

# The Use of Aromatase Inhibitors in Ovulation Induction

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- Ovulation induction and superovulation (COH) are the most widely used treatments for infertility
- Ovarian stimulation can be achieved by administration of exogenous gonadotropins or by augmenting endogenous FSH with clomiphene citrate (CC) treatment.

- For more than 4 decades, CC has been the first line of treatment for ovulatory disorders. CC results in ovulation in most patients (60%–90%), with disappointing pregnancy rates of (10%–40%).
- Gonadotropins are more effective than CC, expensive, associated with higher risk for ovarian hyperstimulation syndrome and multiple gestations do not exert a peripheral antiestrogenic effect.

# Clomiphene Citrate - Problems

- Long tissue half-life (2 weeks)  $\Rightarrow$  prolonged central ER depletion
- High multiple pregnancy rate
- Peripheral anti-estrogenic effects
- Thin endometrium (Gonen et al, 1990)
- Unfavorable cervical mucus
- Reduced uterine blood flow
- Lower pregnancy rate than expected from the high ovulatory rate

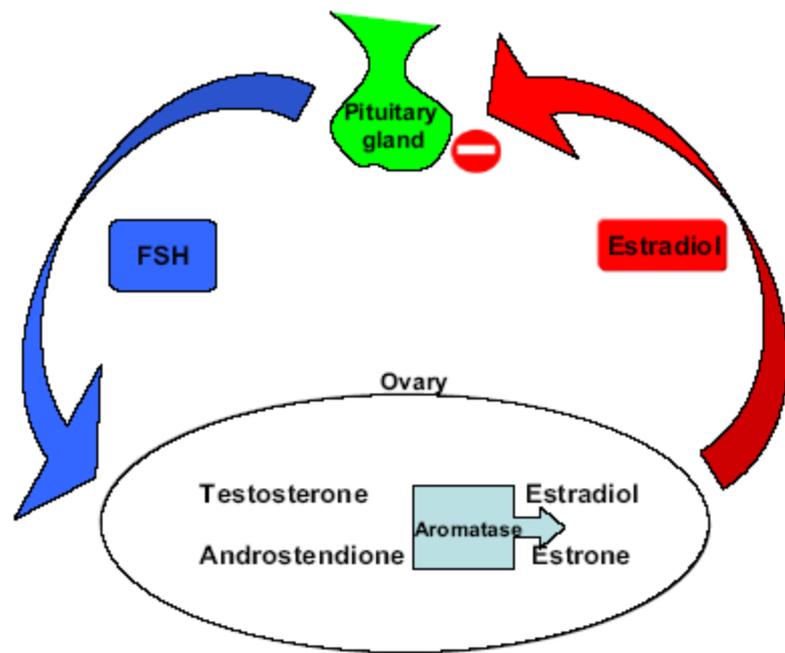
# Aromatase Enzyme

- Have both central and peripheral mechanisms of action
- Aromatase catalyzes the conversion of androgens to estrogens
- Specific non-steroidal, reversible inhibitors, e.g. letrozole, anastrozole
- Have a short half life (~ 45 hours)
- No direct estrogenic or anti-estrogenic effects
- Activity: ovaries, adipose tissue, placenta, brain, muscle, fibroblasts, osteoblasts, liver and breast
- Highly potent (doses of 1-5 mg) decreases E levels by 97->99 %)

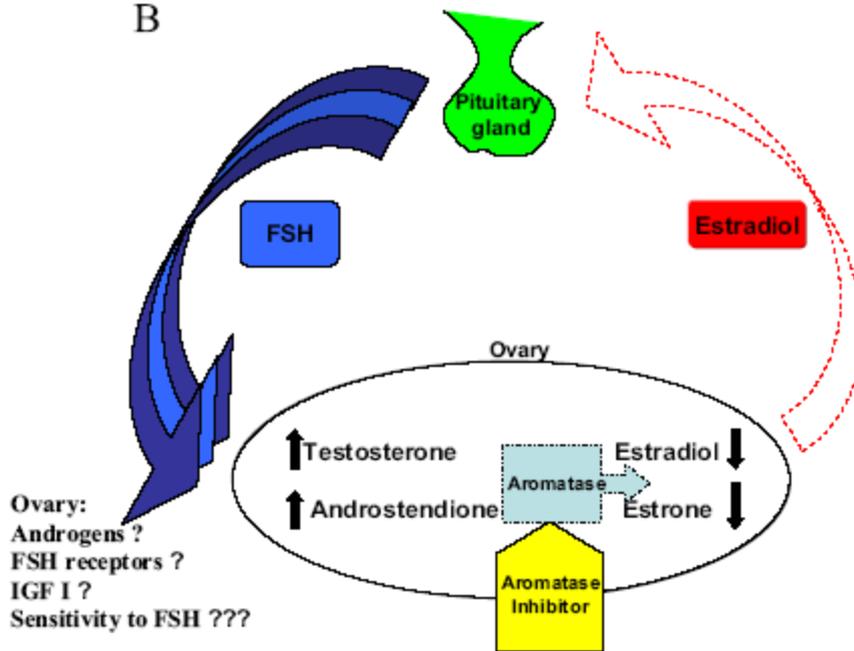
# Hypothesis

- ⦿ Aromatase inhibition decreases estrogenic negative feedback centrally
- ⦿ Increased FSH
- ⦿ Short half-life and no ER effects (no depletion)
- ⦿ Intact central feedback loop for estrogen & FSH (Normal feedback mechanisms centrally)
- ⦿ Avoids the undesirable peripheral anti-estrogen effects of CC = ( no -ve effect on endometrium)
- ⦿ Result in predominantly mono-ovulation when used alone
- ⦿ Ovarian intrinsic accumulation of A, increases GC-FSH sensitivity

A



B



(A) The pituitary– ovarian axis in the follicular phase. Estradiol is produced by the ovarian granulosa cells and exerts a Negative feedback effect on FSH release from the pituitary gland.

(B) Effects of aromatase inhibitor. Aromatization of androgens to estrogens is inhibited, the hypothalamic–pituitary axis is released from the –ve feedback, & FSH secretion is increased. The androgens accumulated in the ovary increase the ovarian sensitivity to FSH. The overall effect is stimulation of development of Ovarian follicles. IGF I insulin-like growth factor I.

# Central Action

- ⦿ May be more vigorous than expected
- ⦿ Blockade of ovarian estrogen production leads to decreased negative feedback and rise of FSH
- ⦿ Blockade of aromatization of androgen to estrogen in the brain may result in a further rise of FSH

# Aromatase inhibitors as a single drug for ovulation induction

- ⦿ Good ovulation rate,
- ⦿ Thick endometrium,
- ⦿ considerable number of pregnancies.
- ⦿ Multiple developing follicles appear on D 7
- ⦿ single dominant follicle only in mid-cycle ( when used alone)

# Aromatase inhibitors for ovulation induction

<b>Authors (reference)</b>	<b>Treatment</b>	<b>No. of patients and diagnosis</b>	<b>Mean E thickness (mm)</b>	<b>Ovulation rate (%)</b>	<b>Conception</b>
Mitwally & Casper Reprod Tech 2000 10:244 –7.	Letrozole	10, PCOS resistant to CC or E <5 mm	<b>7–9</b>	<b>70</b>	<b>2</b> <b>(1 biochemical pregnancy)</b>
Mitwally & Casper Fertil Steril 2001; 75:305–9.	Letrozole	12, PCOS, inadequate response to CC	<b>8.1</b>	<b>75</b>	<b>3 of 12</b>
Mitwally & Casper Fertil Steril 2005; 83:229 –31.	Letrozole, single dose	3 PCOS, 4 unexplained (9 cycles)	<b>9</b>	<b>88.9</b>	<b>1 pregnancy</b>
Al-Omari et al. Int J GynObs 2004 85:289 –91.	Letrozole vs. anastrozole	40 PCOS resistant to CC	<b>8.2</b> <b>Letrozole</b> <b>6.5</b> <b>anastrozole</b>	<b>84.4</b> <b>letrozole</b> <b>60</b> <b>anastrozole</b> <b>e</b>	<b>27%</b> <b>letrozole</b> <b>16.6%</b> <b>anastrozole</b>

*Holzer. A new era in ovulation induction. Fertil Steril 2006*

# Use of Letrozole for superovulation

- Thick endometrium
- Improved stromal blood flow
- Higher pregnancy rates

## Use of Letrozole for superovulation

Authors (reference)	Treatment	No. of pts & diagnosis	Mean no. of dominant follicles	Mean E Thickness (mm)	Pregnancy
Fisher et al. FertilSteril2002; 78:280-5	L (2.5mg) vs. CC (50 mg)	19, N volunteers	1.7 L vs. 2.2 CC	No difference from natural cycles	Volunteers not desiring pregnancy
Sammour et al. Fertil Steril 2001 ;76 Supp1:S110	L (2.5 mg) vs. CC (100 mg)	49, unexplained infertility	1 L vs. 2 CC	8.6 mm L vs. 6.9 mm CC	Pregnancy rate/cycle 16.7% L vs. 5.6% CC
Fatemi Reprod. Biomed online2003;7;5 43-6	L (2.5 mg ) vs. CC (100 mg)	15, unexplained infertility	1 L vs. 2 CC	8.0 mm L vs 8.3 mm CC	Total pregnancies: 37.5% CC vs. 28.6% L

*Note: L letrozole.*

*Holzer. A new era in ovulation induction. Fertil Steril 2006.*

## Letrozole combined with FSH treatment.

Authors (reference)	No. of pts, diagnosis, and treatment	Outcomes
Mitwally and Casper Hum Reprod 2003; 18:1588 –97.	L/FSH (36 pts), CC/FSH (18 pts), FSH only (56 pts). Unexplained infertility, mild male factor	Combined groups received less FSH; no difference in number of follicles, endometrium thinner in CC/FSH; pregnancy rates: 19.1% (L/FSH), 10.5% (CC/FSH), 18.7% (FSH only)
Healey et al. Fertil Steril 2004; 80:1325–9.	FSH alone (165 cycles) vs. L/FSH (60 cycles) for superovulation	Addition of L led to decreased Gn requirement, more follicles, and thinner endometrium; Similar pregnancy rates
Mitwally and Casper JSoc Gyn Invest2004 11:406 –15.	PCOS: L/FSH (26 pts), FSH alone (46 pts). Ovulatory infertility: L/FSH (63 pts), FSH alone (308 pts)	Addition of L is associated with less Gn requirem. similar number of follicles, and higher pregnancy rate in patients with PCOS

**Addition of Letrozol to Gn, ↓ Gn requirement, ↑ nb of preovulatory follicles, & ↓ Endometrium thickness without –ve effect on pregnancy rates**

*Note: pts \_ patients. N.B: L+FSH = Overlapping approach  
Holzer.A New era in ovulation induction. Fertil Steril 2006*

## Letrozole use in assisted reproductive technologies.

Authors (reference)	Treatment	No. of patients	Outcome
Goswami et al. Hum Reprod 2004; 19:2031–5.	L (2.5 mg) D 3–7 + rFSH (75 IU) D 3–8  vs.  long GnRH agonist protocol + FSH	38 poor responders	<b>Addition of letrozole led to :</b>  - <b>less FSH requirement</b>  - <b>comparable outcomes</b>
Schoolcraft et al. Fertil Steril 2002; 78(Suppl 1):S234.	L/FSH  vs.  flare-up protocol	27 poor responders  vs.  258 controls	- <b>More oocytes in controls</b>  - <b>similar pregnancy and implantation rates</b>

*Addition of L to FSH ⇒ effective way of Lowering the FSH requirement and the cost of IVF in poor FSH responders*

*Note: rFSH \_ recombinant FSH. Holzer. A new era in ovulation induction. Fertil Steril 2006.*

In theory the low E2 level in combined L & FSH stimulation could result in:

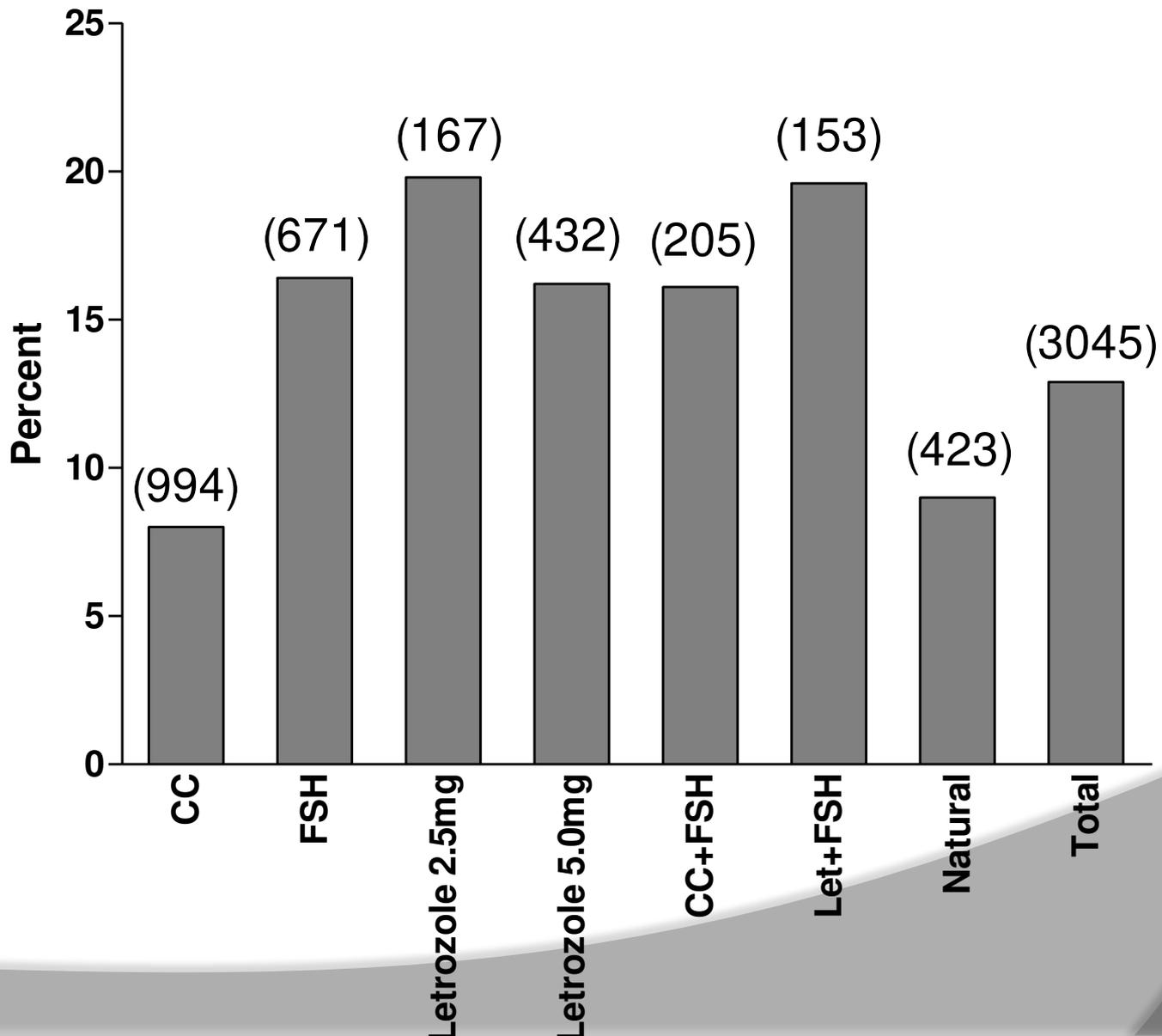
- ⦿ Reduced incidence of ovarian hyperstimulation syndrome
- ⦿ Reduced incidence of Premature lutenization
- ⦿ Favorable Endometrium
- ⦿ High implantation rate
- ⦿ Reduced Gonadotropin requirement

# Composite Pregnancy Rates U of T and McGill

- Over 3000 cycles of ovulation induction or augmentation
- Timed intercourse or IUI
- Retrospective analysis of pregnancy rates
- Women received various ovulation induction protocols
- May have been switched to different treatment in subsequent cycles

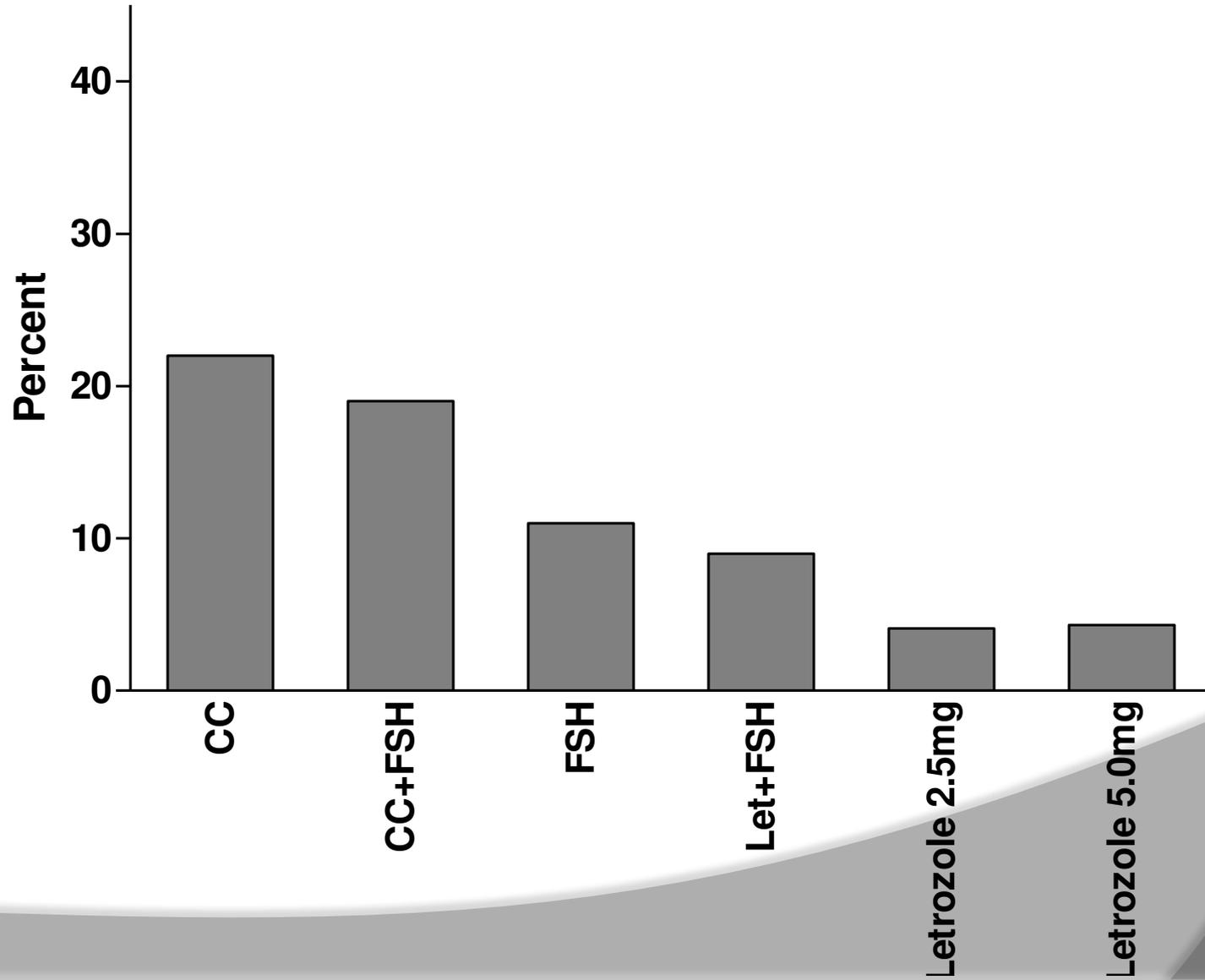
# Pregnancy Rate per Cycle

U of T and McGill



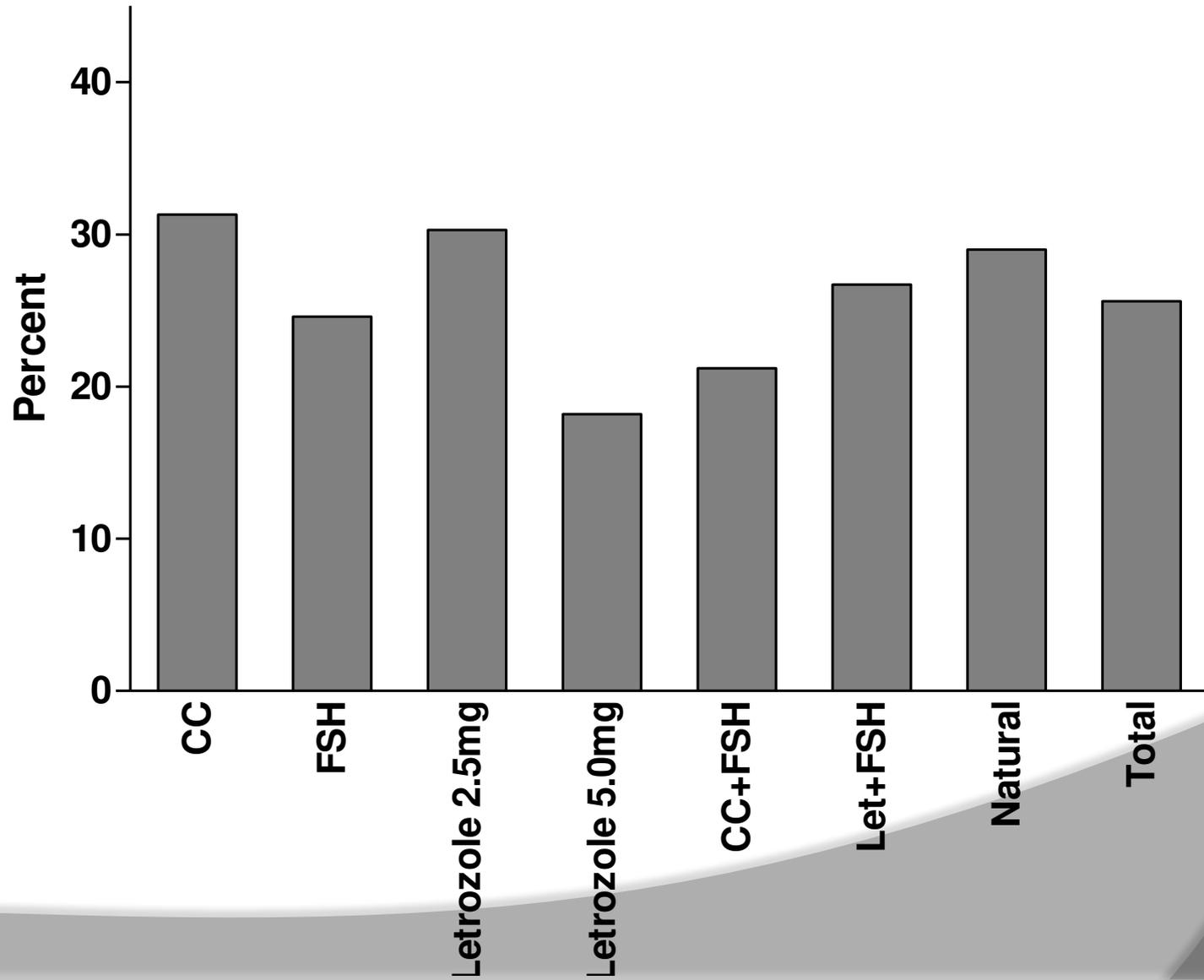
# Multiple Pregnancy Rate

U of T and McGill



# Spontaneous Abortion Rate per Cycle

U of T and McGill



A meta- analysis of four trials showed significant advantage in pregnancy and delivery rates with aromatase inhibitors compared with CC in women with PCOS. Nikolaos P. Polyzos .Fertil Steril 2008;89:278-80

## Baseline characteristics and main outcome measures of trials

Author	Arms (mg)	Patients (eligible)	No.of Cycles	Deliveries (No.)	Pregn. (No.)	Multiple Gestation (No.)	Ectopic Pregn. (No.)
Atay V(2006)	Letrozole 2.5	51 (51)	51	10	11	0	NA
	Clomiphene100	55 (55)	55	5	5	1	NA
Bayar U (2006)	Letrozole 2.5	40 (38)	99	8	9	0	0
	Clomiphene100	40 (36)	95	7	7	0	0
Sohrabvan d F (2006)	Letrozole 2.5+ Metformin	29 (29)	53	10	10	0	NA
	Clomiphene 100+ Metformin	30 (30)	67	3	5	0	NA
Sipe SC (2006)	Anastrazole 1	12 (12)	12	3	3	0	0
	Clomiphene 100	8 (8)	8	1	2	0	1

Note: BMI = Body mass index; NA = not applicable.  
 N. Polyzos. Aromatase inhibitors for PCOS infertility. Fertil Steril 2008

# Treatment protocol & Pregnancy

Administration on days 3-7 of the cycle allows sufficient time for letrozole to be cleared from the body, leaving only negligible levels close to the time of ovulation

# Treatment Protocol

Letrozol	Dose	Duration
2.5-7.5 mg	X 5 days	D3-D7
20 mg	Single dose	D3 Early max E suppression Early clearance
5 mg	X 5 days	D3-D7

Biljan M et al. Fertil Steril 2002;78:S55.

Treatment	pregnancy rate:	Miscarriage rate:	Multiple pregnancy
<p>L or L + FSH</p> <p>vs</p> <ul style="list-style-type: none"> <li>- CC</li> <li>- FSH</li> <li>- CC + FSH</li> <li>- spontaneous pregnancy</li> </ul>	<p>comparable in all except ↓ CC group</p>	<p>similar in all groups</p>	<p>↑ with CC group</p>

*Mitwally MF, et al. Am J Obstet Gynecol 2005;192:381– 6.*

# CONCLUSIONS

Aromatase inhibitors are a new group of drugs to join the arsenal of fertility treatments.

They are orally administered, easy to use, with minor side effects.

letrozole is third-generation aromatase inhibitors that has been used for ovulatory disorders and for superovulation

The data on letrozole suggest that it can be used to replace CC as the first-line treatment for women with ovulatory disorders.

# Conclusion

## AI for Ovulation Induction

- ⦿ Clinical efficacy with lack of side effects demonstrated
- ⦿ Relatively short half-life (~45 hrs)
- ⦿ Presence of intact central feedback mechanisms prevents high multiple ovulation
- ⦿ No adverse effects on endometrium or cervical mucous
- ⦿ Safe for use by community gynecologists without access to ultrasound monitoring

- ⦿ Compared with CC, AI is associated with thicker endometrium.
- ⦿ For superovulation: higher pregnancy rates with letrozole than with CC.
- ⦿ Addition of letrozole to gonadotropin regimens leads to:
  - less gonadotropin requirement
  - pregnancy rate comparable to gonadotropin-only treatment.

- ⦿ It seems that the dose of 5 mg daily for 5 days is the most effective.
- ⦿ Aromatase inhibitors are promising new drugs for the induction of ovulation and superovulation.

**After 4 decades of CC treatment, a new era of ovulation induction has finally arrived.**