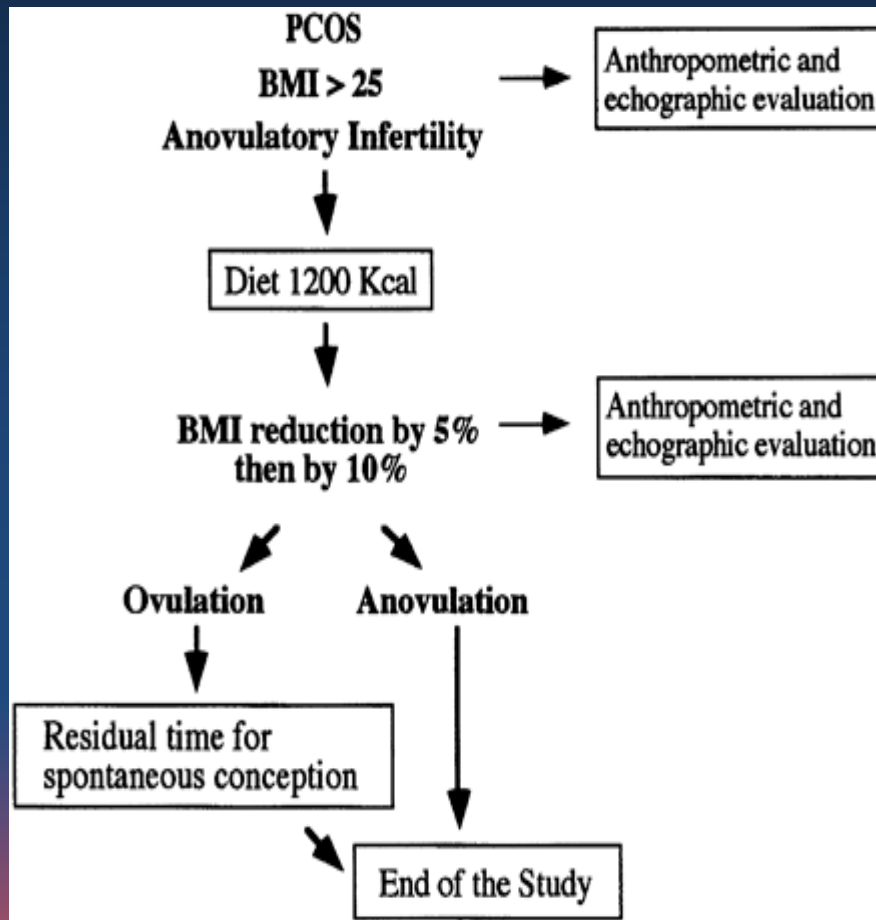
# Most women in our PCOS clinic are obese

<u>BMI</u>	<u>% of PCOS Women</u>
<18.5	0
18.5 – 24.9	9
25 – 29.9	15
30 – 34.9	34
35 – 39.9	20
>40	22

# Management Planning

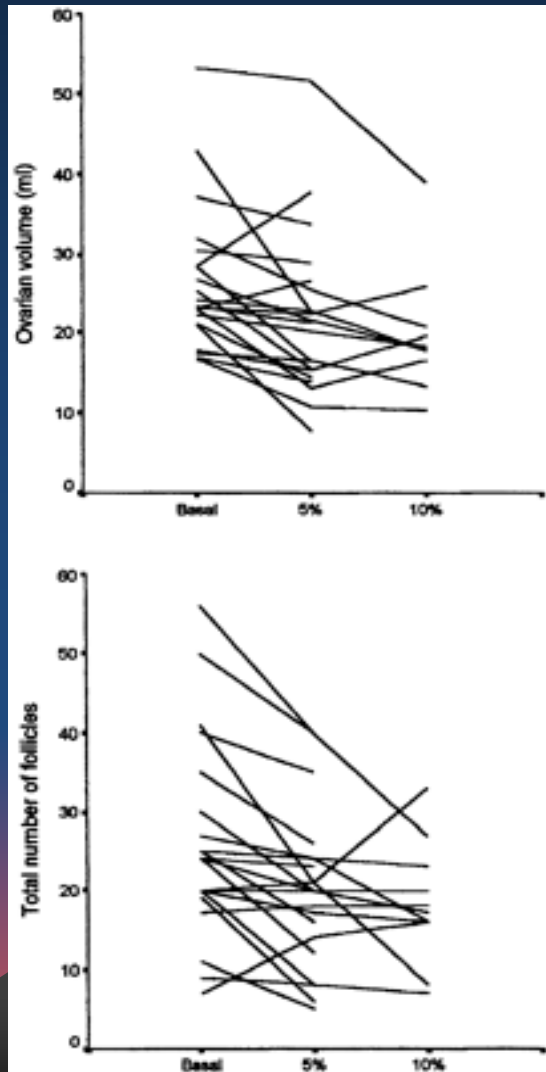


# Effects of Weight Loss on Fertility



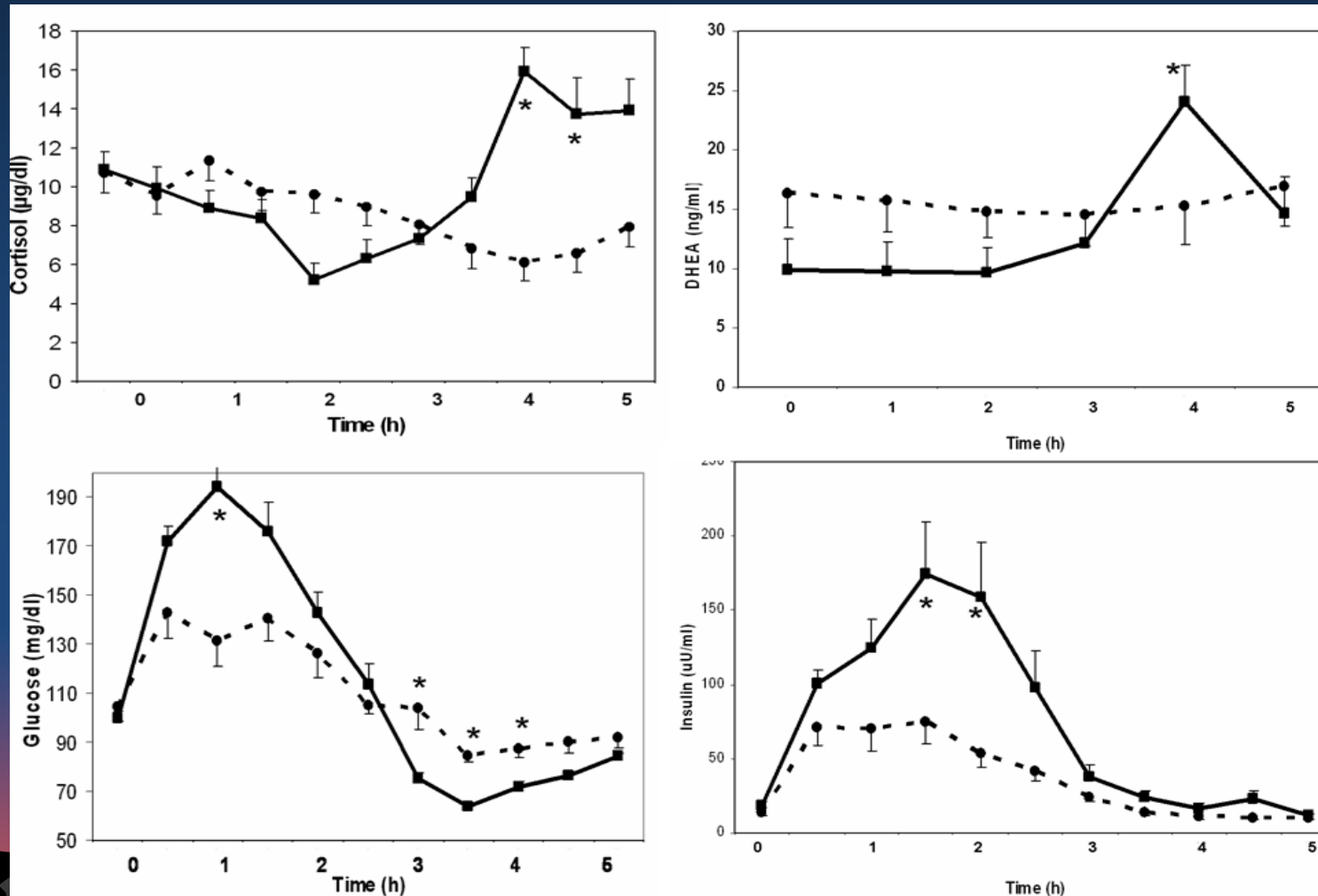
- 33 PCOS patients
- 25 lost 5% weight
- 11 of these lost >10%
- 15 women ovulated
- 10 became pregnant

# Changes in Ovarian Volume and Number of Follicles During Weight Loss

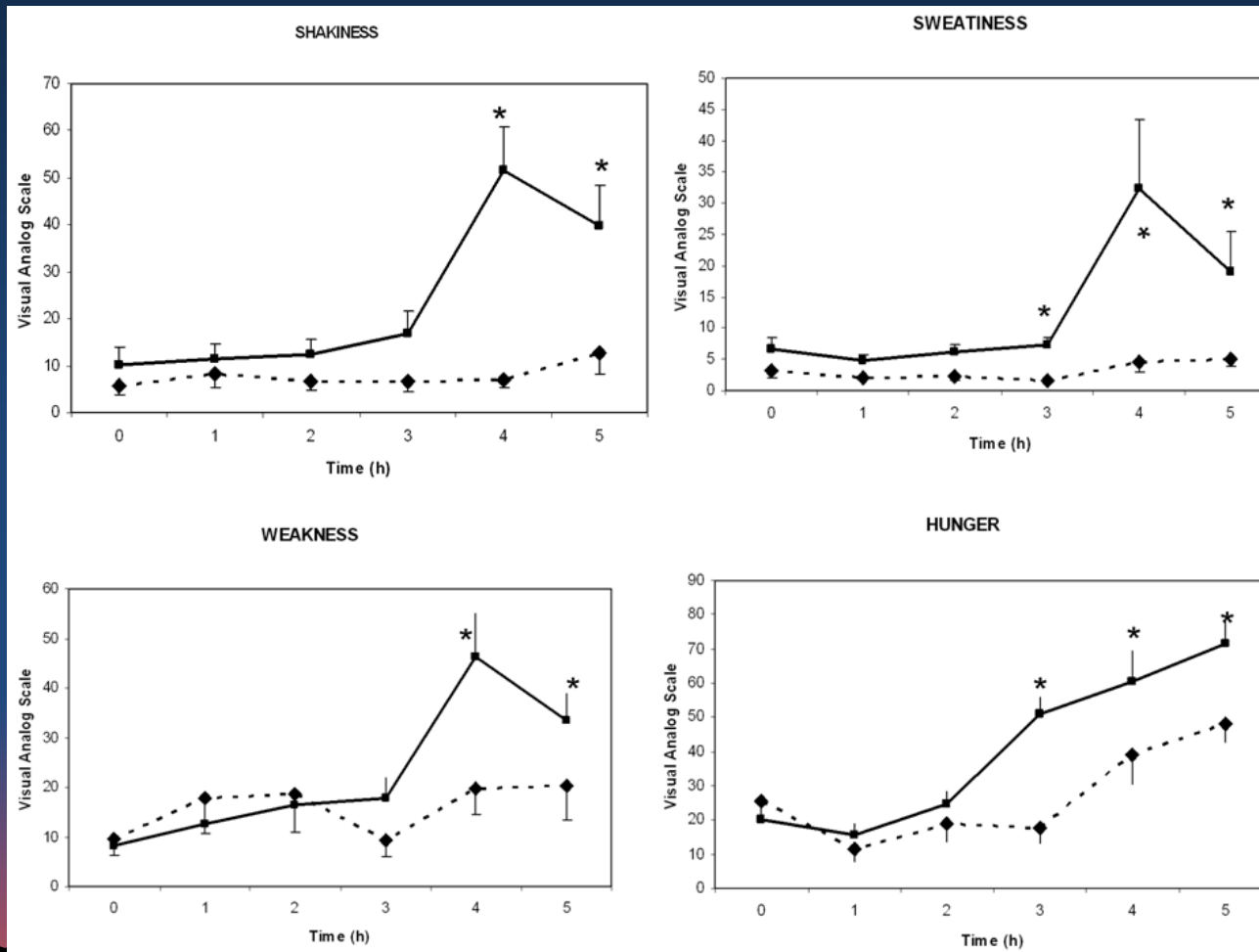


- Ovarian volume decreased by 18% with 5% weight loss  
25% with 10% weight loss
- Follicle number decreased from  $23.5 \pm 11.5$  to  $19.9 \pm 9.9$  with 5%,  
to  $18.3 \pm 7.5$  with 10% weight loss

# Postprandial adrenal steroid secretion in PCOS

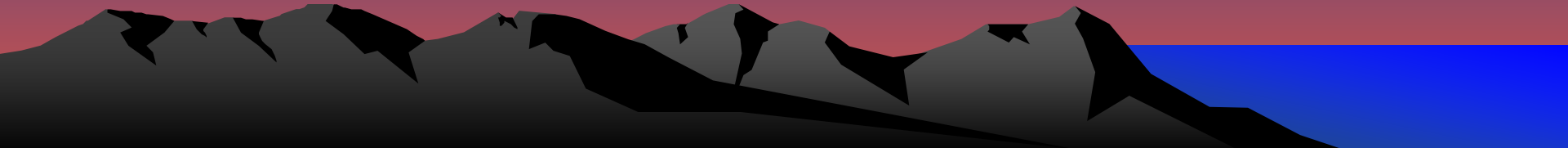


# Symptoms associated with adrenal steroid secretion



# Conclusion

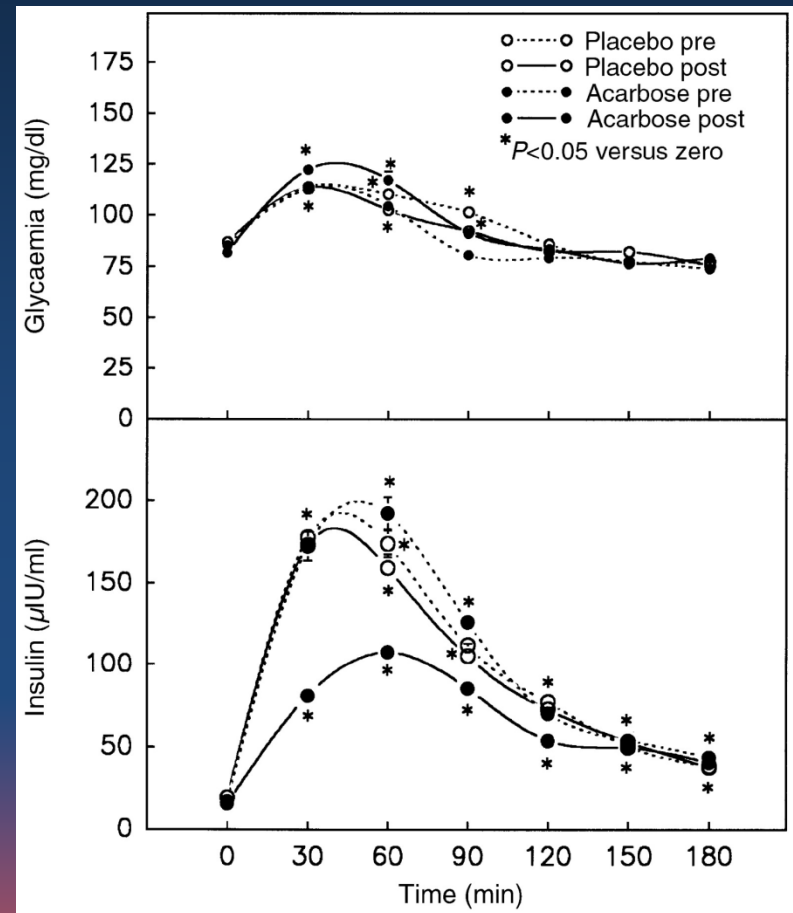
Symptoms of postprandial hypoglycemia are associated with adrenal steroid secretion in PCOS





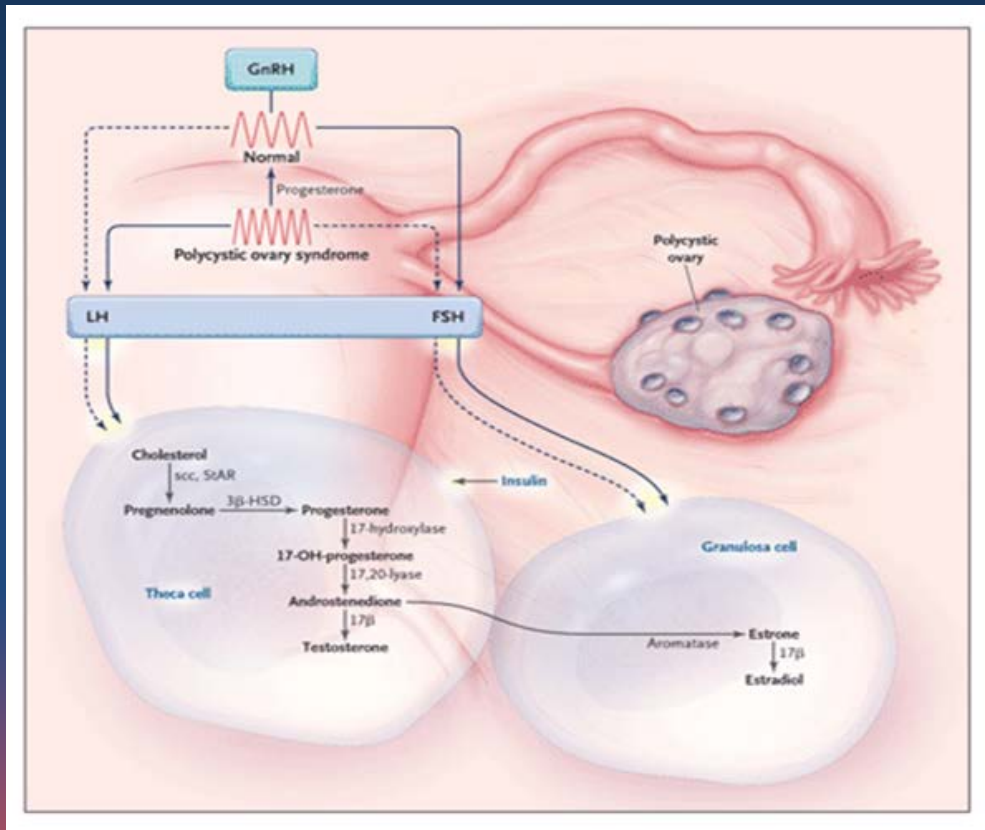
# Tools to decrease insulin response

- Reducing simple sugars and CHO in the diet
- Metformin -- fasting
- Acarbose –postprandial



# Treatment of Hyperandrogenemia

Suppress ovarian androgen production –contraceptives



# Treatment of Hyperandrogenemia

Block androgen receptor  
(spironolactone)



Block conversion of  
testosterone to DHT  
(finasteride)



# Treatment of Infertility

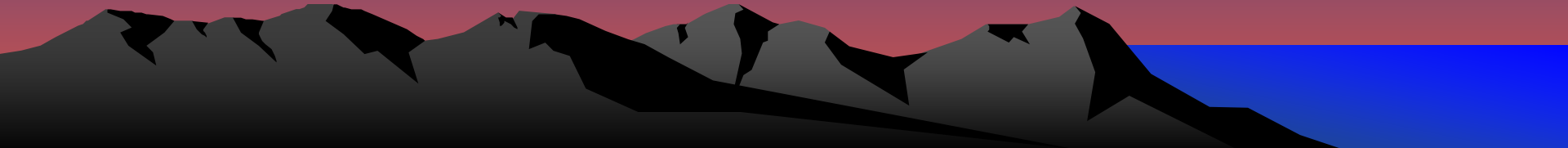
Weight loss

Insulin sensitizers (Metformin, TZD)

Clomiphene citrate

Aromatase inhibitors

Surgery



# ESHRE/ASRM Consensus Statement on infertility in PCOS

	CC	Metformin	Combination
<b>N</b>	<b>209</b>	<b>208</b>	<b>209</b>
<b>Ovulation</b>	<b>49<sup>1</sup></b>	<b>29</b>	<b>60<sup>2</sup></b>
<b>Conception</b>	<b>20<sup>1</sup></b>	<b>12</b>	<b>38<sup>1</sup></b>
<b>Pregnancy</b>	<b>24<sup>1</sup></b>	<b>9</b>	<b>31<sup>1</sup></b>
<b>Live birth</b>	<b>23<sup>1</sup></b>	<b>7</b>	<b>27<sup>1</sup></b>
<b>Multiple</b>	<b>6</b>	<b>0</b>	<b>3</b>

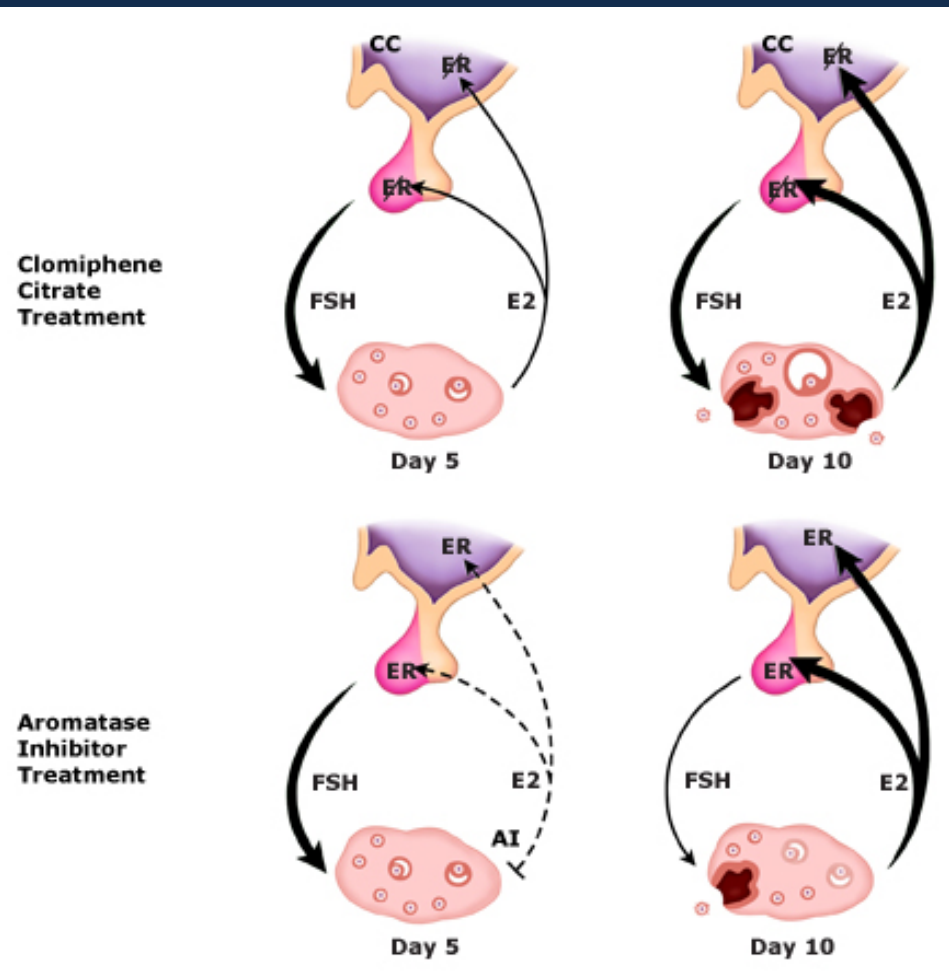
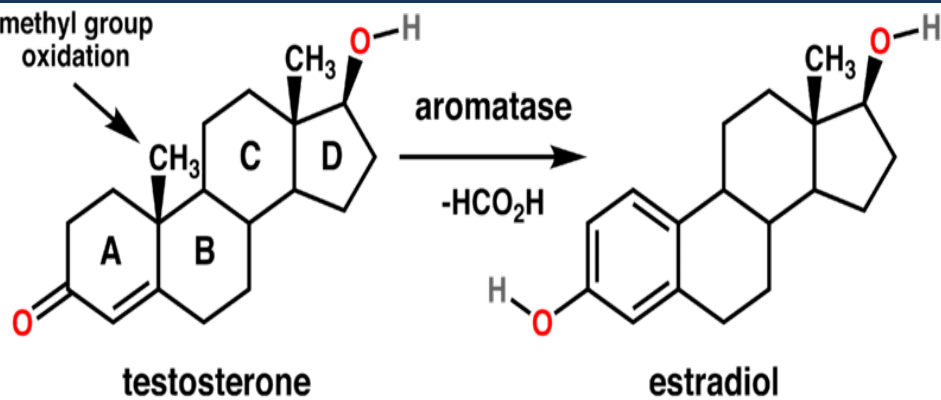
# ESHRE/ASRM Consensus Statement on infertility in PCOS

	CC	Metfor	Comb
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Pregnancy	24 <sup>1</sup>	9	31 <sup>1</sup>
Live birth	23 <sup>1</sup>	7	27 <sup>1</sup>
Multiple	6	0	3

- 1<sup>st</sup>: CC
- 2<sup>nd</sup>: Gonadotropins or laparoscopic ovarian sx
- 3<sup>rd</sup>: IVF
- Metformin: Only in IGT

# New advances in infertility treatment

## Aromatase inhibitors



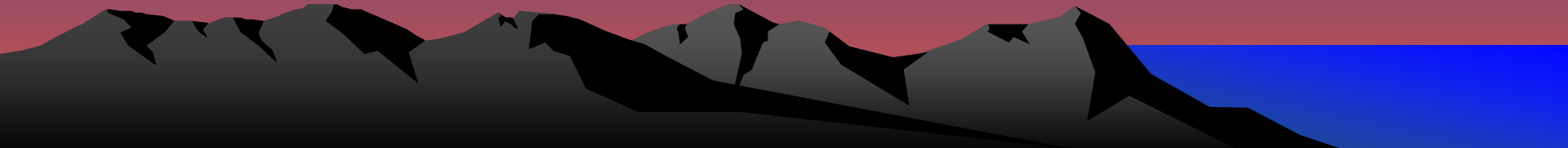
# New advances in infertility treatment—Aromatase inhibitors

## Clomiphene

- 2<sup>nd</sup>- 5<sup>th</sup> d of the cycle
- 50 mg/d
- 150 mg/d maximum
- 70-90% ovulation
- 30-40% pregnancy
- 6-8% multiple
- 10-30% resistant

## Letrozole

- In CC resistant PCOS
- During 3-7 d of cycle
- 2.5 mg/d
- 75% ovulation
- 25% pregnancy





# PCOS After Menopause

*A 21-Year Controlled Follow-Up Study*

*University of Gothenburg, Sweden*

- Anthropometric differences between PCOS and controls diminish: body weight increases in controls, not in PCOS
- Testosterone and DHEAS decrease in both

[Schmidt](#), et al. *JCEM*, 2011

# Update Summary

- Serum AMH is replacing pelvic ultrasound
- Bioavailable testosterone and SHBG are very useful
- OGTT without insulin values is of minimal value
- Controlling both fasting and postprandial hyperinsulinemia is important
- There are new weight loss drugs and infertility management approaches on the horizon