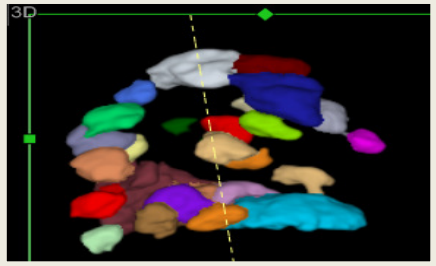
PCOS: Laparoscopic ovarian drilling or gonodotrophin treatment?

AP. Ferraretti, C. Magli, C. Arrivi, L. Gianaroli,

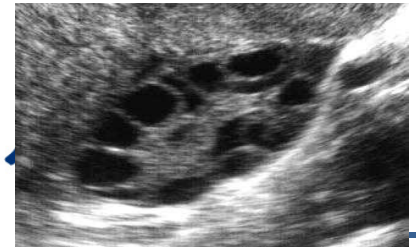
iiarg www.iiarg.com www.sismer.it SISMER

PCOS

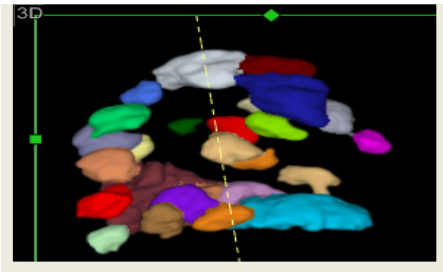


- PCOS is the **most common endocrine** disorder in women (6- > 10%).
- The **prevalence** is similar in various **populations worldwide** (***ancient disorder*** that arose before the migration of humans from Africa)
- Despite its negative effect on reproduction , **PCOS was able to persist** because many women with PCOS are ***able to conceive spontaneously*** and because of its " ***survival advandages effects***" during evolution.
- The **etiology** is still unclear (complex ***genetic*** condition influenced by ***environmental factors*** **)**

- **Different phenotypes** : considerable individual variation and ethnic differences (clinical hyperandrogenism is not expressed in Asian PCOS patients)
- Frequently **associated** with insulin resistance , obesity, infertility obstetrical complication and long-term effects (type 2 diabetes and cardiovascular disease)



PCOS



- **Diagnostic criteria** :
  - ***National Institute of Health*** (1990) : both hyperandrogenism and chronic anovulation.
  - ***Rotterdam criteria*** (ESHRE/ASRM 2003) - Two of the following condition : hyperandrogenism, chronic anovulation , polycysctic ovary
  - ***Androgen Excess Society*** (2006) : hyperandrogenism as a necessary factor (± ovarian dysfunction and /or polycystic ovary)

- **Treatment of** :
  - ***clinical symptoms***
  - ***infertility***

SPECIAL CONTRIBUTIONS

FERTILITY AND STERILITY
AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE 1944

Consensus on infertility treatment related to polycystic ovary syndrome

The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group March 2–3, 2007, Thessaloniki, Greece*

Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome (Review)

Farquhar C, Lilford R, Marjoribanks J, Vanderkerchove P

2010

THE COCHRANE COLLABORATION®

iiarg

SISMER

Consensus on Infertility treatment of PCOS Recommendations

- **First-line treatment : CC (max 6 cycles) ± metformin**
- **Second-line intervention : laparoscopic ovarian surgery (LOS) or Gn stimulation**
- **Third-line treatment : IVF**

RESEARCH www.AJOG.org

REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

Laparoscopic ovarian diathermy vs clomiphene citrate plus metformin as second-line strategy for infertile anovulatory patients with polycystic ovary syndrome: a randomized controlled trial

Stefano Palomba, MD; Angela Falbo, MD, PhD; Lucia Battista, MD; Tiziana Russo, MD, PhD; Roberta Venturella, MD; Achille Tolino, MD; Francesco Orio, MD, PhD; Fulvio Zullo, MD, PhD

2010

OBJECTIVE

Compare the effectiveness of laparoscopic ovarian diathermy (LOD) vs clomiphene citrate plus metformin in infertile patients with CC-resistant polycystic ovary syndrome

RESULTS:

No significant difference per cycle was observed

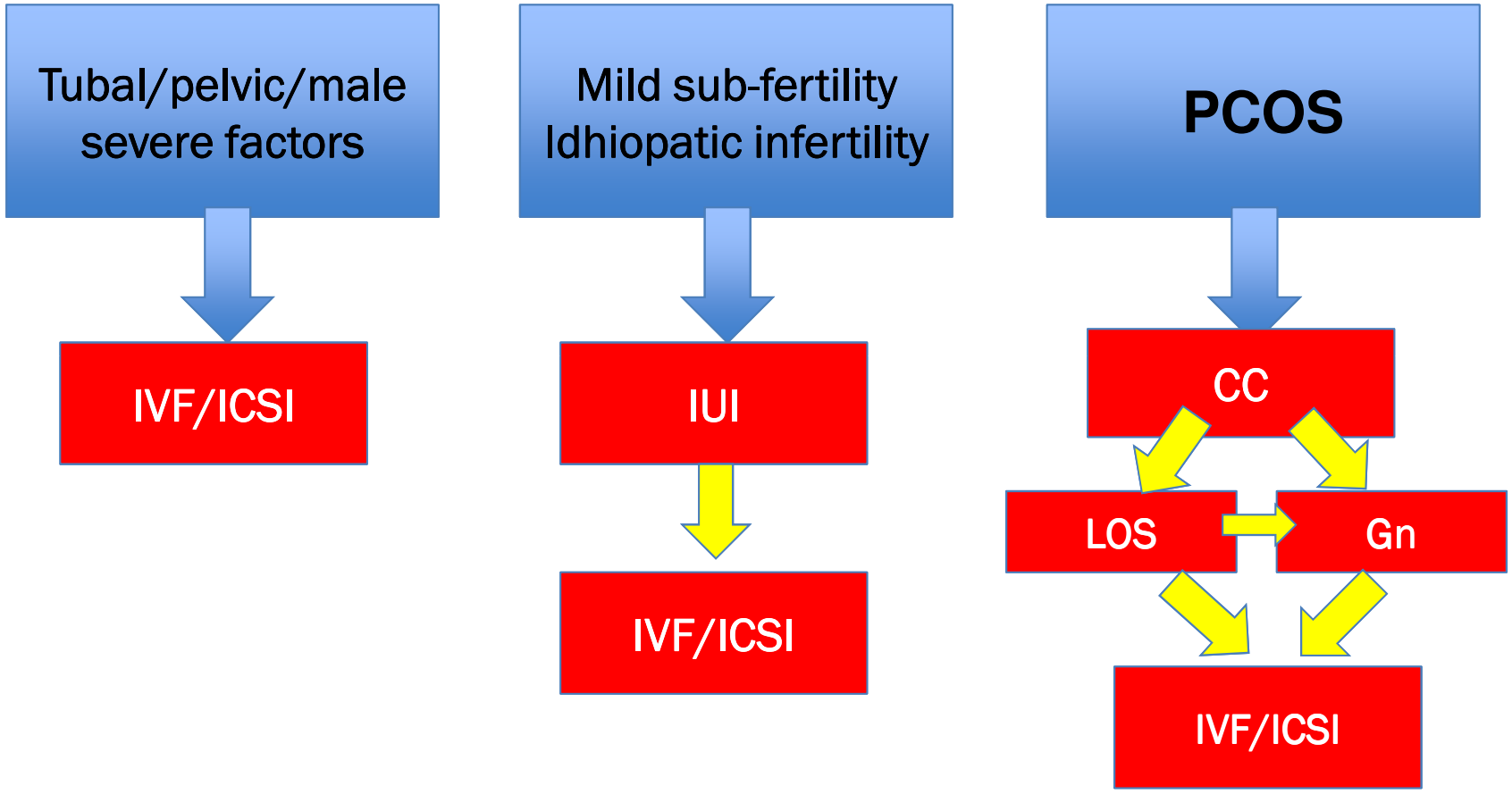
Pregnancy: (15/92 pts [16.3%] vs 14/107 pts [13.1%]; P = .521)
Live-birth (13/92 pts [14.1%] vs 12/107 pts [11.2%]; P = .536)

Cox regression analysis: patients under medical treatment, compared with who received surgical treatment, had
a relative risk of pregnancy of 1.2 (95% confidence interval, 0.61-2.44; P = .582)
a relative risk of live-birth of 1.4 (95% confidence interval, 0.63-2.96; P = .425).

Infertility treatment of PCOS Recommendations

- **Counselling and Lifestyle modifications (**Obesity negatively affects the efficacy of any infertility treatment)
- **First-line treatment : CC (max 6 cycles) ± metformin**
- **Second-line intervention : laparoscopic ovarian surgery (LOS) or Gn stimulation**
- **Third-line treatment : IVF**

Probabily of delivery and Time to delivery



LBR :	60%	70%	85%

Factors to guide for patient-tailored approach (deviation from the 3- lines strategy)

Other (minimal?) factors releated to infertility → IVF/ICSI

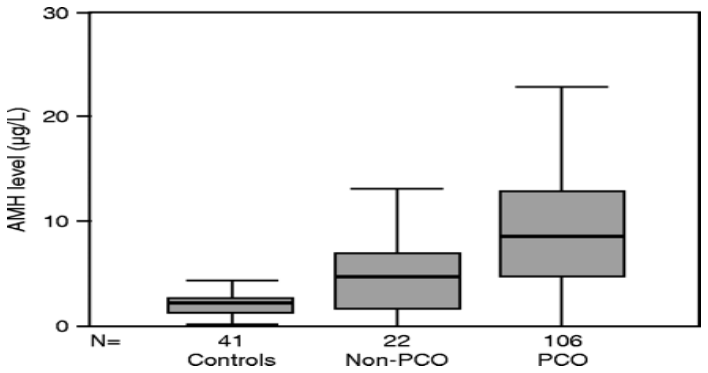
Age

PCOS and Age

Aging

PCOS patients gain regular menstrual cycles when aging

Reduction of the ovarian reserve is less affected by age (?)



Visser et al, Reproduction 2006

Factors to guide for patient-tailored approach (deviation from the 3- lines strategy)

Other (minimal?) factors releated to infertility → IVF/ICSI

Age ?

Duration of infertility (and age) ?

Time to pregnancy can be very long following the 3-lines recommended scheme

BMI ?

Obesity negatively affects the efficacy of any infertility treatment (which more ?)

Initial screening characteristics of women ?

Infertility treatment of PCOS
Recommendations

- **Counselling and Lifestyle modifications**
- **First-line treatment : CC (max 6 cycles) ± metformin**

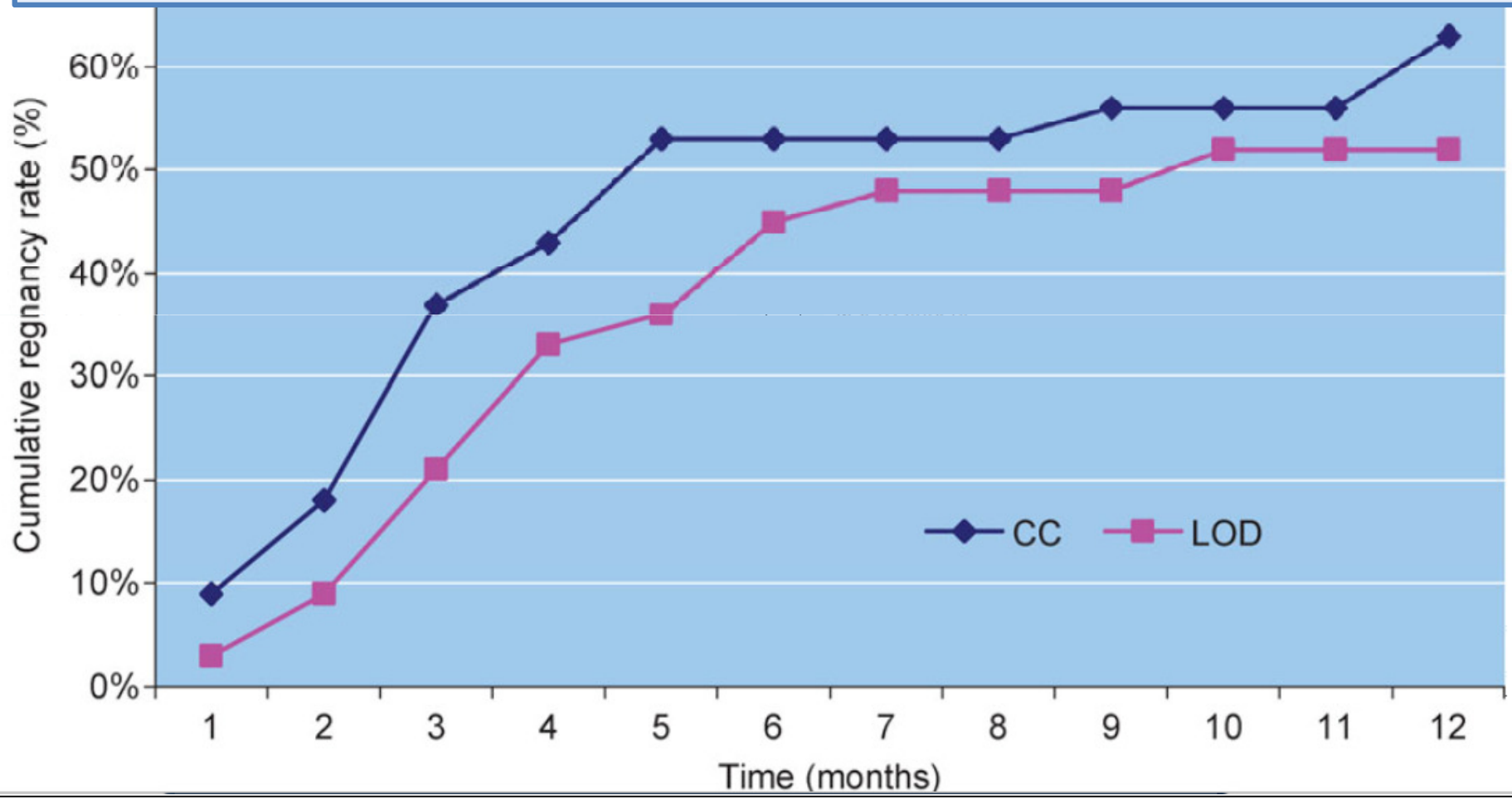
Randomized controlled trial comparing laparoscopic ovarian diathermy with clomiphene citrate as a first-line method of ovulation induction in women with polycystic ovary syndrome

S.A. Amer[1,3], T.C. Li[2], M. Metwally[2], M. Emarh[2], and W.L. Ledger[2]

2009

The aim of this study was to test the hypothesis that LOD may be superior to CC as a first-line treatment.

RESULTS: After randomization, six women conceived before starting treatment and another patient postponed treatment. The remaining 65 women received the treatment (33 underwent LOD and 32 received CC). After the primary treatment, more pregnancies (44%) occurred in women receiving CC than in those undergoing LOD (27%), although the difference did not reach statistical significance [$P = 0.13$, OR 2.1 (0.7 – 5.8)]. After adding the second treatment, the pregnancy rate was still higher, but to a less extent, in the CC group [63% versus 52%, $P = 0.2$, OR 1.6 (0.6 – 4.2)].



Clomiphene Citrate

Starting dose **50** mg/day for 5 days; maximum **150** mg/day.

Should be limited to **six** (ovulatory) **cycles**

• Produces ***ovulation*** **in 75%–80%** and a

• ***Conception*** rate of up **to 22%** per cycle
•Cumulative ***live-birth rates*** vary between **50% to 60%** for up to six cycles

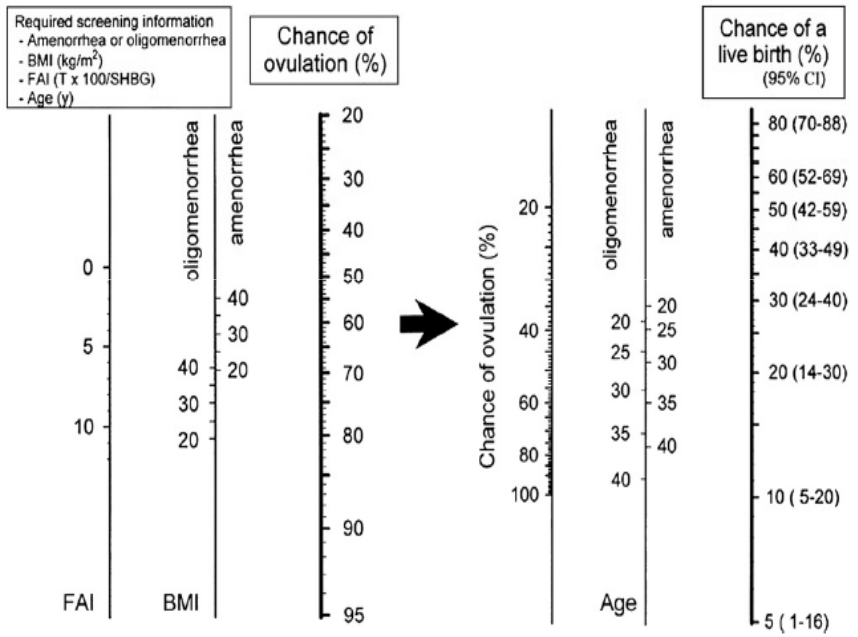
• **US** monitoring is not mandatory (usefull in the fist cycle to allow adjustment in subsequent cycles)
• No evidence that ***HCG*** improves conception

•**Adverse effects :**
OHSS is rare
Multiple pregnancy rates are under 10%, (9% twins. < 1% triplets)

Clomiphene Citrate

FIGURE 2

Nomogram designed to predict chances for live birth in clomiphene citrate induction of ovulation. Note the two different steps. (Imani et al., Fertil Steril 2002;77:91–7. Used with permission.)

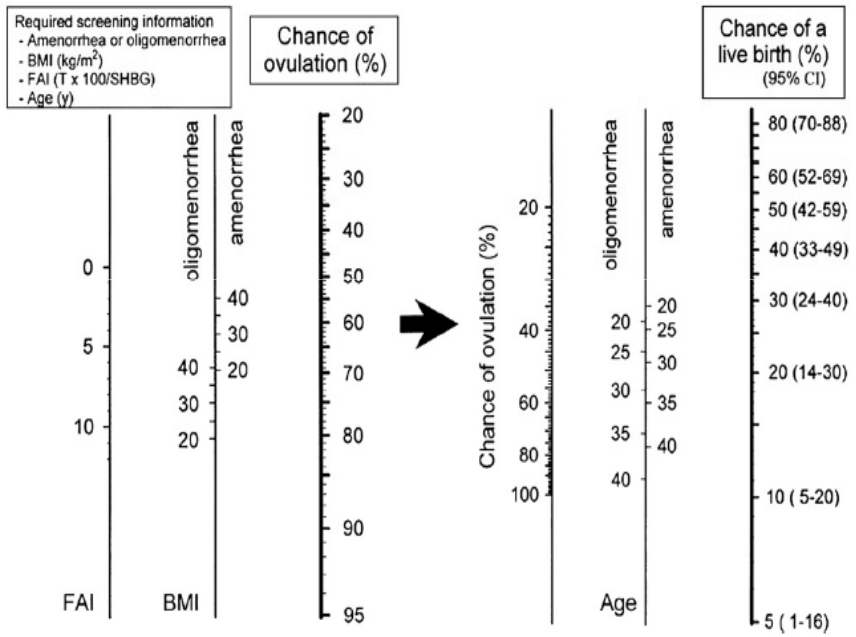


Tarlatzis. Consensus on infertility treatment related to PCOS. Fertil Steril 2008.

Clomiphene Citrate

FIGURE 2

Nomogram designed to predict chances for live birth in clomiphene citrate induction of ovulation. Note the two different steps. (Imani et al., Fertil Steril 2002;77:91–7. Used with permission.)



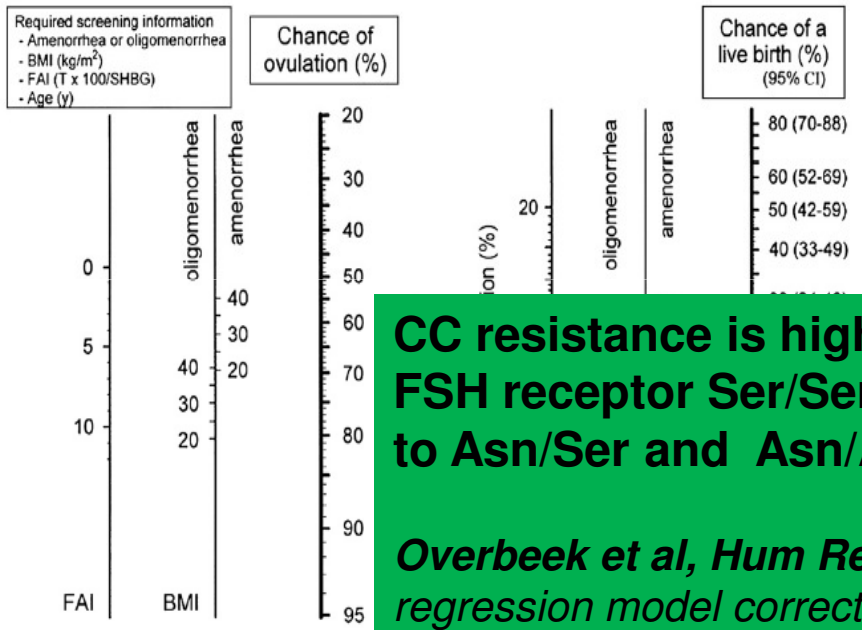
Tarlatzis. Consensus on infertility treatment related to PCOS. Fertil Steril 2008.

Ghobadi et al tested the nomogrram and found it not accurate for use
(Fert Steril , 2007)

Clomiphene Citrate

FIGURE 2

Nomogram designed to predict chances for live birth in clomiphene citrate induction of ovulation. Note the two different steps. (Imani et al., Fertil Steril 2002;77:91–7. Used with permission.)



Tarlatzis. Consensus on infertility treatment related to PCOS. Fertil Steril 200

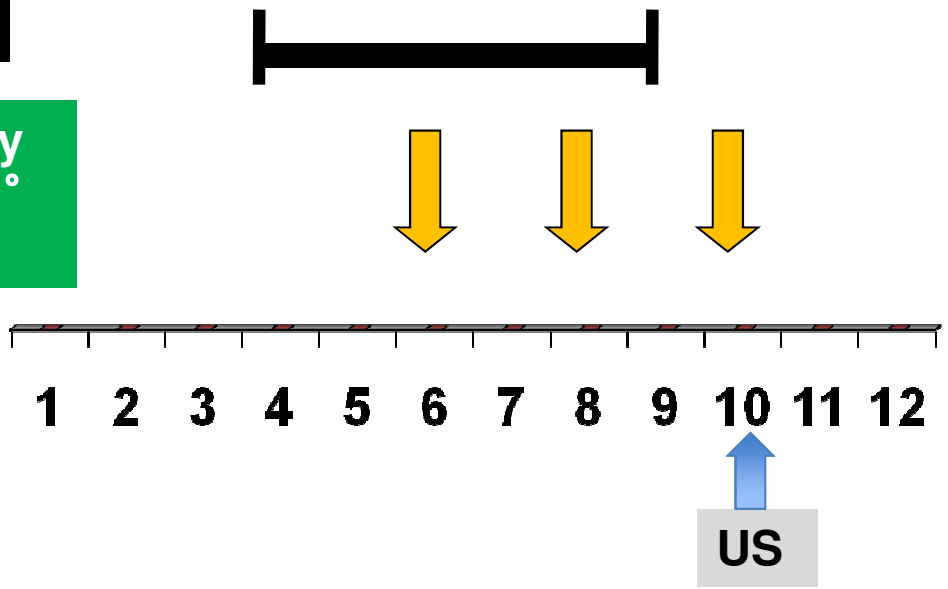
CC resistance is higher in PCOS women with FSH receptor Ser/Ser polymorphism compared to Asn/Ser and Asn/Asn groups (28% vs 14%)

Overbeek et al, Hum Reprod 2009 *(multivariate logistic regression model corrected for age and all other PCOS parameters)*

CC + Iwo FSH doses (± IUI)

Clomiphene citrate (100 mg) for 5 days

FSH (75- 100 IU) every other day from CC 3° day

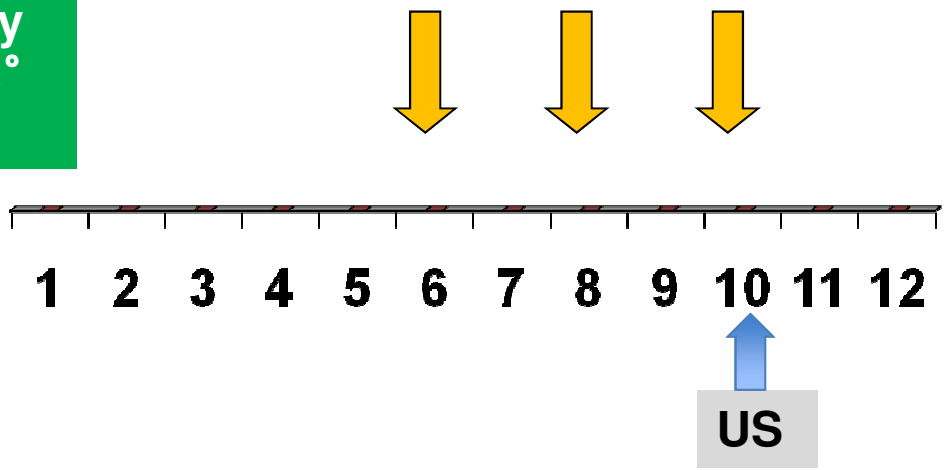


CC + Iwo FSH doses (± IUI)

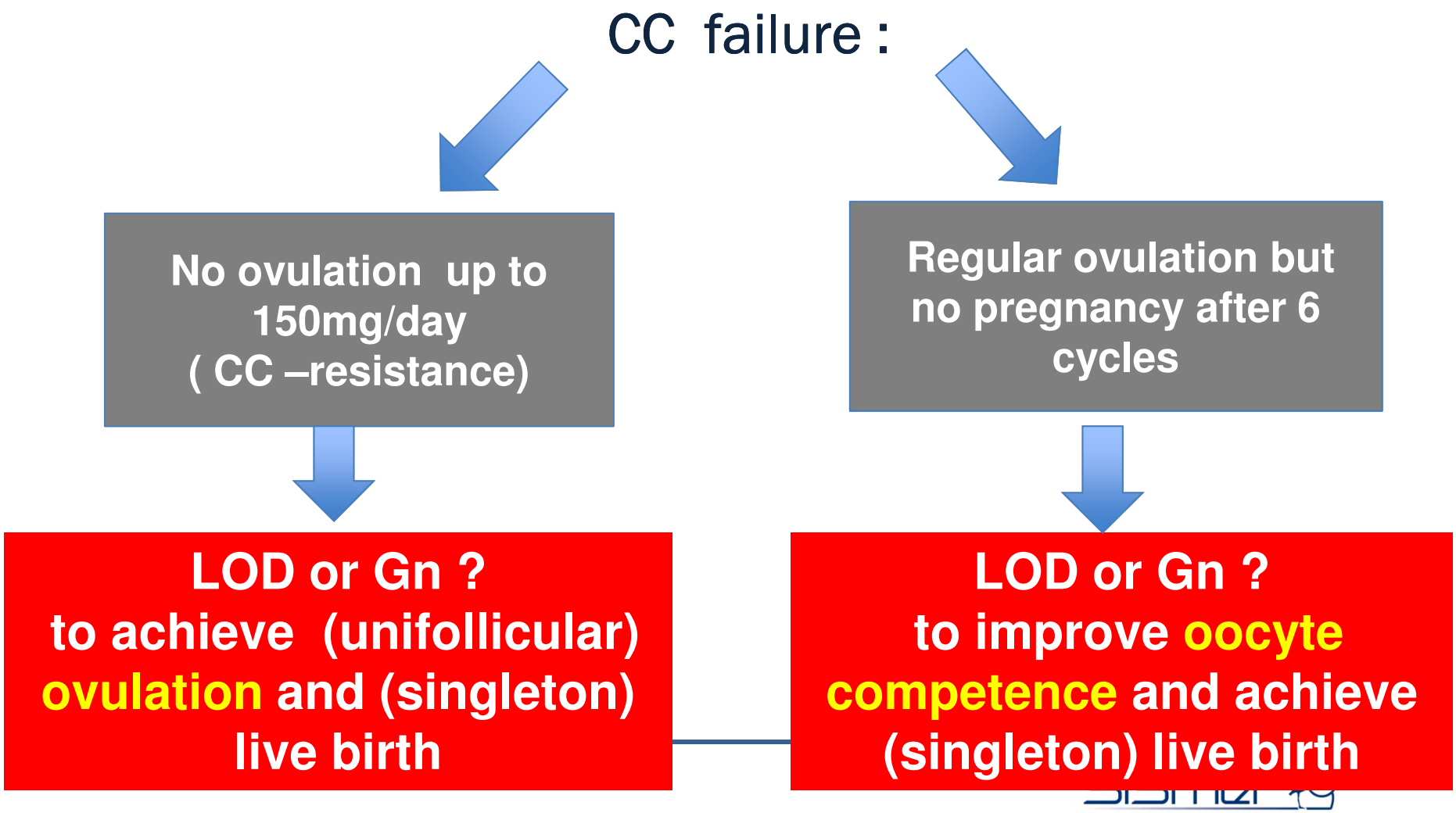
Ovulation in ~50% of CC resistent patients
Mean number of preovulatory follicles : 2.2 ± 1.4
Very few small (> 10 mm) follicles
PR/cyle : 16%

Clom
(100 r

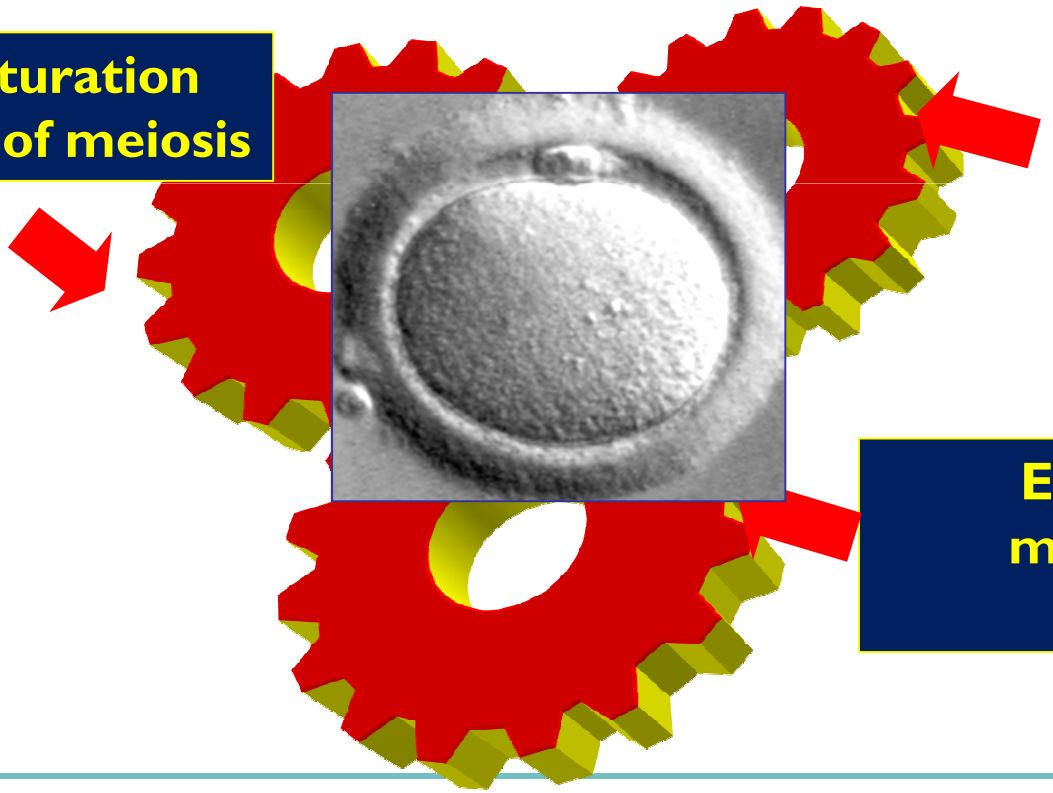
FSH (75- 100 IU) every other day from CC 3° day



LOD or Gn stimulation ?
Second - line intervention after CC failure



Oocyte competence



Meiotic maturation
(resumption of meiosis

Cytoplasmatic
maturation

Epigenetic
maturation

Oocyte competence in PCOS

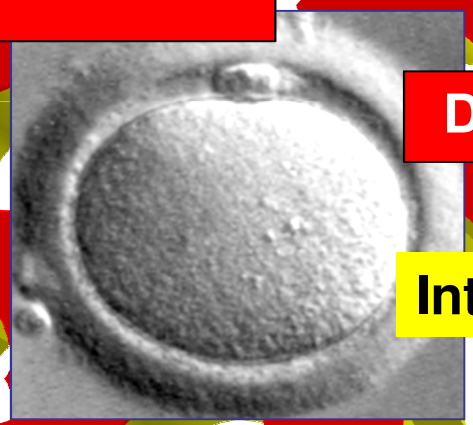
LH persistant hypersecretion

Altered activation of the meiotic process

Meiotic maturation (resumption of meiosis)

Hyperinsulinemia

Stimulate follicle recruitment *(Dumesic et al, 2007)*



Cytoplasmatic maturation

Decreased calcium oscillation

Intraovarian hyperandrogenism

Epigenetic maturation

High level of Leptin

Leptin is a Protein of the ob gene (chromosom 7)
secreted from adipocytes that regulates at the central level the food intake
Discrepancy between elevated leptin and its central action support the concept that obesity is a Leptin resistance condition

Redroductive Target organs are hypothalamus, ovary and endometrium
It regulates the gonadotropins surge that starts pubertal development
Seems to affect steroidogenesis on follicular cells

Insulin resistance and Hyperinsulinemia

Frequent in abdominal obesity with hyperandrogenemia:
Insuline stimulates Androgen production ?
Androgens promotes IR?

Contrary to what occur in other tissues, the ovary remains responsive to insulin and hyperinsulinemia is a key factor for excess androgen production by the theca cells

Infertility treatment of PCOS Recommendations

- Counselling and Lifestyle modifications
- First-line treatment : CC (max 6 cycles) ± metformin
- **Second-line intervention : laparoscopic ovarian surgery (LOS) or Gn stimulation (both efficient)**
- Third-line treatment : IVF

Ovarian surgical treatment for PCOS

- **Surgical ovarian wedge resection :**

  first established treatment for anovulatory PCOS patients (**Stein 1939**). The summated experience in the literature (Donesky, 1995) :**1766** treatments and a PR of **58.8%.** Went out of favour in the 1970s(for the high risk of adhesions with the introduction of medical ovulation

- **Laparoscopic access** :

  1972 (Cohen et al) : **ovarian biopsy** with Palmer forceps

  1984 (Gjonnaess et al) : electrocauterization **(diathermy)** : 5-10 points in each ovary for f 5-6 seconds (300-400 W)

  1988 (Huber et al) : **laser vaporisazion** (3-4 drills 5-10 mm long and 4 mm deep) . All types of laser have been used (CO2, argon,YAG).

  1993 (Armar et al) : **minimal diathermy** (***four puncture*** for 4 seconds)

Laparoscopic Ovarian Drilling (LOD)

- Review of **17 studies, 1664 cases** (Kovacs,2000) :
  - **homogeneous results** (spontaneous ovulation in > 60% of cases and 50% PR) **whatever the technique** (diathermy or laser)
- **Four to ten punctures** are effective.
- More punctures have been associated with **premature ovarian failure** *(Amer,2203; Malkawi,2003)*
- **Adhesion formation rate: 0-100%***(Gurgan et al review 1994). Higher risk with CO2 laser vs cauterization.*
- LOD of **one vs two** ovaries : 2 RCT , 40 cases : no evidence of difference *(Cochrane review , Farquar et al .2010)*

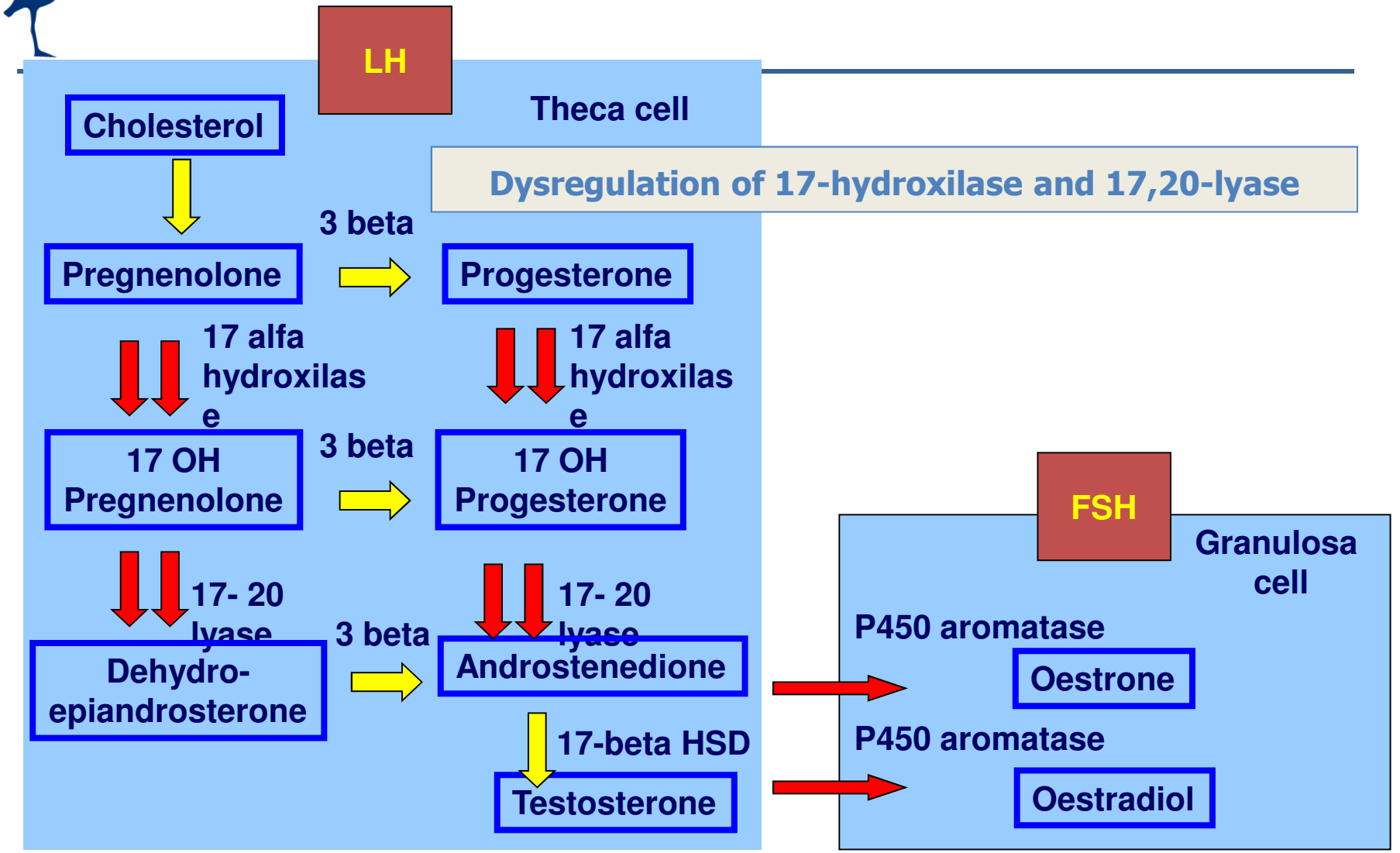
Laparoscopic Ovarian Drilling (LOD)

- Review of 17 studies, 1664 cases (Kovacs,2000) :
  - h… …ases an…
- Fo… as… *Ma…*
- Ad… *Higher ris…*
- LO… …

LOS has been suggested for nonfertlity indications such menagement of irregular cycles or hyperandrogenism. Because of the lack of long-term evidence and the risks of surgery, this approach cannot be recommended

LOS may be useful at any time when infertile PCOS **patients need** to be evaluated by laparoscopy to asess their pelvis
????

Ovarian Steroidogenesis in PCOS



Low aromatase activity (multiple small follicles)

Mechanism of action of LOD : unclear

LOD destroy ovarian androgen-producing tissue (effect on the ovarian steroidogenesis ⟹ reductions in intraovarian androgens production)

The local effect is followed by a fall in the serum levels of androgens and luteinsing hormone (LH) and an increase in follicle-stimulating hormone (FSH) levels *(Armar 1990; Greenblatt 1987)*

Thus both local and systemic effects are thought to promote follicular recruitment, maturation and subsequent ovulation

LOD is able to restore CC sensitivity (and to preventi OHSS in IVF ??)

Changes in blood flow?

Stimulation of ovarian nerves?

The beneficial effect may continue for years (few data)

Gn stimulation

(PCOS women are specifically prone to execessive follicle development)

- **Conventional protocol** (starting dose of 150 IU) : high rate of ovulation but unacceptable rate of multiple follicular development (23%) and high risk of severe OHSS (> 4%) . **No longer recommended**.

- Since early 90', **low-dose protocols** have been used for PCOS patients .

- **Currently** , two low dose regimens are used:
  - **Step-up regimen** : FSH starting dose of 37.5 – 50 IU/day for 14 days and small weekly dose increment (50%) .
  - **Step-down regimen** : FSH starting dose of 75-100 IU and stepwise reduction as soon as follicular development is observed Intense ovarian response

Low –dose Gn protocols

	Step – up (3 trials ,1991-1994)	Step-down (1 trial , 1995)
Ovulation rate	68- 74%	91%
Monofollicular cycles	73%	62%
Pregnancy rate/ cycle	16-20%%	17%
Cumulative PR in 3- 6 cycles	55- 73%	47%
Multiple PR	4-18%	8%
OHSS	1%	2%

Preventing all multiple gestation and OHSS is not possible at this time

Consensus on infertility treatment related to PCOS,2008

Gn stimulation in PCOS

Intense **monitoring** (US and E2) is required to reduce complications and cycle has to be cancelled when ***more two follicles > 14 mm***

The duration of gonadotropin therapy generally should not exceed **six ovulatory cycles. No pregnancy with 6 cycles signifies resistance**

Different Gn preparation

uFSH vs rFSH **:** no differences

FHS vs HMG *: similar results (LH exogenous administration in PCOS has not detrimental effects,)*

FSH different isoforms *(to reproduce normovulatory cycles) : no tested in PCOS*

Sequential protocols *(FSH ⇨ LH/HCG) to drive selective maturation of one single follicle and atresia of small follicles (tested by Hugues et al 2005 in normogonadotropic oligo- anovulation)*

GnRH analogues to normalize LH secretion :

The addition of ***Gn RH agonist*** increases the OHSS risk and does not increases the PR. Its use is not justify in PCOS

GnRH antagonist : no data in ovulation induction for PCOS

PCOS in ART

GnRH antagonist

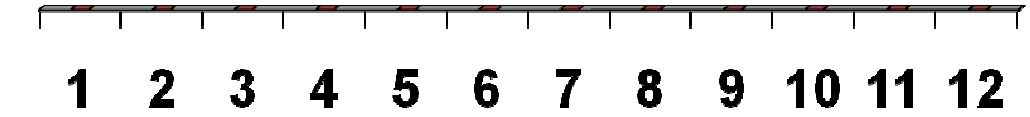
Single dose (3mg)

HCG

Multiple dose (0.25

from day I

FSH



Day of FSH

Benefit in PCOS
(Laines et al Hum Reprod 2007)

Laparoscopic ovarian drilling or gonodotrophin treatment?

- Efficacy
- Safety
- Costs

Cochrane review (2010)
5 RCT trials (1998-2005)
174 vs 165 patients

LOD vs Gn?
Efficacy

	LOD	Gn
Ovulatory cycles	78%	90%
PR/cycle	9%	15%
Miscarriage rate	14%	16%
LBR 6 months follow –up vs 3 FSH cycles	15%	20%
LBR 12 months ± medical ovulation vs 6 FSH cycles	67% Only LOD 34% Plus CC 49% Plus Gn 67%	60%
LBR after 24 months ±medical ovulation	82%	

LOD vs Gn?
Safety and costs

	LOD	Gn (step-up low dose)
Monofollicular ovulation	100%	73%
Multiple PR	1%	17%
OHSS	0%	3%
Risks related to surgery	Present	Absent
Ahesions formation	Low risk (< 10 holes)	Absent
Premature ovarian failure	Rare (< 10 holes)	Absent
Quality of life	No differences	
Costs / term pregnancy	11.301 €	14.489 €
Duration of the beneficial effect	Years (few data)	Stimulated cycles

LOD vs Gn?

Specific indications	LOD	Gn
Amer et al ,2004 *Retrospective study (200 PCOS women)*	**Persistent high LH levels (> 10 IU/ML)**	**Advanced age (> 35 ? > 38?)**
	Need of laparoscopic evaluation of the pelvis	**Long duration of infertility**
		Obesity
		Marked hyperandrogenism
Saleh et al ,2001	**Hyperinsulinemia**	
Logistic factors	**Patient living too far from the hospital for intensive monitoring**	**No doctor skill for LOD ?**

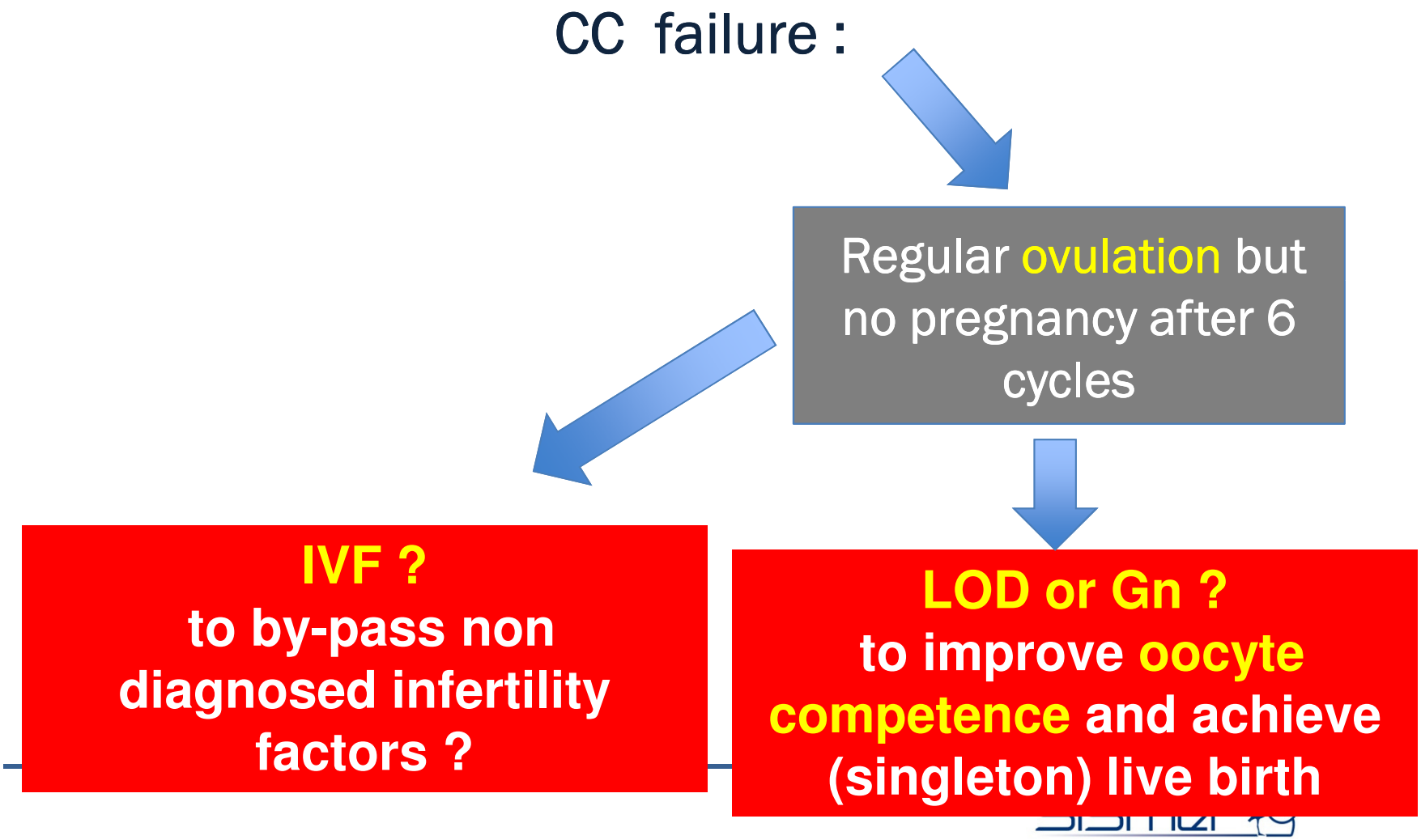
LOD or Gn stimulation ?
Second - line intervention after CC failure

CC failure :

No ovulation up to 150mg/day
(CC – resistance)

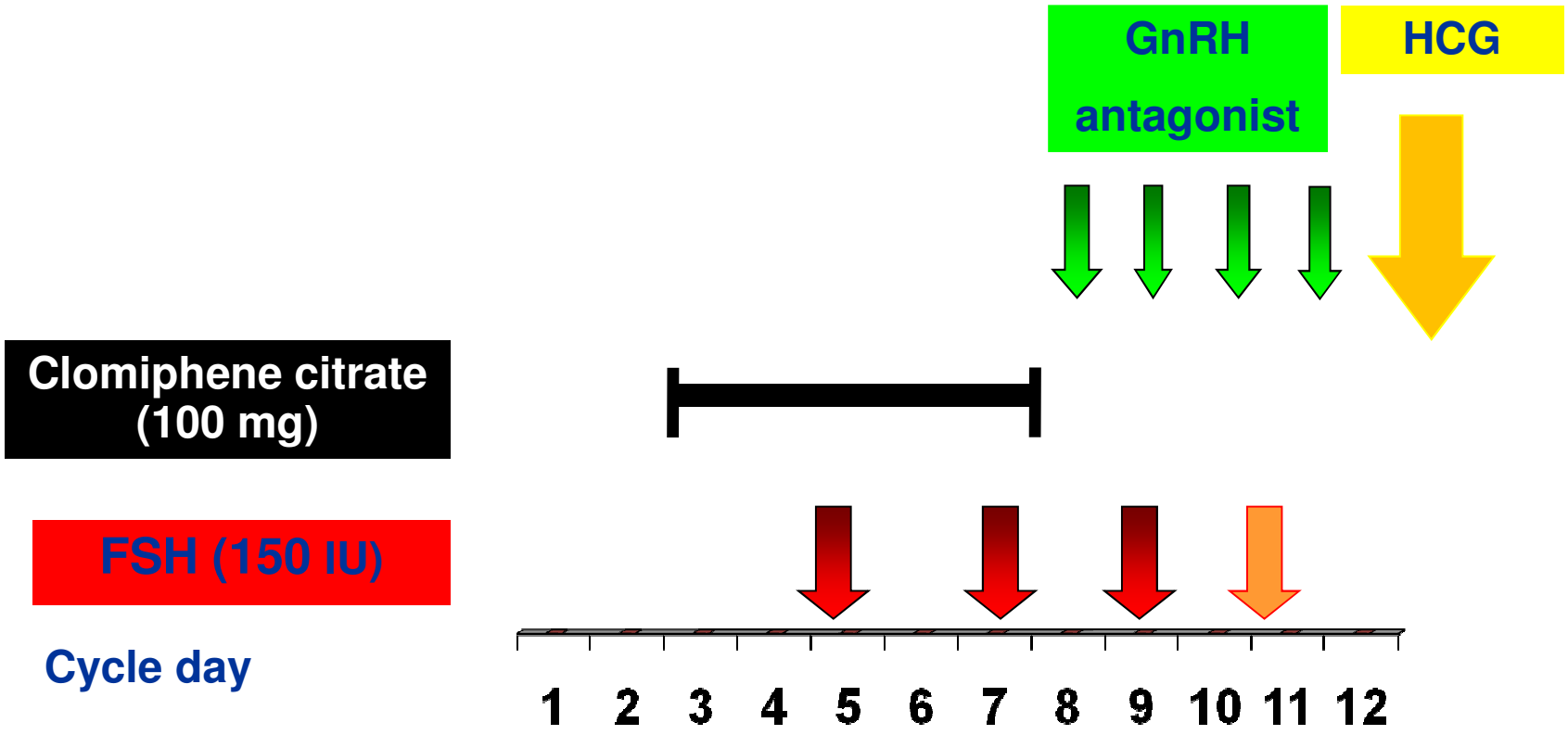
LOD or Gn ?
to achieve (unifollicular) ovulation and (singleton) live birth

LOD or Gn stimulation ?
Second - line intervention after CC failure



IVF Lite

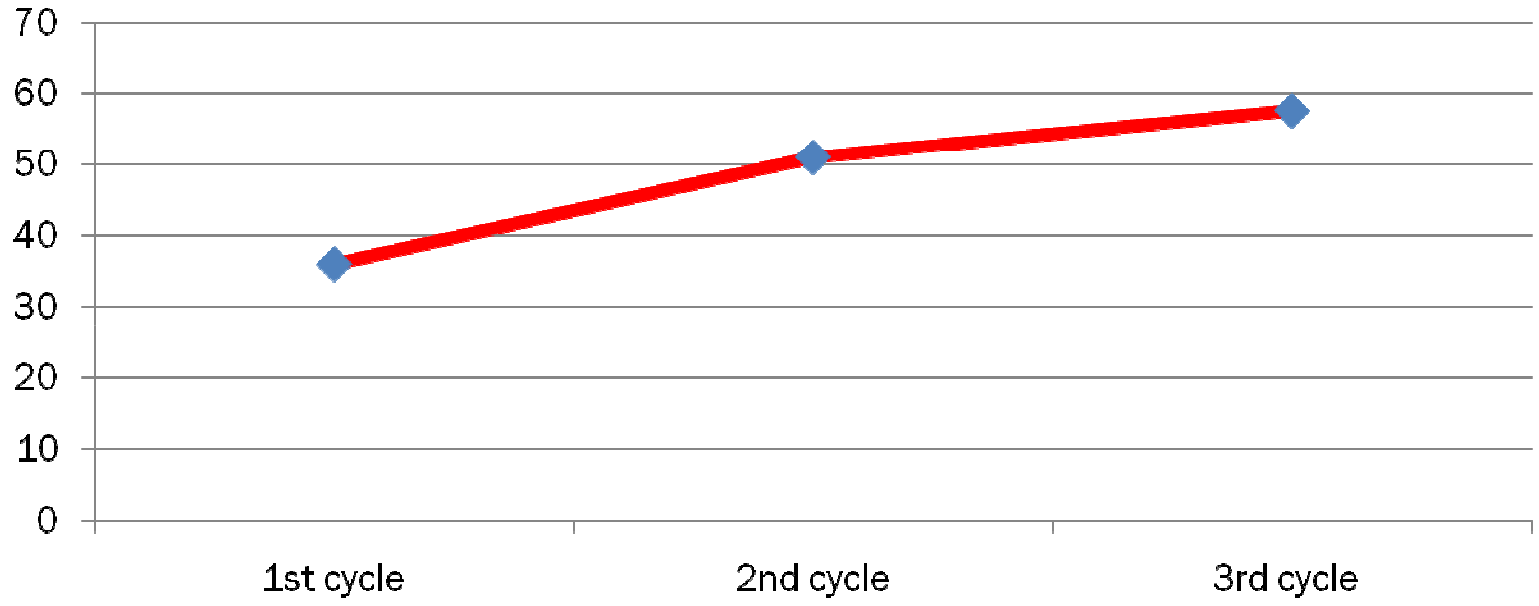
Fixed stimulation protocol



IVF LITE in PCOS

Cycles	42
Patients	23
N° oocytes	185 (5,8 ± 2.4)
M2	114 (3.6 ± 2.5)
Inseminated	91
2 PN (%)	76 (83,5)
Embyos day 2 (%)	76 (100)
Gr.1 (%)	68 (89,5)
Embryos Transferrred	73 (1.8 per cycle)
OHSS	0

Cumulative ongoing pregnancy rate per PCOS patient (23 patients)



	1° cycle	2° cycle	3° cycle
LBR	36%	51%	60%

Ovarian drilling : different approaches

- Laparoscopic diathermy or laser
- Transvaginal Hydrolaparoscopy (next lecture)
- Transvaginal ultrasound-guided ovarian drilling
  - 1991 Yasuyuki, Japan (8 patients)
  - 2001 Ferraretti et al, Italy (11 patients)
  - 2009 Badawy et al, 2009

Ovarian drilling

- Laparoscopic diathermy or laser
- Transvaginal Hydrolaparoscopy (next lecture)
- Transvaginal ultrasound-guided ovarian drilling

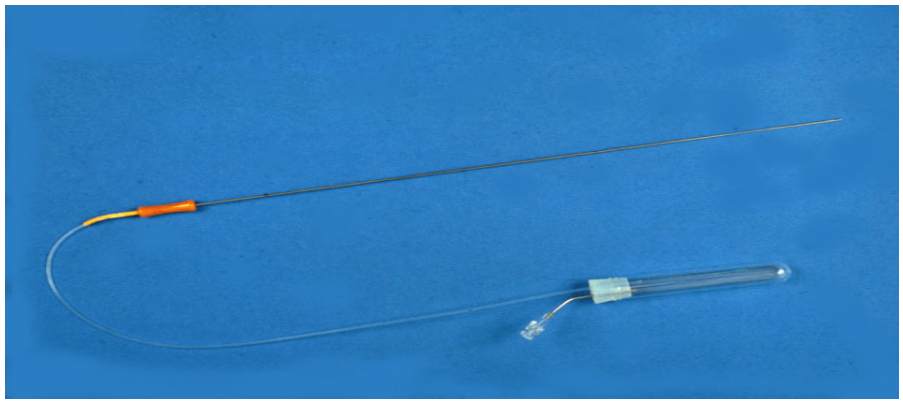
A new surgical treatment for improving ART Outcome in PCOS patients

Ferraretti et al, Fertility and Sterility 2001;76:812

PCOS patients undergoing ART vs Control

	Control (tubal infertility)	PCOS with adequate response	PCOS with poor performance
No. of patients	502	32	24
No. of cycles	873	47	34
No. of cancelled cycles	137(15%)	0	21 (56%)
No of oocytes/retrieval	11.7 ± 7	13.8 ± 5	11.3 ± 4
Fertilization rate	73%	56%	48%
Cleavage rate	78%	83%	52%
No of transferred cycles	537*	44	11
No of pregnancies (%)	226(42)	18 (41)	0
Implantation rate	26%	24%	/
Abortion rate	11%	14%	/

US guided TVOD in ART



Ferraretti et al Fertility and Sterility 2001;76:812

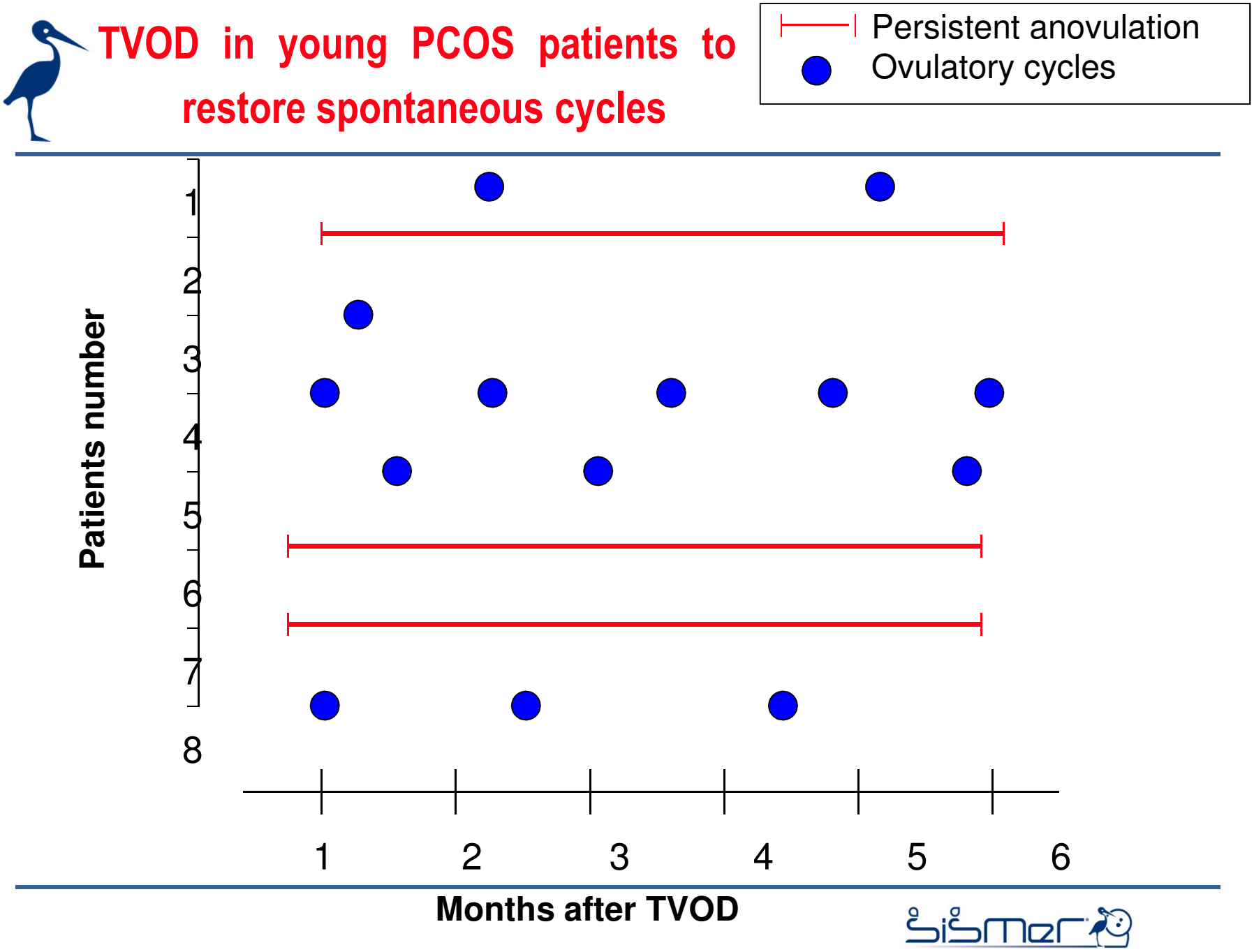
Results (24 PCOS)

	Before TVOD	After TVOD
No of patients	24	23**
No of cycles	34	30
No cancelled	21	5*
No of eggs	11.3± 4	13.2 ± 3
Fertilization rate	48%	70%*
Cleavage rate	52%	73%*
Fresh transfers	8	21
Thawed transfers	3	10
Clin.pregnancies	0	15
Delivery rate/cycle	0	47%*
Delivery rate/patient	0	64%*

* p < 0.05

**One patient had a spontaneous pregnancy after TVOD

TVOD in young PCOS patients to restore spontaneous cycles



US guided transvaginal ovarian drilling for PCOS (Badawy et al , Fertil Steril 2009)

- RCT
- 163 PCOS patients with CC resistance
- LOD (81 pat) vs UDTN (82 patients)
- Main Outcome results : hormonal changes , ovulation and pregnancy
- Results : no differences (PR in six months : 22%vs 25%)
- Conclusions :

  the ease to sheduling, reduced costs , rapid recovery and no risk of adverse effects suggest it as a first-line treatment for PCOS patients resistant to CC

Treatment of PCOS clomiphene-resistant :

Laparoscopic ovarian drilling
or
Gonodotrophin treatment
or
US- guided transvaginal ovarian drilling
???