

Indirect Ovarian Stimulation:  
*Anti-estrogens, Aromatase Inhibitors,  
Insulin Sensitizers*

Prof. Dr. Basil C. Tarlatzis

*Unit for Human Reproduction  
1<sup>st</sup> Department of Obstetrics and Gynecology  
Aristotle University of Thessaloniki, Greece*



---

---

---

---

---

---

---

---

Indirect Ovarian Stimulation

- Anti-estrogens
- Aromatase inhibitors
- Insulin sensitizers

---

---

---

---

---

---

---

---



ESHRE/ASRM Consensus, Thessaloniki 2007

---

---

---

---

---

---

---

---

## Indirect Ovarian Stimulation

- Anti-estrogens
- Aromatase inhibitors
- Insulin sensitizers

---

---

---

---

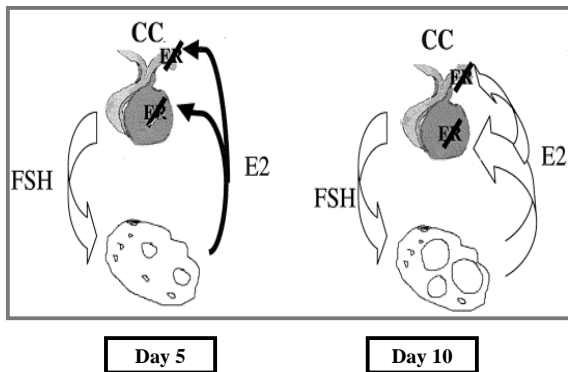
---

---

---

---

## Clomiphene Citrate Treatment



---

---

---

---

---

---

---

---

## CC ADMINISTRATION

- For 5 days
- Onset on days 2 - 5
- No difference between different days of onset
- Starting dose 50 mg/day per os

---

---

---

---

---

---

---

---

## RESULTS OF TREATMENT WITH CC

### 5 STUDIES

(1968-1983): A total of 5878 cases

- Ovulation rate: 70-86%
- Pregnancy rate: 34-43%
- Miscarriage rate: 13-25%

Messinis I, 2002

---

---

---

---

---

---

---

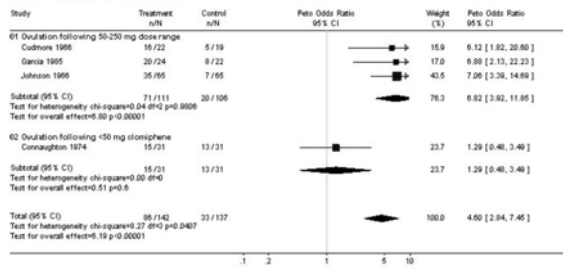
---

---

---

### CC for Ovulation Induction in Women with Oligo/Amenorrhea

Review: Clomiphene citrate for ovulation induction in women with oligo-amenorrhea  
 Comparison: 01 Clomiphene citrate in oligo-amenorrheic women vs placebo  
 Outcome: 01 Ovulation following all dose ranges



Hughes et al 2000 Cochrane Database Syst Rev

---

---

---

---

---

---

---

---

---

---

## CC VS PLACEBO

### 4 studies (cross-over)

- CC increased ovulation (OR: 6.8) [3 studies] and pregnancy rate (OR: 3.41) [2 studies]

Hughes et al., 2000 Cochrane Database Syst. Rev. (2): CD000056

### 3 RCTs

- CC increased pregnancy rate (OR 5.8, 95% CI 1.6 to 21.5)

Beck et al., 2005 Cochrane Database Syst. Rev. (1): CD002249

---

---

---

---

---

---

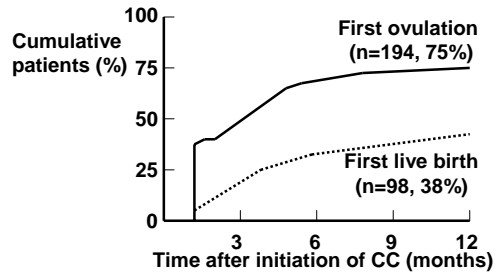
---

---

---

---

## OVULATION INDUCTION WITH CC (Chances to ovulate and conceive)



Van Santbrink et al, Trends Endocr. Metab. 16, 382-9, 2005

---

---

---

---

---

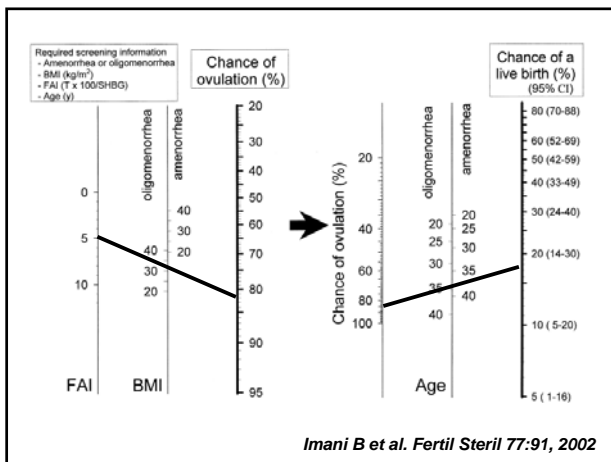
---

---

---

---

---




---

---

---

---

---

---

---

---

---

---

## Clomiphene Citrate: *Summary Points*

- CC remains the treatment of first choice for induction of ovulation in most anovulatory women with PCOS.
- Selection of patients for CC treatment should take account body weight / BMI, female age and the presence of other infertility factors.
- The starting dose of CC should be 50 mg/day (for five days) and the recommended maximum dose is 150 mg/day.

---

---

---

---

---

---

---

---

---

---

Clomiphene Citrate: *Summary Points*

- Results of large trials suggest monitoring by ultrasound or progesterone may not be mandatory to ensure good outcome.
- Life-table analysis of the largest and most reliable studies indicates a conception rate of up to 22% per cycle in those women ovulating on CC.

---

---

---

---

---

---

---

---

Clomiphene Therapy in PCOS

*Clomiphene Resistance:* Failure to ovulate after 2-3 successive cycles of CC at the maximal dose (20-30%)

*Clomiphene Failure:* Failure to conceive after 6 to 12 cycles of treatment in women who respond normally to CC

---

---

---

---

---

---

---

---

Indirect Ovarian Stimulation

- Anti-estrogens
- Aromatase inhibitors
- Insulin sensitizers

---

---

---

---

---

---

---

---

<p><b>CONTROVERSY: LETROZOLE FOR OVULATION INDUCTION</b></p> <p><b>Effects of letrozole on superovulation with gonadotropins in women undergoing intrauterine insemination</b></p> <p>David Hwang, M.D., Sheng-Lin Tan, M.D., Tapan Talsani, M.D., and Marlene M. Blain, M.D.</p> <p>Department of Obstetrics and Gynecology, McGill University, Montreal, Quebec, Canada</p>	<p><b>COMPARISON AND CONTRAST</b></p> <p><b>Comparison of the effects of letrozole and clomiphene citrate on ovarian follicles, endometrium, and hormone levels in the rat</b></p> <p>Ezgi Kiliç Özgür, M.D.,* Mustafa Kucuk, M.D.,* and Samir Akbar, M.D.*</p> <p>Pakistan University of Medicine, Sialkot, Punjab</p>
<p><b>LETROZOLE: OVULATION OR SUPEROVULATION?</b></p> <p>Robert F. Casper, M.D.</p> <p>Division of Reproductive Medicine, Peter and Alexandra Baynes, Department of Obstetrics and Gynecology, Mount Sinai Hospital, and the University of Toronto, Toronto, Ontario, Canada</p>	<p><b>OVULATION INDUCTION IS NOT THE SAME AS SUPEROVULATION: THE EFFECT OF SELECTIVE ESTROGEN RECEPTOR MODULATORS AND AROMATASE INHIBITORS</b></p> <p>David W. Tougas, M.D.</p> <p>West School of Medicine of the University of Southern California, Los Angeles, California</p>
<p><b>OVULATION INDUCTION IN WOMEN WITH INFERTILITY: A NEW INDICATION FOR AROMATASE INHIBITORS</b></p> <p>David W. Tougas, M.D.</p> <p>Department of Obstetrics and Gynecology, Northwestern University, Feinberg School of Medicine, Chicago, Illinois</p>	<p><b>LETROZOLE AND GONADOTROPINS: WHAT IS THE IDEAL PATIENT PROTOCOL?</b></p> <p>David Hwang, M.D., Sheng-Lin Tan, M.D., Marlene M. Blain, M.D., and Tapan Talsani, M.D.</p> <p>Department of Obstetrics and Gynecology, McGill University, Montreal, Quebec, Canada</p>

---

---

---

---

---

---

---

---

---

---

**3<sup>rd</sup> generation Aromatase Inhibitors**

*Steroidal derivatives:*

- Exemestane (Aromasin)

*Non-Steroidal imidazole derivatives:*

- Fadrozole.

*Non-Steroidal triazole derivatives:*

- Anastrozole (Arimidex)
- Letrozole (Femara)

*Both approved in USA for the treatment of breast cancer*

---

---

---

---

---

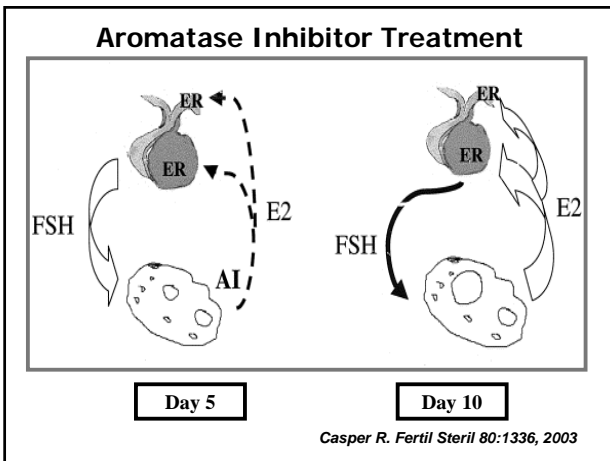
---

---

---

---

---




---

---

---

---

---

---

---

---

---

---

## AI Dose

- 2.5 mg/day, days 3 to 7  
or
- Single dose of 20 mg on day 3

*(Mitwally & Casper, 2001)*

---

---

---

---

---

---

---

---

## Letrozole Results

- Clinical Pregnancy Rate (6 studies)  
Letrozole 49/350 = 14%/cycle  
CC 32/372 = 8.6% /cycle  
( $P < 0.025$ )
- Live Birth Rate (4 studies)  
Letrozole 31/174 cycles = 17.8%/cycle  
CC 20/293 cycles = 6.8%/cycle  
( $P < 0.001$ )

---

---

---

---

---

---

---

---

## Letrozole: Safety Results

- **Incidence of all malformations was not different between letrozole babies and normal deliveries**  
( $p = 0.25$ ; 95%CI 0.78-4.71)

The incidence of locomotor malformations  
 $p = 0.0005$ ; 95% CI 2.64-27.0

The incidence of cardiac anomalies  
 $p = 0.0006$ ; 95% CI 3.30-58.1

*Biljan et al. ASRM, Abstract O-231, 2005*

---

---

---

---

---

---

---

---

Aromatase Inhibitors: *Summary Points*

- Further studies should demonstrate efficacy and safety of aromatase inhibitors.

---

---

---

---

---

---

---

---

Indirect Ovarian Stimulation

- Anti-estrogens
- Aromatase inhibitors
- Insulin sensitizers

---

---

---

---

---

---

---

---

Indirect Ovarian Stimulation:  
*Insulin Sensitizers*

- Lifestyle modification (diet and exercise)
- Metformin (1000-2500 mg)
- Troglitazone (discontinued)
- Rosiglitazone (4-8mg/day)
- Pioglitazone
- D-chiroinositol

---

---

---

---

---

---

---

---



## Metformin: Mechanism of Action

- Biguanide used for diabetes mellitus type 2
- Rapid clearance and low side-effects
- Lowers serum insulin and glucose without hypoglycaemia
- Works in at least two ways
  - improved uptake of glucose into the tissues
  - suppression of hepatic glucose output and gluconeogenesis
- Side effects are largely gastrointestinal
- Effects directly on the ovary are uncertain

---

---

---

---

---

---

---

---

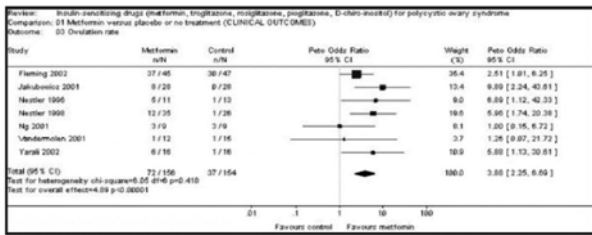
---

---

---

---

## Metformin vs Placebo/No Treatment Ovulation rate



Lord et al 2003, Cochrane Database Syst Rev

---

---

---

---

---

---

---

---

---

---

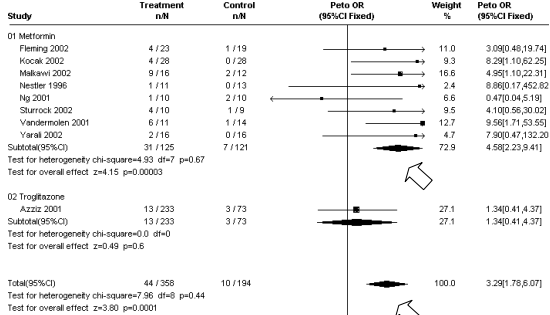
---

---

## Metformin and Pregnancy

Comparison: 15 Pregnancy Rates - all trials

Outcome: 01 Crude pregnancy rate



Lord et al 2003, Cochrane Database Syst Rev

---

---

---

---

---

---

---

---

---

---

---

---

## CC+Placebo vs. CC+MET in PCOS

**Table 2** Rates of ovulation, pregnancy, and spontaneous abortion. Figures are numbers (percentages) of women in each group

	Clomifene citrate + metformin (n=111)	Clomifene citrate + placebo (n=114)	Risk difference % (95% CI)	Relative risk (95% CI)
Ovulation	71 (64)	82 (72)	-8 (-20 to 4)	0.89 (0.7 to 1.1)
Ongoing pregnancy	44 (40)	52 (46)	-6 (-20 to 7)	0.87 (0.6 to 1.2)
Spontaneous abortion	13 (12)	12 (11)	1 (-7 to 10)	1.11 (0.5 to 2.3)

Moll et al, *BMJ*, 2006

---

---

---

---

---

---

---

---

---

---

## NIH – Reproductive Medicine Network

*Legro, et al., NEJM, 2007*

	Clomiphene 209	Metformin 208	Combination 209
%			
Ovulation	49*	29	60**
Conception	20*	12	38*
Pregnancy	24*	9	31*
Live birth	23*	7	27*
Multiple	6	0	3

\*P < 0.001

\*\*P < 0.001 combination vs. clomiphene

---

---

---

---

---

---

---

---

---

---

## Metformin: *Summary Points*

- At present, use of metformin in PCOS should be restricted to those patients with glucose intolerance.
- Decisions about continuing insulin sensitizers during pregnancy in women with glucose intolerance should be left to obstetricians providing care and based on a careful evaluation of risks and benefits.

---

---

---

---

---

---

---

---

---

---

### Metformin: *Summary Points*

- Metformin alone is less effective than CC in inducing ovulation in women with PCOS.
- There seems to be no advantage to adding metformin to CC in women with PCOS.

---

---

---

---

---

---

---

---

### Ovulation Induction: *General Conclusion*

- More patient-tailored approaches should be developed for ovulation induction based on initial screening characteristics of anovulatory women.

---

---

---

---

---

---

---

---

Thank you !

---

---

---

---

---

---

---

---