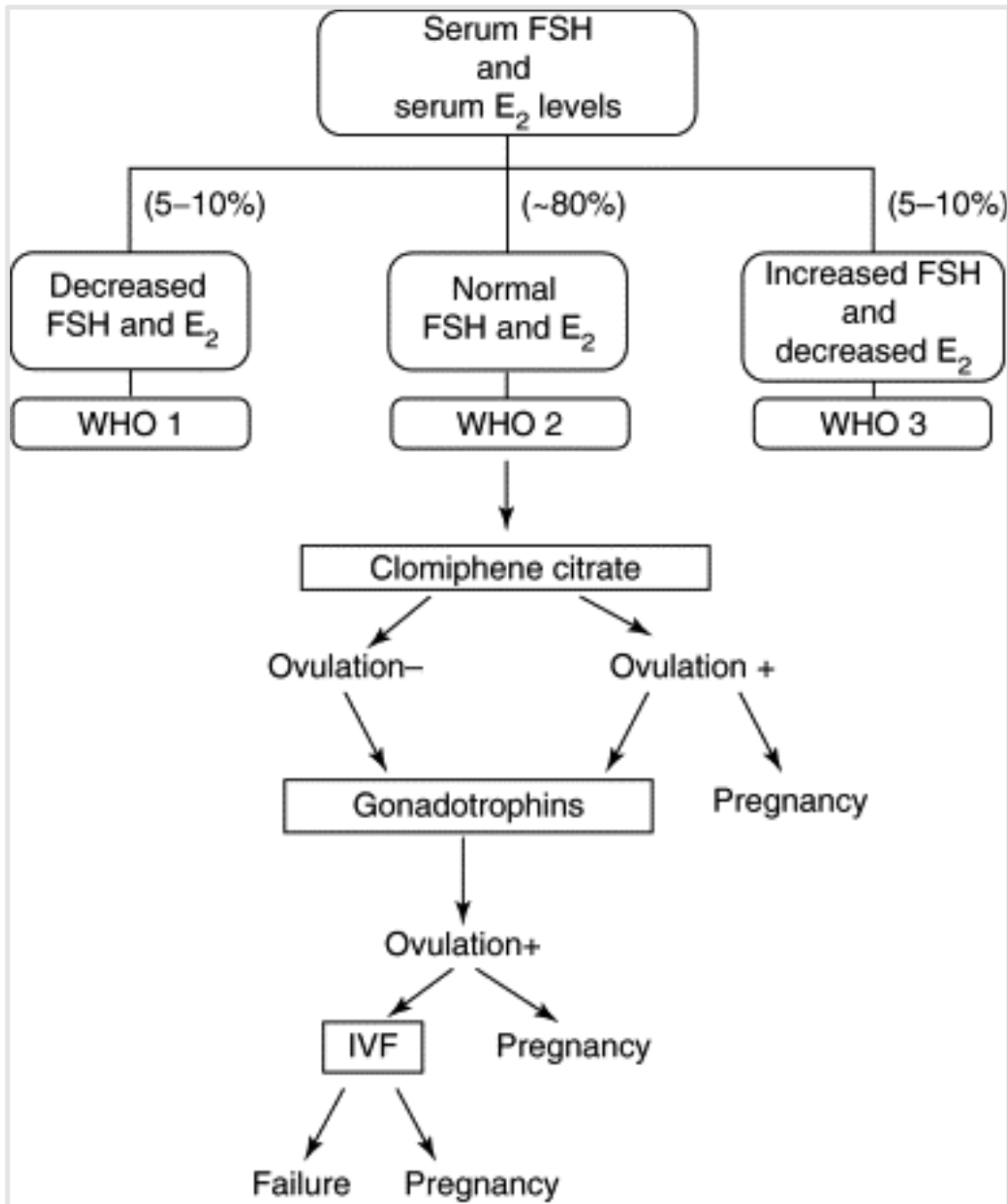


# Blagi vs. standardni protokoli ovarijske stimulacije kod PCOS

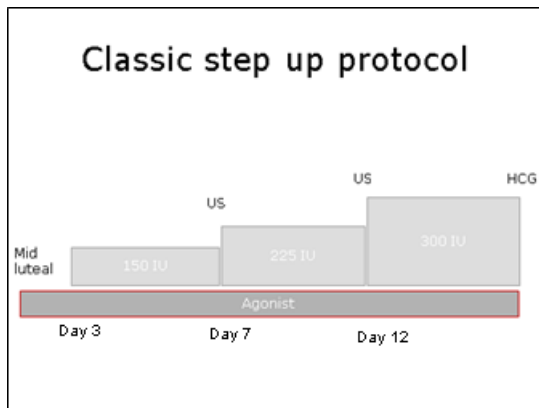
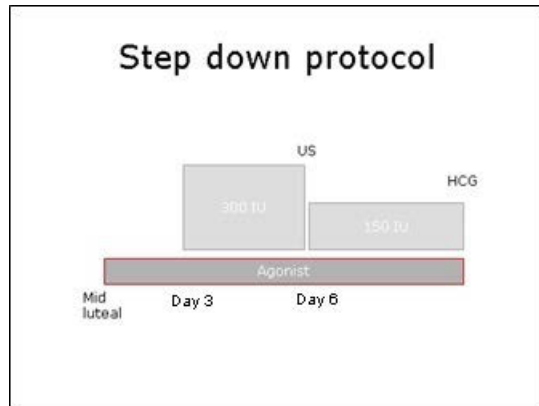
## Mild vs. standard ovarian stimulation protocols in PCOS

Romana Dmitrović



# Ovulation induction algorithm

# PCOS – problems with standard IVF



- High number of antral follicles
- Increased sensitivity to gonadotropins
- Excessive ovarian response/ OHSS
- High number of immature oocytes
- Low fertilization rates
- Reduced cleavage rates
- Low implantation rates
- High miscarriage rates

# Mild ovarian stimulation for IVF - definitions

- **Mild IVF**
  - 2-7 oocytes
  - oral compounds, low dose FSH/HMG, GnRh antagonist
- **Conventional IVF**
  - >8 oocytes, GnRh agonist or antagonist with conventional FSH/HMG dose

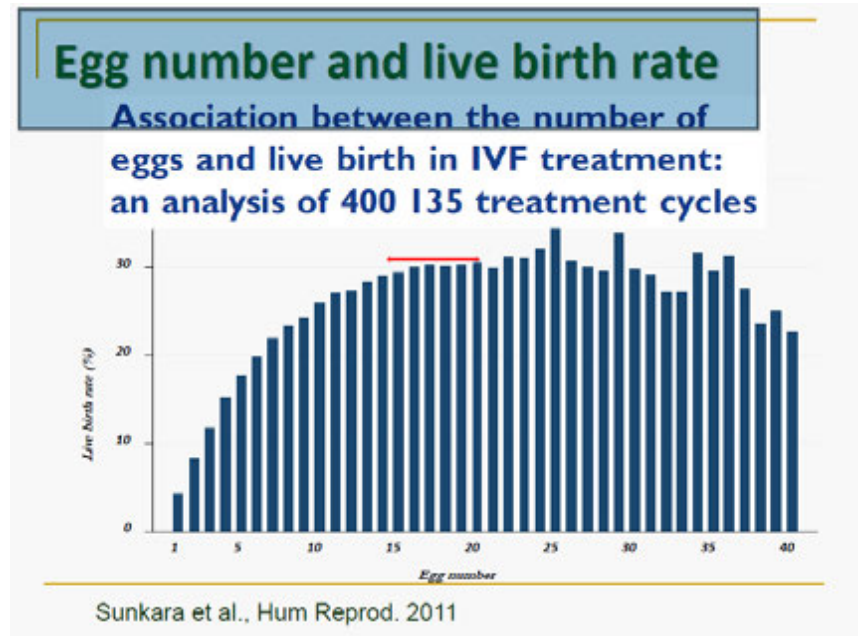
**ISMAAR 2007 (International Society for Mild Approaches in Assisted Reproduction)**

- **Mild IVF** - a procedure in which the ovaries are stimulated with gonadotropins and/or other compounds, with the intent to limit the number of oocytes obtained for IVF to fewer than seven

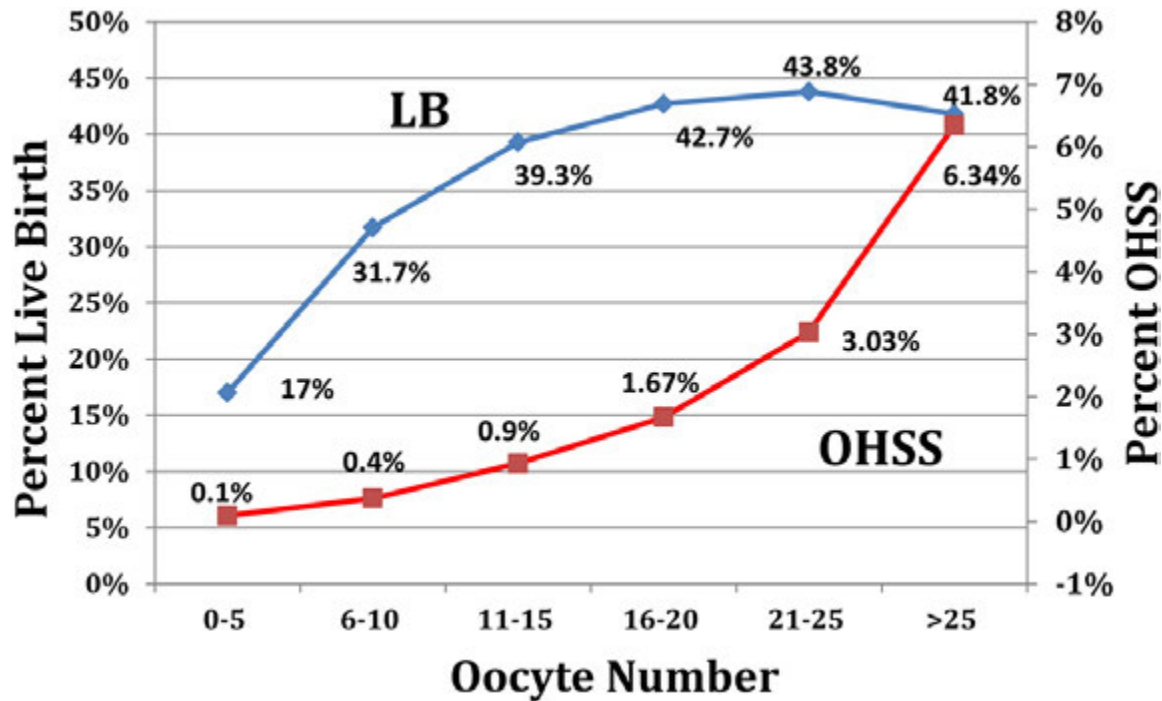
**The ICMART (International Committee Monitoring Assisted Reproduction Technologies) and WHO revised glossary on ART terminology, 2009. Hum Reprod 2009;24:2683–2687.**

# Current ovarian stimulation approaches

- High number of oocytes
- Time consuming, complex, high costs, patient discomfort, high drop-out rates, often OHSS
- Advantage: cryopreserved embryos
- Cycle programming
- Higher cumulative success rates?

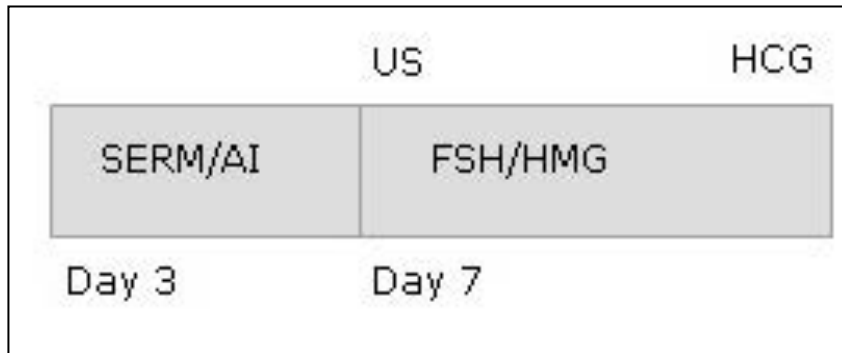


Oocyte number as a predictor for ovarian hyperstimulation syndrome and live birth: an analysis of 256,381 in vitro fertilization cycles



# Mild stimulation

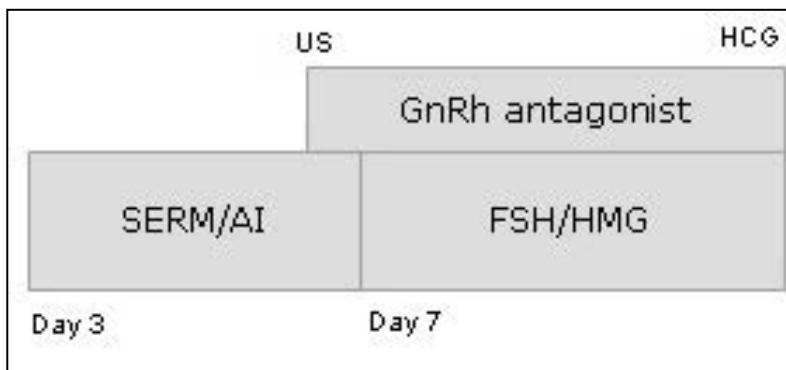
Beta+  
↓



- Short protocols
- Patient friendly
- Reduced risk of OHSS
- Reduced cost
- Chromosomally normal oocytes

But

- Lower cumulative success rate?
- Rarely cryopreservation



# Pregnancy rates with mild stimulation

## CC + hCG

- Trounson 1981, LBR **17%**/ET
- Marrs 1983, PR **11%**/asp
- MacDougall 1994 (RCT), PR **13%**
- Ingerslev 2001 (RCT), PR **18%**

## CC + gonadotropins + hCG

- Dhont 1995, PR **25%**
- Weigert 2002, PR **35%**
- Engel 2003, LBR **40%**
- Lin 2006, PR **41.7%**



# Mild vs. Standard stimulation – (B + 2012-2014)

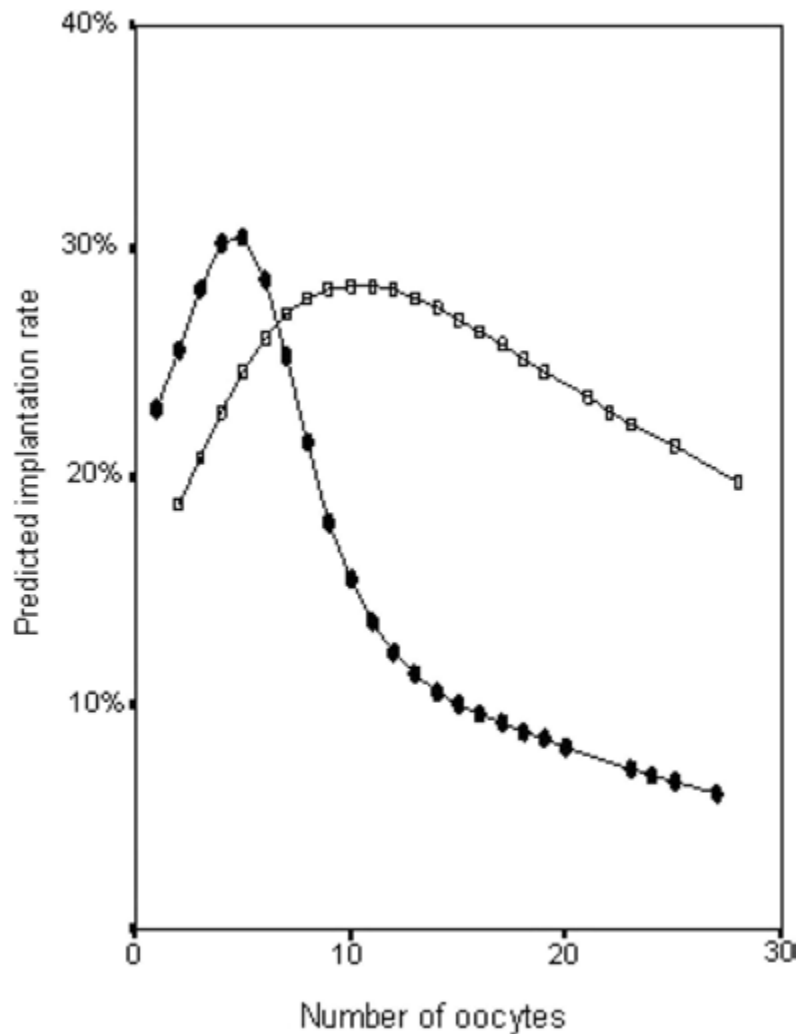
	Mild stimulation	Standard stimulation	p
<b>Pregnancy rate per cycle</b>	21/40 52.2%	29/81 35.8%	0.153
<b>Total number of cryopreserved embryos</b>	27	119	
<b>Pregnancies per cryopreserved embryos used up-to-date</b>	3/8	15/29	
<b>Cummulative pregnancy rate (fresh and cryopreserved cycles)</b>	21+3=24/40 60/ <b>47,5%</b>	29+15=44/81 54,3/ <b>48,1%</b>	

# 2013 SART (Society for Assisted Reproductive Technology; USA) DATA (standard stimulation)

	<b>&lt;35</b>	<b>35-37</b>	<b>38-40</b>	<b>41-42</b>
Number of cycles	36958	18508	16853	9026
Percentage of cycles resulting in pregnancy	46	37,8	28,6	18,8
Percentage of cycles resulting in live birth	40,1	31,4	21,2	11,2

<b>Mild stimulation B +</b>	<b>&lt;35</b>	<b>35-37</b>	<b>38-40</b>	<b>41-42</b>
Number of cycles	66	31	7	21
Percentage of cycles resulting in pregnancy	30	42,1	28,8	4,2

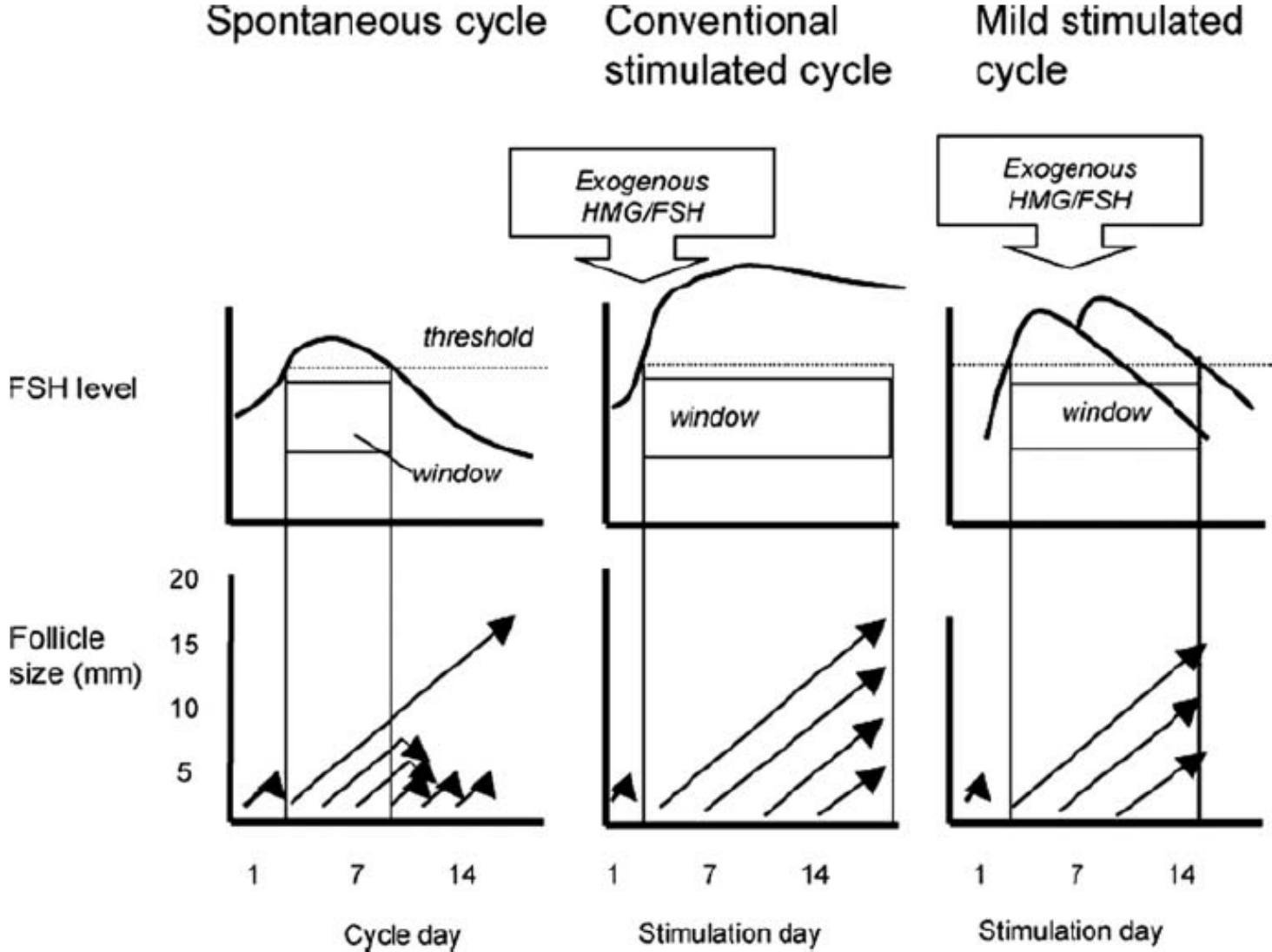
Ongoing pregnancy rate per embryo transferred (implantation rate) according to the number of oocytes retrieved following mild or conventional ovarian stimulation for IVF (P = 0.045).



M.F.G. Verberg et al. Hum. Reprod. Update 2009;15:5-12

Black dots, mild ovarian stimulation; open squares, conventional ovarian stimulation.

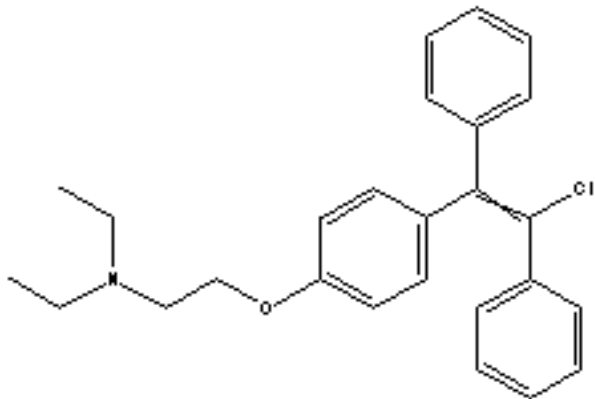
# Mild vs. Standard stimulation



# Mild stimulation

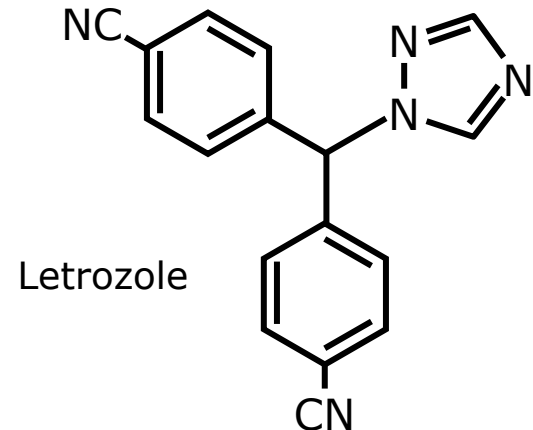
- Clomiphene

- Selective estrogen receptor modulator
- 100 mg (2 tbls) from day 2-5, for 5 days – followed by 150IU FSH/HMG for 3-5 days



- Letrozole

- Aromatase inhibitor
- 5 mg (2 tbls) from day 2-5, for 5 days – followed by 150IU FSH/HMG for 3-5 days

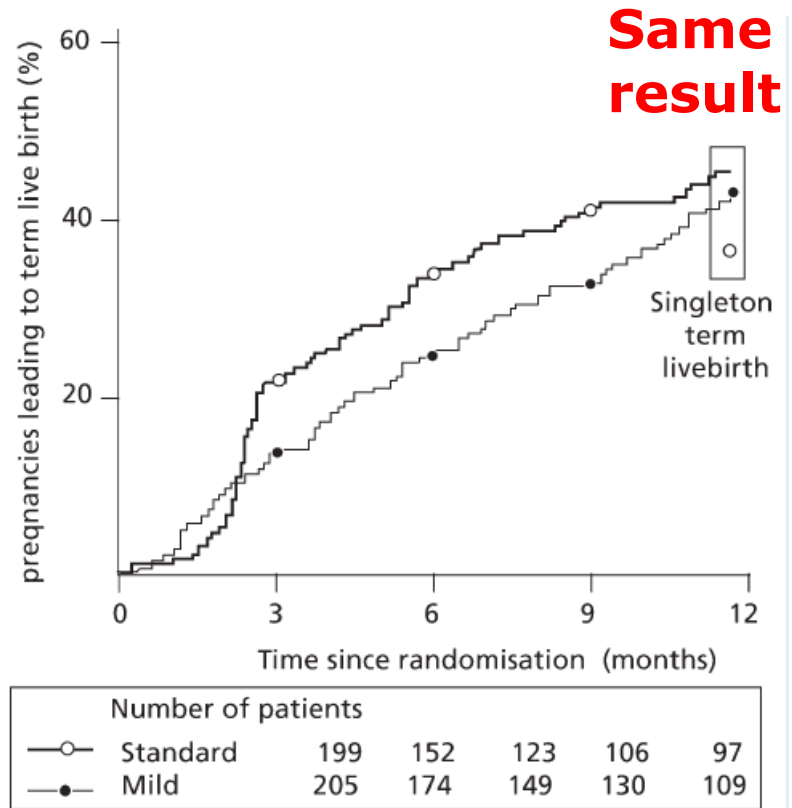


# Letrozole in ovulation induction in PCOS

Outcome	Clomiphene Group (N = 376)	Letrozole Group (N = 374)
<b>Primary outcome</b>		
Live birth — no. (%)	72 (19.1)	103 (27.5)
Singleton live birth — no./total no. (%)	67/72 (93.1)	99/103 (96.1)
<b>Ovulation</b>		
Women who ovulated — no. (%)	288 (76.6)	331 (88.5)
No. of ovulations/total treatment cycles (%)	688/1425 (48.3)	834/1352 (61.7)
<b>Fecundity among women who ovulated — no./total no. (%)</b>		
Conception	103/288 (35.8)	154/331 (46.5)
Singleton pregnancy	75/288 (26.0)	113/331 (34.1)
Singleton live birth	67/288 (23.3)	99/331 (29.9)

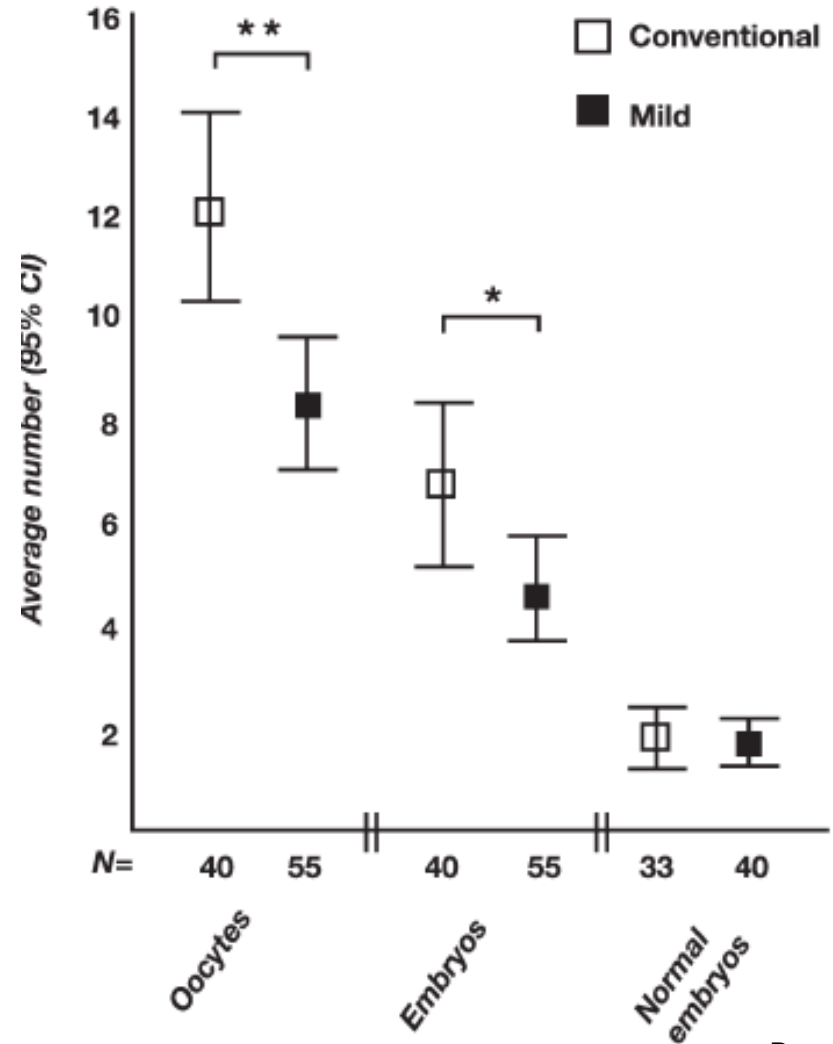
- Mild treatment (**4 cycles, SET**) vs. standard treatment (**3 cycles, 2 embryos**), **1 year**

- Mild treatment: 5.d.c. start, 150 IU FSH + GnRH antagonist
- Standard treatment: GnRH long protocol



# Better quality embryos with mild stimulation

- despite “mild” stimulation obtained significantly fewer oocytes and embryos, both regimens finally generated the same number (1.8/cycle) of chromosomically normal embryos





# Mild IVF - conclusions

- Comparable pregnancy rates
- Lower multiple pregnancy rates
- Lower OHSS rates
- Price
- Oocyte and embryo quality
- Patient-friendly