

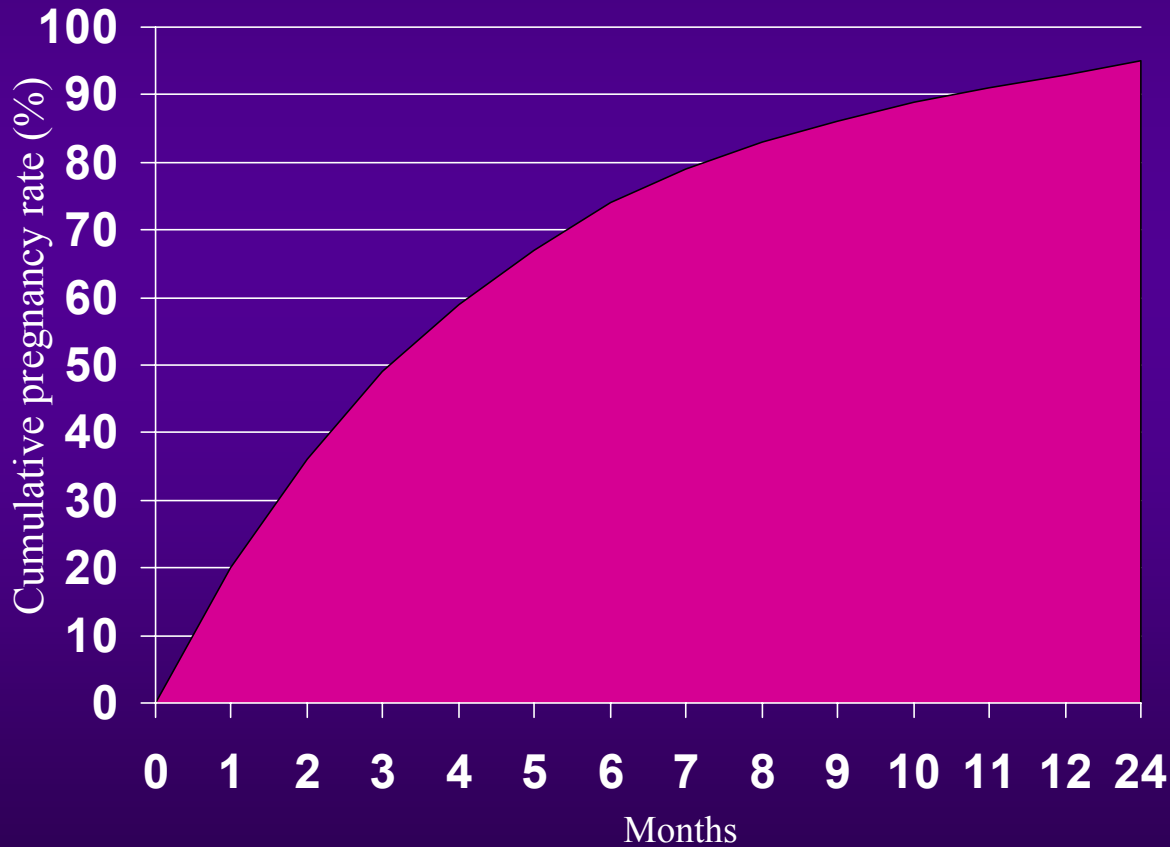


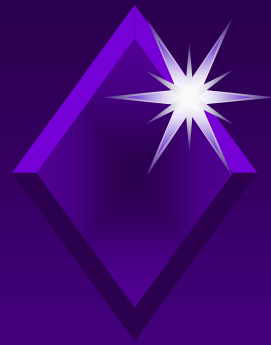
Ovarian stimulation

Didier Chardonnes



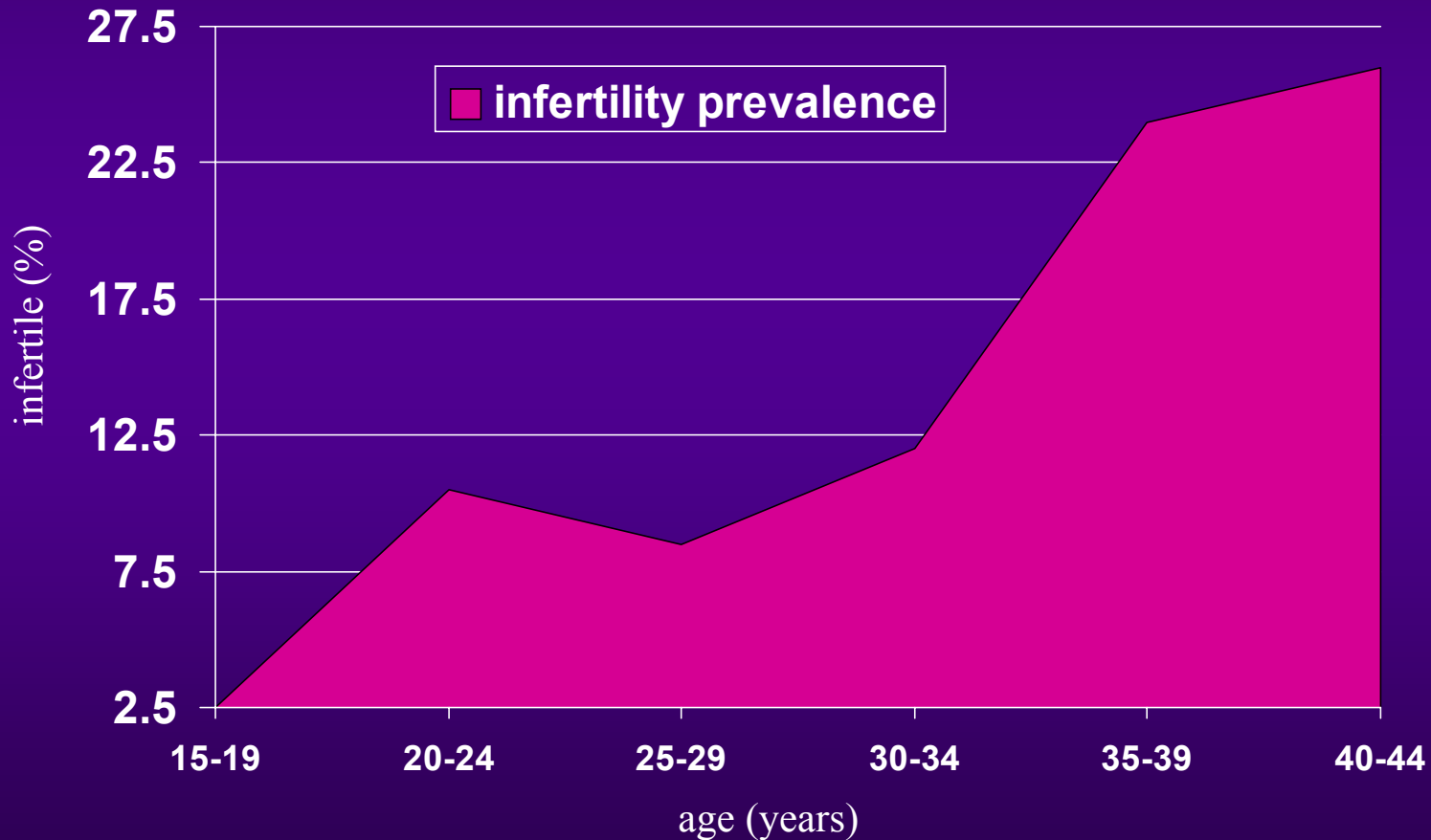
Infertility definition

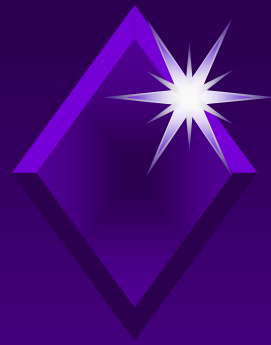




Fertility and age

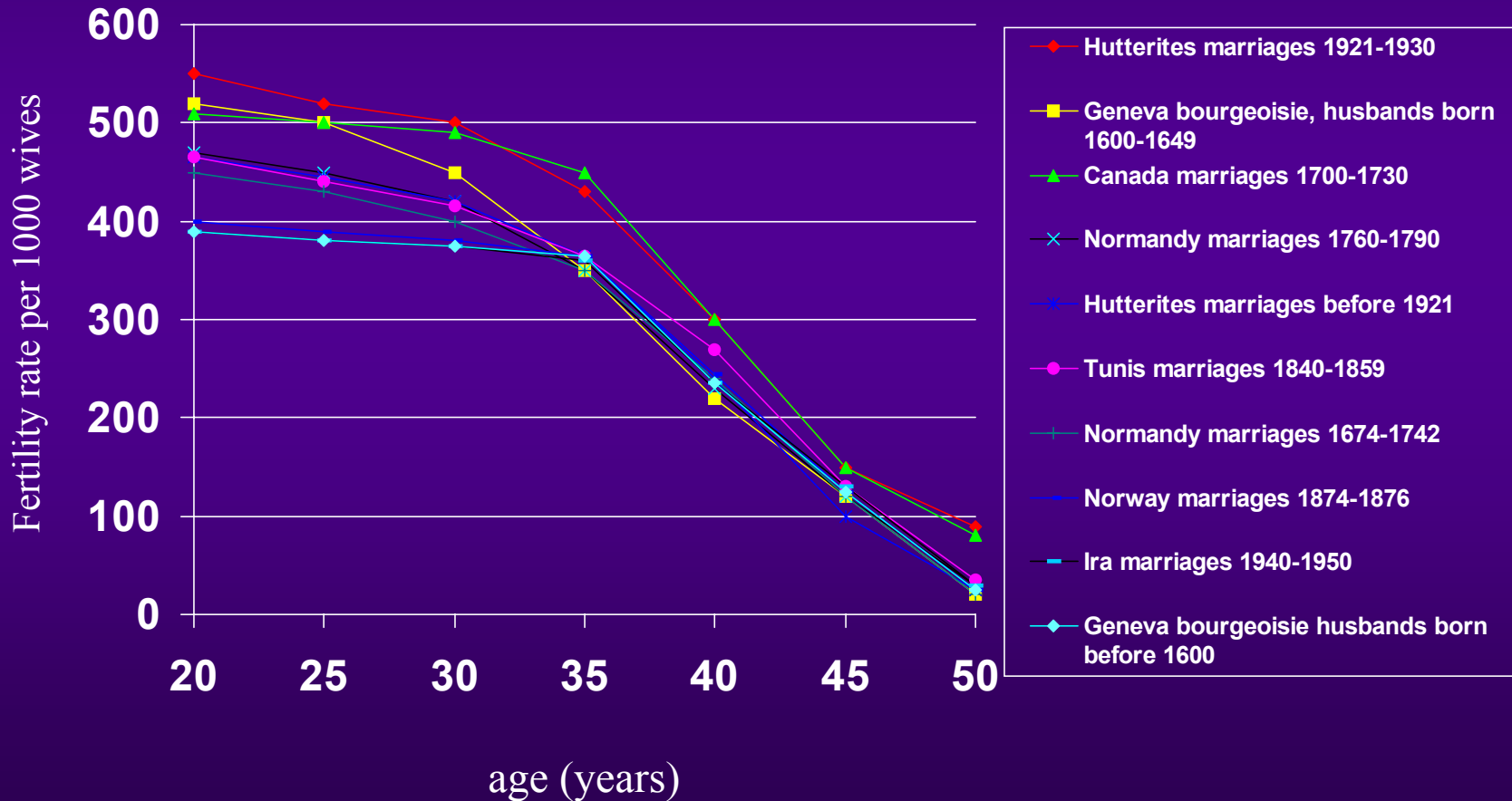
Menken et al., 1986, Science, 233: 1389 - 1394





Fertility and age

Trussel et al., 1985, *Popul. Stud.*, 29: 269-286

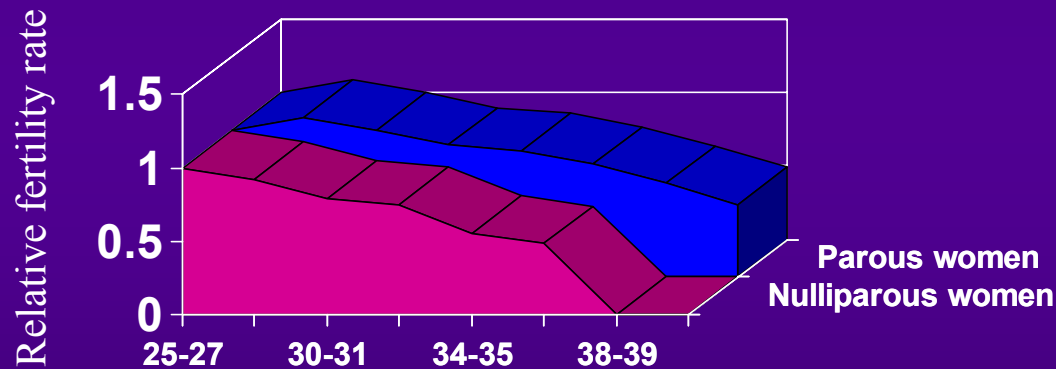




Fertility and age

Federation CECOS et al., 1982, N. Eng. J. Med., 306: 404 - 406

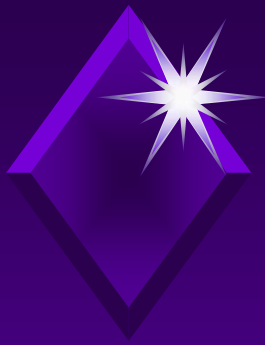
**Relative fertility rates by age group in the Oxford Family Planning Association
Contraceptive Study (N = 4104)**





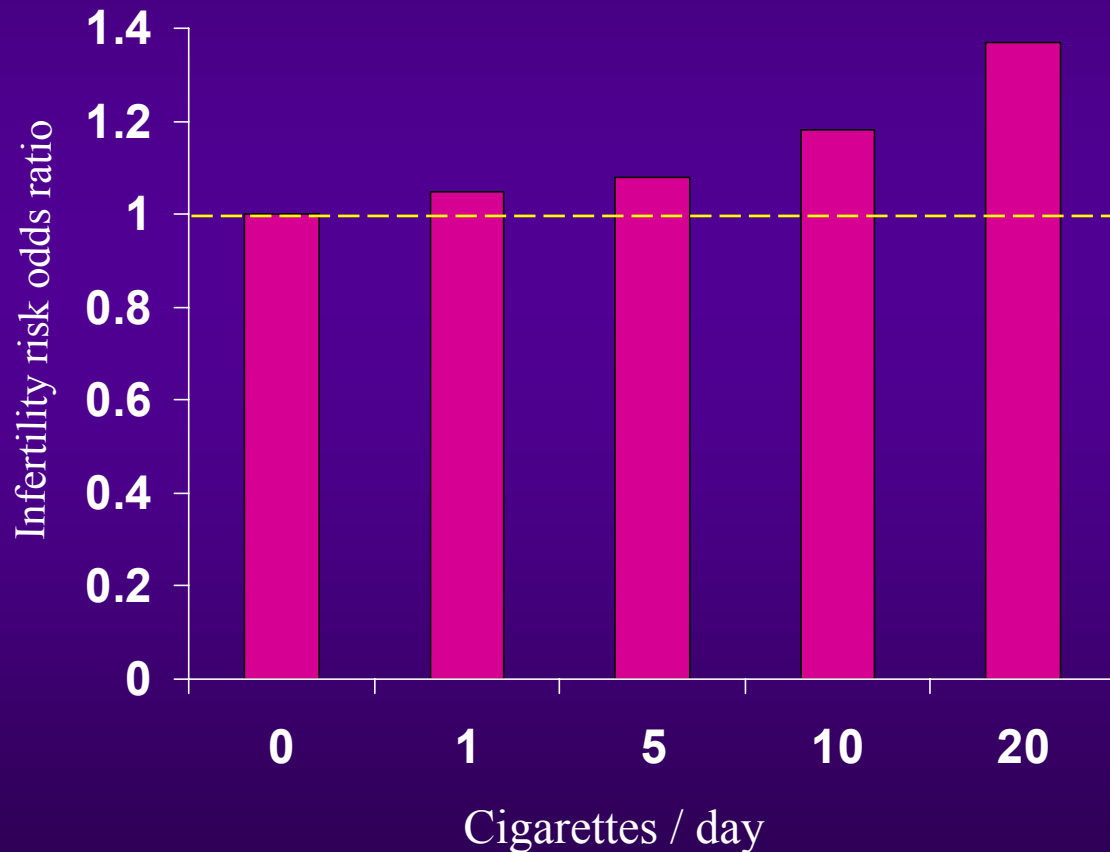
Fertility and life style factors

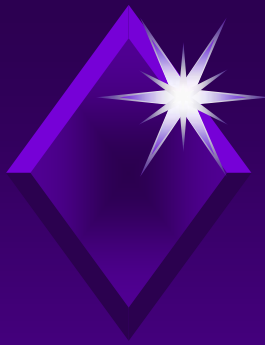
- ◆ Smoking
- ◆ Body weight
- ◆ Infectious disease



Fertility and smoking

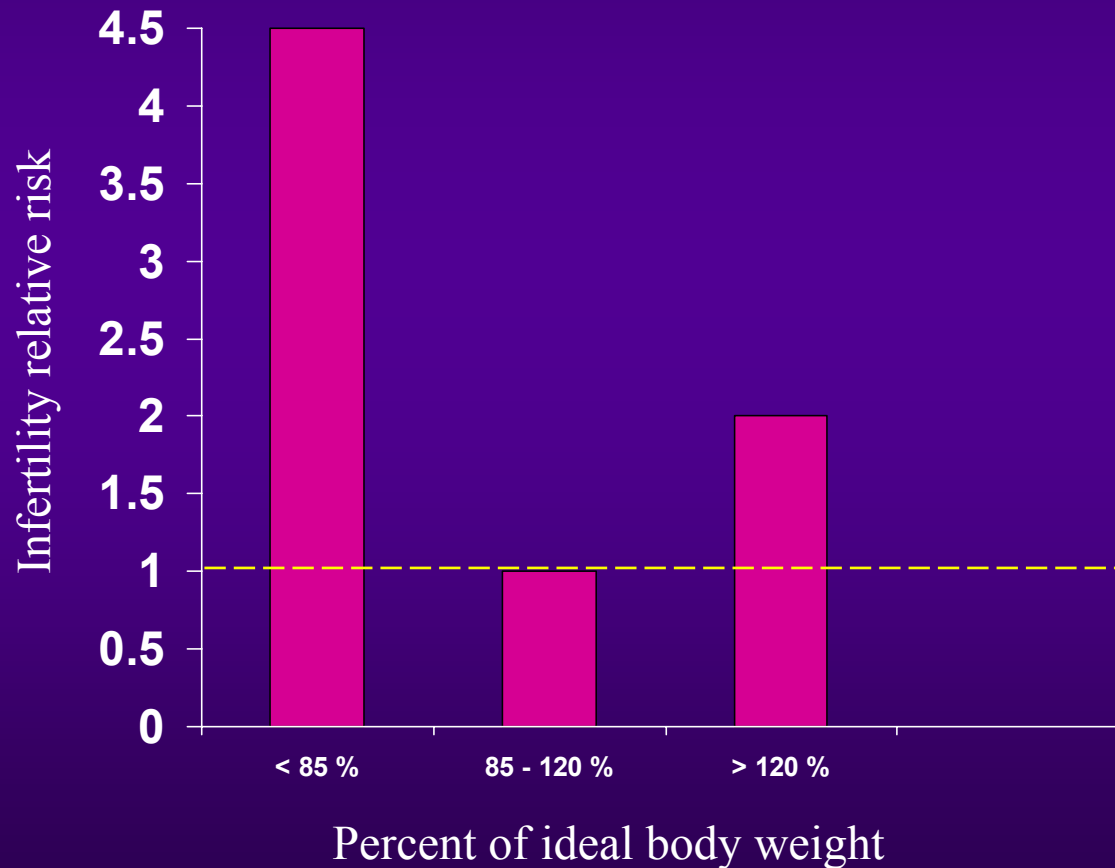
Laurent et al., 1992, Fertil. Steril., 57: 565 - 572





Fertility and body weight

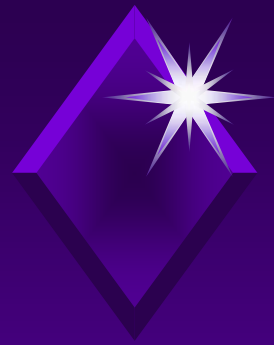
Green et al., 1988, Fertil. Steril., 50:721 - 726





Changing a life style

- ◆ Stop smoking
- ◆ Diminish alcohol consumption
- ◆ Body weight back to normal
 - ◆ Diet counseling
 - ◆ Adapt physical activity
- ◆ Reduce stress
 - ◆ Psychological counseling

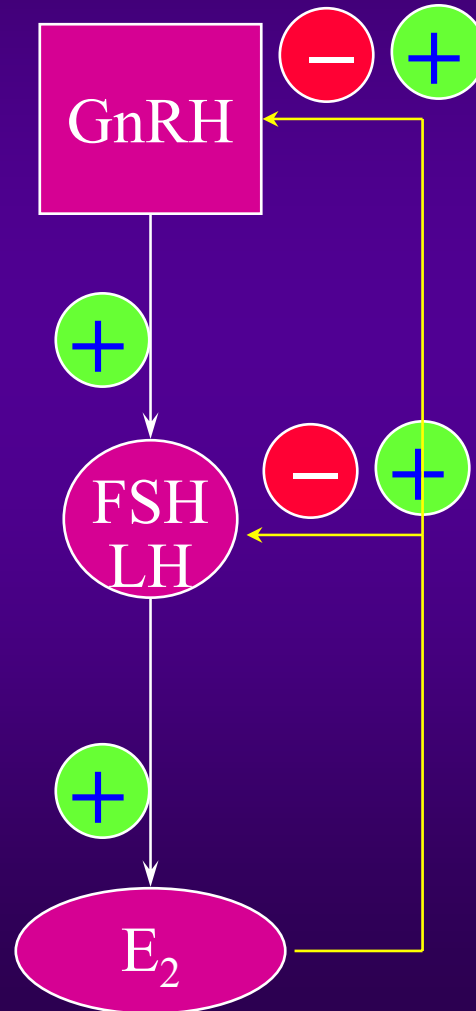


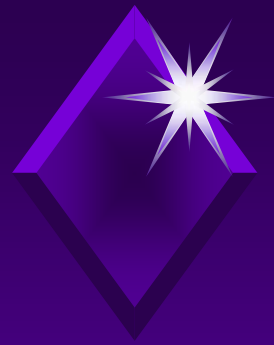
The axis

Hypothalamus

Pituitary

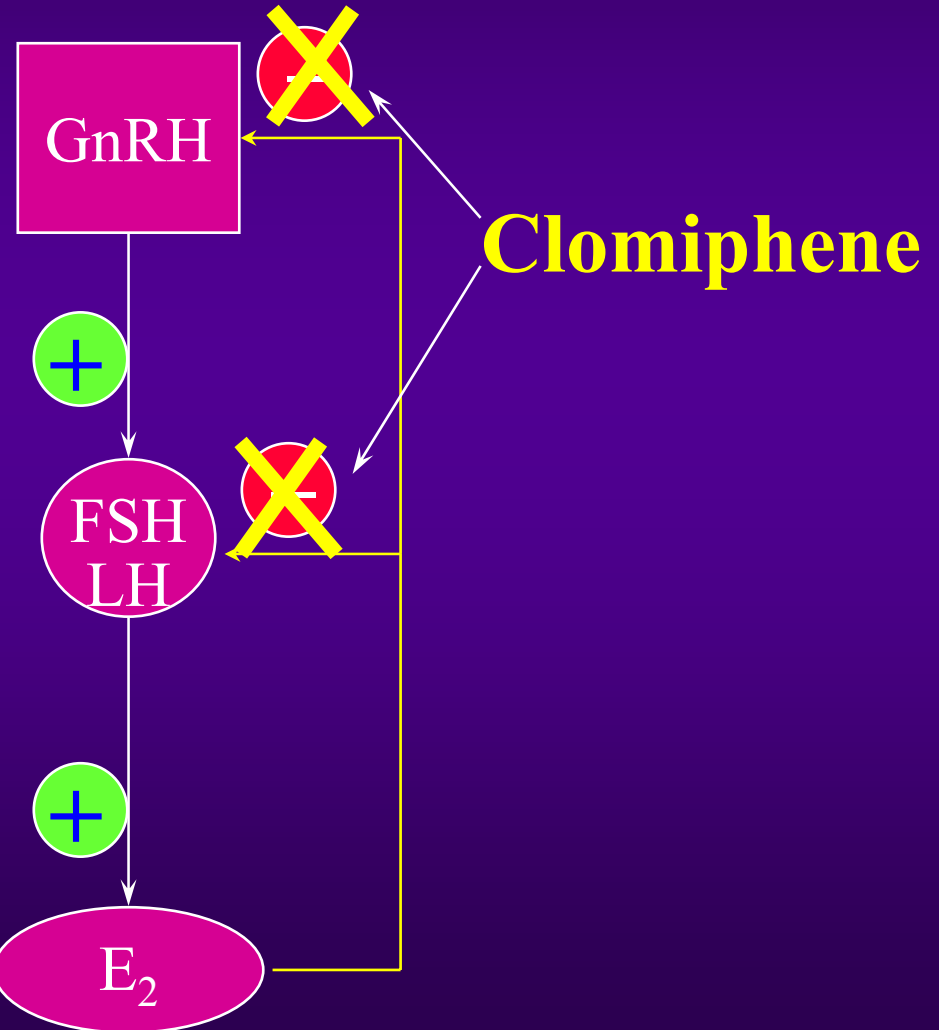
Ovary





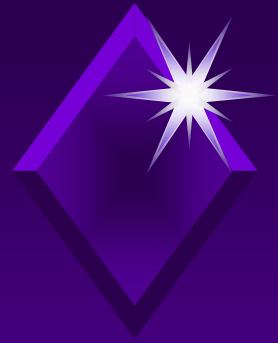
Clomiphene citrate

Hypothalamus



Pituitary

Ovary

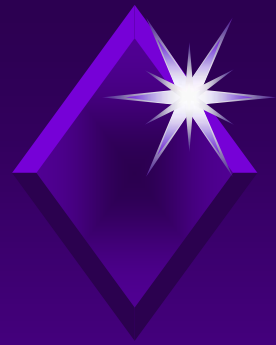


Clomiphene citrate indications

- ◆ PCO

- ◆ Oligoanovulation

 - ◆ Progesterone positive test



Clomiphene citrate administration regimen

◆ Dose

- ◆ 50-200 mg p.o. daily

◆ Initiation

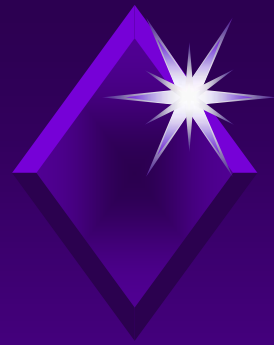
- ◆ D3-5 spontaneous or progesterone-induced cycle

◆ Duration

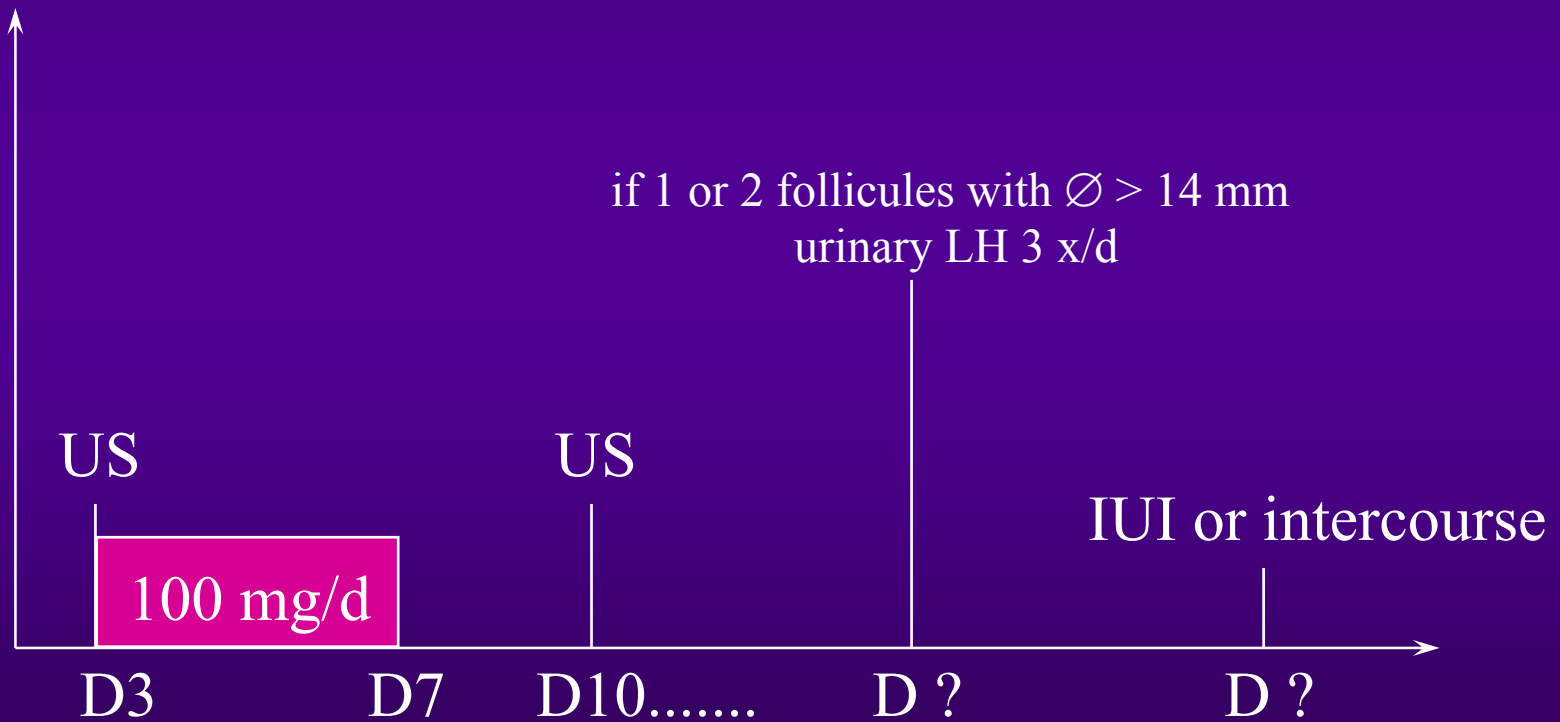
- ◆ 5 days

◆ Optional

- ◆ hCG at mid-cycle



Clomiphene citrate stimulation





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 potential



Clomiphene citrate overall results

◆ Ovulatory rates

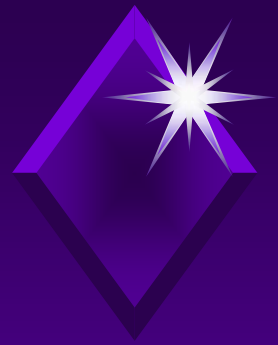
- ◆ oligomenorrhea 90 %
- ◆ secondary amenorrhea 67 %

◆ Pregnancy rates

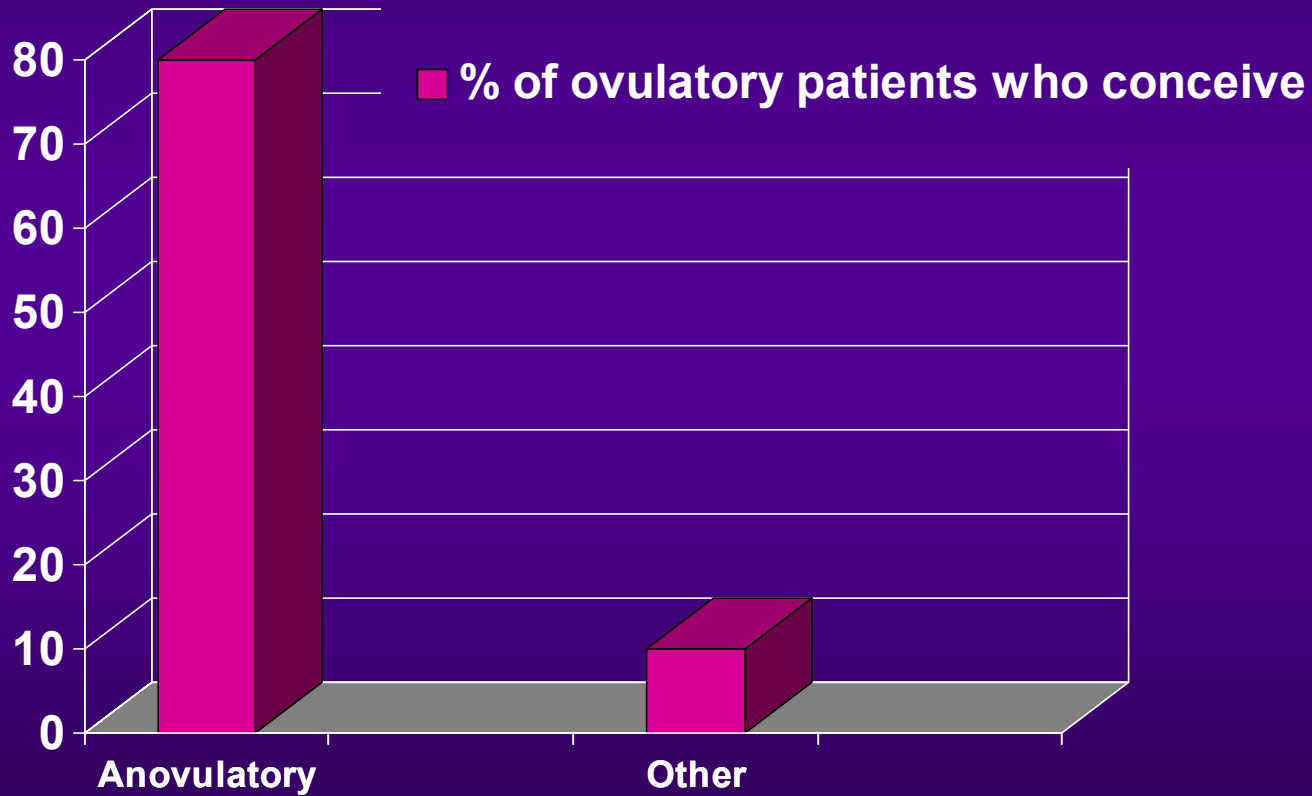
- ◆ overall 40 %
- ◆ no other infertility factor 80 %
- ◆ abortion 20 %

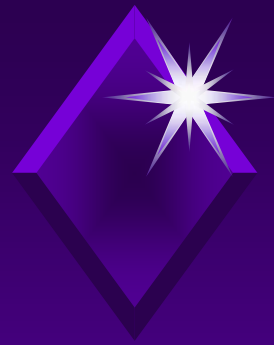
◆ Side effects

13 %



Clinical results (Gysler et al. 1982)



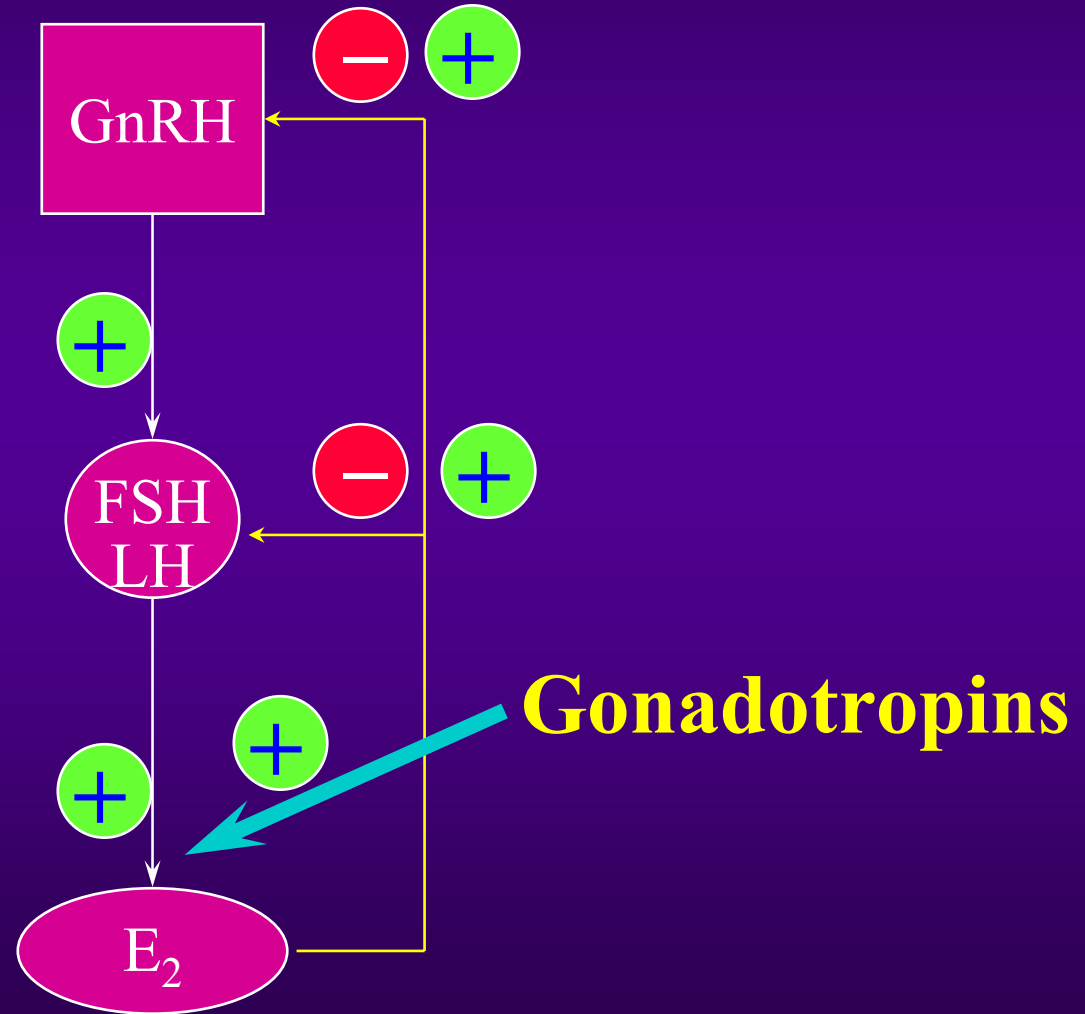


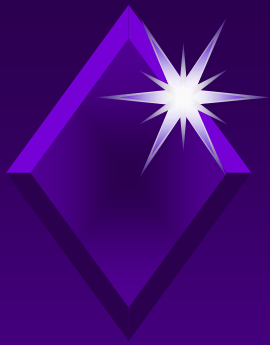
Gonadotropins

Hypothalamus

Pituitary

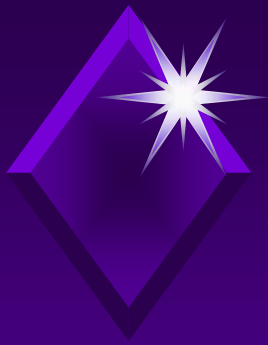
Ovary





Gonadotropins indications

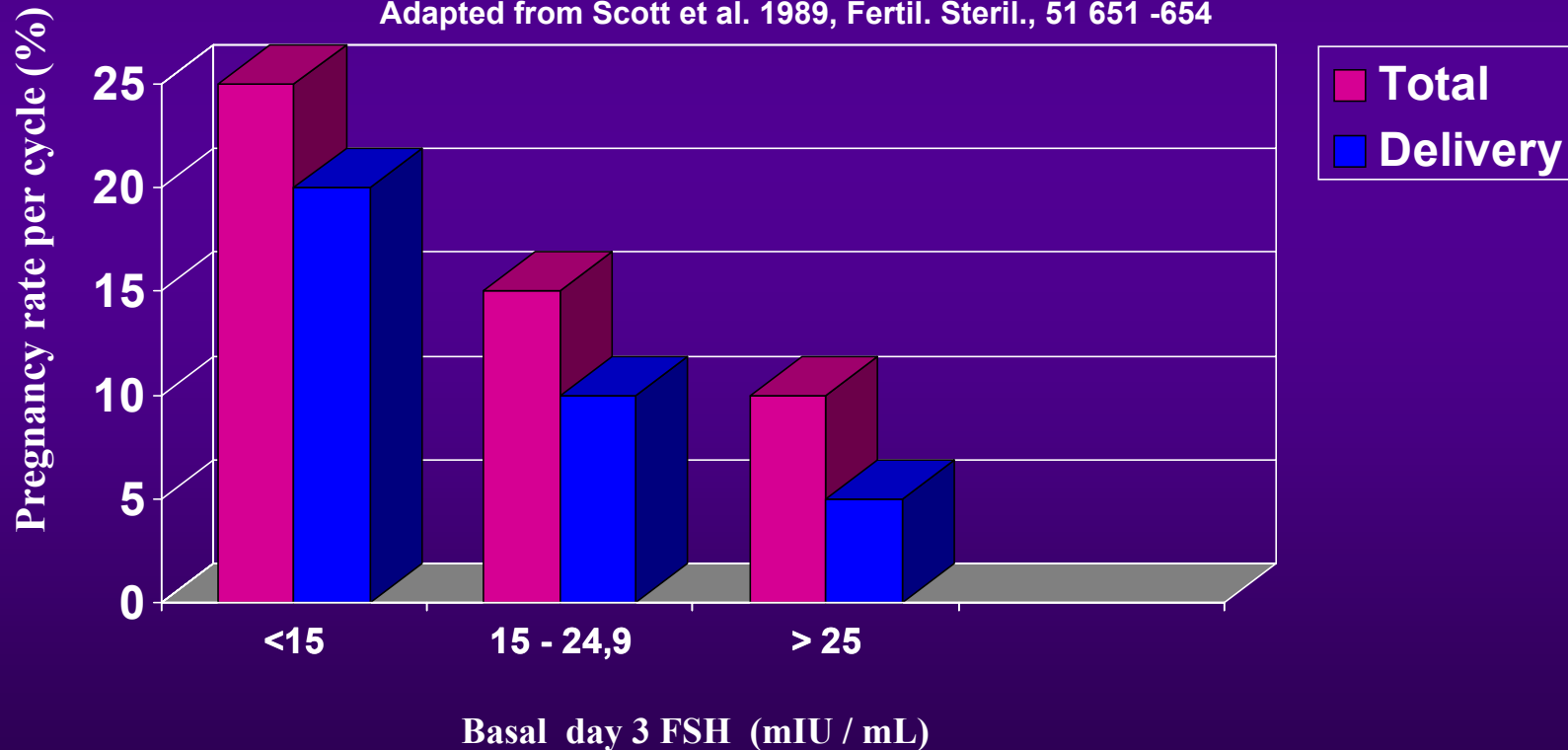
- ◆ Anovulatory patients
 - ◆ Hypothalamic disorders
 - ◆ Pituitary failure
 - ◆ PCOS
- ◆ Reproductive technology
- ◆ Poor candidates
 - ◆ > 40 years old
 - ◆ elevated D3 FSH
- ◆ Contraindication
 - ◆ Primary hypogonadism

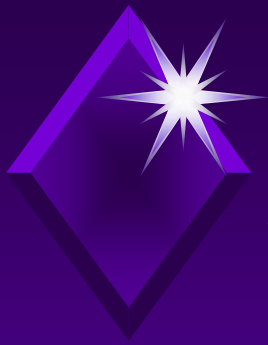


Hormonal assays: FSH

**Prognostic value of day 3 FSH levels in 758 patients
undergoing an IVF cycle**

Adapted from Scott et al. 1989, Fertil. Steril., 51 651 -654

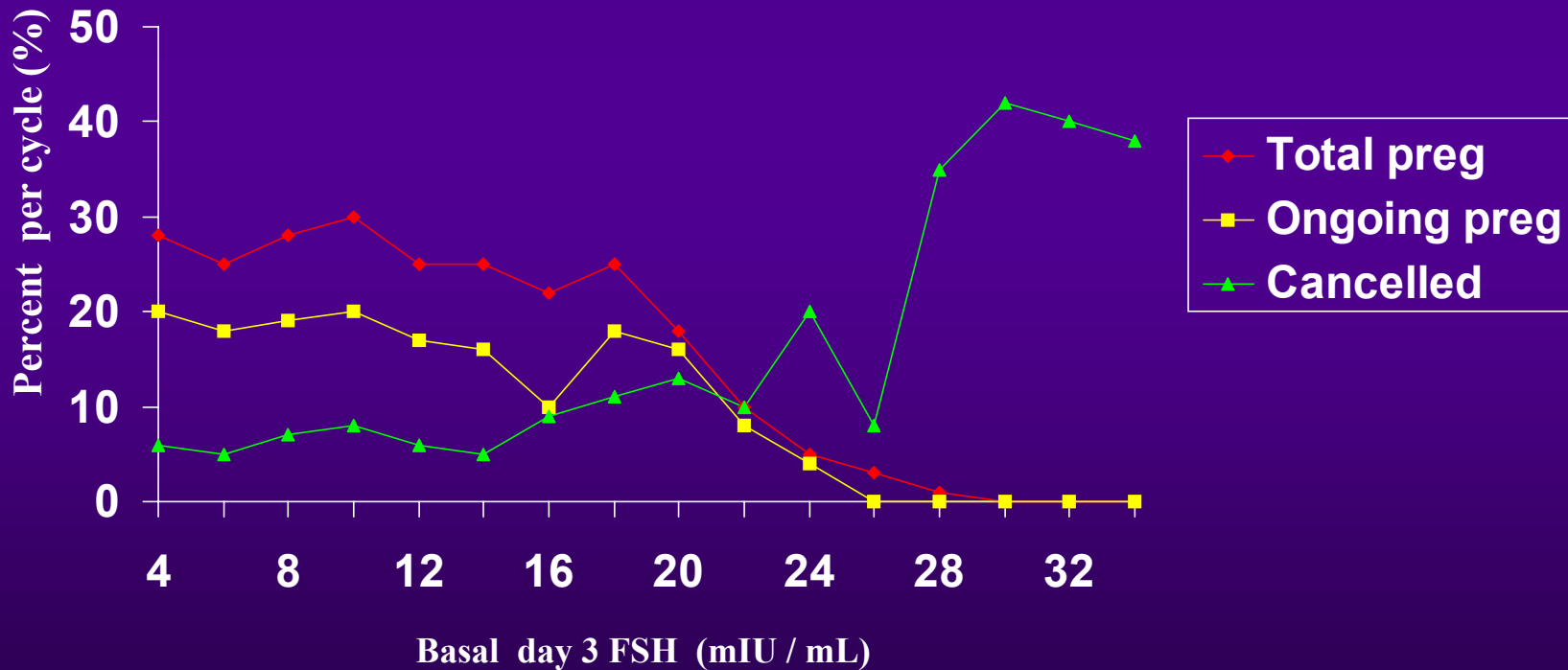


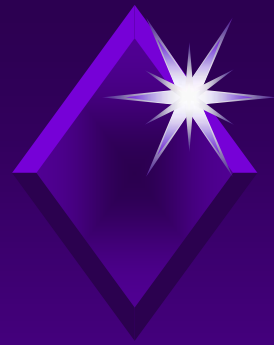


Hormonal assays: FSH

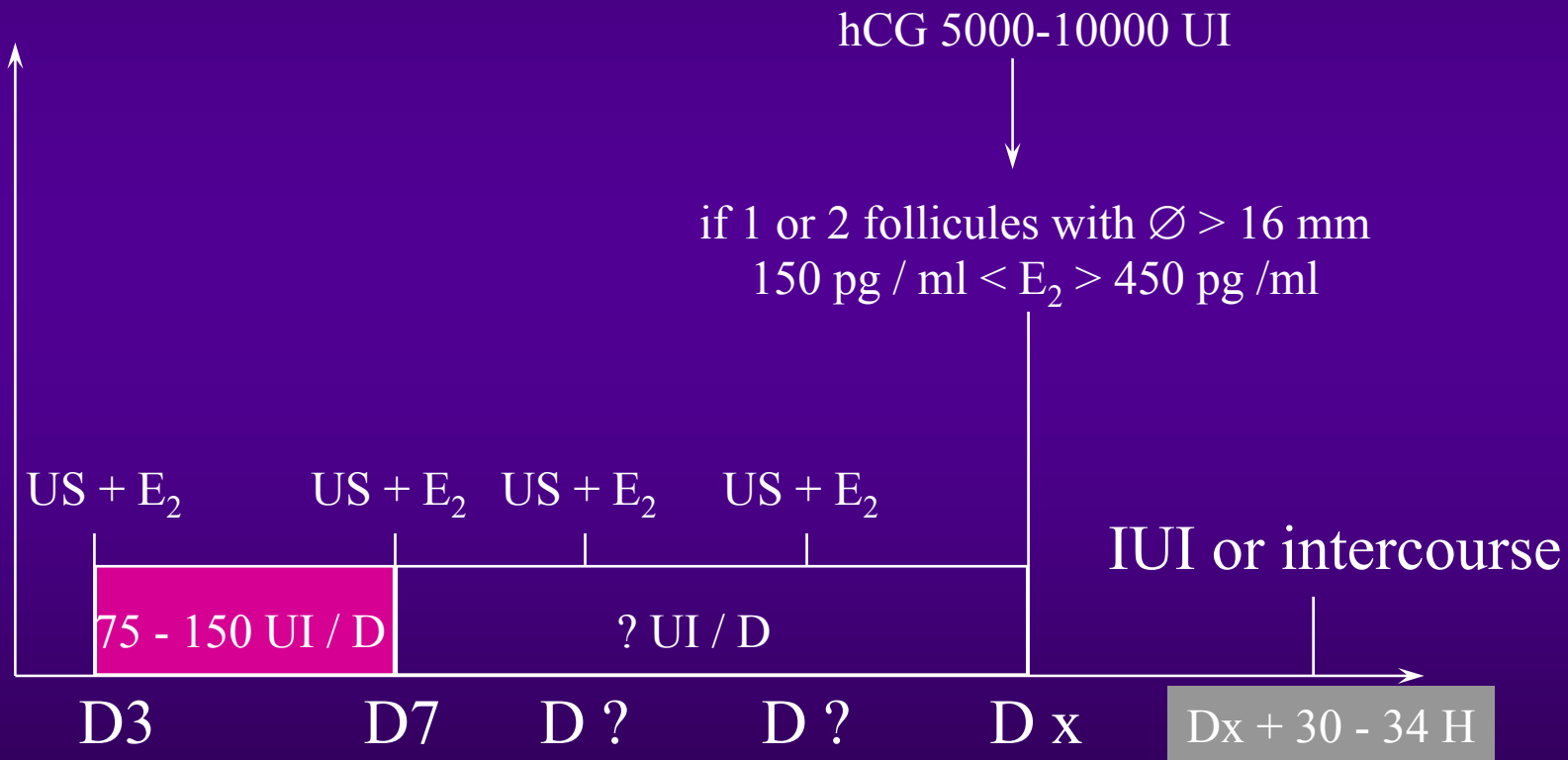
Day 3 FSH levels: pregnancy rate and cancellation rate in 1478 IVF cycles

Adapted from Toner et al. 1991, Fertil and Steril., 55: 784 - 791





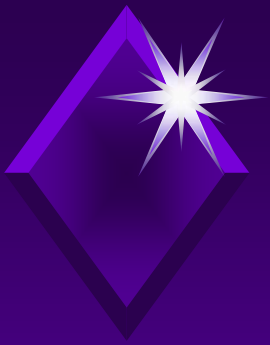
Gonadotropin stimulation





Preparations

	FSH	LH	PRICE (SFr)
HMG (Pergonal Humegon)	75	75	31
purified HMG (Metrodin HP)	75	<0.1	63
recombinant FSH (Gonal F Puregon)	75 50 37.5	0	95



Advantages for recombinant gonadotrophins in IVF

- ◆ Diminished total dose of gonadotrophins
- ◆ Diminished duration of treatment
- ◆ Higher number of mature oocytes retrieved
- ◆ Higher take home baby rate

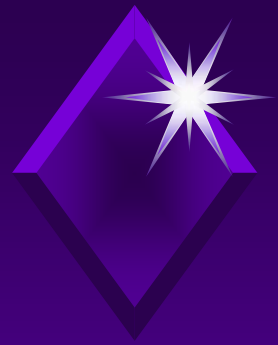
(OR 1.2 95% CI 1.1 -1.5)

Daya, Hum Reprod 1999, 14; 2207-2215

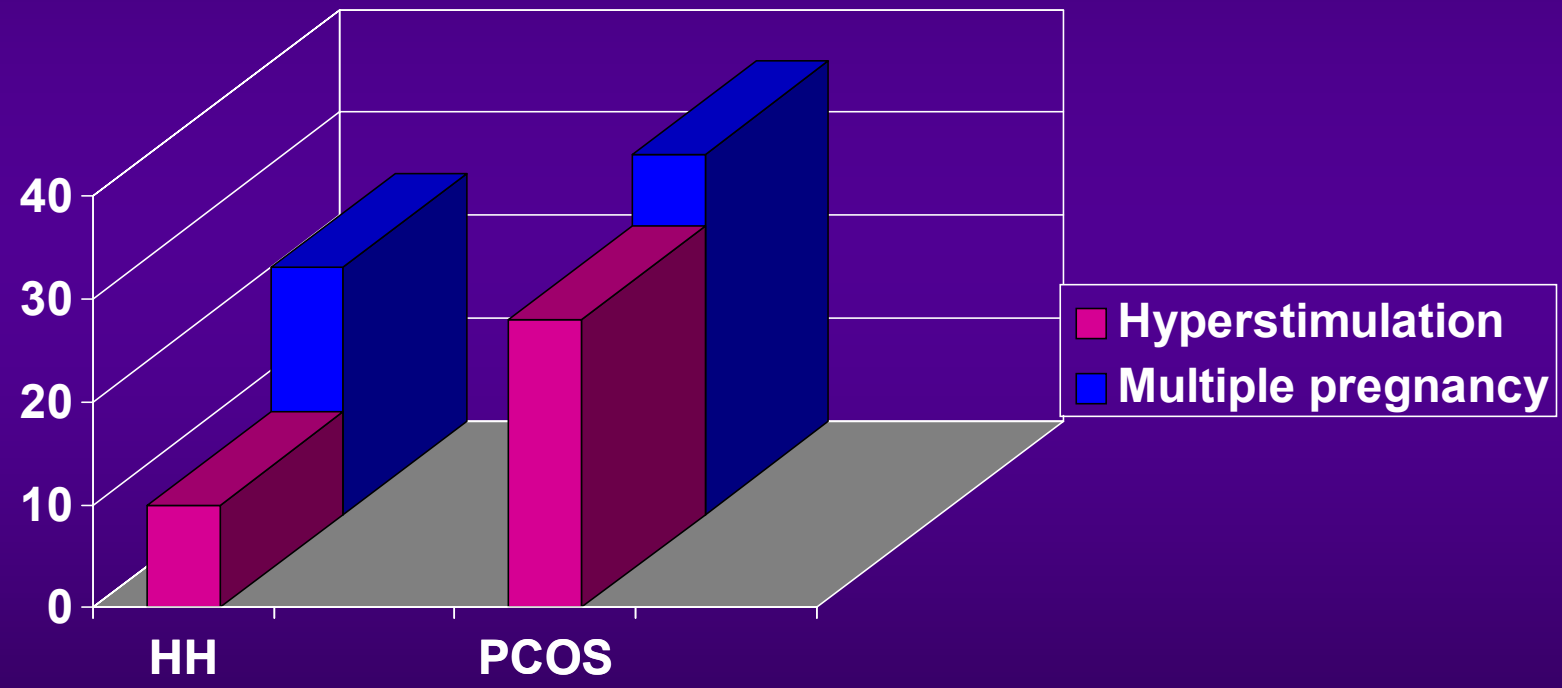


Gonadotropins overall results

◆ Ovulation	> 99 %
◆ Pregnancy	70 %
◆ Multiple pregnancies	10 %
◆ Abortion	28 %
◆ Ovarian enlargement	5 %
◆ Hyperstimulation	< 0.1 %
◆ Teratogenicity	none



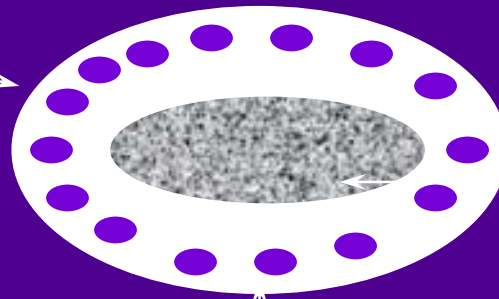
Gonadotropins complications



Wang et al 1980

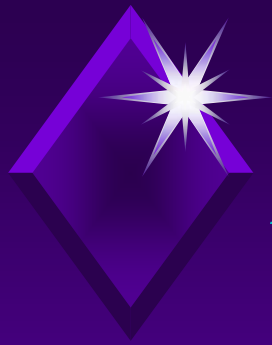


↑ Volume ovarien



↑ Stroma ovarien

> 10 follicules \varnothing <10 mm situés à la périphérie
(signe du collier de perles)



PCO

?

PCOS

• Critères échographiques

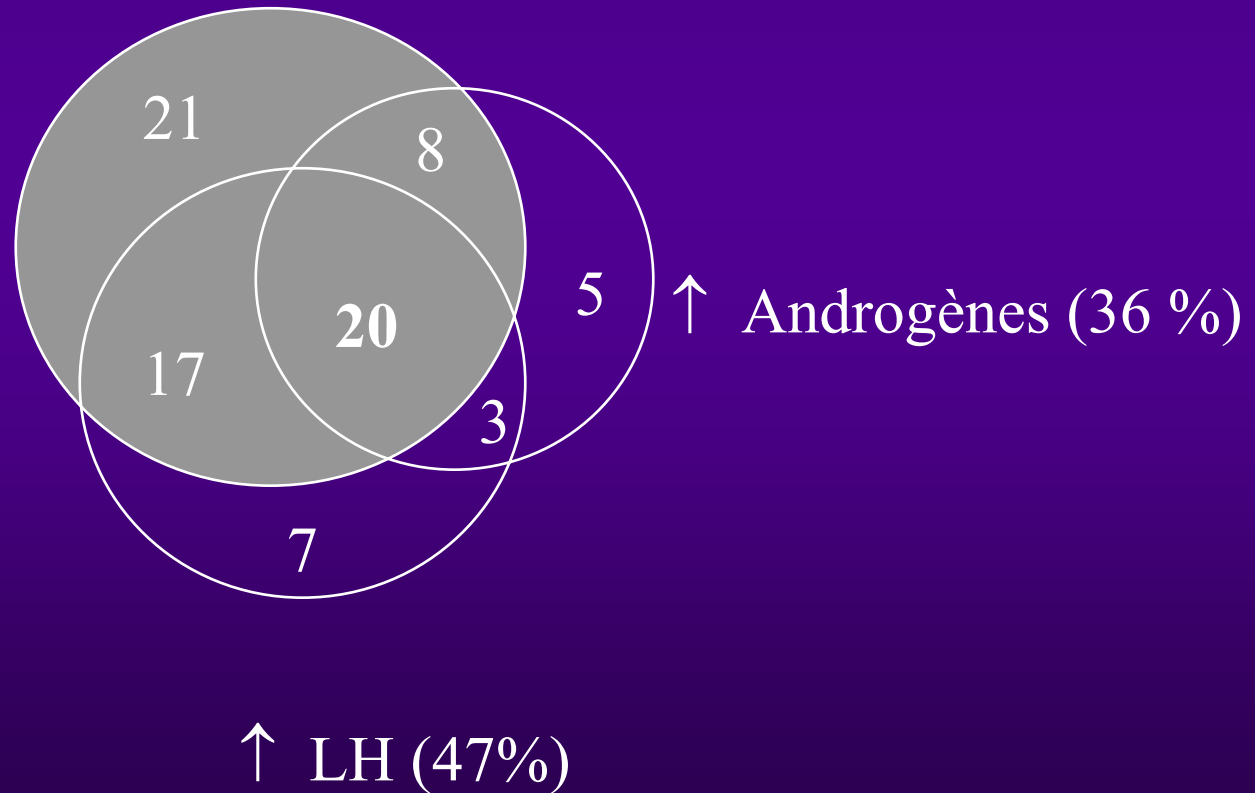
- Infertilité 88 %
- Résistance à l'insuline 70 %
- Hirsutisme 62 %
- Troubles du cycle 50 %
- Obésité 38 %
- Acné 35 %

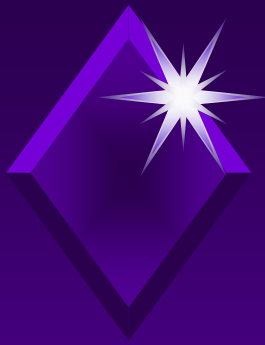


PCO versus PCOS

van Santbrink et al. 1997 Fertil Steril

Critères échographiques (66%)

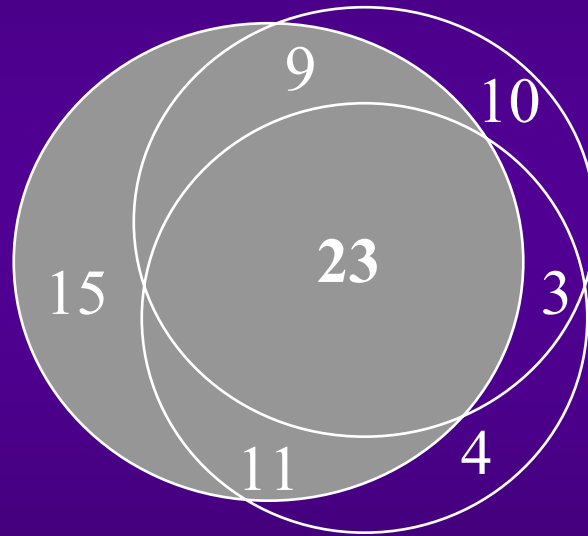




PCO

van Santbrink et al. 1997 Fertil Steril

↑ nb follicules (58%)

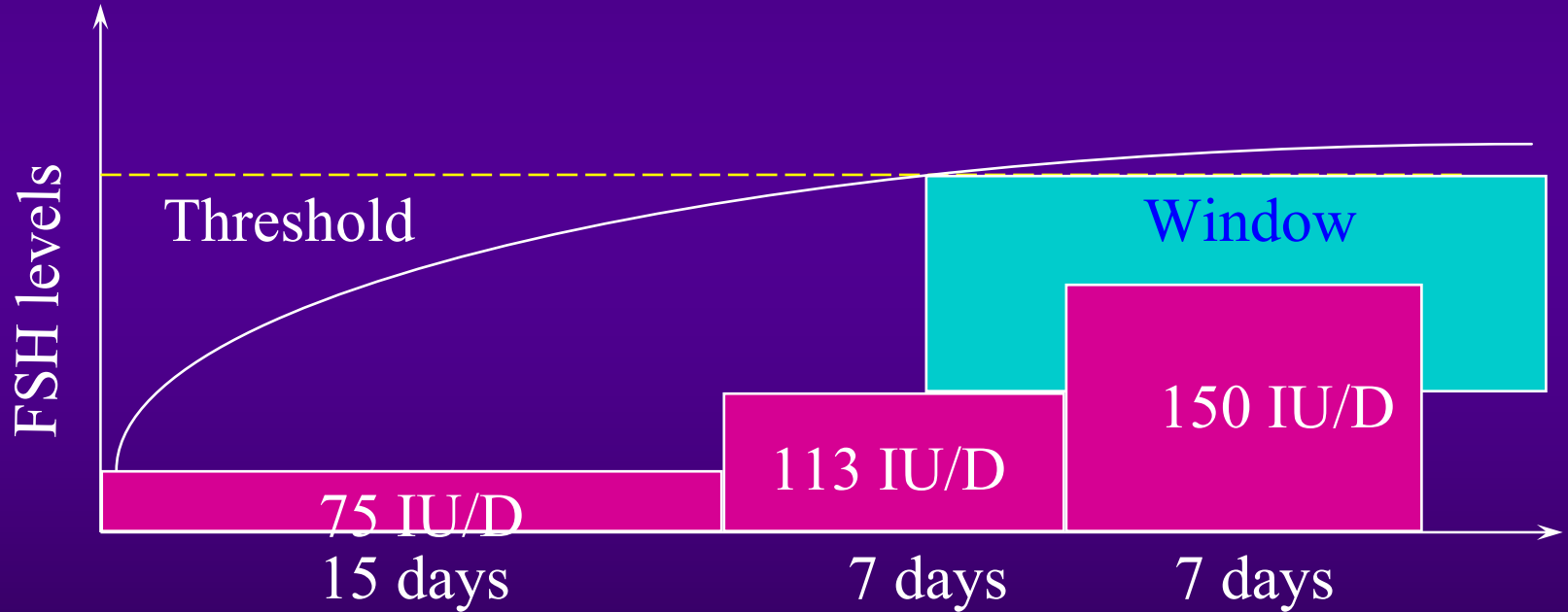


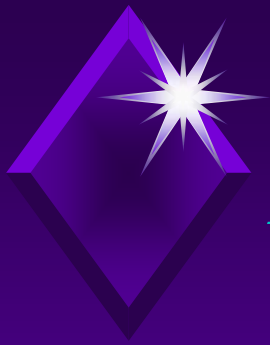
↑ Stroma ovarien (45%)

↑ Volume ovarien (41%)



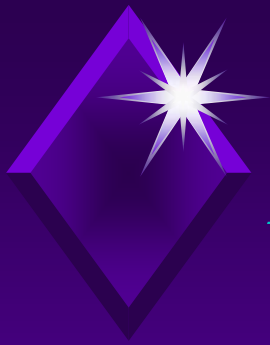
Low dose step up regimen





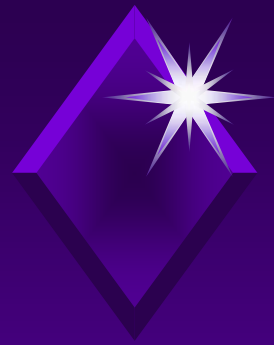
Low dose step up regimen

Nb of cycles /patients	505 / 134
% ovulatory	73
% monovulatory	72
% non responders	5
% pregnancies	43
% multiple preg.	7
% miscarriages	30

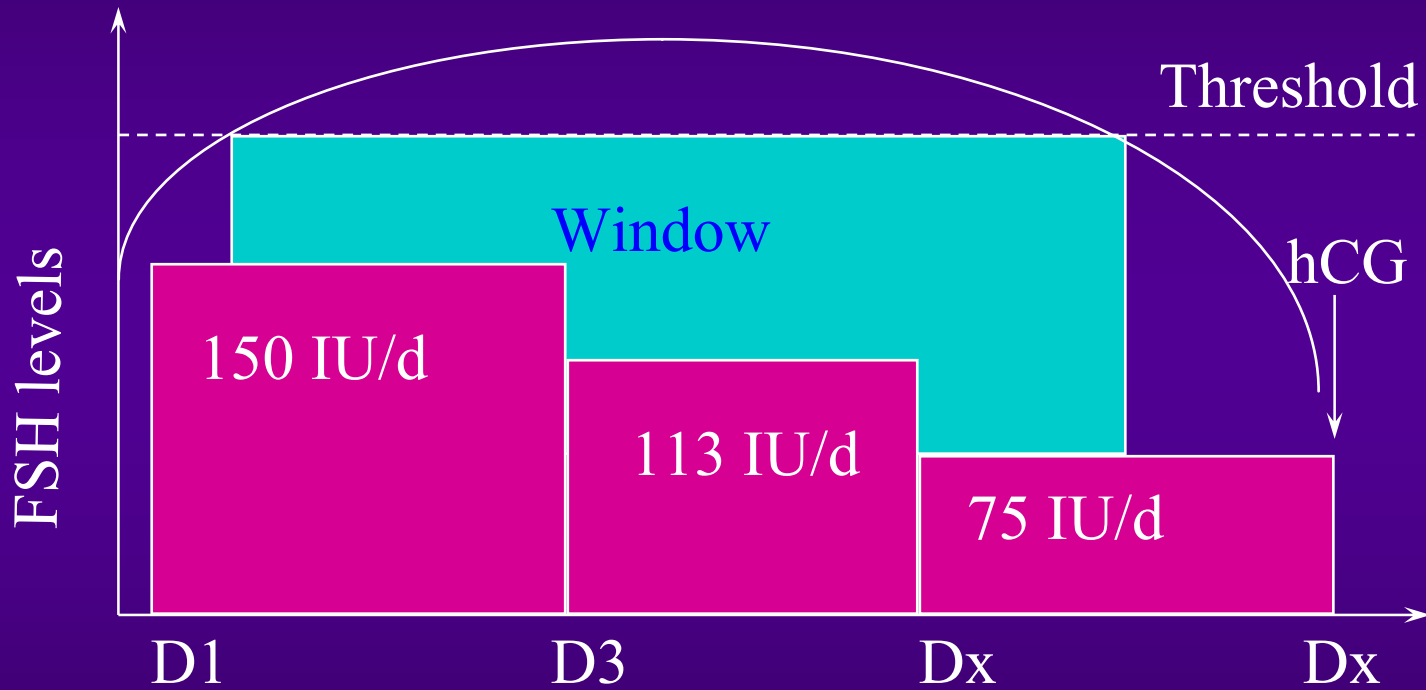


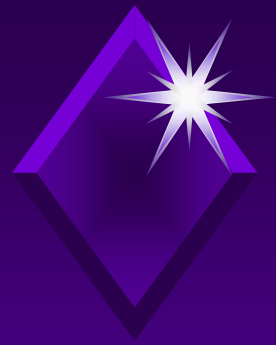
Low dose step up regimen

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)
Pregnancy rate per cycle	10 %



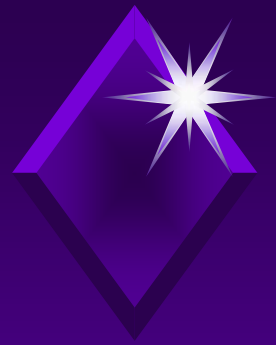
Stepdown regimen





Stepdown regimen

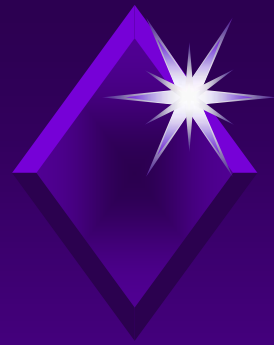
	Mizunuma et al. 1991	van Stanbrink et al. 1995
N° cycles	17	234
Ovulatory rate	100	91
Conception rate	29	16
Multiple pregnancy rate	20	12
Abortion rate		19
Hyperstimulation rate		2



GnRH agonists indications

- ◆ Pituitary downregulation
 - ◆ Ovarian stimulation (ultrashort, short and long protocol)
 - ◆ Endometriosis
 - ◆ Myomatous uterus
 - ◆ Hyperandrogenemia

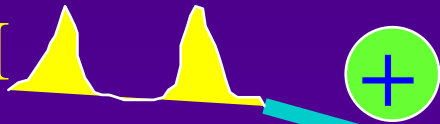
- ◆ Ovarian stimulation
 - ◆ Pulsatile administration



Pulsatile GnRH

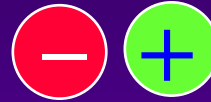
Hypothalamus

GnRH

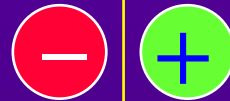


Pituitary

GnRH

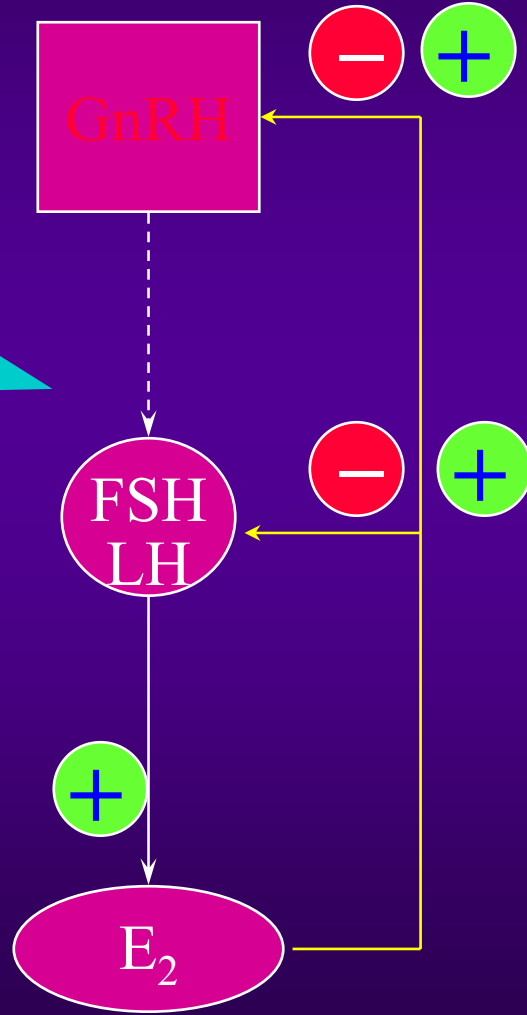


FSH
LH



Ovary

E₂





Pulsatile GnRH

◆ Route

- ◆ Intravenous or subcutaneous

◆ Dose

- ◆ theoretical 2-40 μg
- ◆ practical 5 μg

◆ Frequency

- ◆ 60 - 90 min

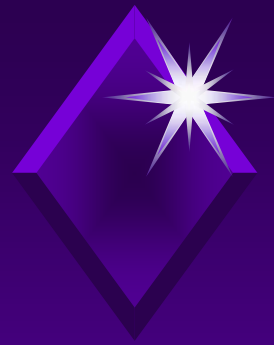
◆ Duration

- ◆ optimal until menstruation or + pregnancy test
- ◆ minimum until ovulation then luteal phase support



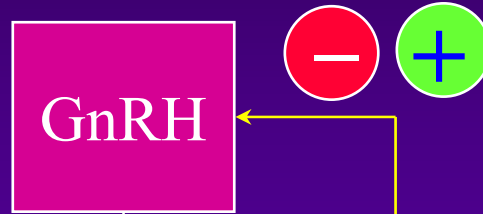
Pulsatile GnRH in hypothalamic hypogonadism and PCOS Jacobs et al. 1994

	Ovulation rate (%)	Pregnancy rate (%)	Pregnancy rate per ovulation (%)
Hypogonadotropic hypogonadism	90	28.6	32
PCOS	50.7	14.6	28.7



Continuous GnRH

Hypothalamus



GnRH



Pituitary

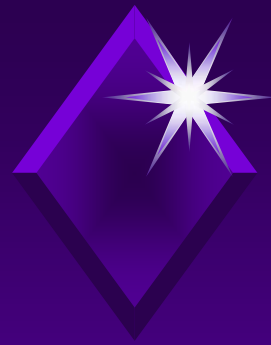


Ovary



Gonadotropins

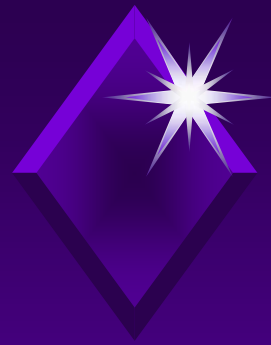




GnRH agonists continuous and ovulation induction

◆ Advantages

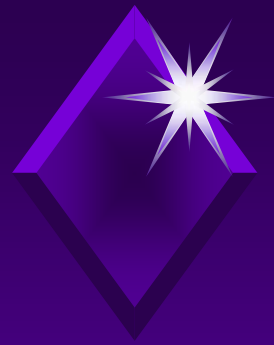
- ◆ lower cancellation rate
- ◆ more oocytes
- ◆ no premature LH surge



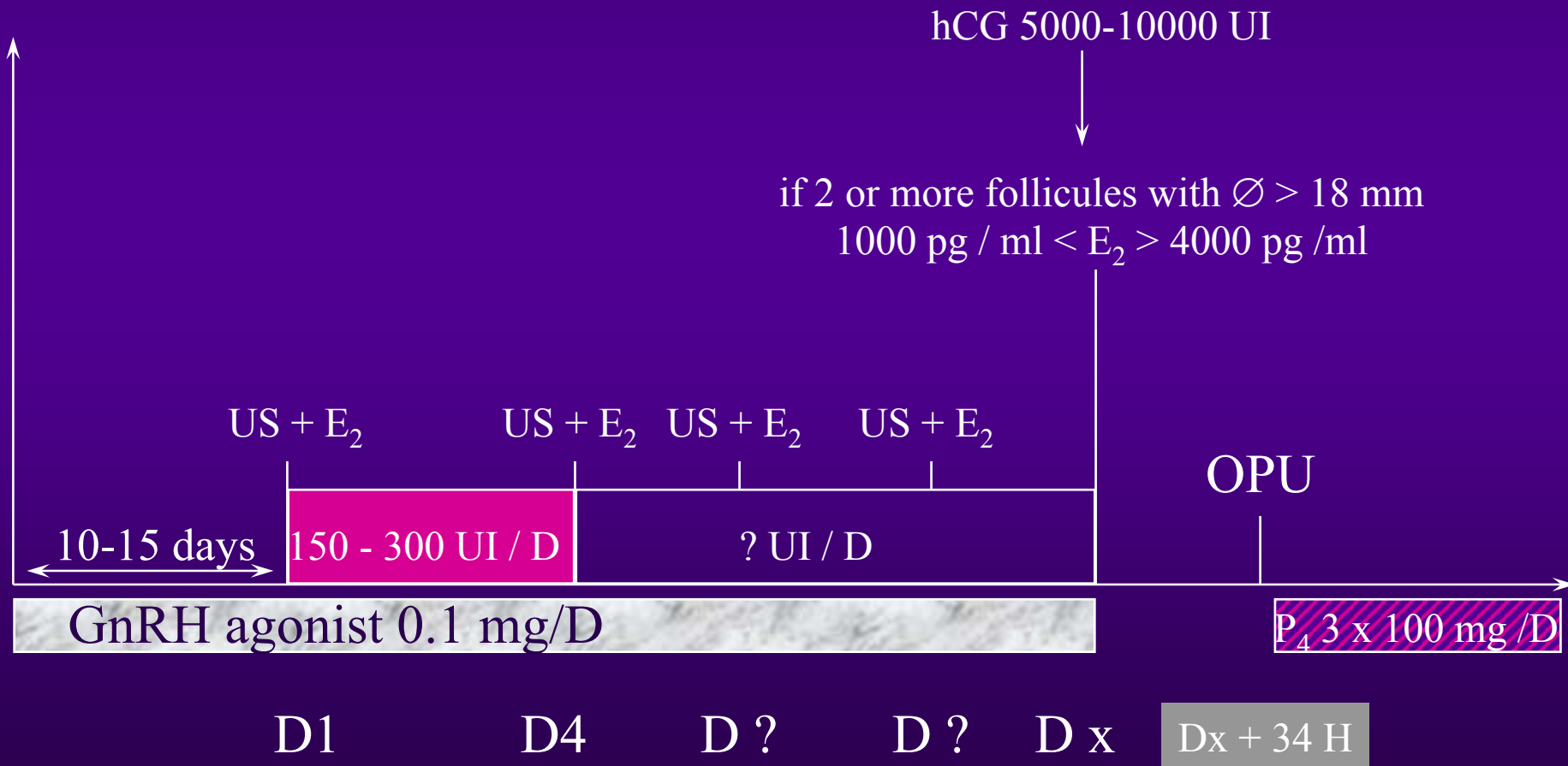
GnRH agonists continuous and ovulation induction

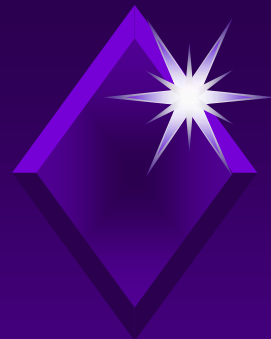
◆ Disadvantages

- ◆ More gonadotrophins needed
- ◆ Ovarian cysts
- ◆ Unwanted pregnancy exposure



Gonadotrophin stimulation with GnRH agonist





GnRH-agonists in IVF

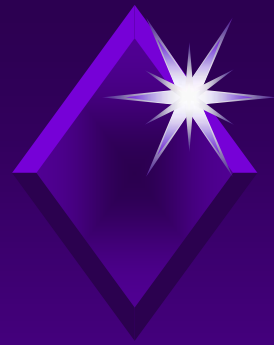
(Prospective studies long /short Protocol)

	HMG (amp) Short	HMG (amp) Long	Embryos (n) Short	Embryos (n) Long	Preg rate (%) Short	Preg rate (%) Long
Hedon 88	27.3	36.5	2.9	4	12.8	37.5
Zorn 88	20.5	39.5	1.8	2.3	25.3	26.6
Remorgida 89	23.7	31.7			34.7	36.4
Ton 90	24	27	1	3	16.6	25.7
Tarlatzis	27.9	37.7	4	6.3	19.4	25.8



Incidence of OHSS

	HMG %	Clomid %	Spontaneous %	TSH %
Mild	3 - 23			
Moderate	3 - 16	< 1	< 1	< 1
Severe	< 2			



Risk factors fo OHSS

◆ Gonadotrophin therapy

◆ Rapid E₂ rise

◆ PCO

◆ Younger age

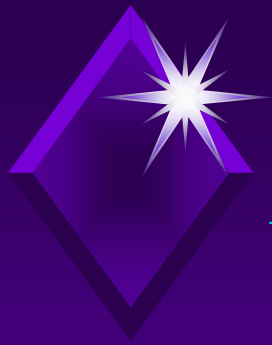
**Multiple small and
intermediate follicule**

◆ Pregnancy

◆ Multiple gestation

◆ Molar pregnancy

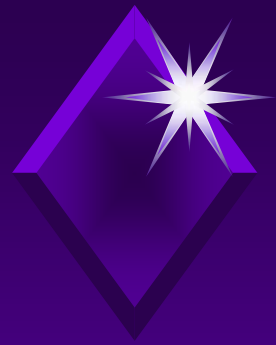
hCG rise



Mediators of OHSS

◆ VEGF

◆ Renin angiotensin



OHSS pathophysiology

hCG



Ovarian VEGF



**Angiogenesis
Hyperpermeability**



OHSS classification

Mild OHSS

- grade 1 abdominal distention
- grade 2 nausea
vomiting or diarrhea
enlarged ovaries

Moderate OHSS

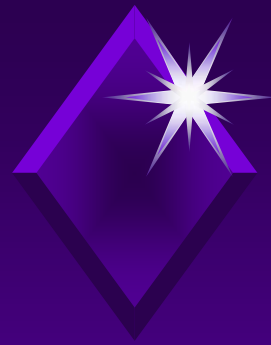
- grade 3 US evidence of ascites

Severe OHSS

- grade 4 clinical ascites
- grade 5 Hct >45%
WBC > 15000
oliguria
creat clearance > 50 ml/min

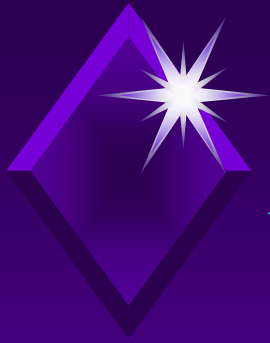
Critical OHSS

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



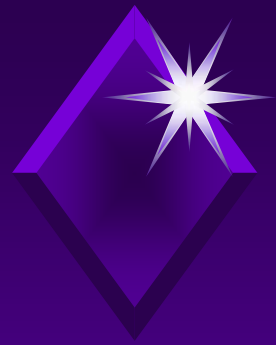
Thromboembolic disease in OHSS

- ◆ Haemoconcentration
- ◆ High E₂ levels



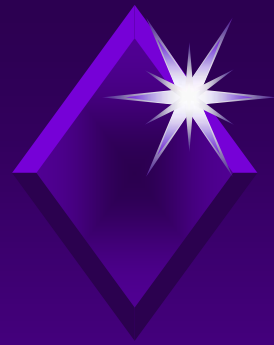
Mild to moderate OHSS treatment

- ◆ Clinical assessment
 - ◆ daily abdominal diameter and weight
- ◆ Off work
 - ◆ home rest

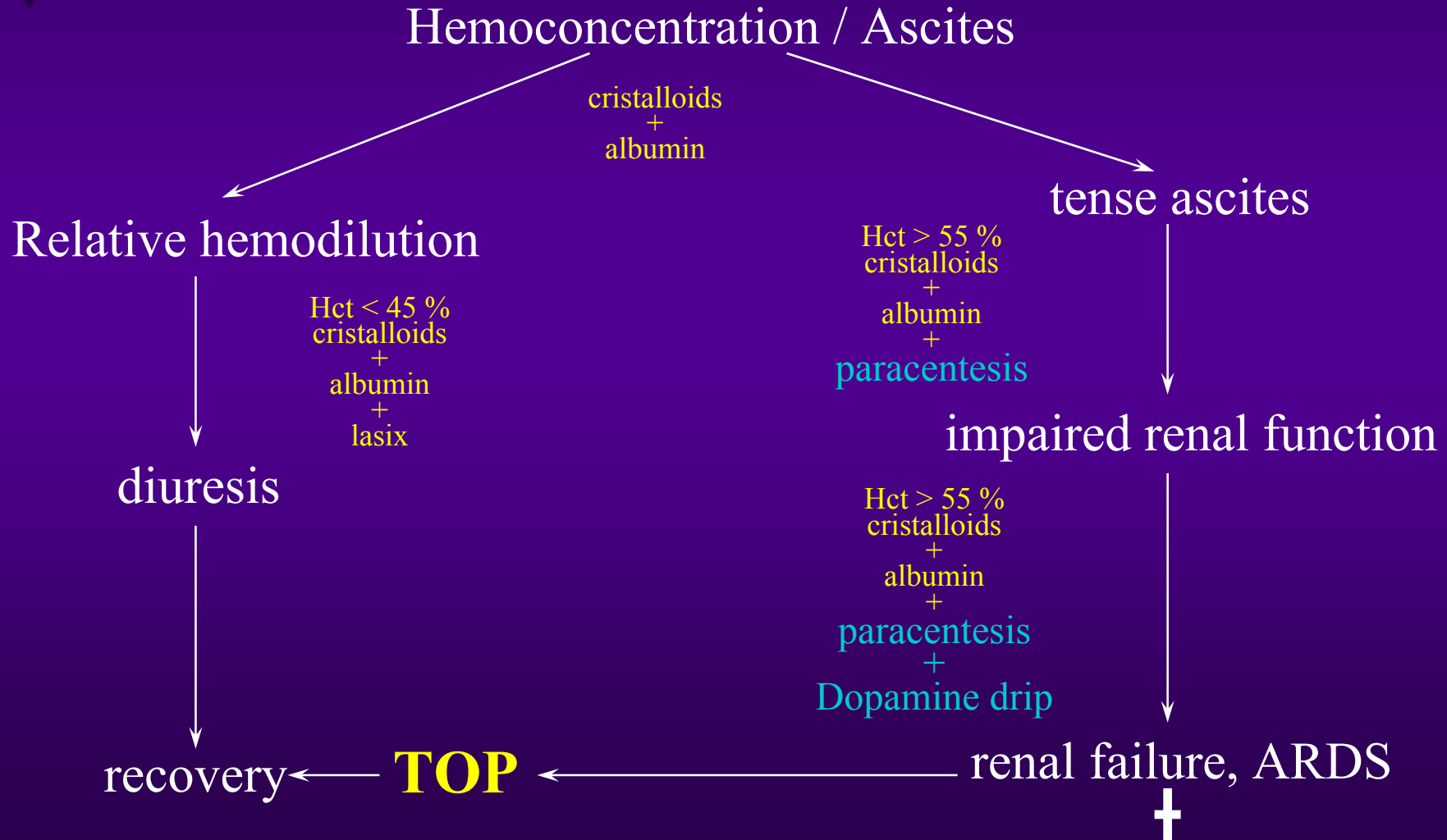


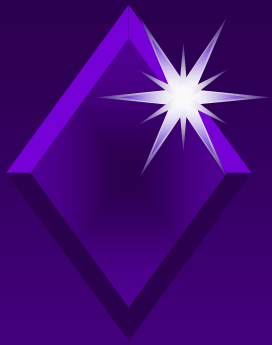
Severe OHSS treatment

- ◆ Hospital admission
 - ◆ monitor input output
 - ◆ daily FBC, urea, creatinine, ultrasound
 - ◆ prophylactic anticoagulation
 - ◆ bed rest



Critical OHSS treatment





Treatment choices for ovulatory dysfunction

	CC	HMG/FSH	Pulsatile GnRH	Dopaminergic
Oligoanovulation	++	+	+	-
Hypothalamic amenorrhea	-	++	++	-
Hyperprolactinemia	-	-	-	++
Pituitary insufficiency	-	++	-	-