PCO

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PCO

- Epidemiology
- Neurodendocrine aspects
- Ovarian and adrenal function
- Insulin resistance
- Genetics
- Diagnosis
- Treatments

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Prevalence of PCOS

• PCO on ultrasound	20 %	
• Oligomenorrhea	4 - 7 %	whites
	21 %	pima
• Oligomenorrhea + hyperandrogenemism	9 %	greeks
	4.5 %	whites
	3.5 %	blacks

Long term risks in PCOS

- **Definite**
  - Type 2 diabetes
  - Dyslipidemia (Hypercholesterolemia with diminished HDL2 and increased LDL)
  - Endometrial cancer (OR 3.1 95% CI 1.1 - 7.3)

Long term risks in PCOS

- **Possible**
  - Hypertension
  - Cardiovascular disease
  - Gestational diabetes mellitus
  - Pregnancy-induced hypertension
  - Ovarian cancer
- **Unlikely**
  - Breast cancer

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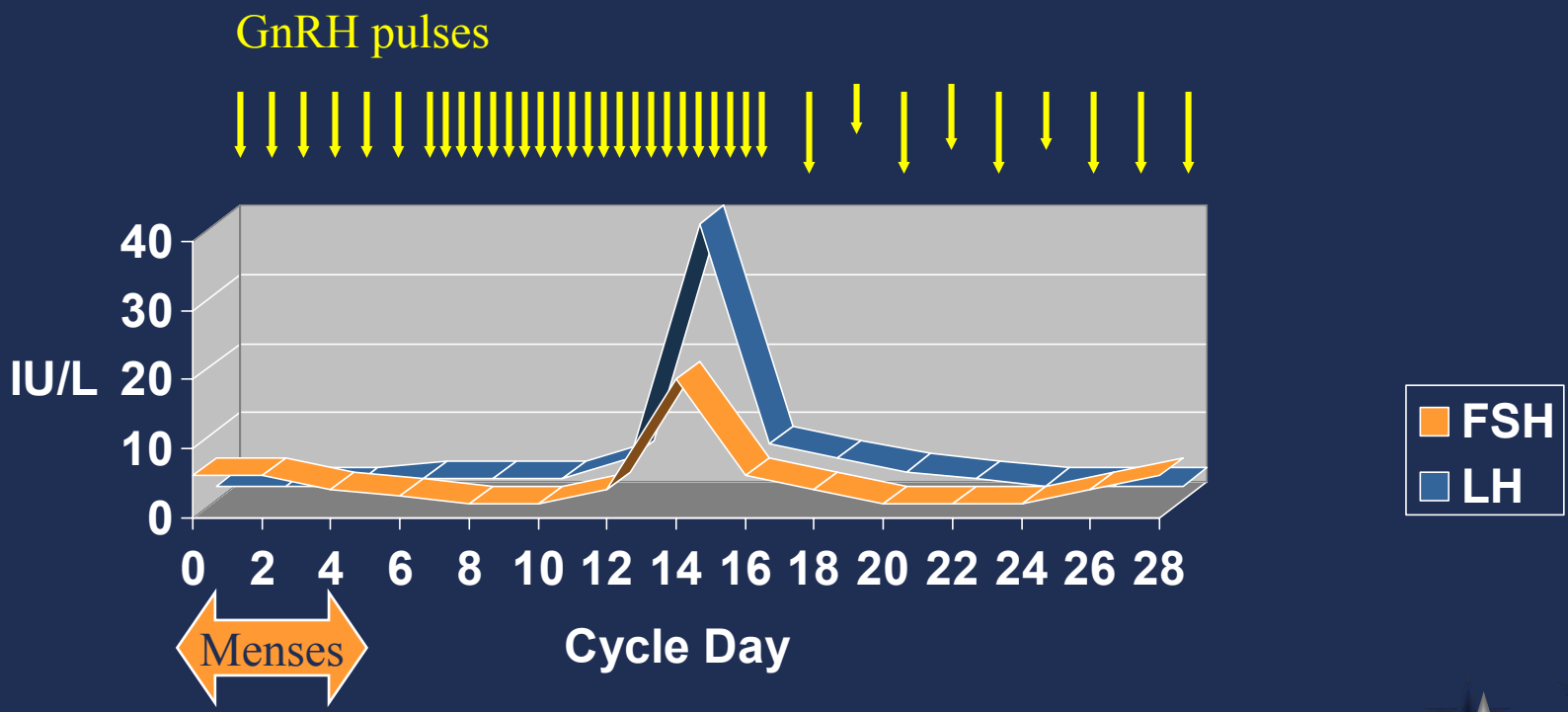
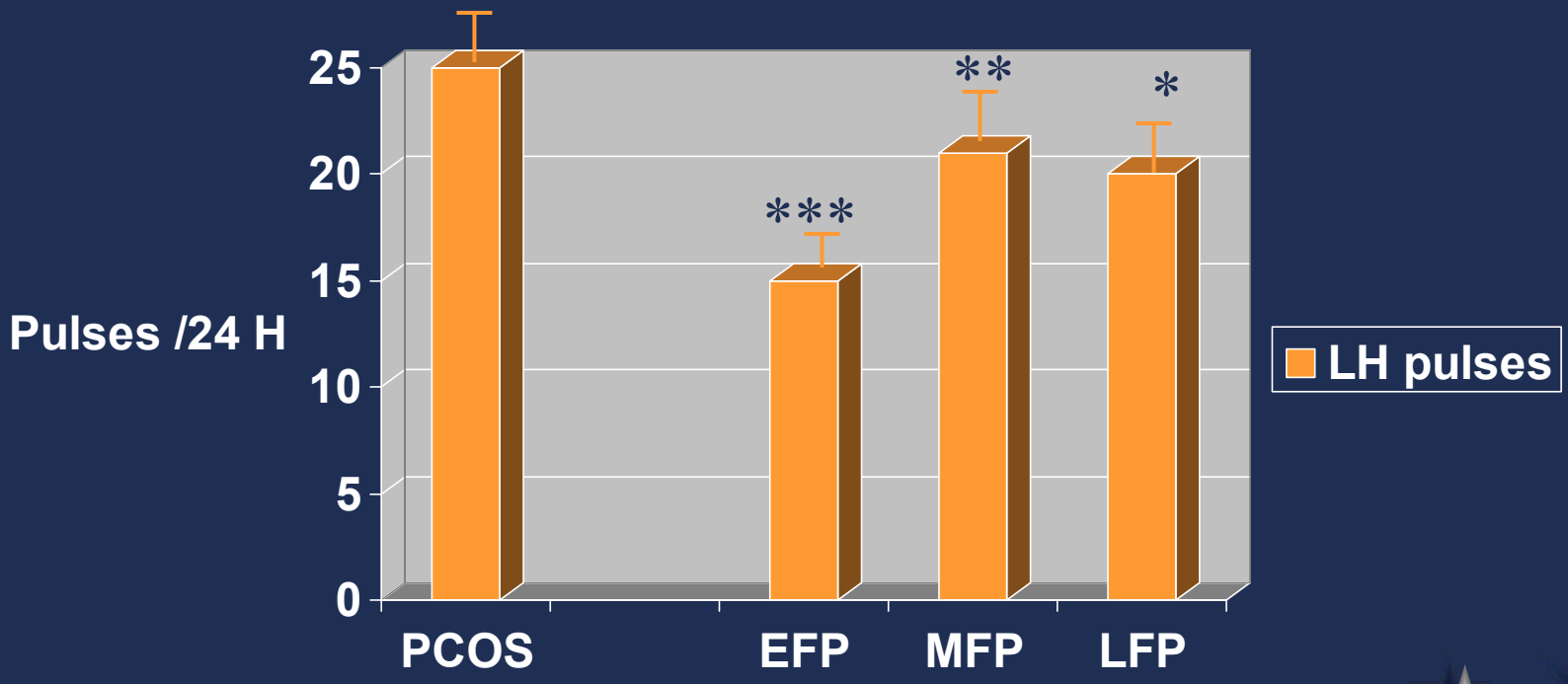
Normal menstrual cycle

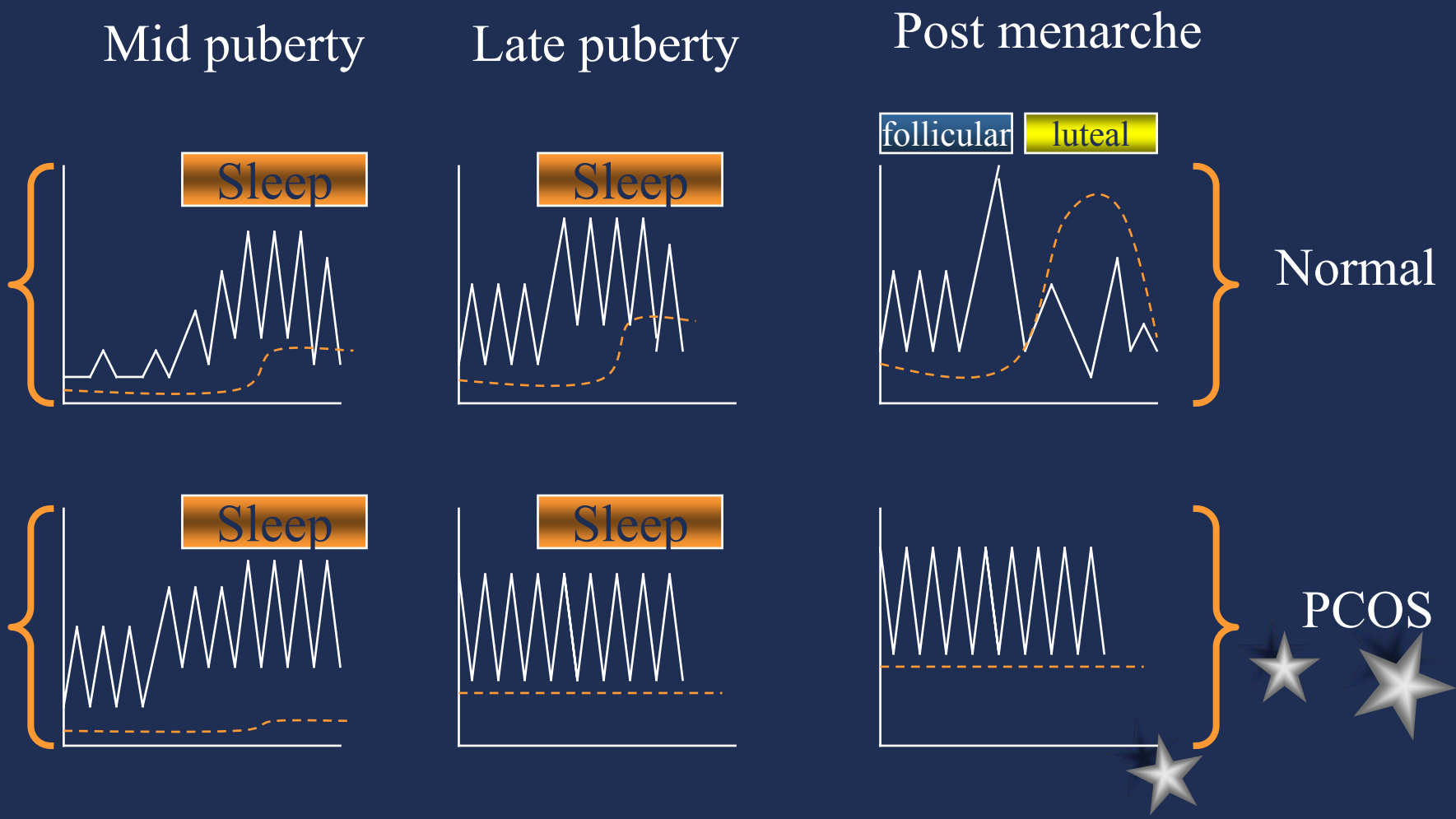


LH pulses and PCO

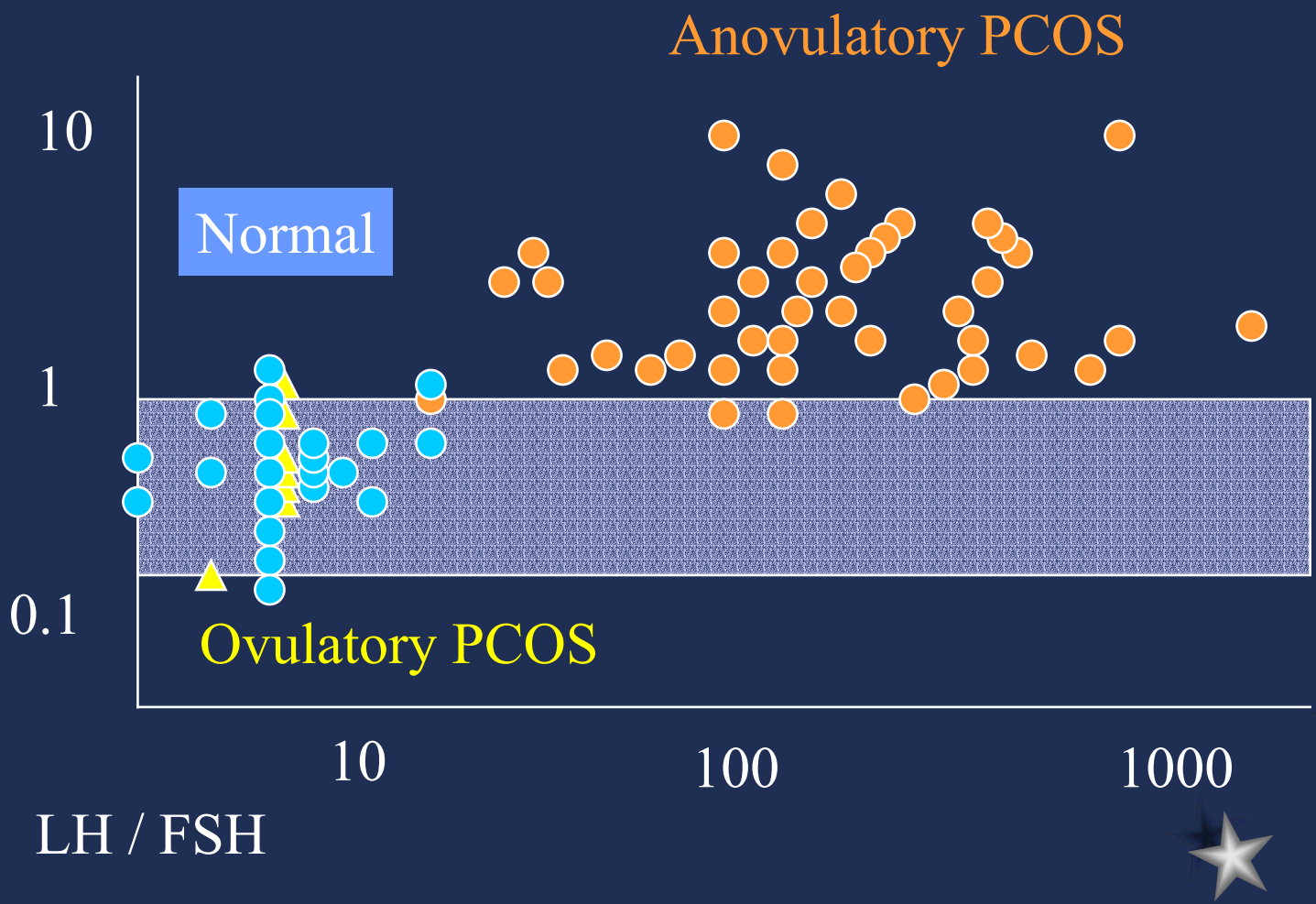
Waldstreicher et al. JCEM 1988



Evolution of pulsatile GnRH



LH and PCO Taylor et al JCEM 1997



PCOS hypothesis

- Fast frequency LH pulses reflect unrestrained postpubertal GnRH secretion
- PCOS is associated with a relative insensitivity of the GnRH pulse generator
- Preferential FSH secretion does not occur with increased LH response

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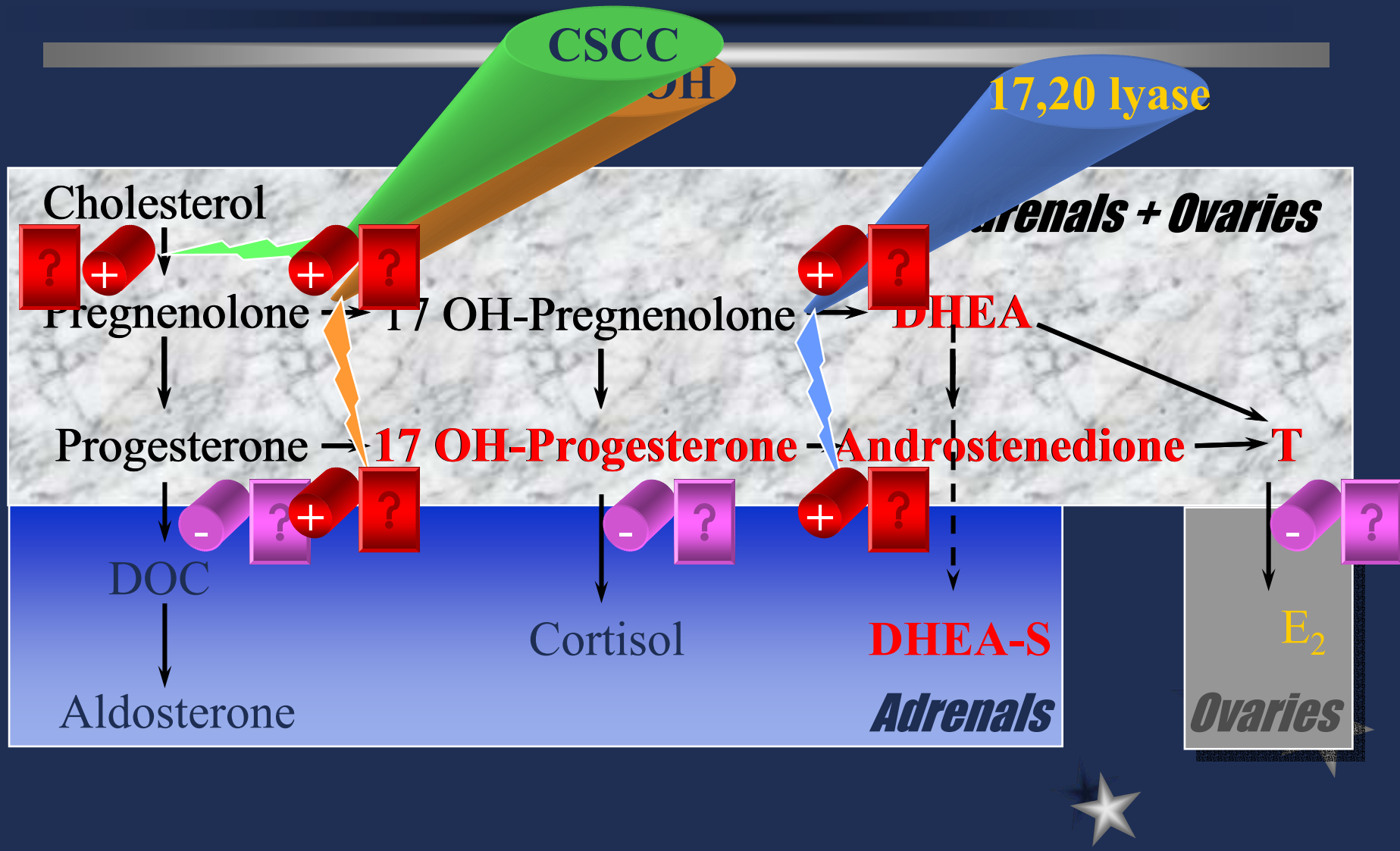
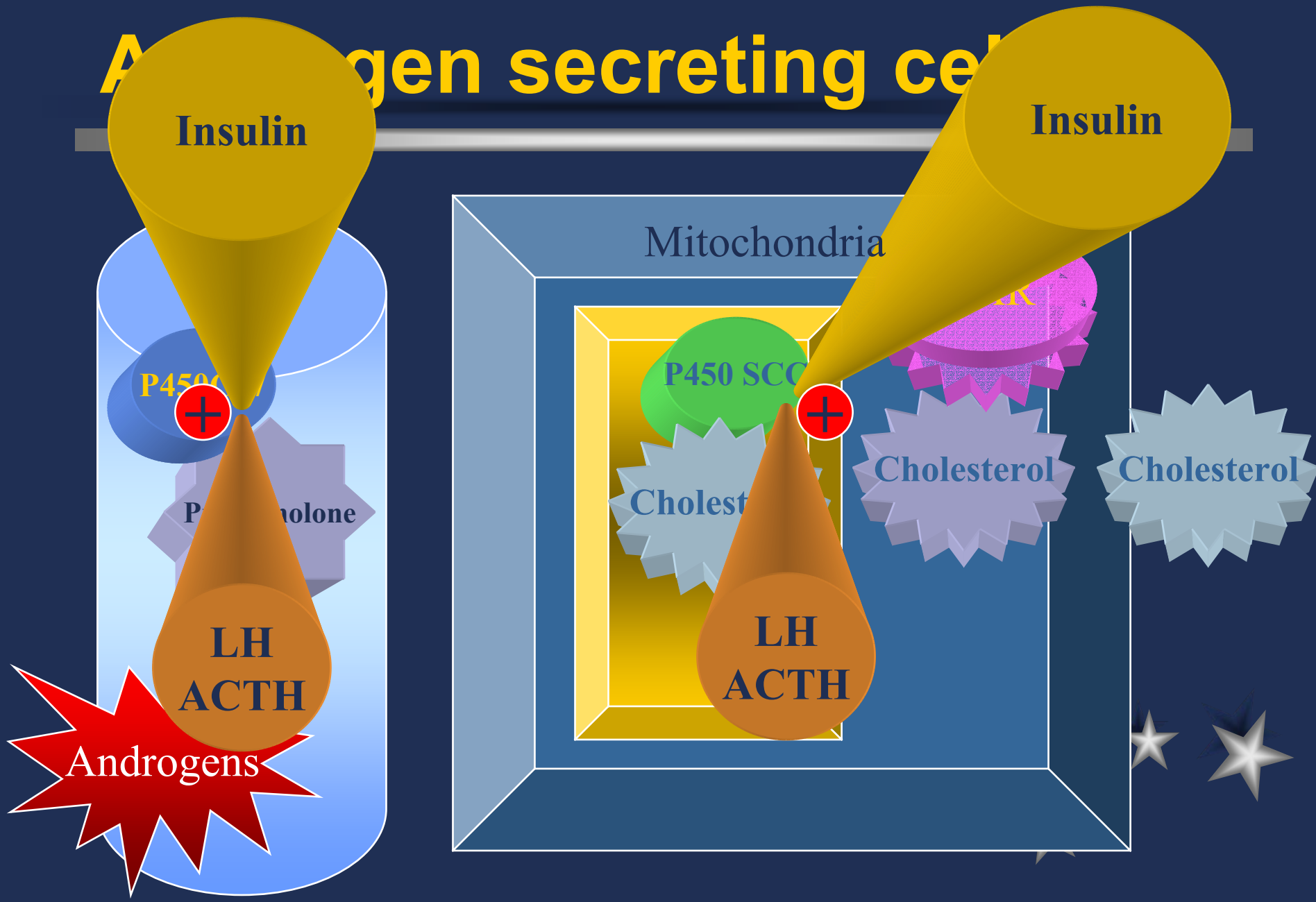
Steroid synthesis in PCOS

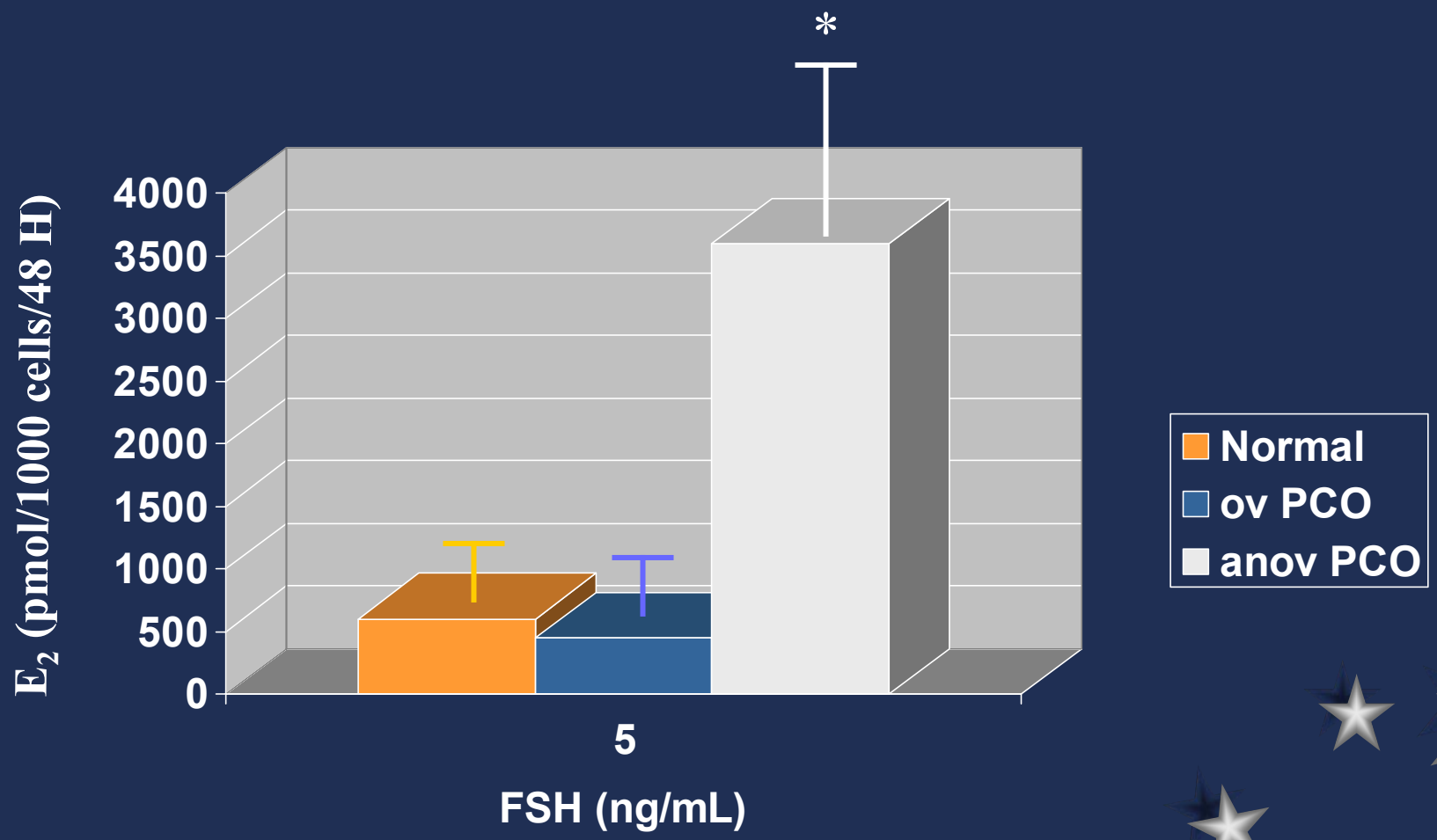


A gen secreting ce



PCO and granulosa cells

Franks et al. 1991 J Ster Biochem Mol Biol



PCO and granulosa cells

Almahbobi et al. 1996 Clin Endocrinol

- **Increased binding of FSH in anov PCO**
  - Increased receptors number?
  - Increased receptors affinity ?

PCO

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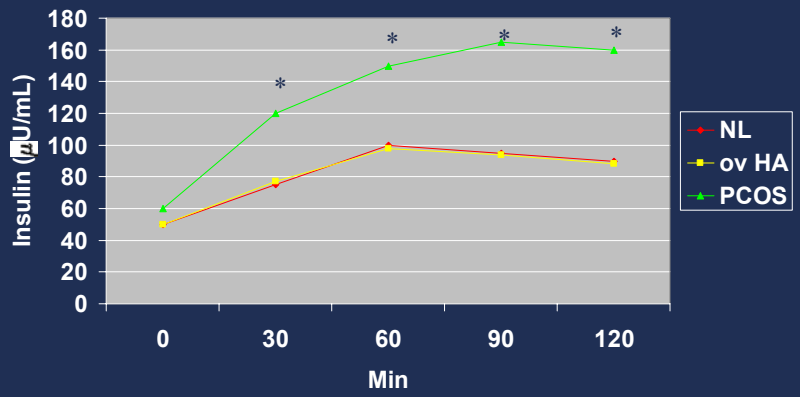
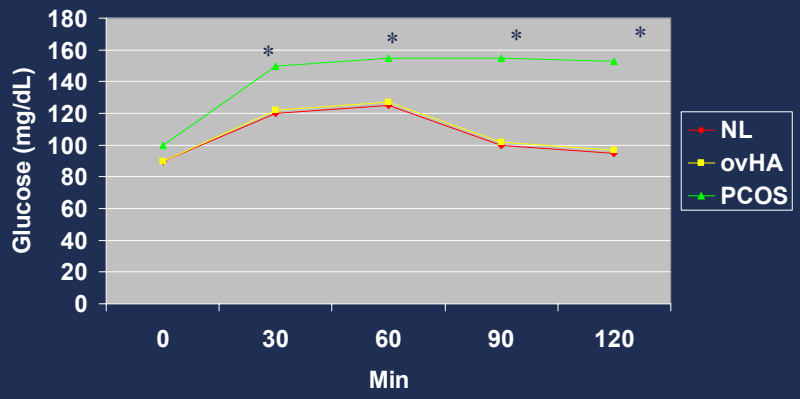
Insulin resistance in PCOS

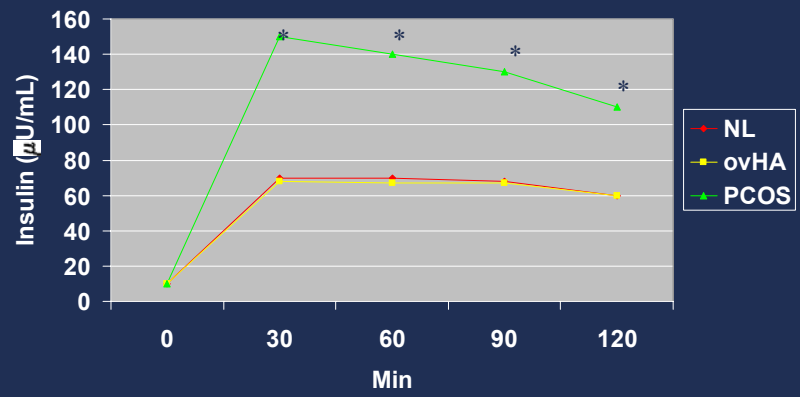
Dunaif et al JCEM 1987

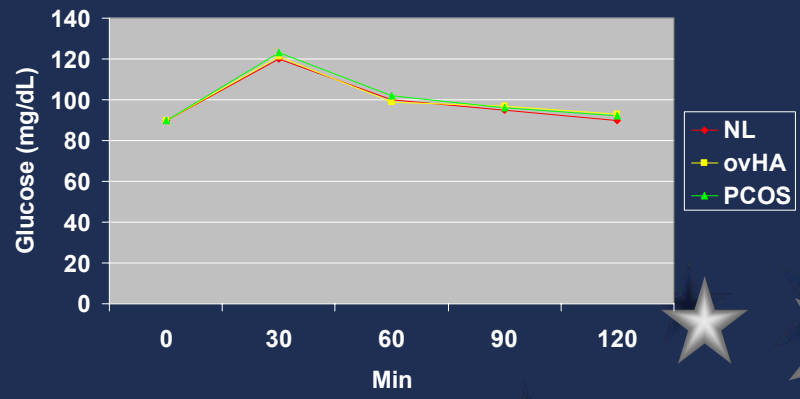
Obese





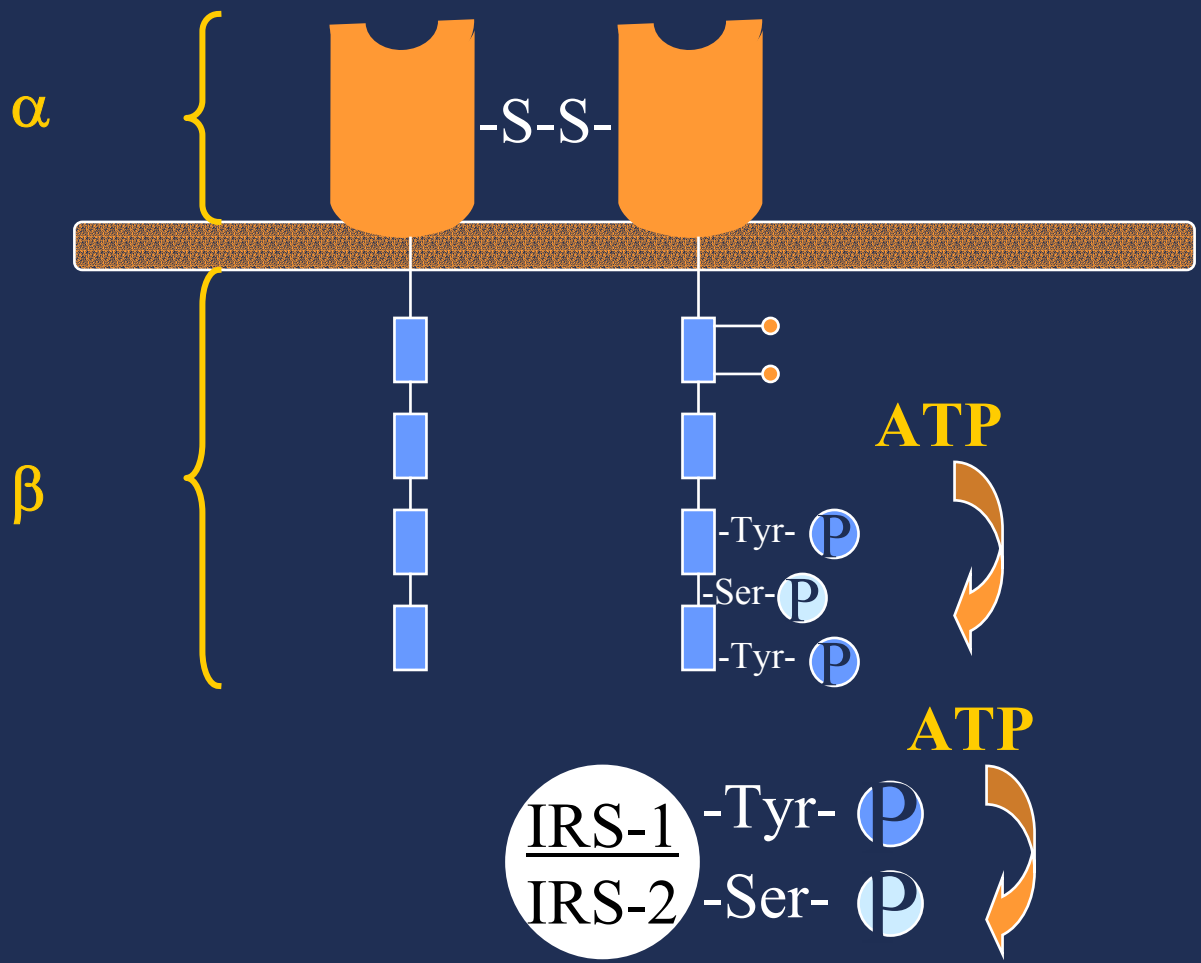
Lean





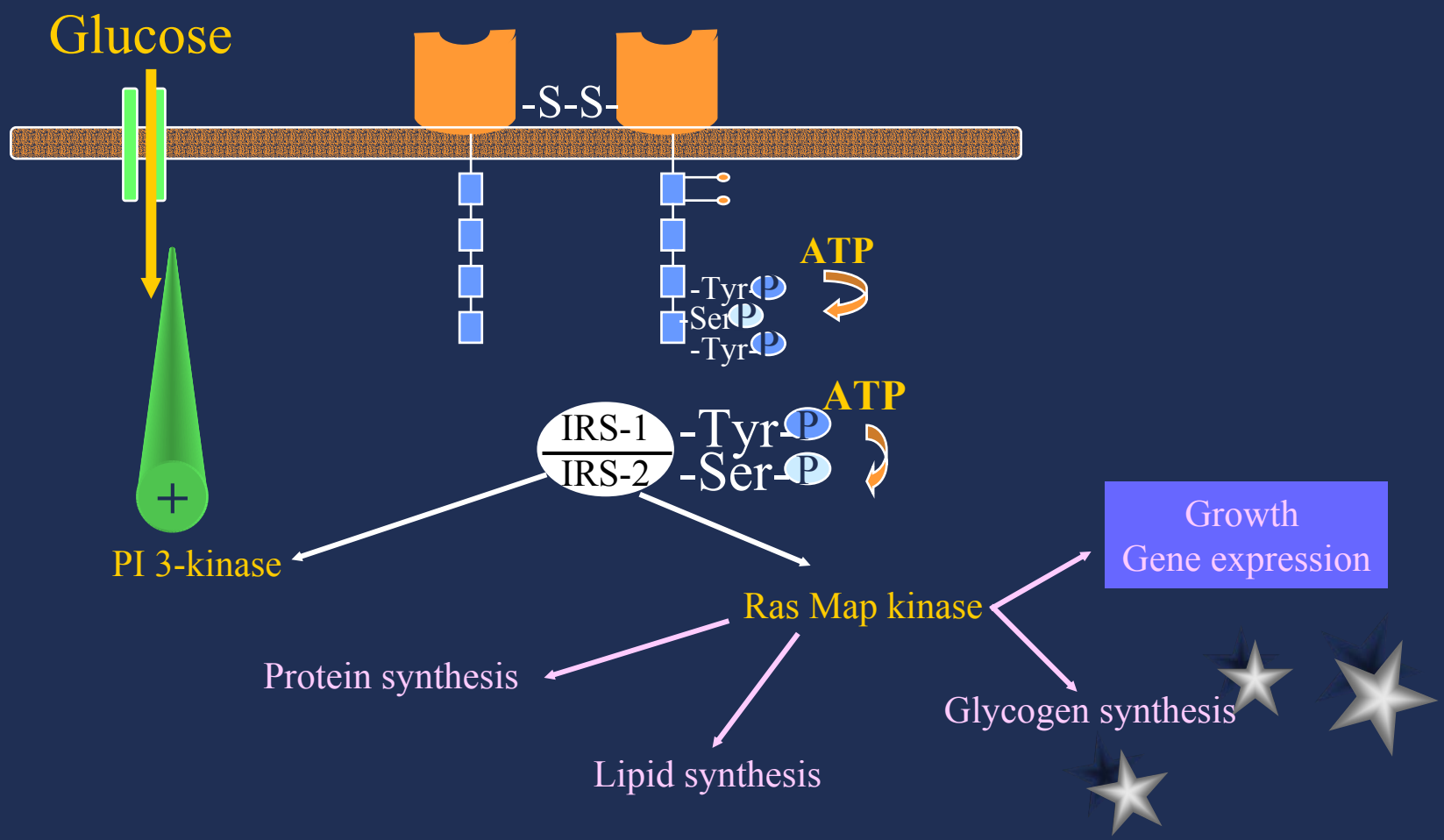
Insulin receptor

Kahn et al 1994 Diabetes

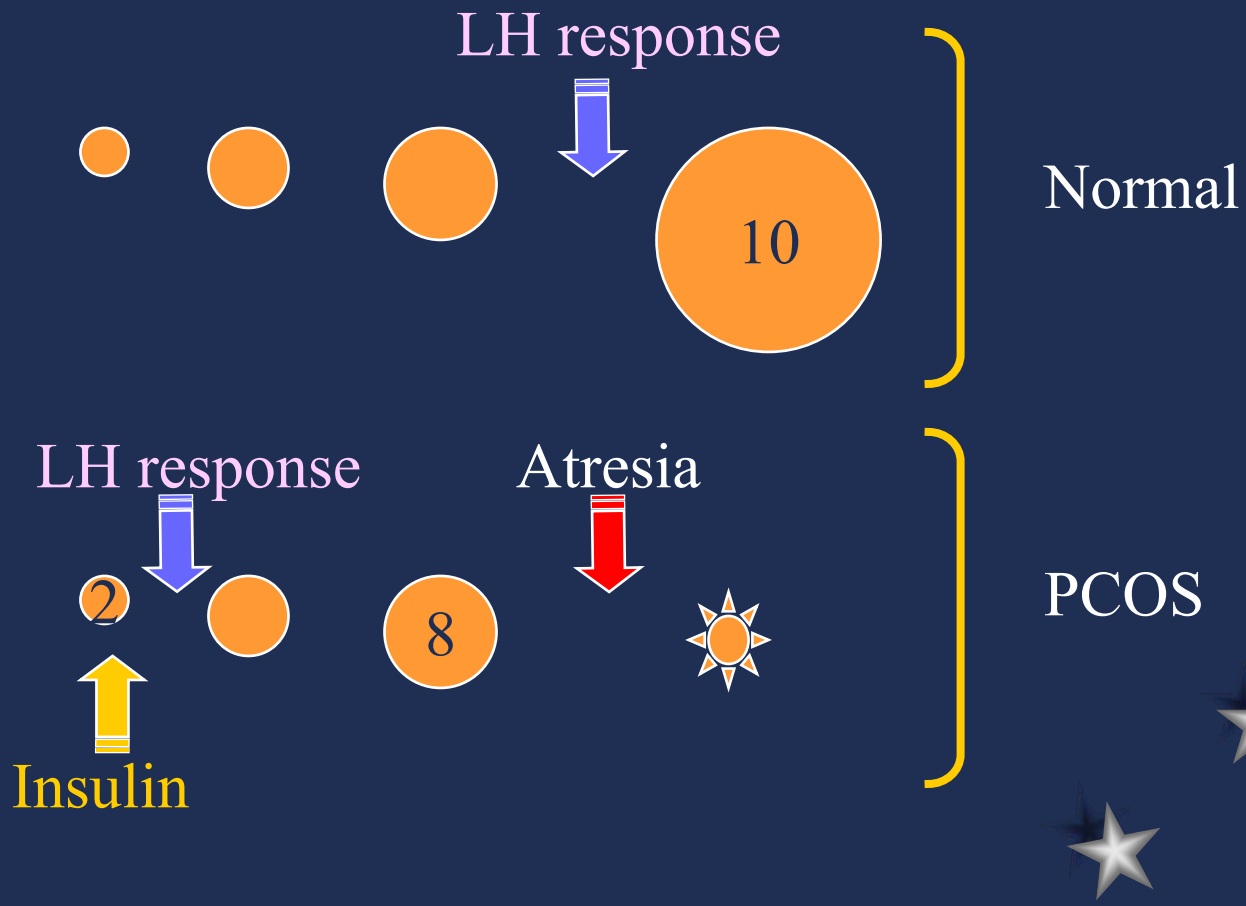


Insulin receptor

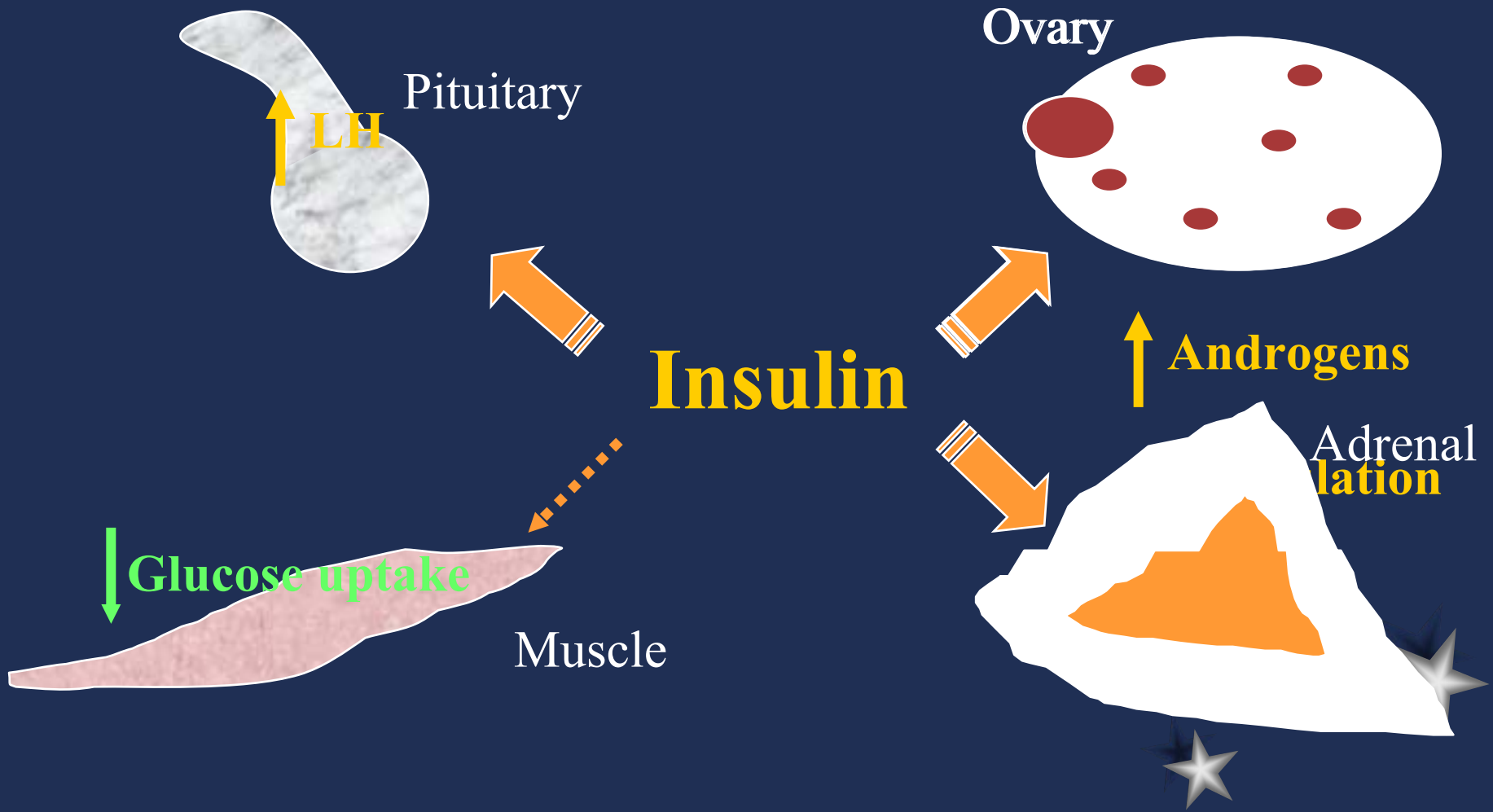
Kahn et al 1994 Diabetes



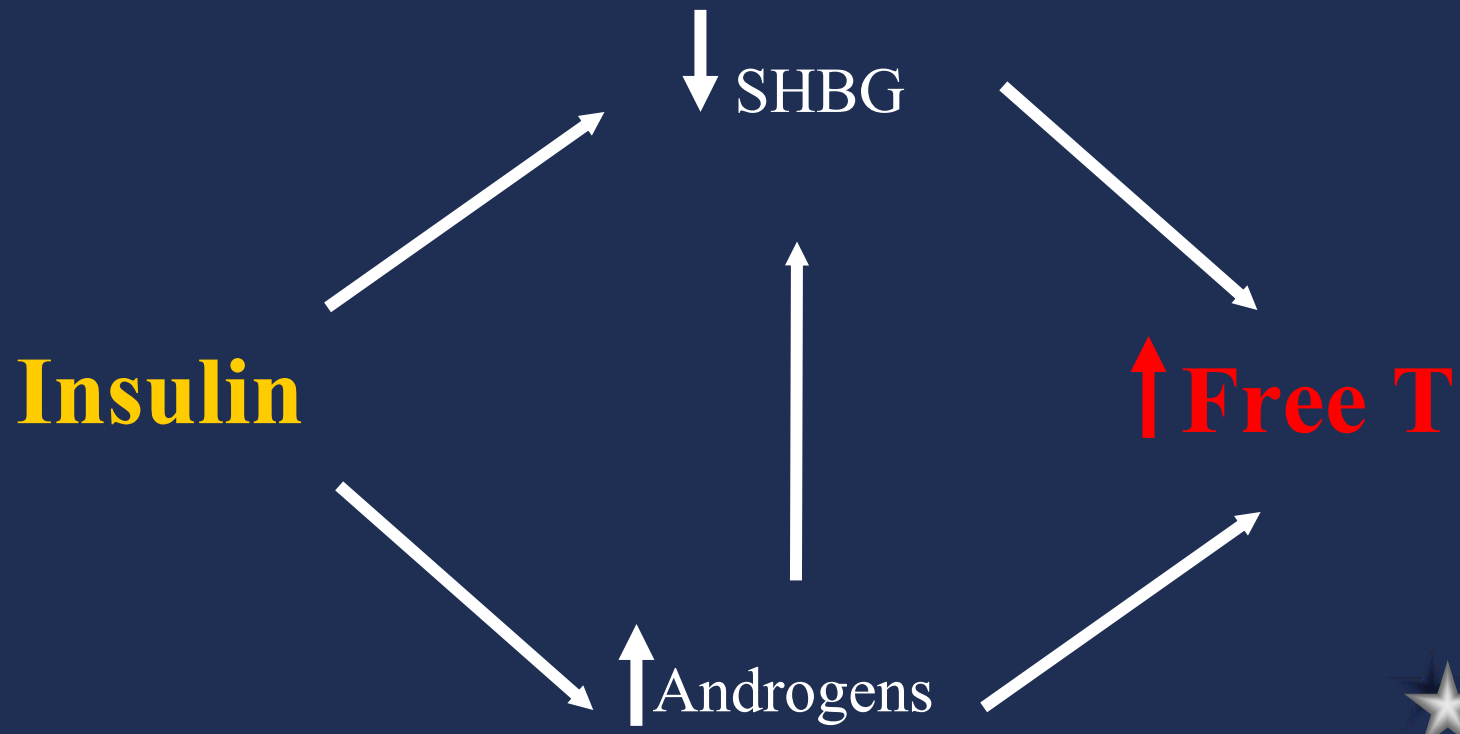
Insulin and anovulation



Insulin resistance and PCOS



Insulin and androgens



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PCOS and genetics

- **Familial clustering**
  - Premature balding in men
  - PCO in sisters
- **Autosomal dominant**
- **Polygenic**
  - CYP 11a (cholesterol side chain cleavage)
  - insulin / insulin receptor gene
  - follistatin

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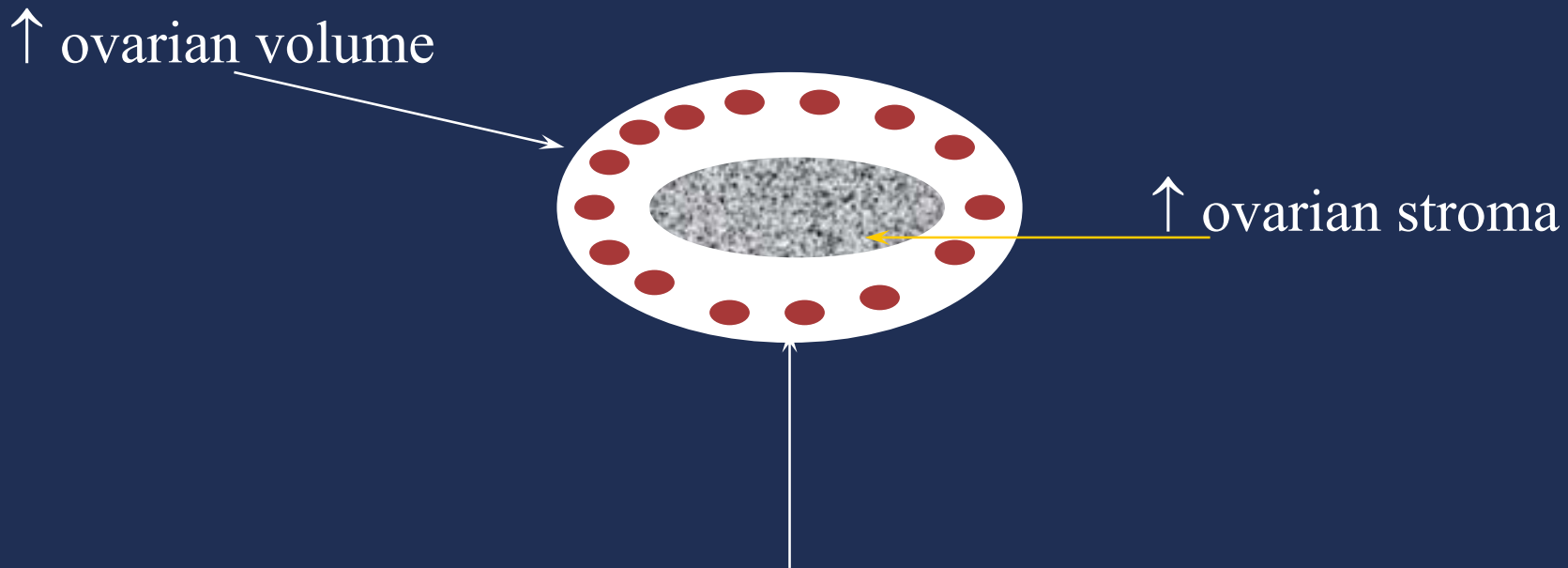
PCO ? PCOS

- Ultrasound criteria

• Infertility	88 %
• Insulin resistance	70 %
• Hirsutism	62 %
• Irregular cycles	50 %
• Obesity	38 %
• Acnea	35 %

PCO and ultrasound criteria

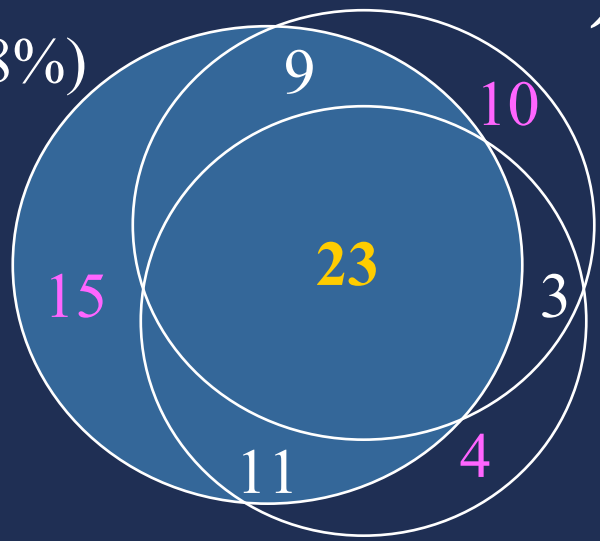


PCO and ultrasound criteria

van Santbrink et al. 1997 Fertil Steril

↑ Follicules number(58%)

↑ Ovarian stroma (45%)

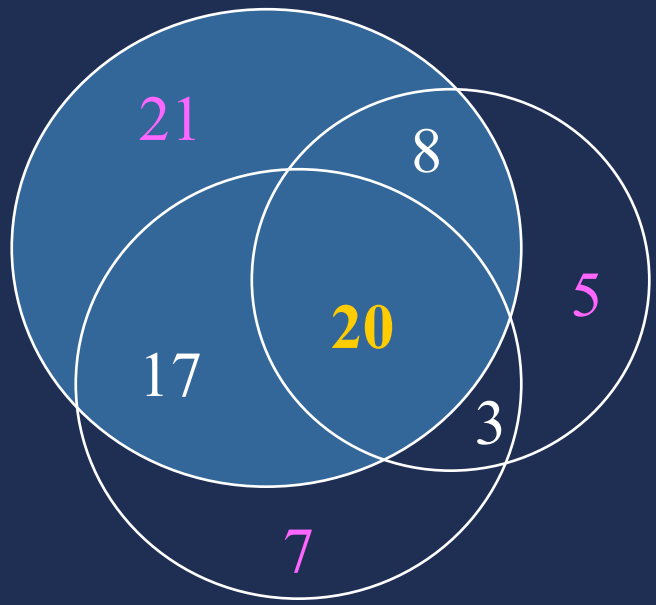


↑ Ovarian volume (41%)

PCO versus PCOS

van Santbrink et al. 1997 Fertil Steril

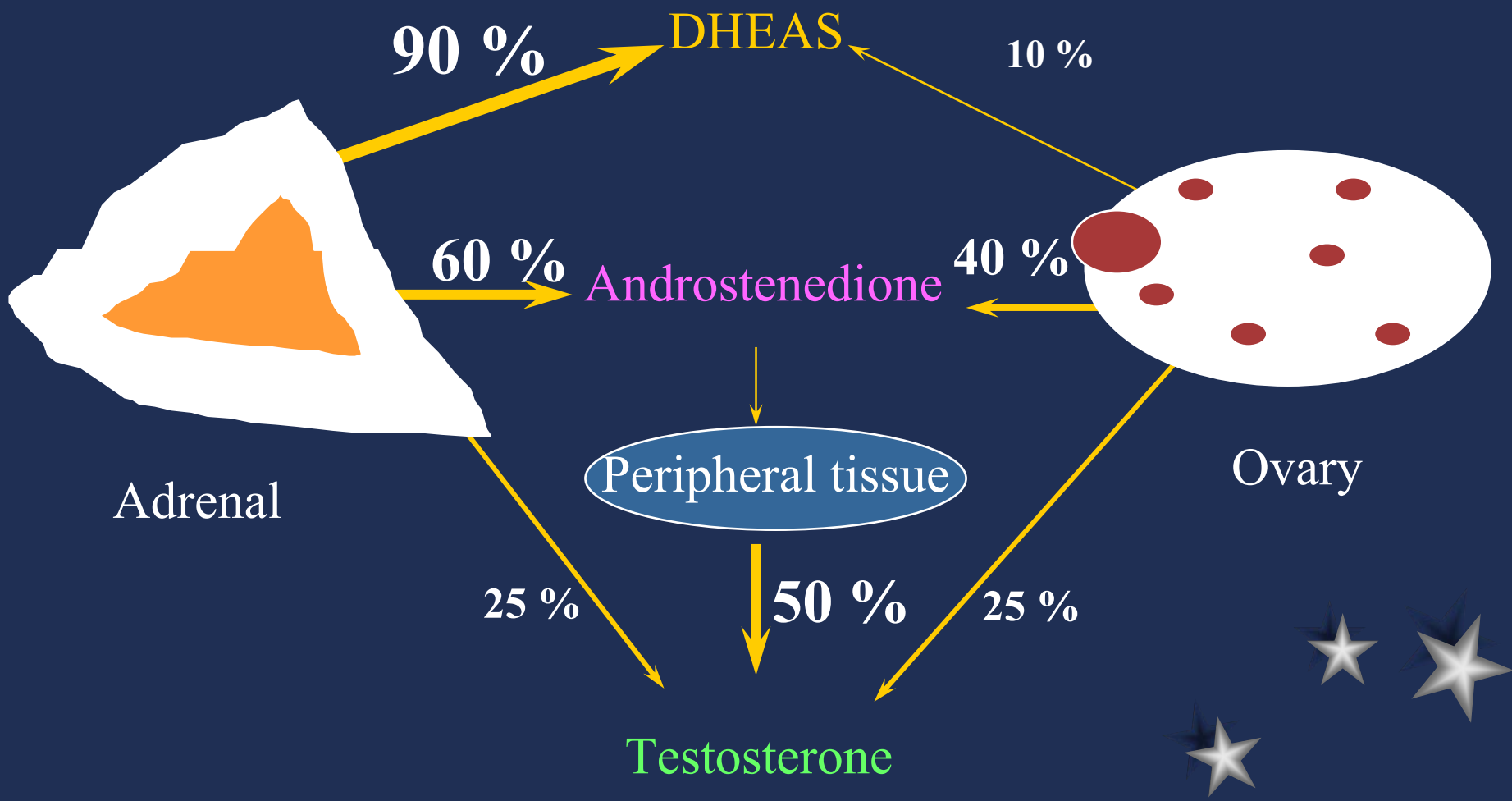
Ultrasound criteria (66%)



↑ Androgens (36 %)

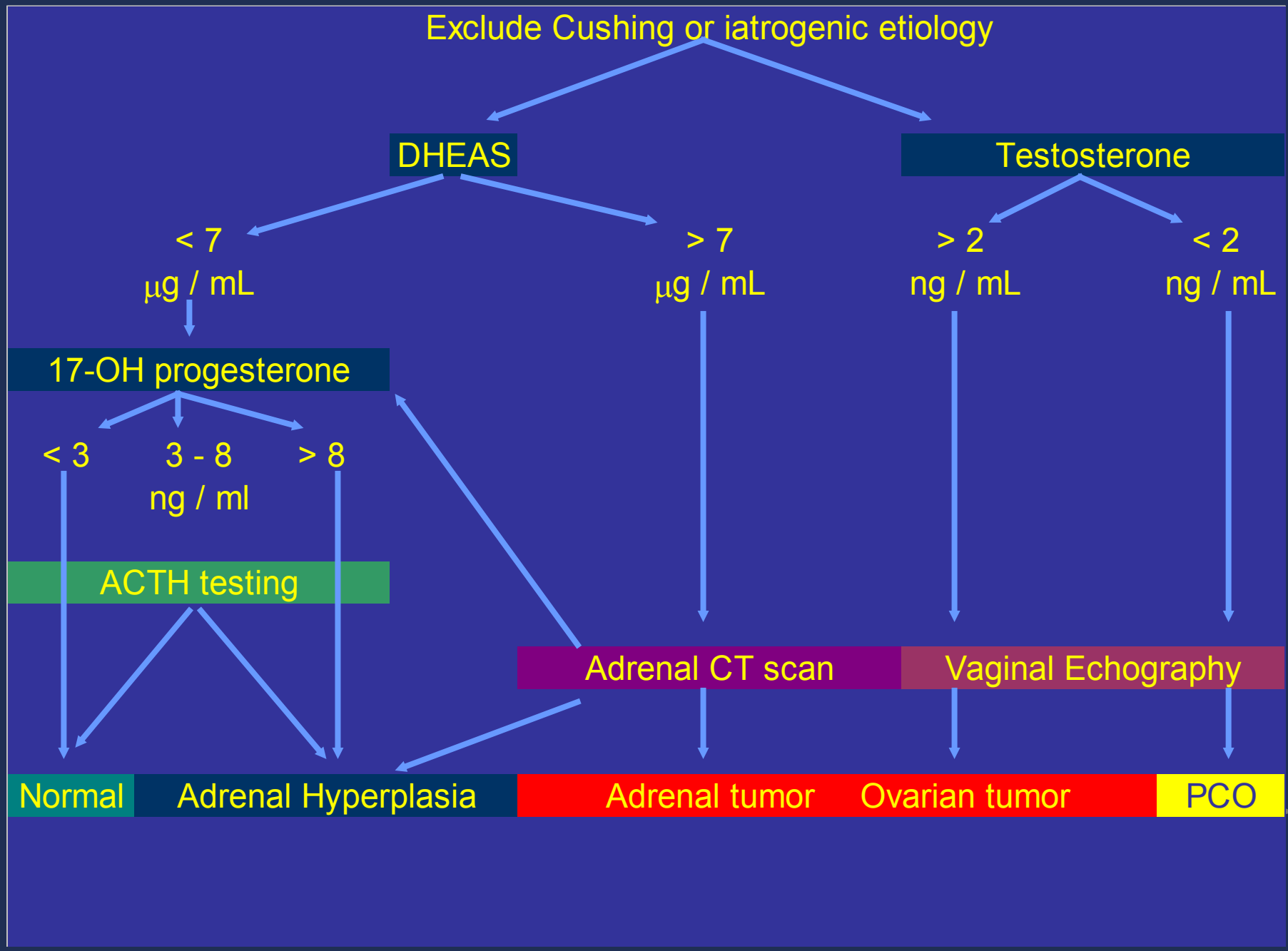
↑ LH (47%)

Origin of androgens



Transport of androgens

	SHBG	Albumin	CBG	Free
Testosterone	**66**	30,5	2	1,5
Androstenedione	7	**84,5**	1	7,5
DHEA	8	<0,1	**88**	4


Exclude Cushing or iatrogenic etiology
DHEAS
Testosterone
< 7 μg / mL
> 7 μg / mL
> 2 ng / mL
< 2 ng / mL
17-OH progesterone
< 3
3 - 8 ng / ml
> 8
ACTH testing
Adrenal CT scan
Vaginal Echography
Normal
Adrenal Hyperplasia
Adrenal tumor
Ovarian tumor
PCO

Testing for insulin resistance

- Anovulation and signs of hyperandrogenism
- Anovulation without signs of hyperandrogenism but elevated free testosterone
- Anovulation and a family history of insulin resistance or type II diabetes
- Anovulation and waist circumference over 90 cm

Insulin sensitivity testing in PCOS

Legro et al. JCEM 1998

	PCOS (n=40)	Controls (n=15)	P
Age	26.9 ± 5.4	28.7 ± 5.2	NS
BMI	39.0 ± 7.1	37.1 ± 6.2	NS
T (ng/dL)	86.2 ± 34.5	33.4 ± 9.7	<0.0001
uT (ng/dL)	31.2 ± 12.5	8.3 ± 3.8	<0.0001
DHEAS (ng/mL)	2472 ± 1570	1501 ± 553	<0.001
Fasting glucose (mg/dL)	90 ± 8.4	86 ±.10.4	NS
Fasting insulin (μU/mL)	27 ± 18.1	13.3 ± 10.1	<0.001

Insulin sensitivity testing in PCOS

Legro et al. JCEM 1998

- **Fasting Glycemia / fasting insulinemia**

(mg / dL) / (μU / mL)

< 4.5

(mmol / L) / (pmol / L)

<0.035

– Sensitivity	95 %
– Specificity	84 %
– PPV	87 %
– NPV	94 %

2H oral 75 g glucose testing

- **Normal** < 7.8 mmol/L
- **Impaired** 7.8 - 11.1 mmol/L
- **Non insulin- dependant diabetes** > 11.1 mmol/L

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Treatment goals

Speroff Clinical gynecologic endocrinology and infertility 2000

- Reduce the production and the circulating levels of androgens
- Protect the endometrium against unopposed estrogens
- Support lifestyle changes to achieve normal body weight
- Lower the risk for cardiovascular disease and diabetes mellitus
- Induction of ovulation to achieve pregnancy

Treating hyperandrogenic effects

- **Ovarian suppression**
  - Oral contraception
  - GnRH agonist
  - ketokonazole

Ketokonazole

- **Enzyme Inhibitor**
  - 17,20 desmolase,
  - 17 α hydroxylase
  - 11 β hydroxylase
- **Starting dose :**
  - 400 mg / day up to 1200 mg / day
- **Side effects.**
  - Scalp hair loss, dry skin
  - Nausea, vomiting
  - Fatigue, headache
  - Hepatotoxicity

Treating hyperandrogenic effects

- **Adrenal suppression**
  - Dexamethasone: 0.25 - 0.375 mg / d
  - Prednisone: 2 mg / d
  - Ketokonazole

Treating hyperandrogenic effects

- **Lowering peripheral actions of androgens**
  - cyproterone acetate
  - Spironolactone : 50 - 200 mg / d
  - Flutamide (*Flucinome*): 250 - 375 mg / d
  - Finasteride (*Proscar*): 5 mg / d

Cyproterone acetate

- **Actions:**
  - potent progestin
  - moderately potent antiandrogen
  - weak glucocorticoid
  - Increases testosterone clearance and hepatic metabolism
- **Dosage**
  - 2 mg /d + 35 μg EE
  - 50 mg / d d 5 - d 15

Ciproterone acetate

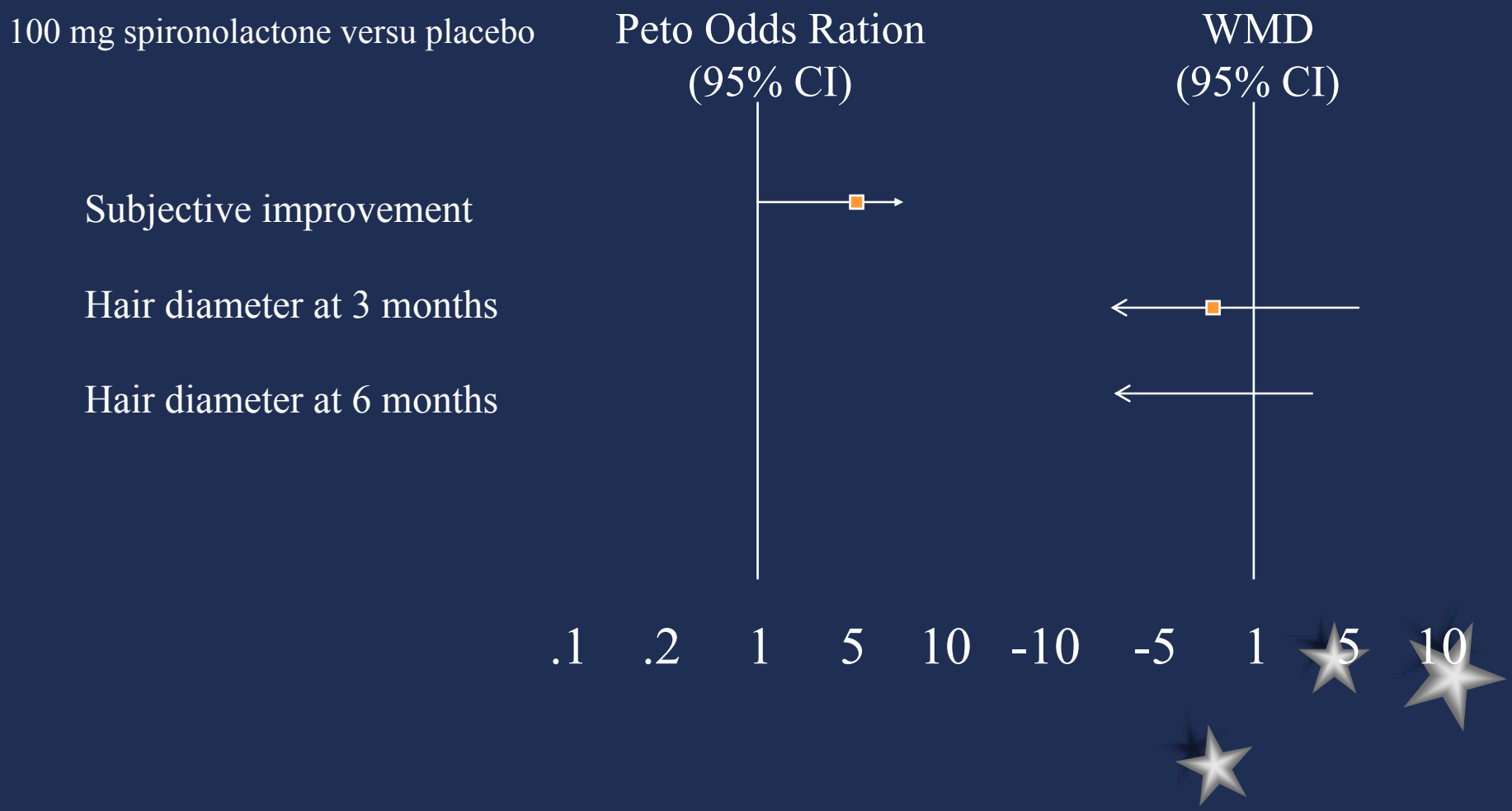
- **Side effects**
  - Menstrual delay (2 - 3 days)
  - Amenorrhea
  - Weight gain
  - Edema

Spironolactone

- **Antialdosterone**
- **Affinity to T receptor : 67 % of DHT**
- **Usual starting dose: 50 mg bid**
- **May be combined to OC**
- **Side effects.**
  - Short cycles 25 %
  - Breast tenderness
  - Polyuria (usually disappears after a few weeks)
  - Hyperkalemia (Cave diabetic and renal patient)

Spironolactone versus placebo for hirsutism

Lee O et al, Cochrane Library, 4 ;2000



Finasteride

- **Action**
  - 5 α reductase type 2 inhibitor
- **Dose:**
  - 5 mg / d
- **Minimal side effects**

Flutamide

- **Action**
  - Nonsteroidal antiandrogen
- **Dose:**
  - 250 mg / j - 500 mg / j
- **Secondary effects**
  - Nausea, gastralgia
  - Breast tenderness
  - Hepatotoxicity (strict monitoring of liver function tests)

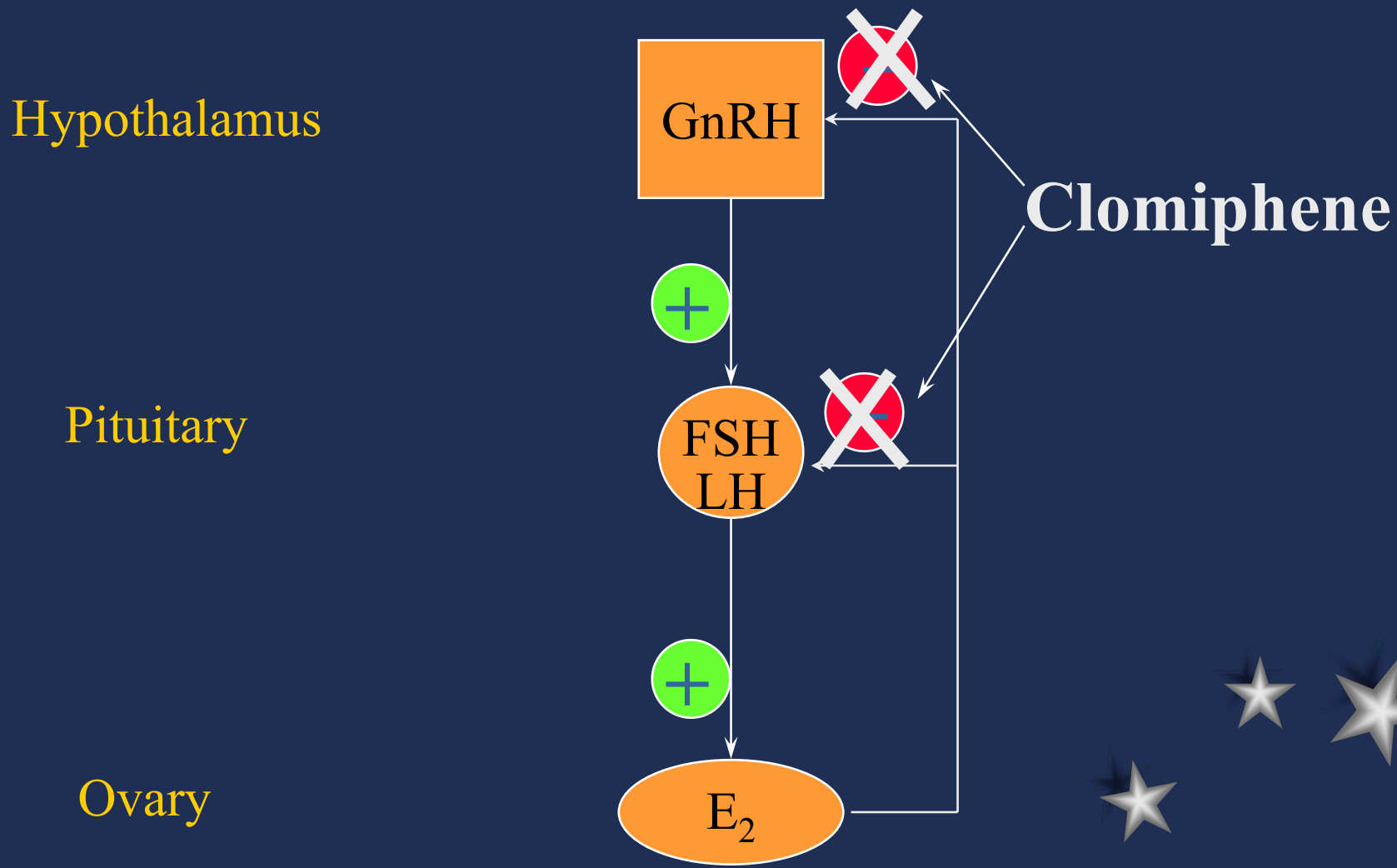
Antiandrogens

- Wait 6 months for assessment of efficacy
- All have similar documented effects on hirsutism with approximately a 50% reduction of FG score
- All are contraindicated during pregnancy

Ovulation induction

- Clomiphene citrate
- Gonadotropins
- Surgical
- Insulin lowering agents

Clomiphene citrate



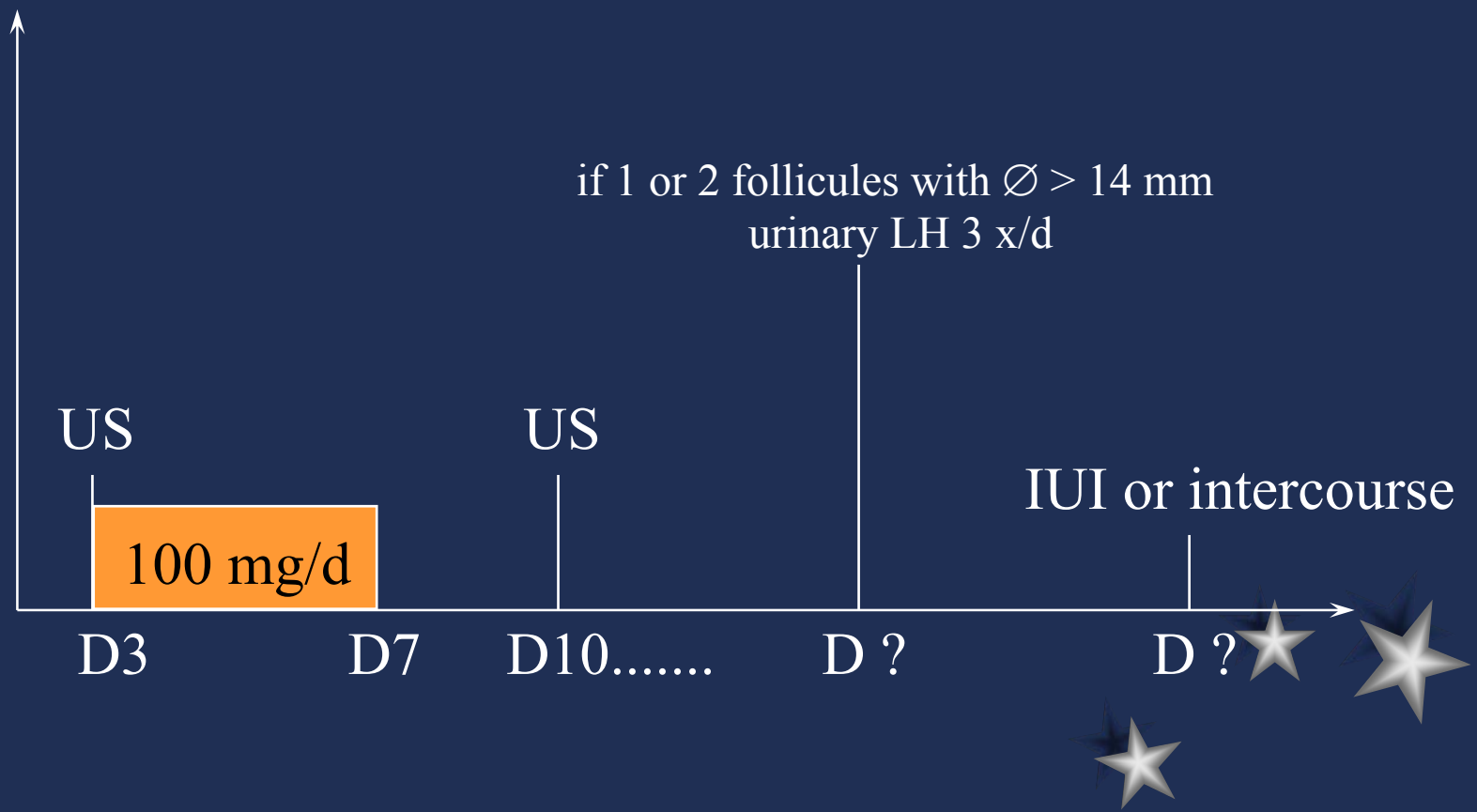
Clomiphene citrate indications

- **PCO**
- **Oligoanovulation**
  - Progesterone positive test

Clomiphene citrate administration regimen

- **Dose**
  - 50-200 mg p.o. daily
- **Start**
  - D3-5 spontaneous or progesterone-induced cycle
- **Duration**
  - 5 days
- **Optional**
  - hCG at mid-cycle

Clomiphene citrate stimulation



Clomiphene citrate overall results

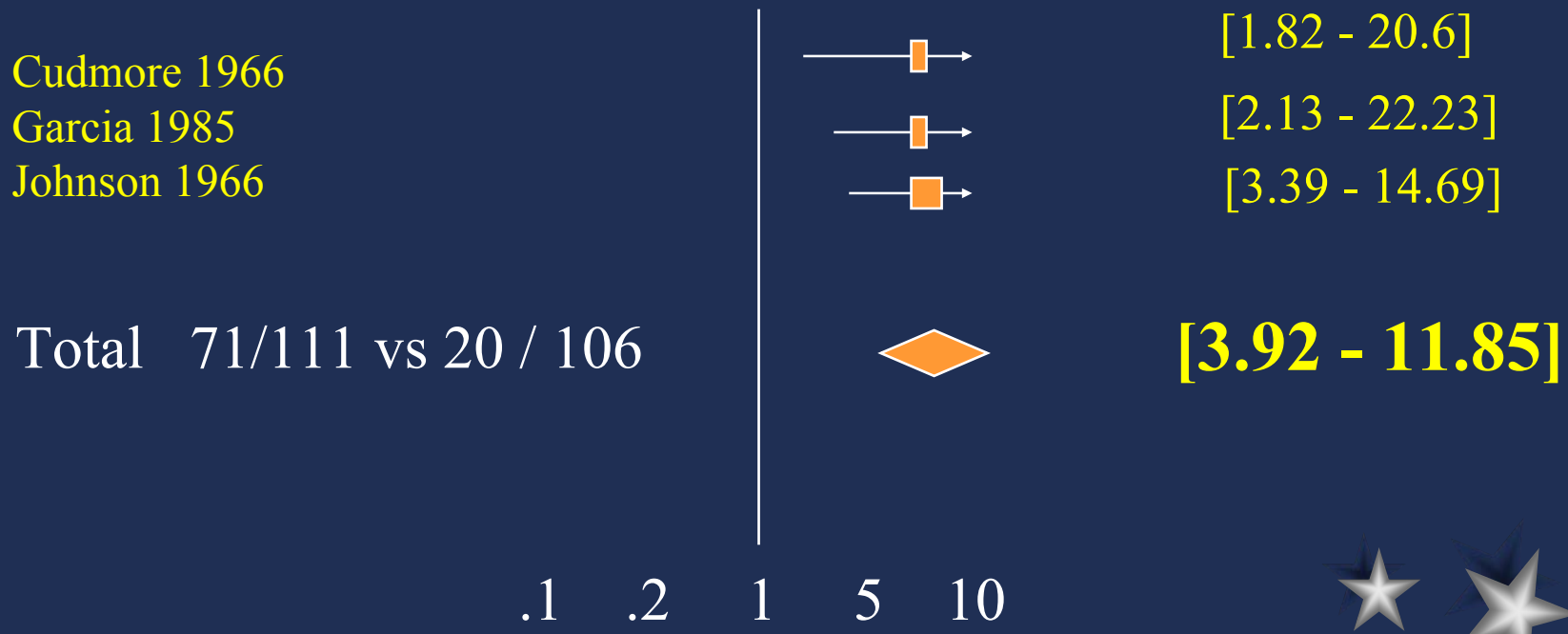
- **Ovulatory rates**
  - oligomenorrhea - 90 %
  - secondary amenorrhea - 70 %
- **Pregnancy rates**
  - overall - 40 %
  - no other infertility factor - 80 %
  - abortion - 20 %
- **Side effects**

  - 10 %

Clomiphene citrate for ovulation induction in women with oligo-amenorrhea

Hughes et al. The Cochrane library, 4: 2000

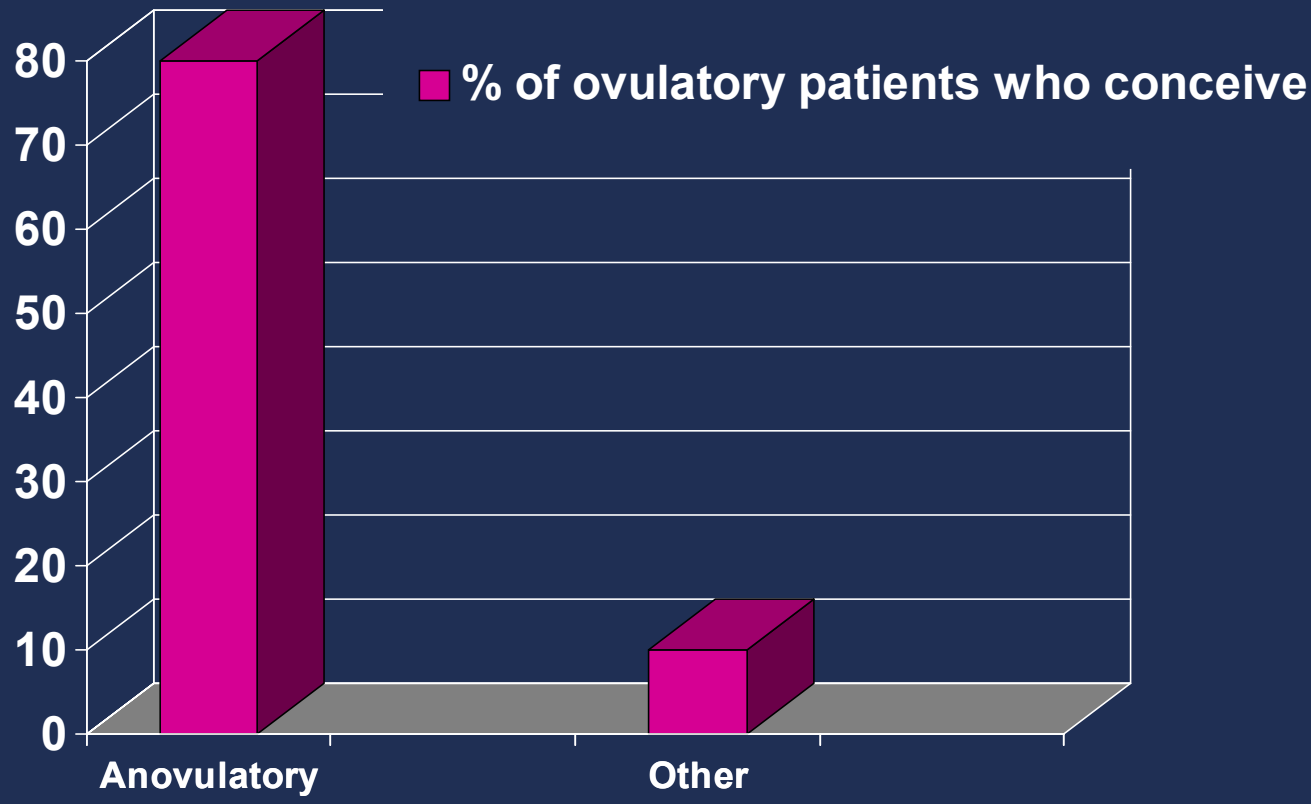
Ovulation following 50 - 250 mg dose range



Clomiphene citrate side effects

- vasomotor flashes (10 %)
- poor cervical mucus (10%)
- multiple pregnancies (7%)
- abdominal distension (5.5%)
- nausea vomiting (2.2 %)
- headaches (1.3%)
- visual disturbances
- teratogenic protential

Clinical results (Gysler et al. 1982)



Ovarian drilling: indications

- Clomiphene insensitive patients
- Endoscopic pelvic assessment
- Persistent LH hypersecretion
- Patients unable to attend for intensive monitoring for gonadotrophin therapy

Laparoscopic ovarian drilling

	Ovulation rate (%)	Pregnancy rate (%)	Adhesion rate (%)
Cautery	70 – 92 %	70	19
Laser	62 – 99 %	57	80

Ovarian drilling and HMG

- Decrease in the duration and the amount of HMG *(Fahri et al 1995)*
- Decrease OHSS *(Fukaya et al 1995)*

Ovarian drilling and IVF

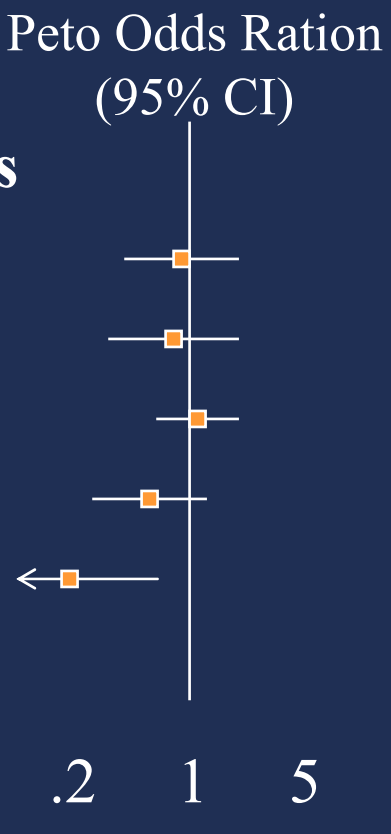
- Decrease cancellation rate
- Decrease OHSS
- Higher pregnancy rate *(Colacurci et al. 1997)*

Ovarian drilling for PCOS

Farquar et al. Cochrane Library, 4; 2000

Ovarian drilling vs gonadotrophins

- Pregnancy rate (6months / 6 cycles)
- Pregnancy rate per cycle
- Ovulation rate
- Miscarriage rate
- Multiple pregnancy rate

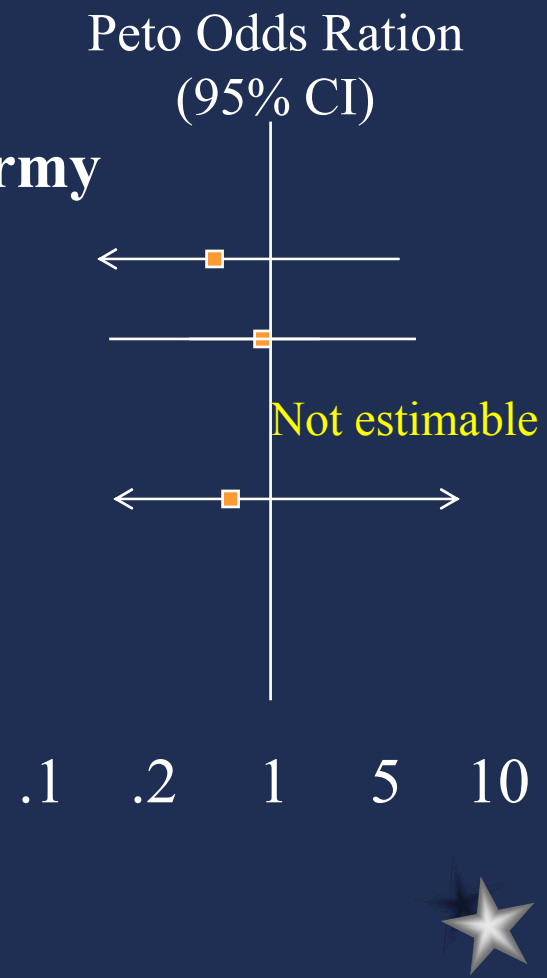


Ovarian drilling for PCOS

Farquar et al. Cochrane Library, 4; 2000

Ovarian drilling laser vs diathermy

- Pregnancy rate (6 months / 6 cycles)
- Ovulation rate per cycle
- Miscarriage rate
- Severe adhesions



PCOS and insulin lowering agents

- **Five different modalities to lower insulin levels in PCOS**
  - weight loss
  - metformin *(Glucophage, Diabiformine)*
  - troglitazone
  - diazoxyde *(Proglicem)*
  - D-Chiro-inositol

Metformin

- **Biguanide**
- **Dose: 500 - 850 mg tid**
- **Multiple modes of action**
  - Diminishes endogenous glucose production
    - Inhibits hepatic gluconeogenesis
    - Inhibits glycogen breakdown
  - Increases glucose transport to muscle
  - Weight loss

Metformin

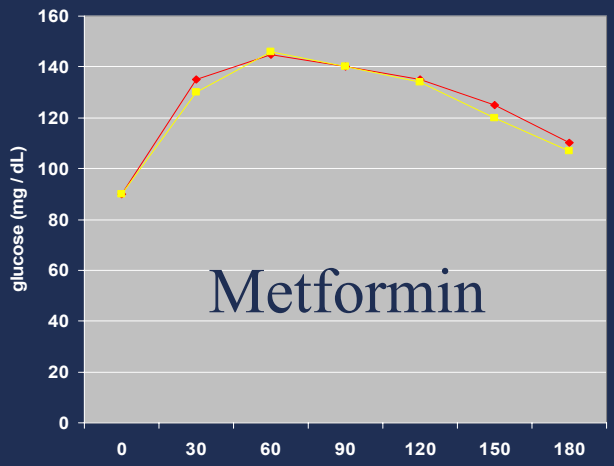
- **Adverse effects**
  - Lactic acidosis
- **Exclusion criteria**
  - Renal and hepatic disease
  - Cardiac or respiratory insufficiency
  - Severe infection
  - Alcohol abuse
  - Pregnancy

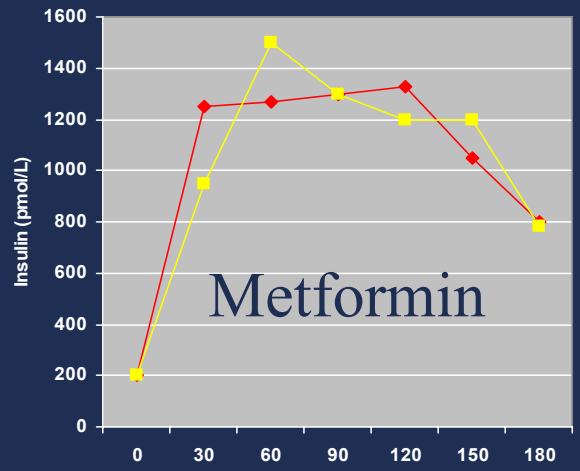
Troglitazone

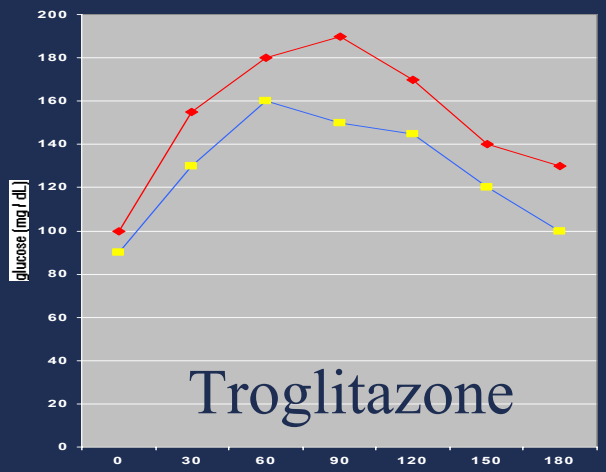
- **Thiazolidinedione**
- **dose: 200 - 500 mg daily**
- **peroxysome proliferator-activated receptor γ (PPARγ2)**
  - enhances insulin action on muscle, adipose tissue and liver

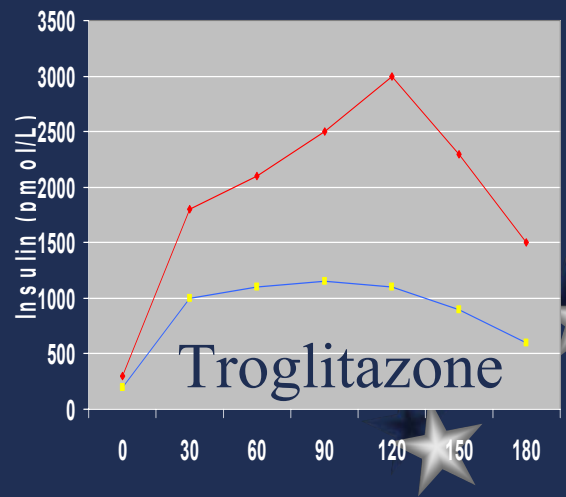
Metformin versus troglitazone in PCOS

Adapted from Ehrmann et al JCEM 1997









Metformin and Ovulation in PCOS

Nestler et al. NEJM 1998

Study Design

- **Multicentric**
- **Randomized, single blind, placebo controlled**
- **61 obese (BMI > 28 kg/m^2) PCOS**
  - 35 assigned to Metformin (500 mg tid)
  - 26 assigned to placebo

Metformin and Ovulation in PCOS

Nestler et al. NEJM 1998

- **Results :**

spontaneous ovulation

	Ovulation	Percent
Metformin alone	12 / 35 (+2?)	34
Placebo alone	1 / 26	4

p<0.005 Fisher Exact Test

Metformin and Ovulation in PCOS

Nestler et al. NEJM 1998

- **Results :**

CC-induced ovulation

	Ovulation	Percent
Metformin + CC	19 / 21	90
Placebo + CC	2 / 25	8

p<0.0001 Fisher Exact Test

Metformin and Ovulation in PCOS

Nestler et al. NEJM 1998

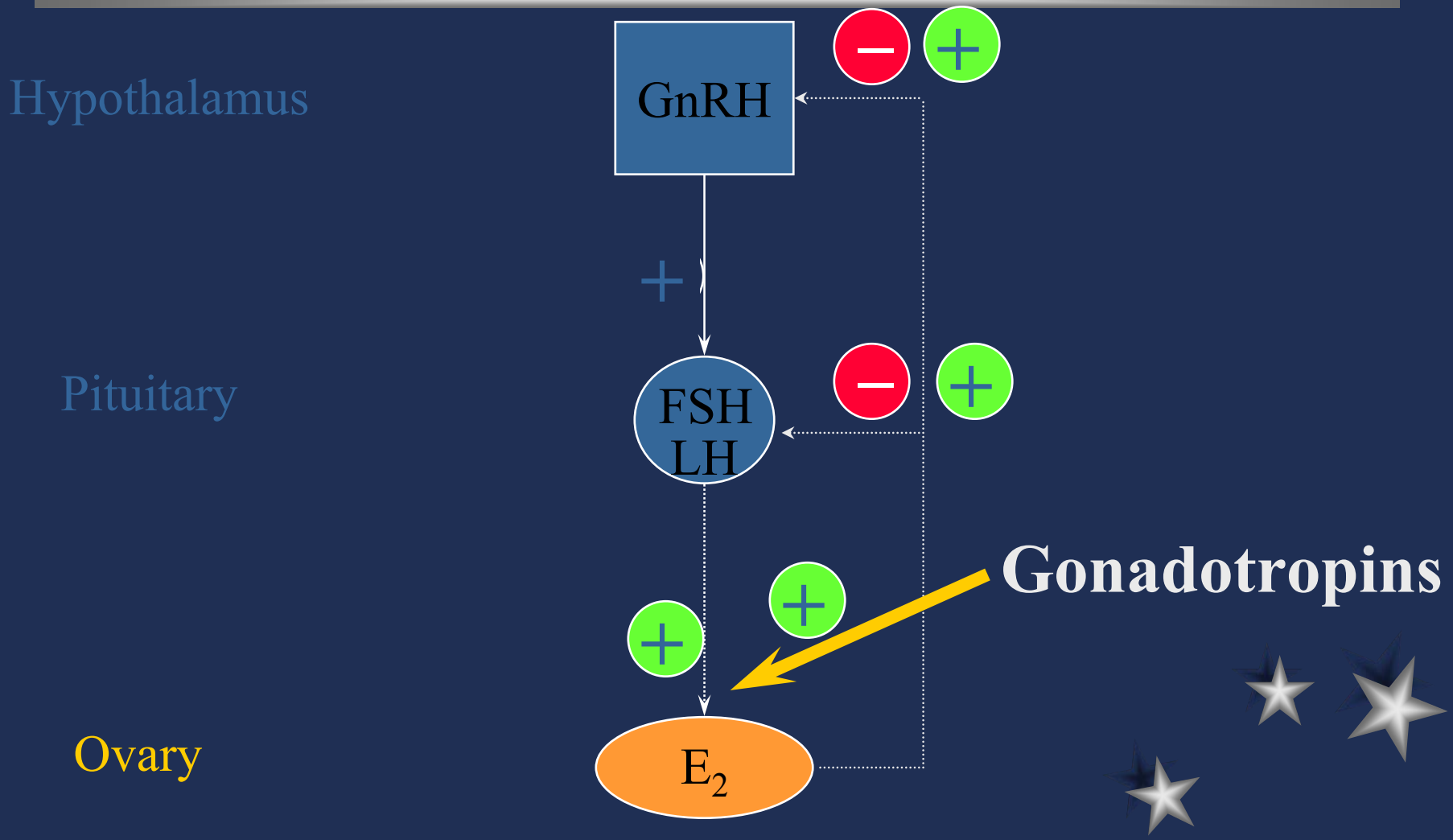
- **Results :**

spontaneous ovulation

	Ovulation	Percent
Metformin group	31 / 35	88
Placebo group	3 / 26	4

p<0.0001 Fisher Exact Test

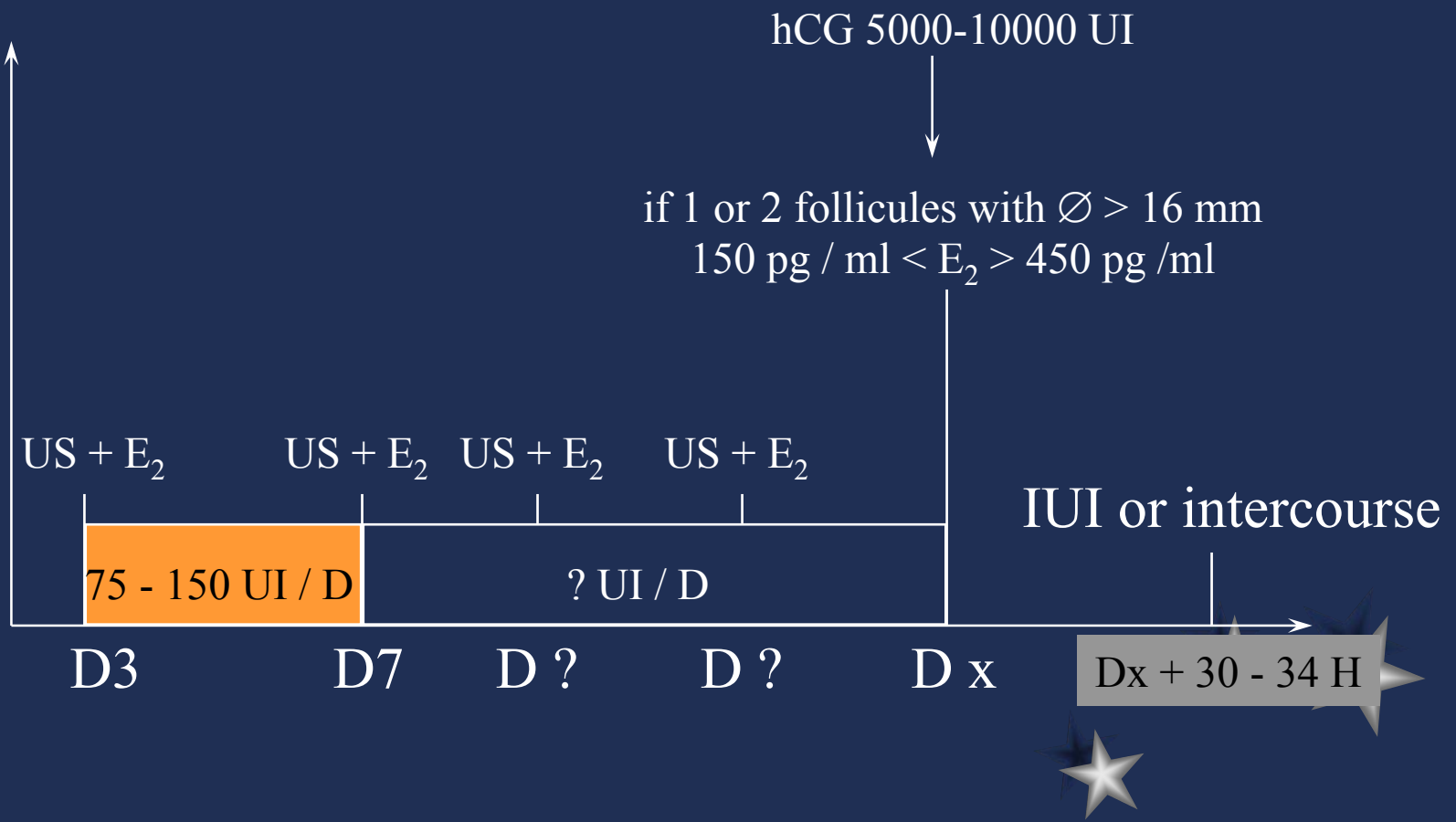
Gonadotropins



Gonadotropins indications

- **Anovulatory patients**
  - Hypothalamic disorders
  - Pituitary failure
  - PCOS
- **Reproductive technology**
- **Poor candidates**
  - > 40 years old
  - elevated D3 FSH
- **Contraindication**
  - Primary hypogonadism

Gonadotropin stimulation

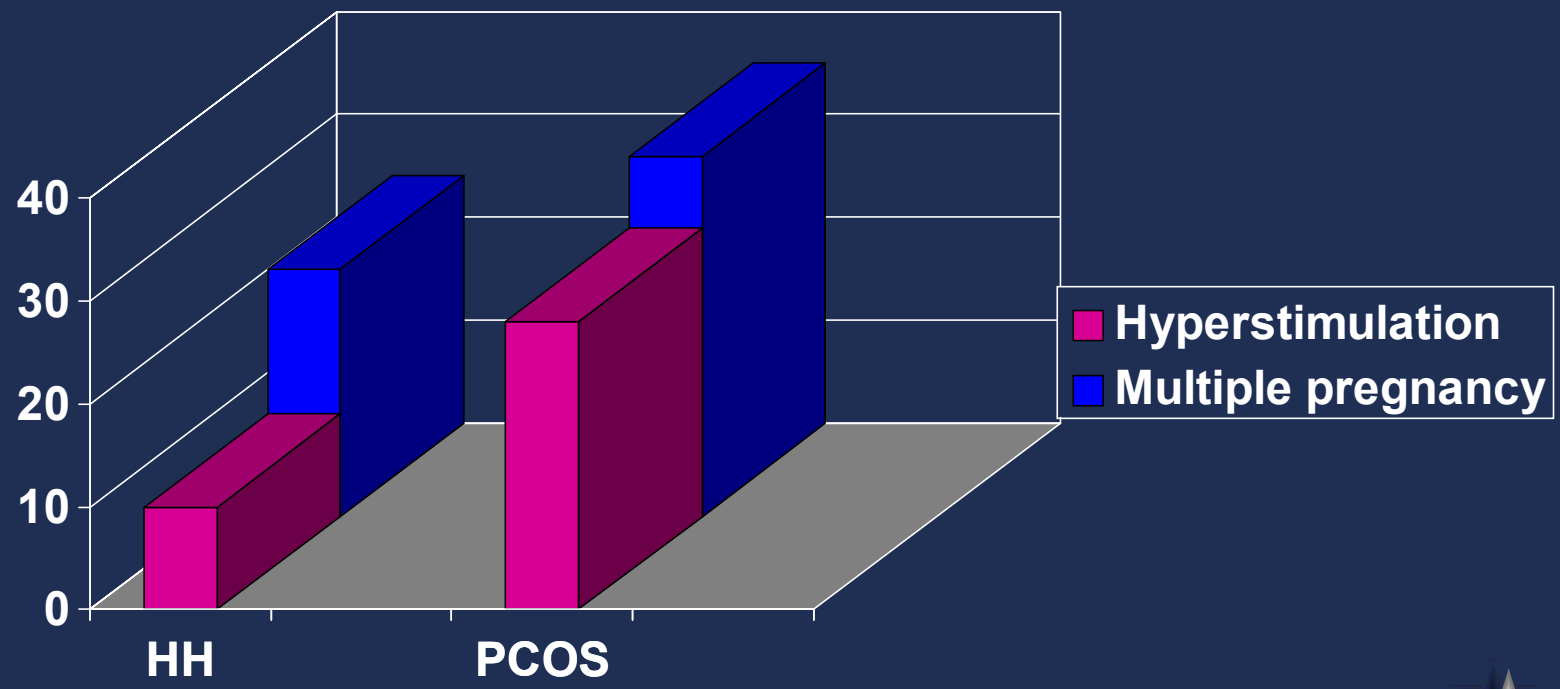


Gonadotropins overall results

- Ovulation > 99 %
- Cumulative pregnancy rate - 70 %

  (6 cycles)
- Multiple pregnancies - 30 %
- Abortion - 30 %
- Hyperstimulation - 10 %

Gonadotropins complications



Wang et al 1980

OHSS classification

Mild OHSS

grade 1 abdominal distention

grade 2 nausea
vomiting or diarrhea
enlarged ovaries

Moderate OHSS

grade 3 US evidence of ascites

Severe OHSS

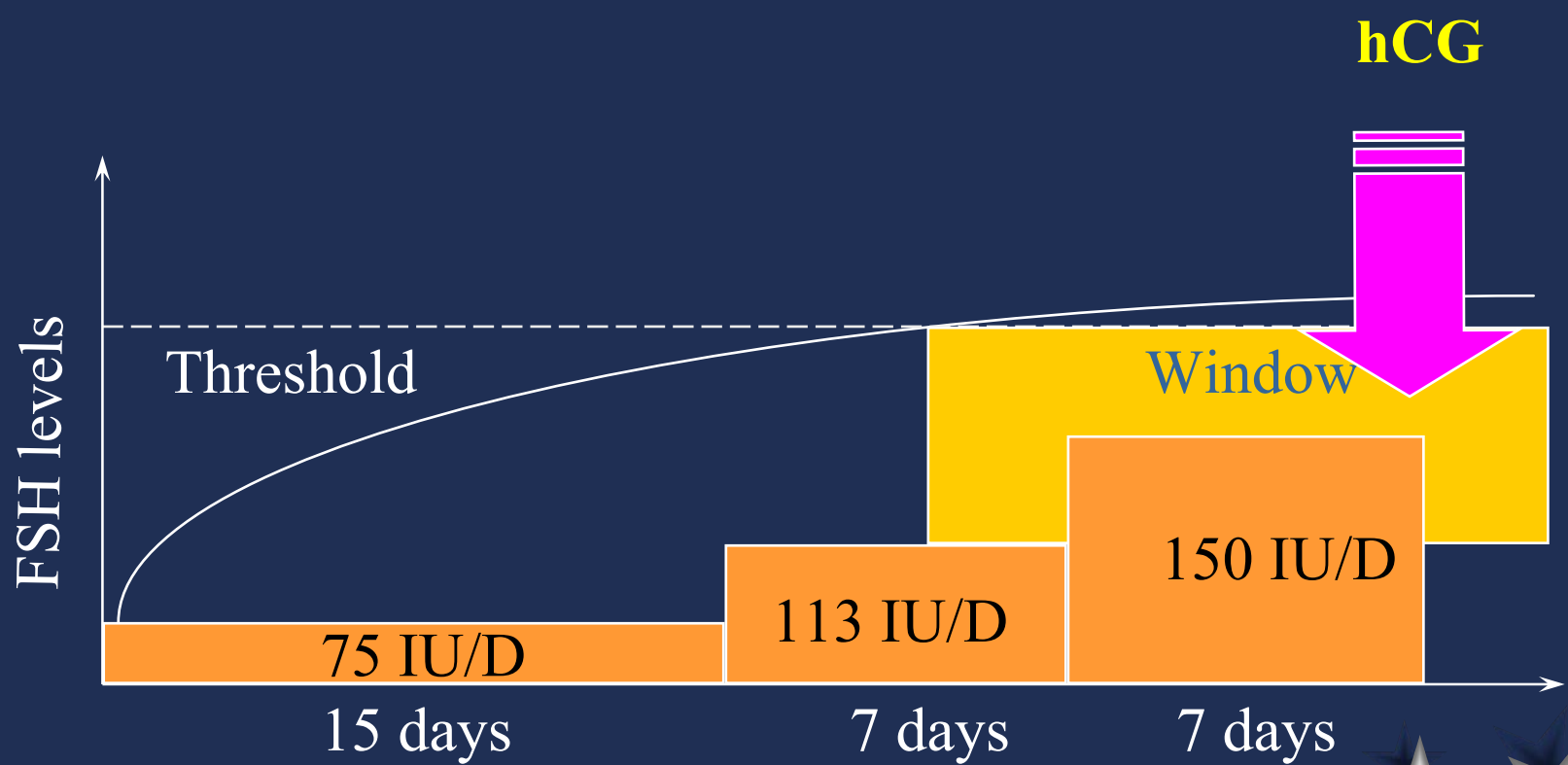
grade 4 clinical ascites

grade 5 Hct >45%
WBC > 15000
oliguria
creat clearance > 50 ml/min

Critical OHSS

grade 6 Tense ascites
Hct > 55 %
WBC > 25000
creat clearance < 50 ml min
renal failure
thromboembolic phenomena
ARDS

Low dose step up regimen



Low dose step up regimen

Adapted from Franks et al. 1996

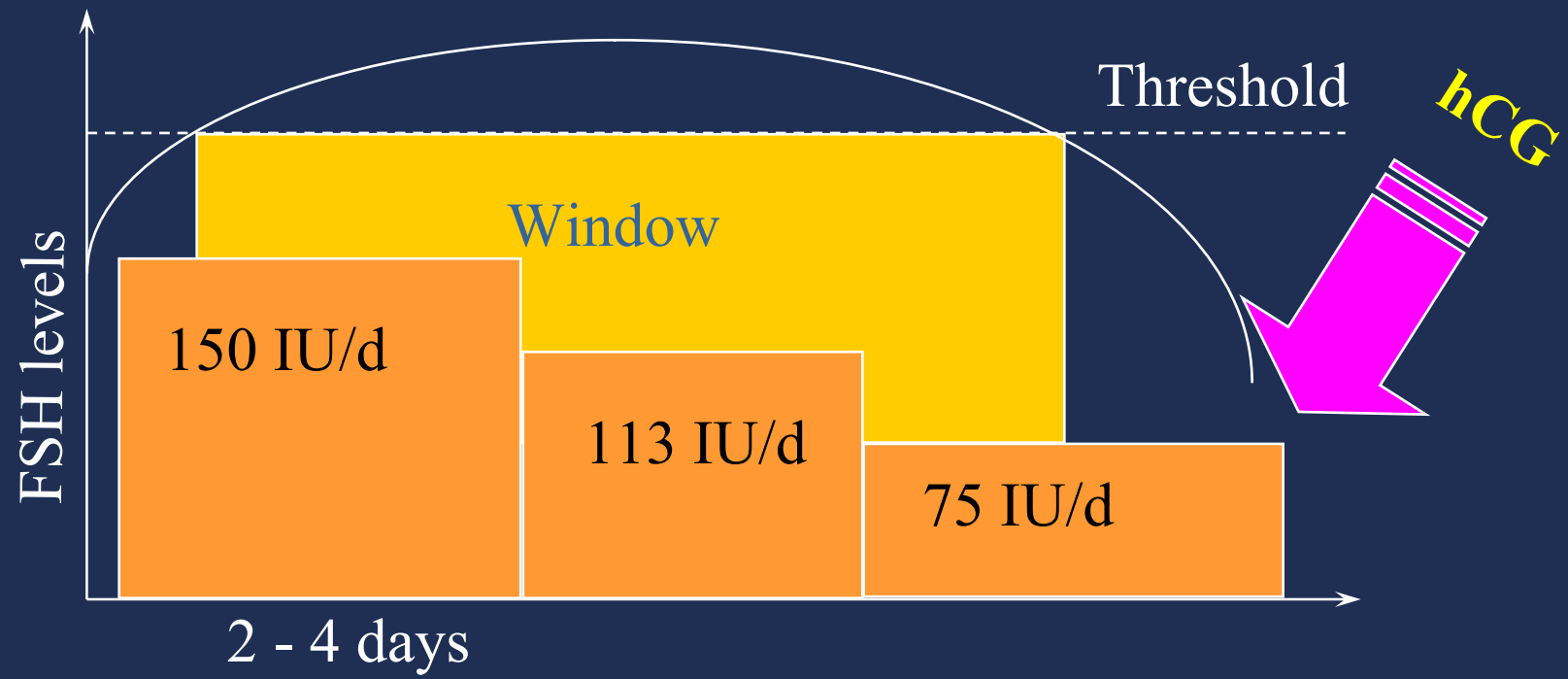
Nb of cycles /patients	505 / 134
% ovulatory	73
% monovulatory	72
% non responders	5
% pregnancies / cycle	11
Cumulative PR (6 cycles)	55
% multiple preg.	7
% miscarriages	30

Low dose step up regimen

Adapted from Franks et al. 1996

Mean threshold dose (range)	95 IU (52-225)
Mean total dose (range)	18.5 amps (5 - 81)
Mean duration to hCG (range)	14.2 days (5 - 34)

Stepdown regimen



Stepdown regimen

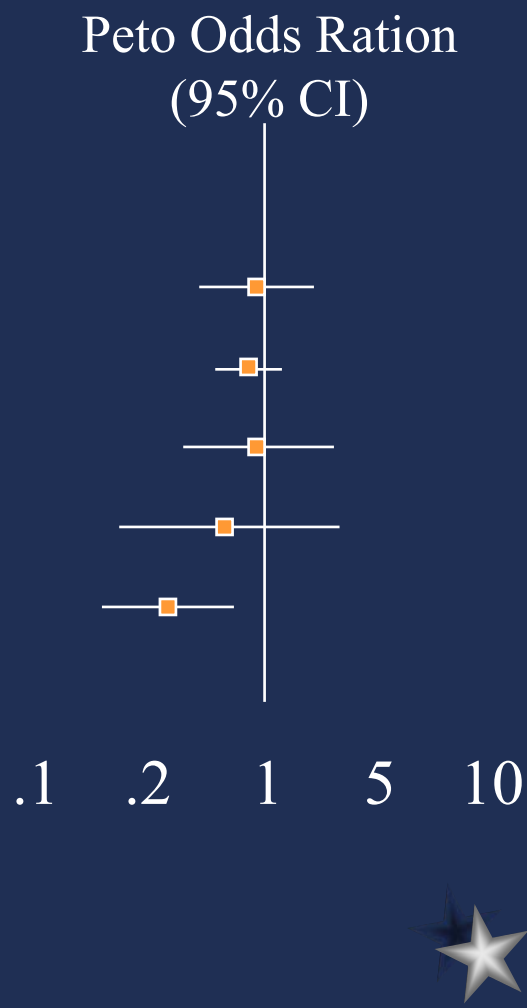
	Mizunuma et al. 1991	van Stanbrink et al. 1995
N° cycles	17	234
Ovulatory rate	100	91
Conception rate	29	16
Multiple pregnancy rate	20	12
Abortion rate		19
Hyperstimulation rate		2

Gonadotropin therapy for ovulation induction in PCOS

Nugent et al. Cochrane Library, 4; 2000

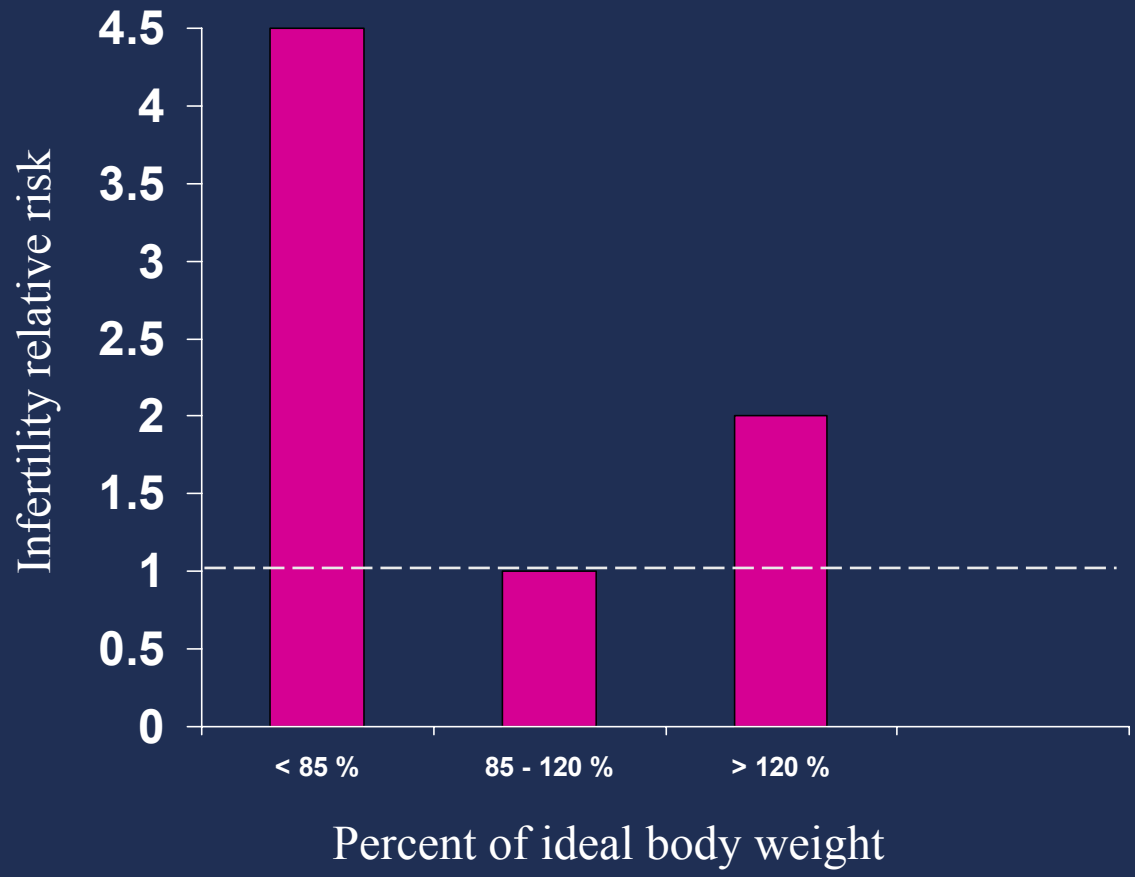
FSH versus hMG

- Pregnancy rate per cycle
- Ovulation rate per cycle
- Miscarriage rate
- Multiple pregnancy
- OHSS



Fertility and body weight

Green et al., 1988, Fertil. Steril., 50:721 - 726

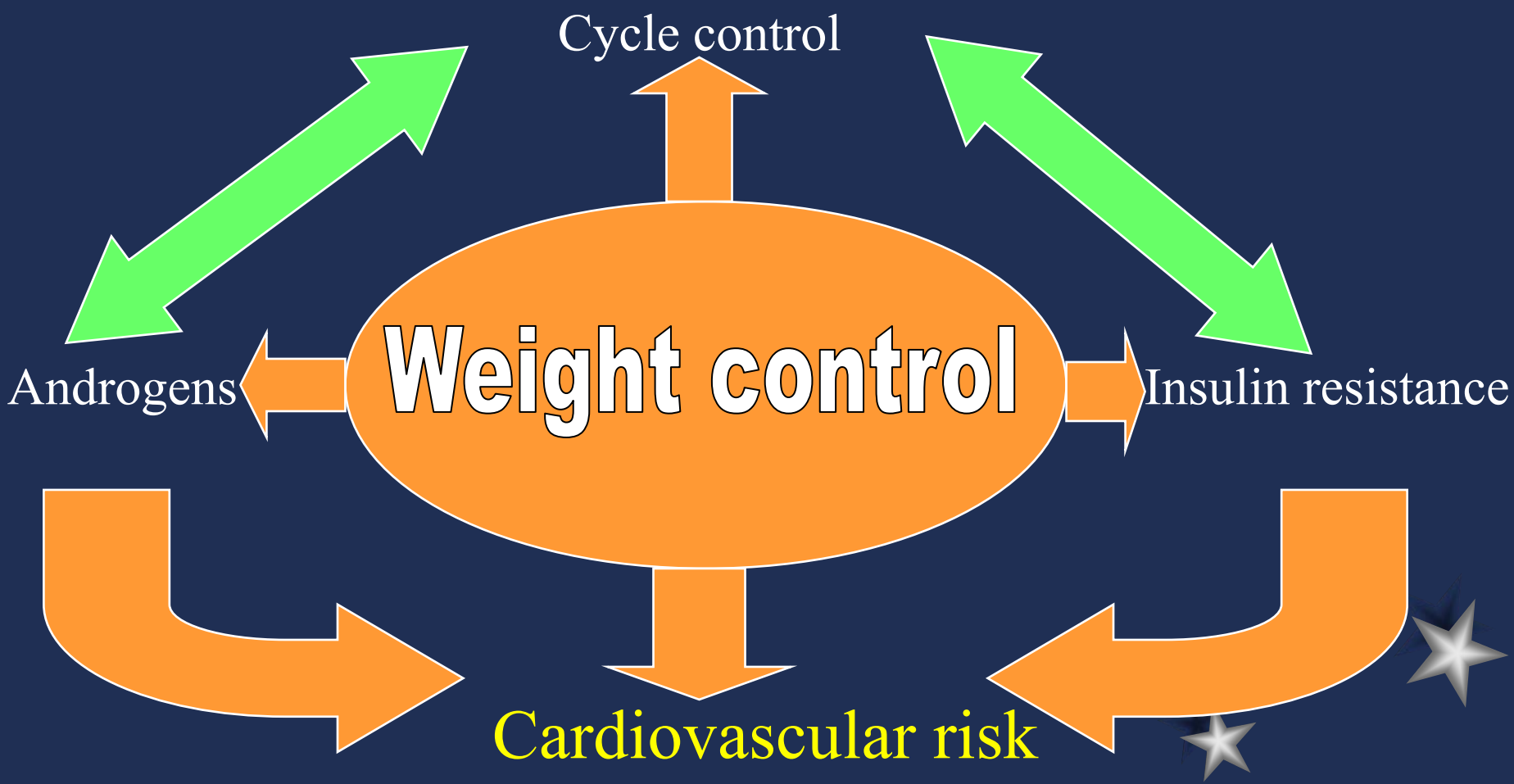


Weight reduction in obese anovulatory women

Bates et al. *Fertil Steril 1982*	*Pasquali et al.* *JCEM 1989*	*Kiddy et al.* *Clin Endocrinol 1992*
18 women	20 women	24 women
13 lost > 15 % of BW	Mean decreased from 86 to 76 kg	Mean BMI from 34.7 to 30.6
10 conceived	8 had menstrual cyclicity improvement	6 pregnancies

Beneficial metabolic effects of weight reduction

- ↗ SHBG
- ↗ IGFBP
- ↘ fasting insulin
- ↘ free androgens


Cycle control
Androgens
Weight control
Insulin resistance
Cardiovascular risk