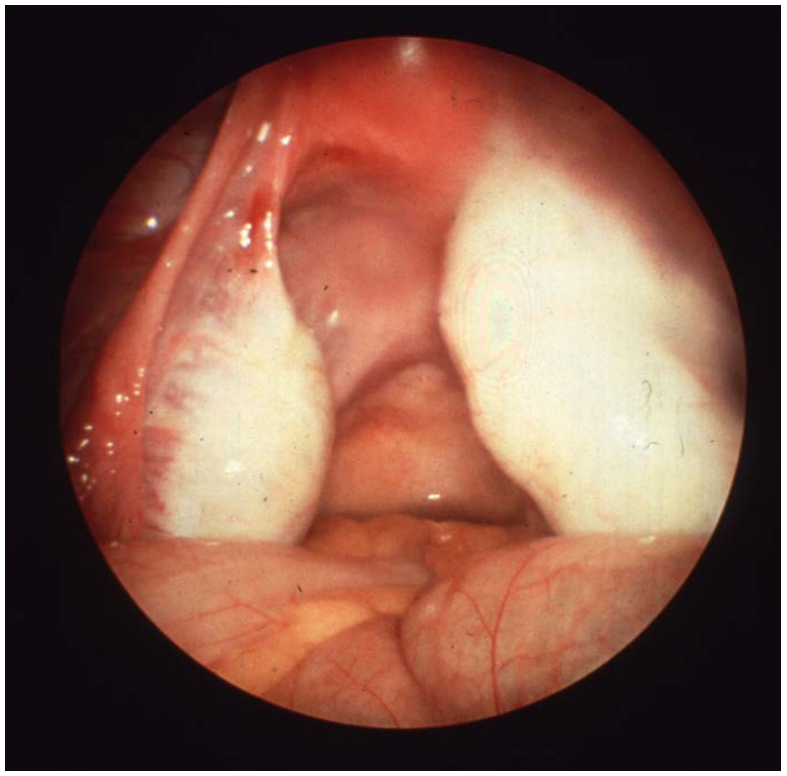
Letrozole for Ovulation Induction in PCOS

Robert F Casper
TRIO Fertility and
University of Toronto

Disclosures

- SABs: Abbvie, EMD Serono
- Consultant: Fertility Nutraceuticals, Fertilify
- Stock: Circadian-ZircLight
- Royalties: Teva, Up-To-Date
- Medical Director: Insception-LifeBank cord blood bank
- Scientific Director: TRIO Fertility

Polycystic Ovarian Syndrome

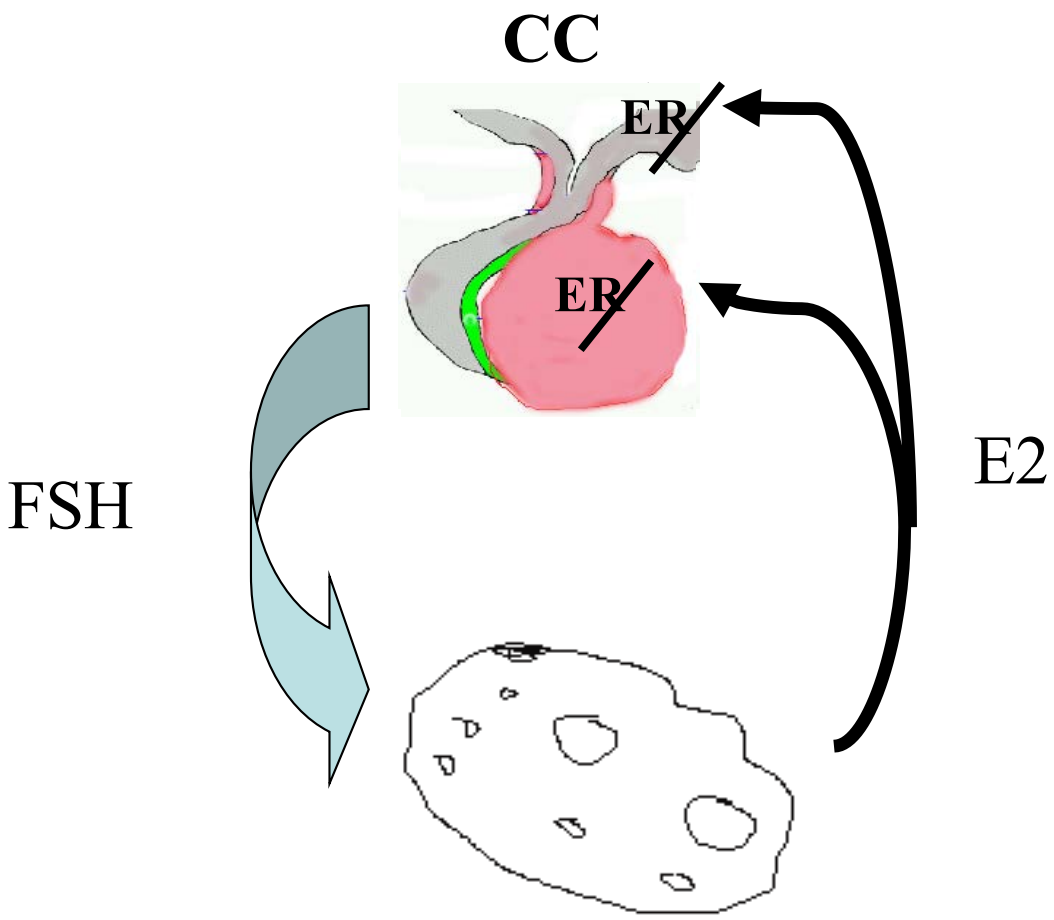


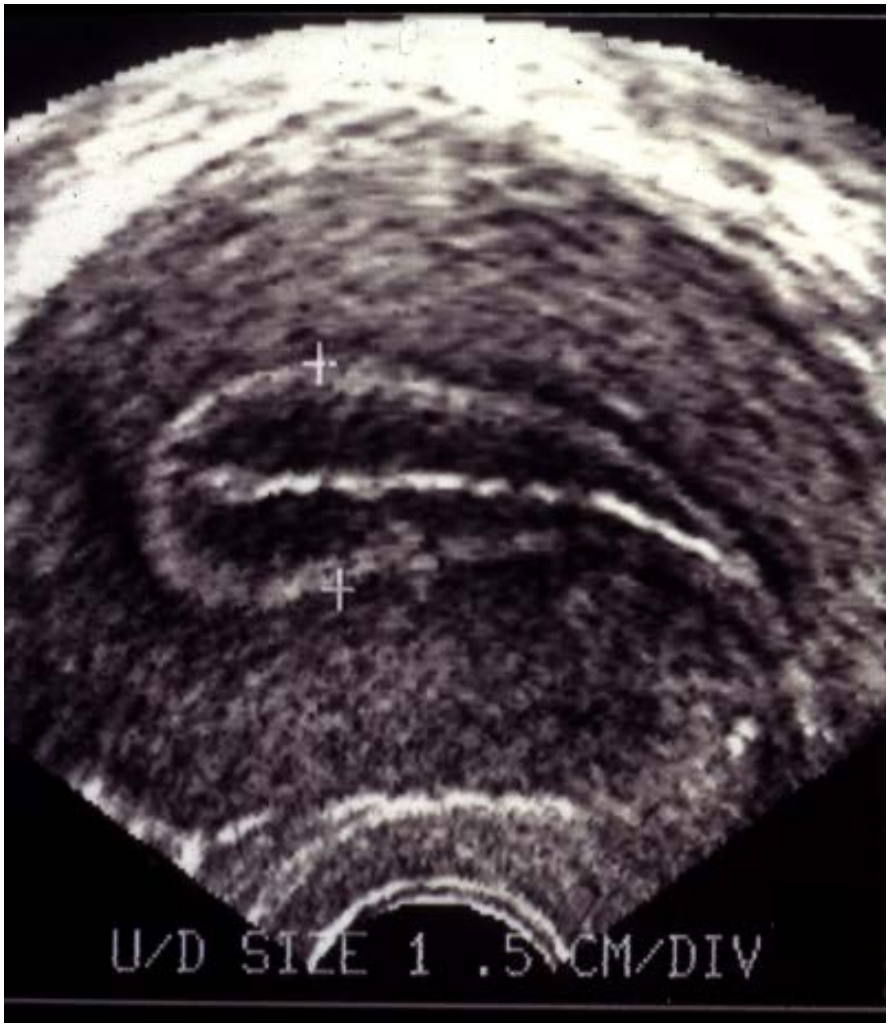
- Most common anovulatory cause of infertility
- Key features are:
  - Anovulation
  - Hyperandrogenism
  - Typical polycystic ovarian pattern on U/S
  - Insulin resistance

Induction of Ovulation

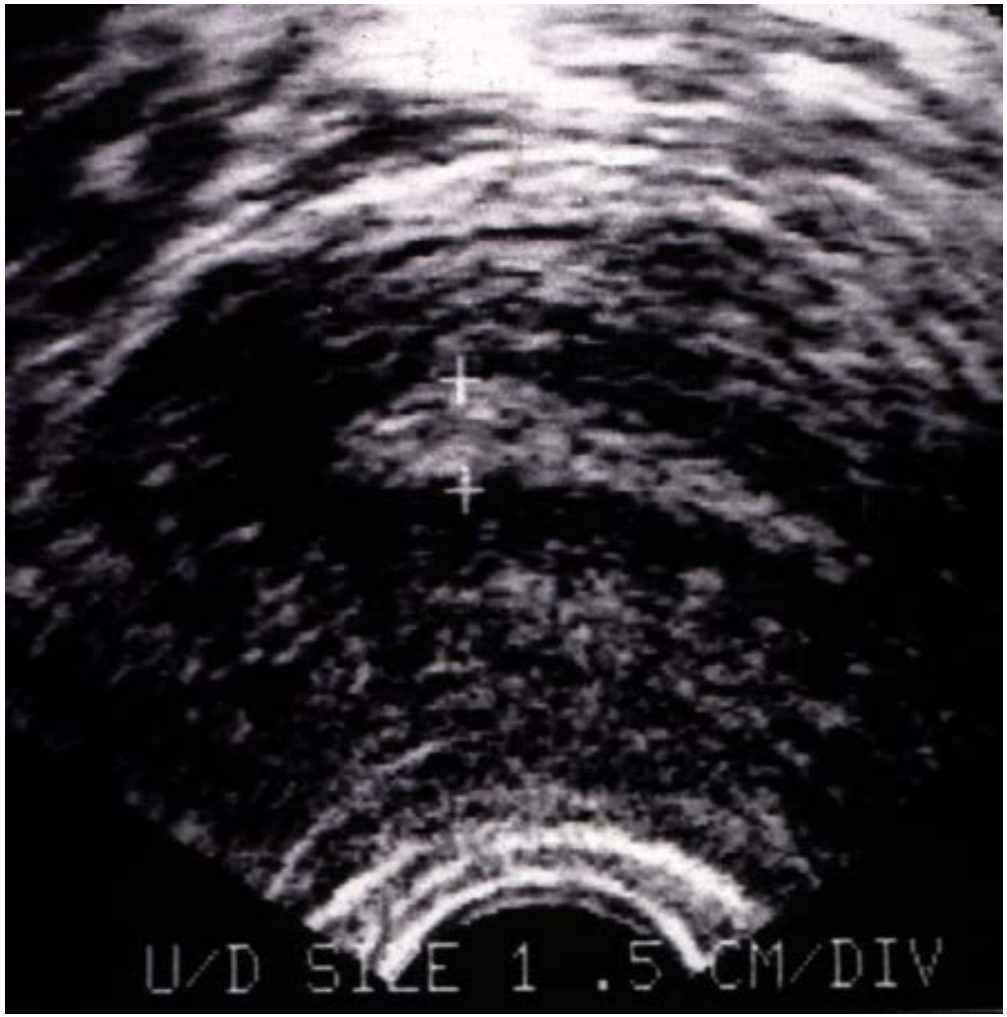
- In women with PCOS and anovulatory infertility, the first choice for the induction of ovulation has been clomiphene citrate (CC)
- In the 1960s, CC the only choice for ovulation induction
- Orally active, inexpensive, relatively few side effects
- With introduction of gonadotropins, CC still had many advantages and fewer risks
- Widespread adoption for ovulation induction was warranted

Clomiphene Citrate Treatment

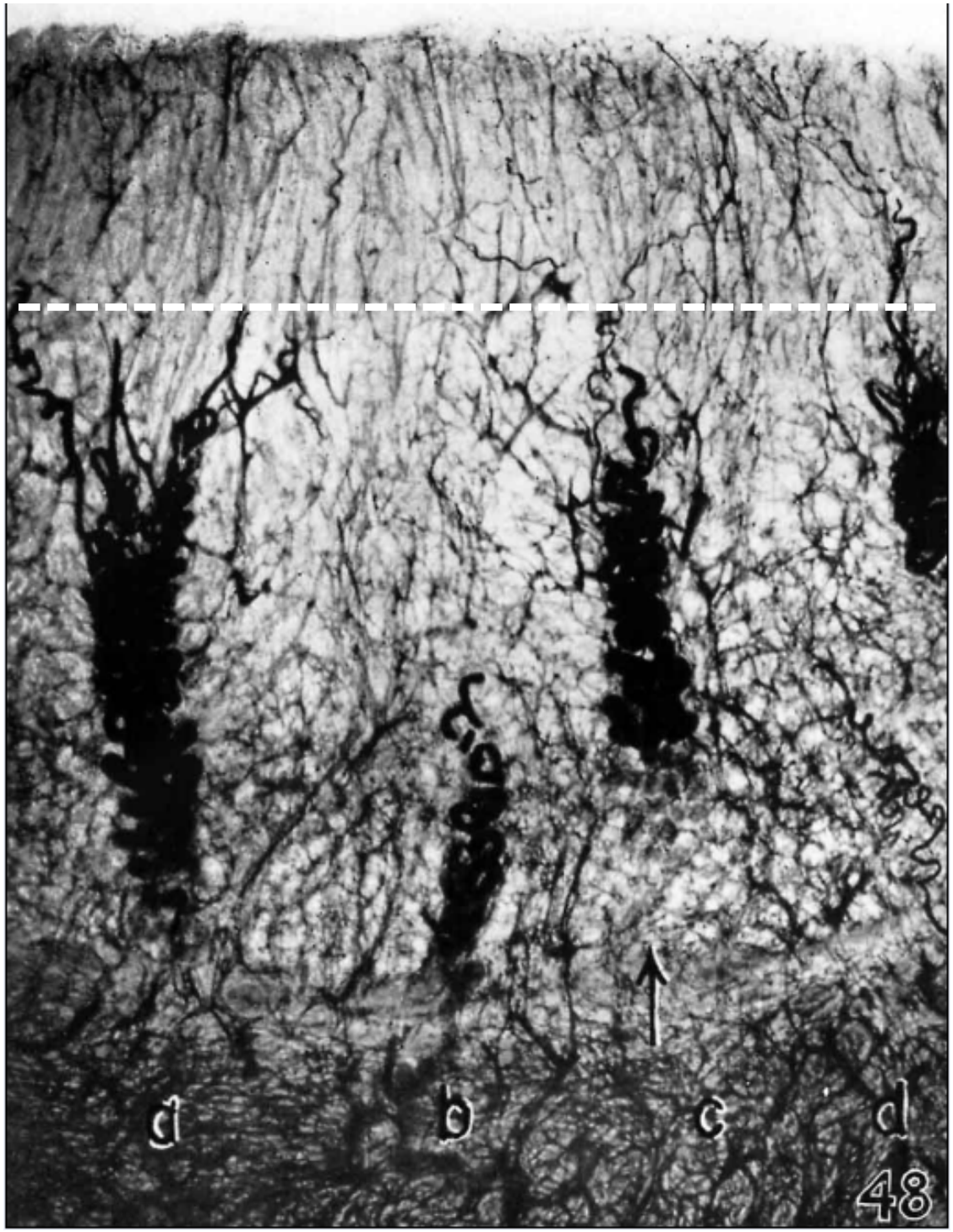




Natural Cycle



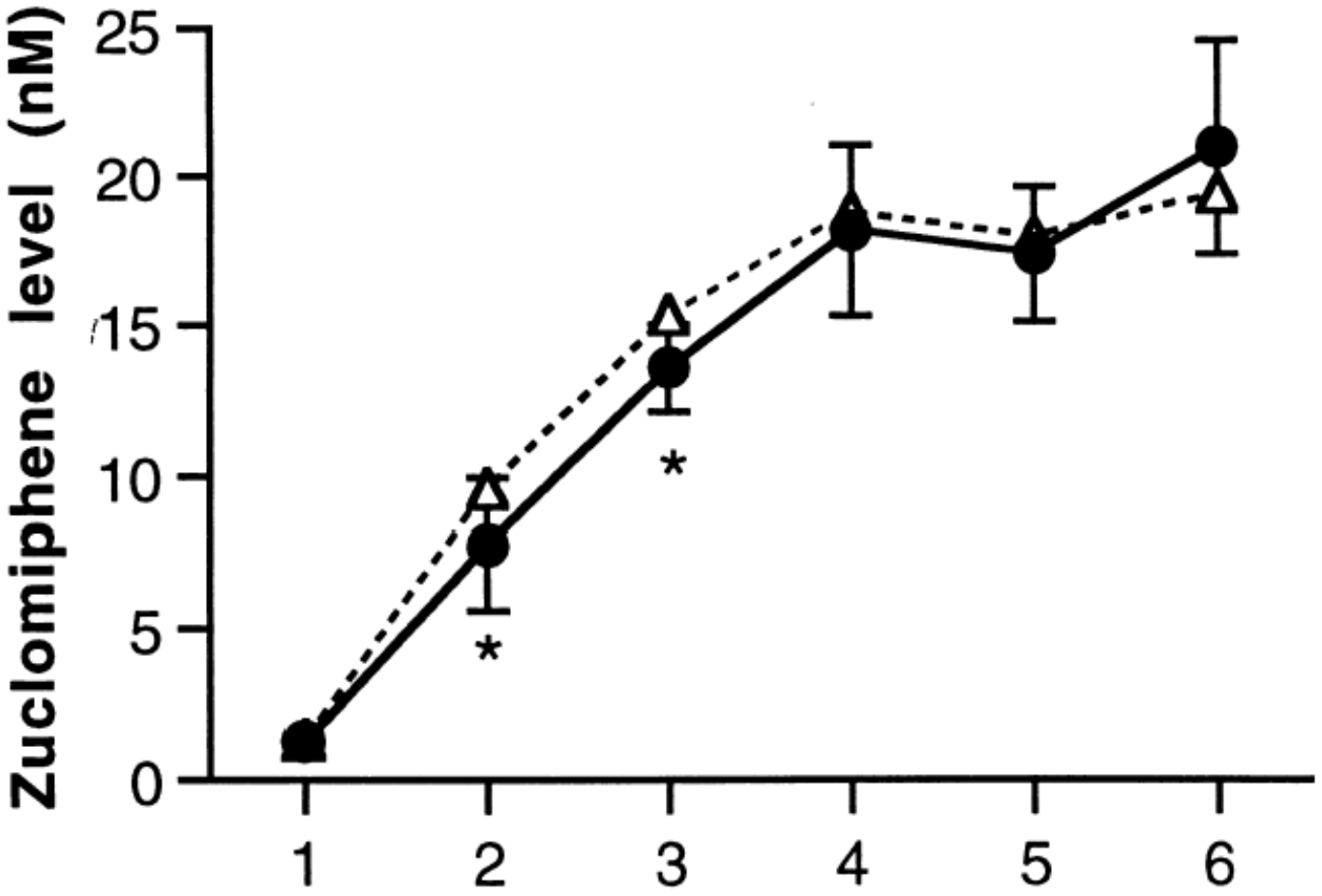
CC Cycle



Bartelmez, GW (1957) The form and the functions of the uterine blood vessels in the rhesus monkey. Contributions to Embryology, 36, 154-183.

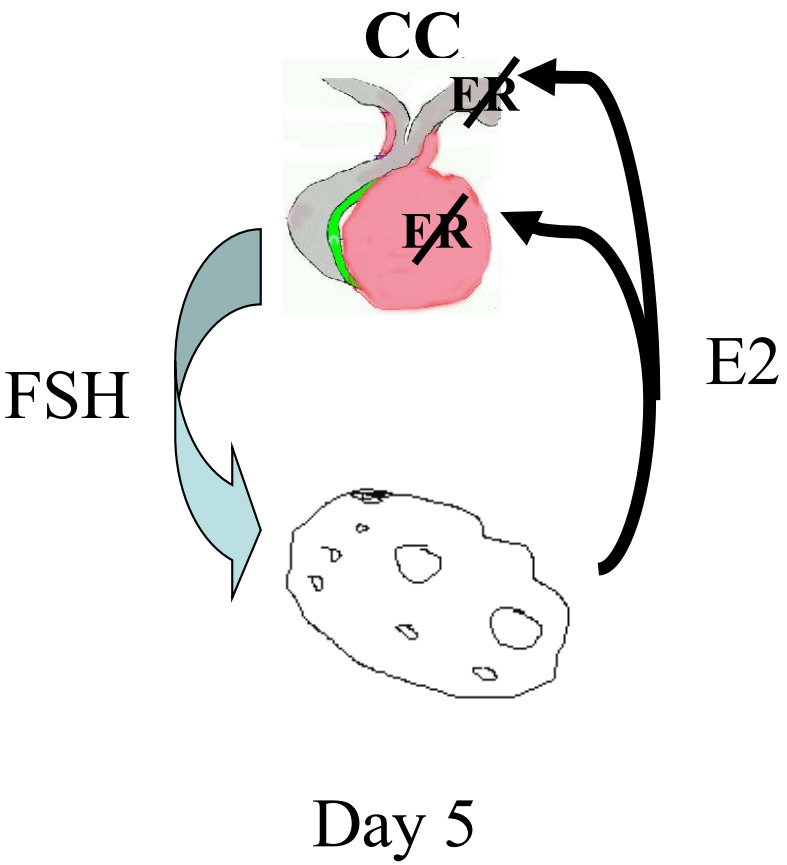
(Courtesy of Professor Graham Burton, Cambridge)

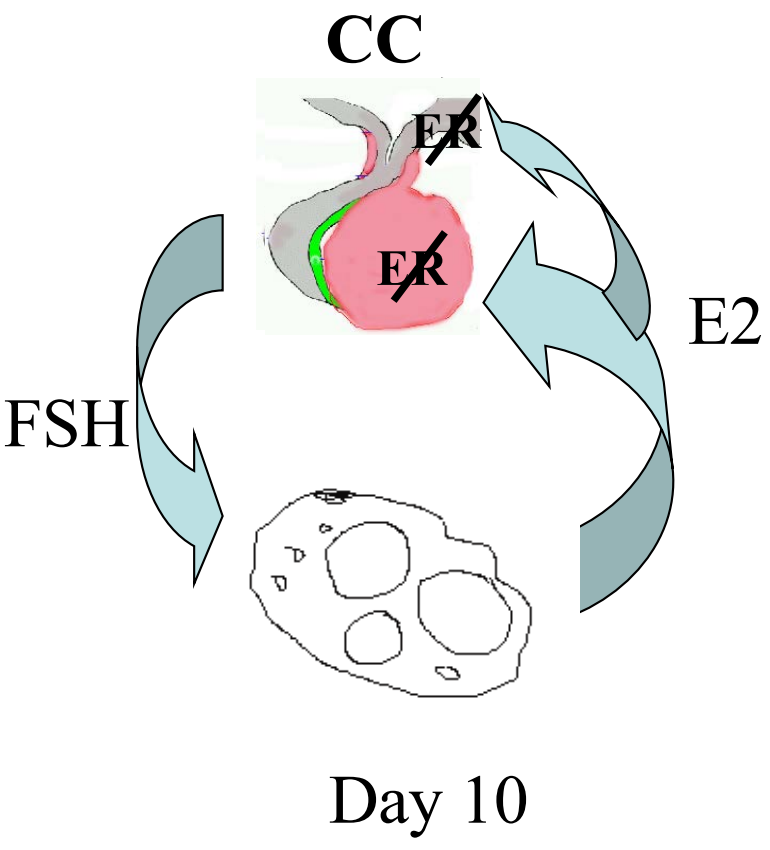
Day 3 zuclomiphene concentrations. *Solid line*: All subjects with an ovulatory response (n = 6–9). *Stippled line*: Subjects with an ovulatory response to 50 mg CC (n = 3–5). Data are presented as means ± SE. *$P<.05$ compared with previous point in post hoc analysis.

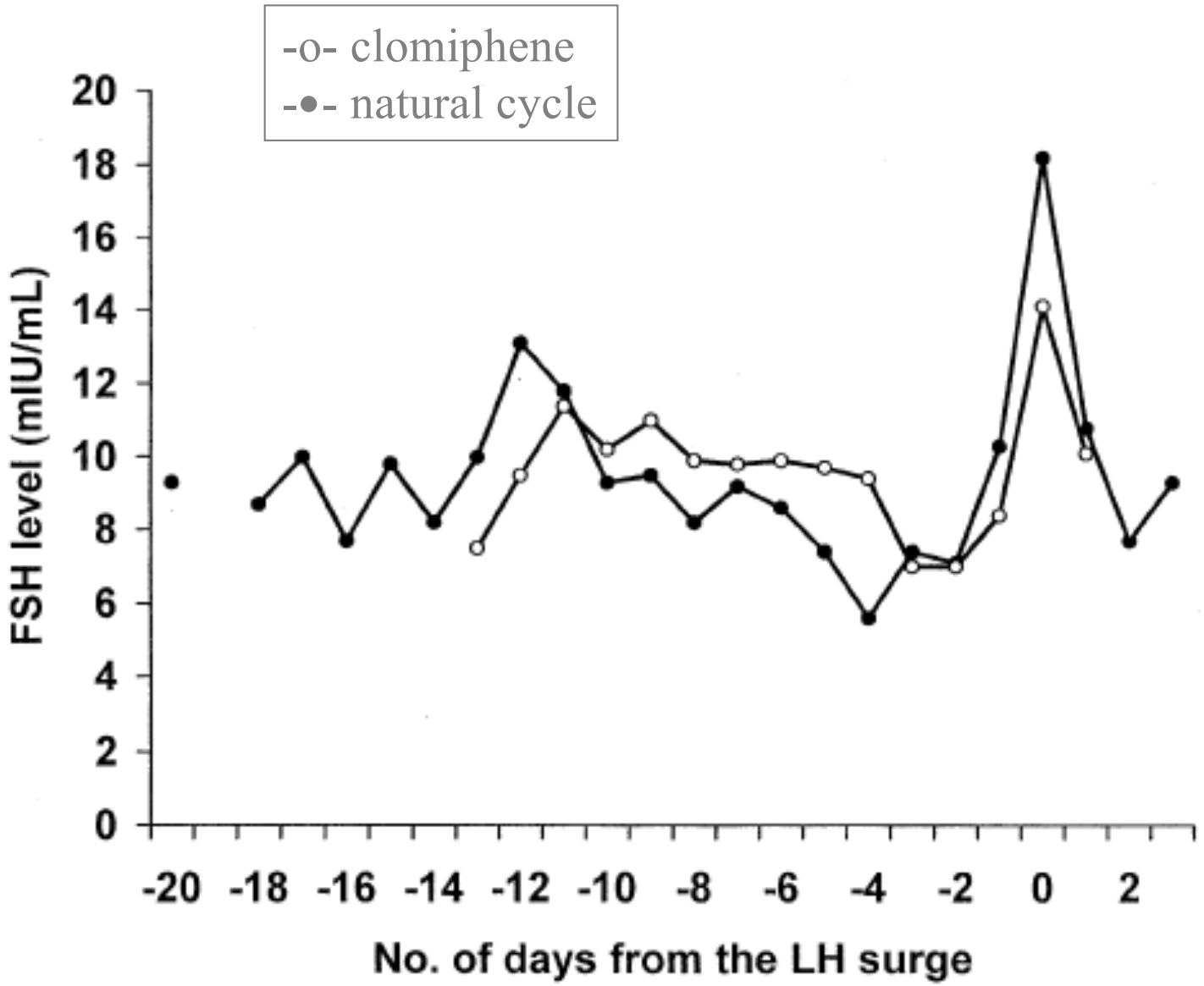


Young et al, Fertil Steril 1999

Clomiphene Citrate Treatment







Fisher et al, Fertil Steril 2002

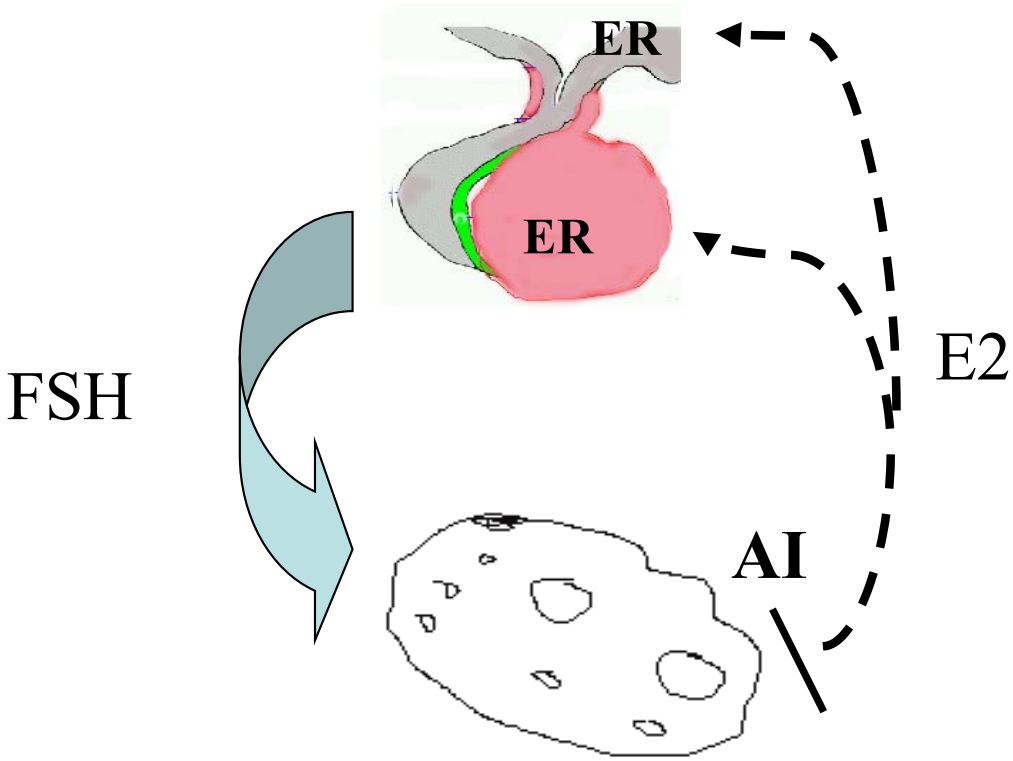
Clomiphene Citrate - Problems

- 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
- Long tissue half-life
- High multiple pregnancy rate

Aromatase Enzyme

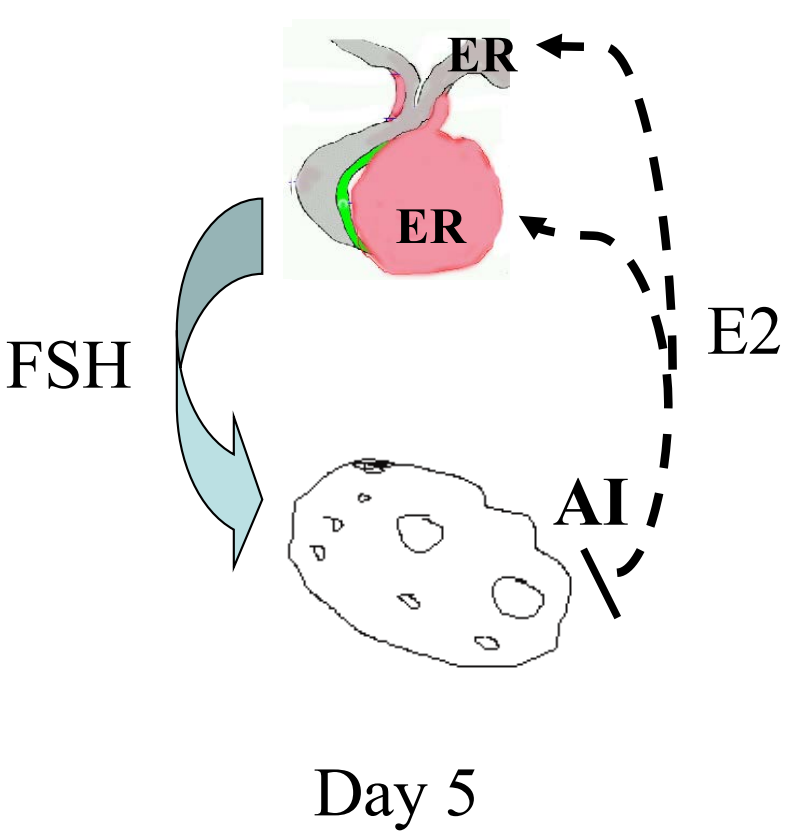
- Aromatase catalyzes the conversion of androgens to estrogens
- Specific non-steroidal, reversible inhibitors, e.g. letrozole, anastrozole
- Have a short half life (~ 45 hours)
- No direct estrogenic or anti-estrogenic effects

Aromatase Inhibitor Treatment

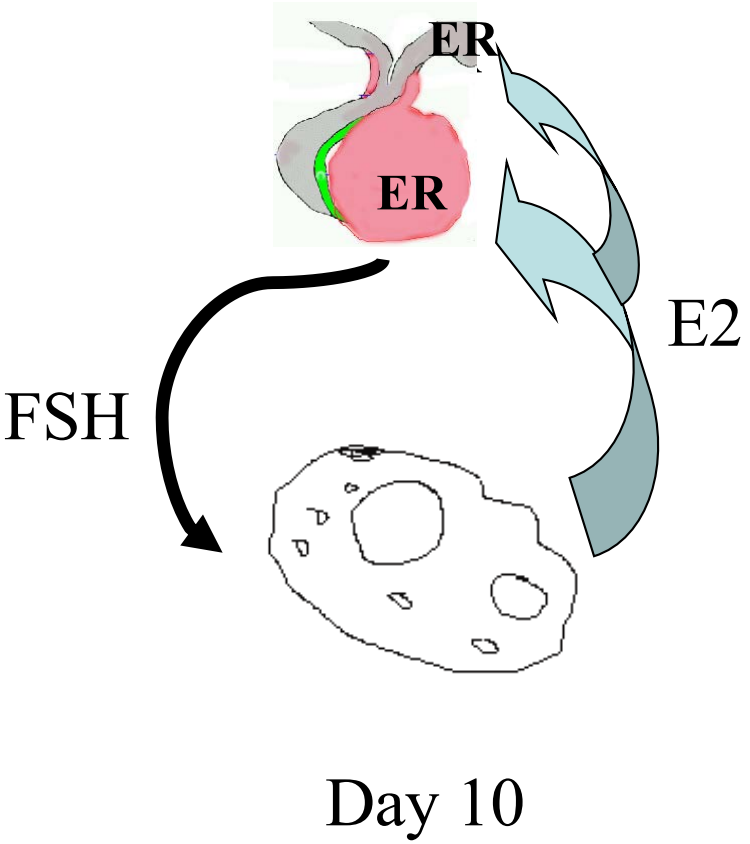


Day 5

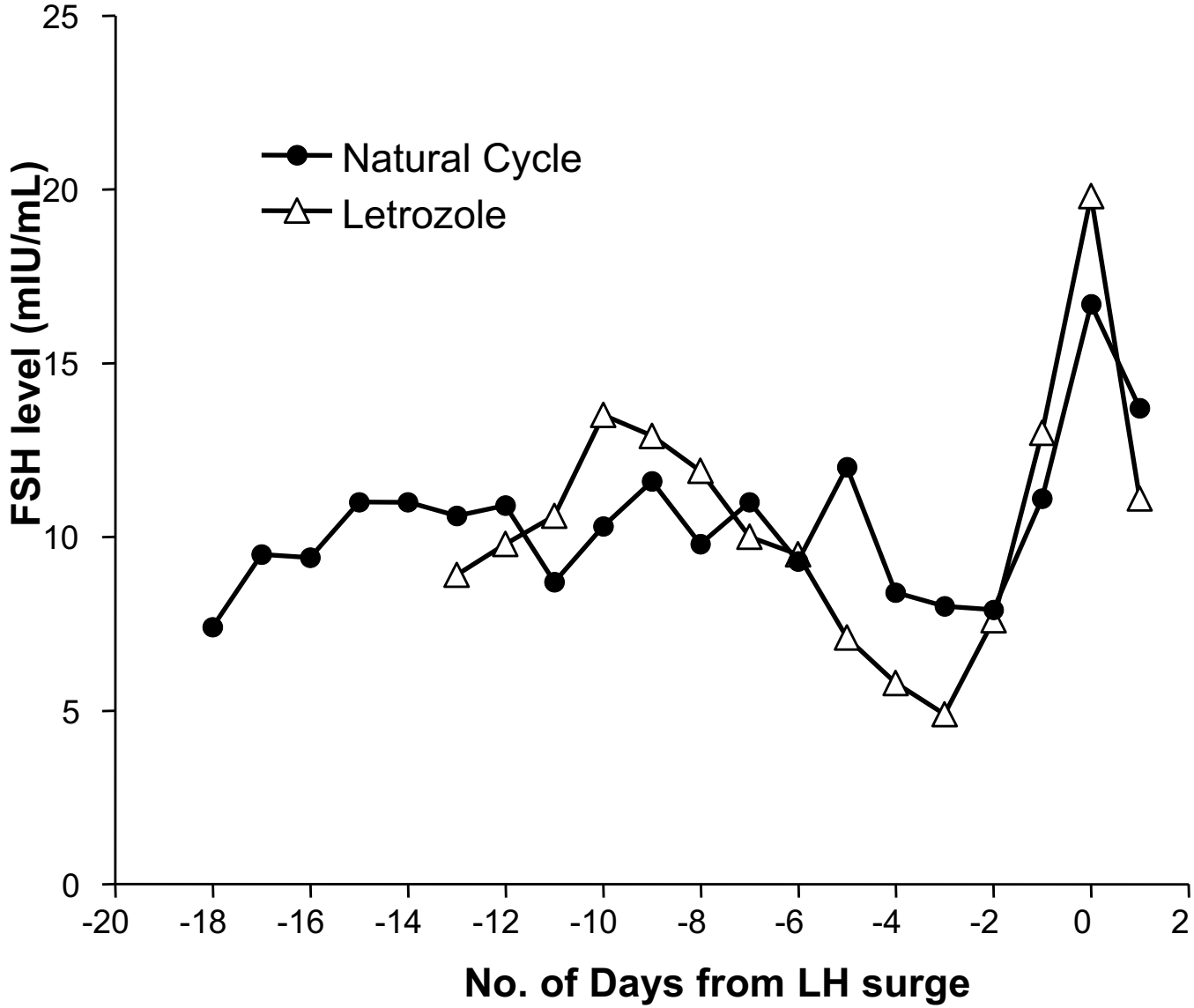
Aromatase Inhibitor Treatment



Day 5



Day 10



Fisher et al, Fertil Steril 2002

Aromatase Inhibitors Increase Ovarian FSH Sensitivity

- AI block intraovarian conversion of androgen to estrogen
- Result is increased intraovarian T and A_4
- Animal studies in 3 species all show increase in ovarian FSH receptor activity by androgens

Aromatase Inhibitors for Ovulation Induction

- Have both central and peripheral mechanisms of action
- No adverse ER effects and short half life
- Intact central feedback loop for estrogen and FSH
- Result in predominantly mono-ovulation when used alone

Letrozole Dose Response

TABLE 2

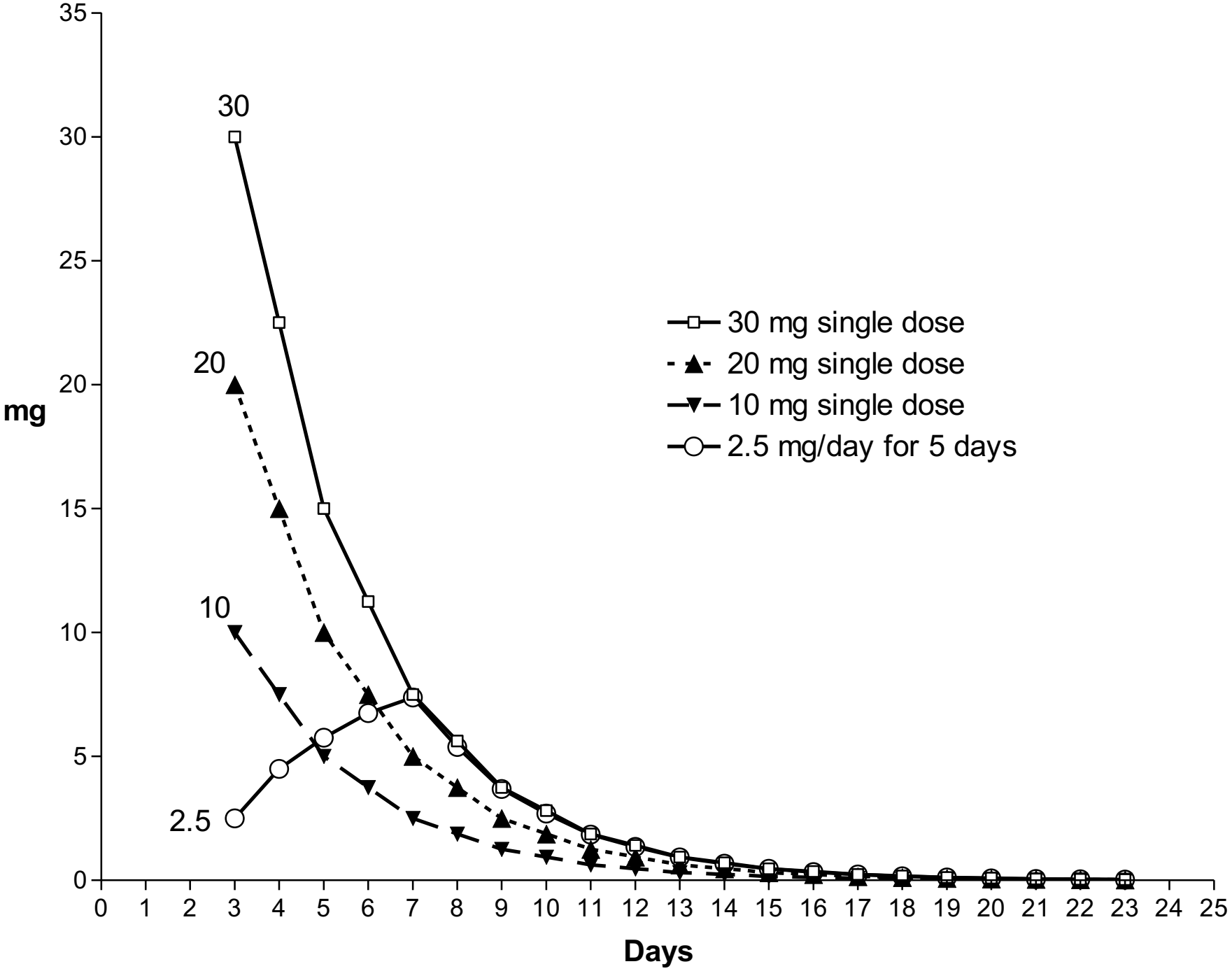
Results of superovulation with 2.5 mg and 5 mg of letrozole daily.

	Patient group		
	Letrozole 2.5 mg	Letrozole 5 mg	*P* value
No. of patients	34	38	
No. of days required to achieve follicular maturity	11.4 ± 0.4	11.7 ± 0.4	NS
No. of follicles >14 mm on day of hCG administration	1.3 ± 0.1	2.0 ± 0.1	<.001
No. of follicles ≥18 mm on day of hCG administration	1.1 ± 0.0	1.3 ± 0.1	<.05
Endometrial thickness (mm)	7.5 ± 0.3	7.8 ± 0.3	NS
Pregnancy rate per cycle started (%)	5.9%	26.3%	<.05

Note: NS = not statistically significant.

Al-Fadhli. RCT of two different doses of letrozole. Fertil Steril 2006.

Al-Fadhli et al, Fertil Steril 85:161, 2006


Letrozole Dose Remaining in Body
mg
Days
30
20
10
2.5
30 mg single dose
20 mg single dose
10 mg single dose
2.5 mg/day for 5 days
0
5
10
15
20
25
30
35
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25

Single dose letrozole

TABLE 1

Various characteristics of the letrozole single-dose regimen (alone or plus FSH) compared with the 5-day regimen (alone or plus FSH) treatment cycles.

	Letrozole only			Letrozole plus FSH		
	Single dose	*P*	5-Day regimen	Single dose	*P*	5-Day regimen
Day of hCG administration	11.9 ± 2.2	.26	11 ± 4.3	12.6 ± 2.7	.61	12 ± 3.4
Endometrial thickness (mm)	8.5 ± 2.4	.77	8.8 ± 1.9	0.84 ± 0.1	.14	9.2 ± 1.6
Follicles >1.5 cm	1.7 ± 0.7	.35	1.9 ± 0.8	2.8 ± 2.5	.97	2.8 ± 1.5
E_2 level (pmol/L)	642 ± 425	.30	784 ± 398	904 ± 430	.25	1,338 ± 976
FSH dose (unit/cycle)	NA	NA	NA	784 ± 532	.19	490 ± 330
Clinical pregnancy rate per cycle	15%	.27	18%	20%	.21	16.7%

Note: Data are presented as mean ± SD on the day of hCG administration (except pregnancy rate, which is presented as clinical pregnancy rate per cycle). $P < .05$ was considered statistically significant. NA = not available.

Mitwally. Single-dose aromatase inhibitor for ovarian stimulation. Fertil Steril 2005.

Mitwally and Casper, Fertil Steril 83:229-31, 2005

Comparison of CC and Aromatase Inhibitors for Ovulation Induction

RMN PPCOS II Study

- 750 infertile PCOS women
  - *Diagnosis of PCOS* via Modified Rotterdam Criteria (Must have ovulatory dysfunction and either hyperandrogenism or polycystic ovaries)
  - Exclude other endocrinopathies (thyroid, prolactin excess, NC-CAH, etc)
- In good health, no confounding medications
- Ages 18-39
- No BMI limits (but BMI counseling)

Legro et al, NEJM 2014

Improved Rate Ratio of Ovulation with Letrozole vs Clomiphene

CC 76.6% vs Let 88.5%

RR 1.16 (95% CI 1.08- 1.34)

Legro et al, NEJM 2014

Improved Rate Ratio of Total Ovulations with Letrozole vs Clomiphene

CC 688/1425 = 48.3%

Let 834/1425 = 61.7%

RR 1.28 (95% CI 1.19- 1.37)

Legro et al, NEJM 2014

Improved Rate Ratio of Live Birth with Letrozole vs Clomiphene

- RR 1.44 (95% CI 1.10- 1.87)

Legro et al, NEJM 2014

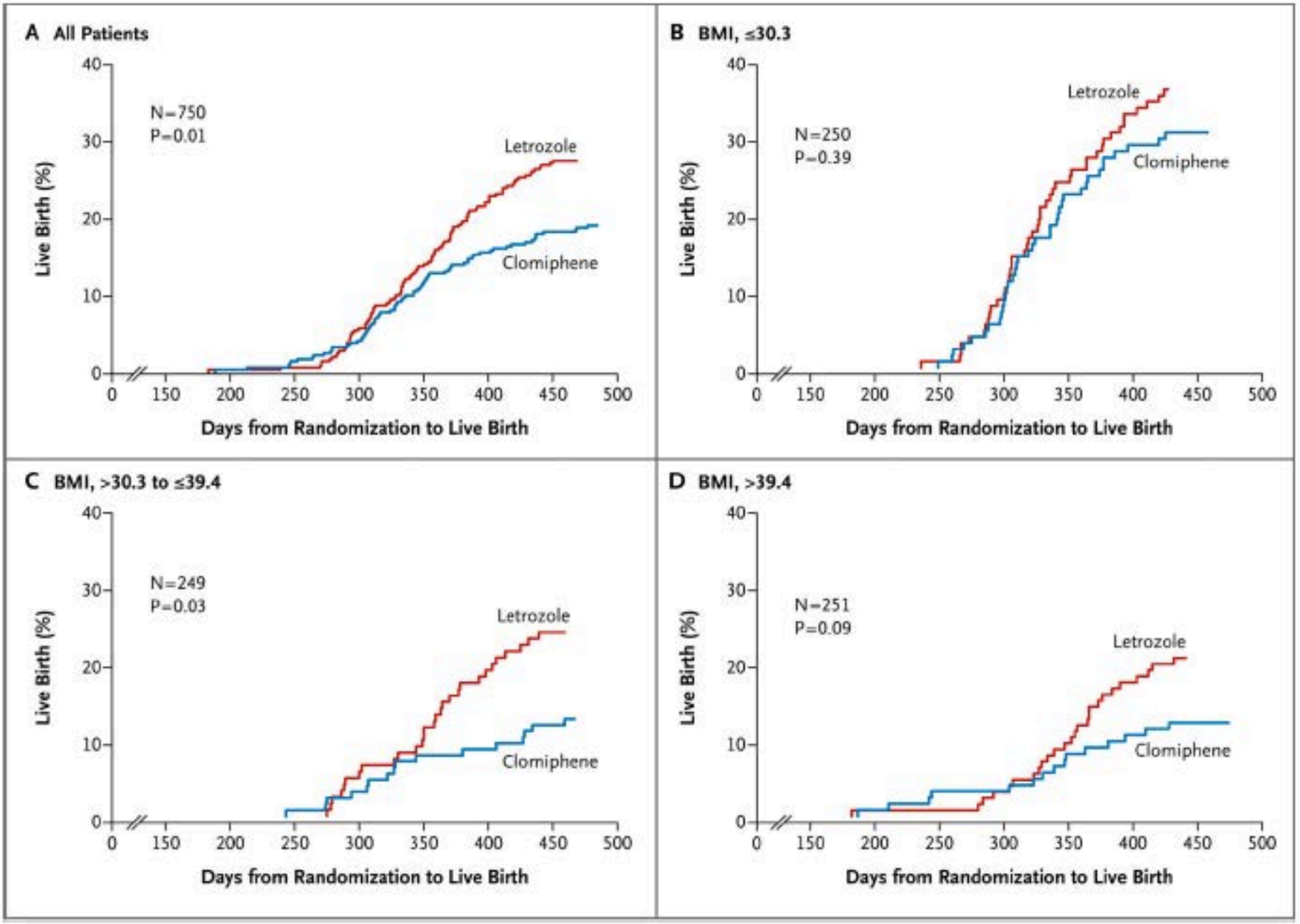


Figure 1. Kaplan–Meier Curves for Live Birth

Infant Outcomes

Outcome	Clomiphene group	Letrozole group	P value *
Infant birth weight (grams)	3230 ± 715	3232 ± 657	0.82
Twin live birth Rate (all diamnionic-dichorionic)	7.4%	3.2%	0.49

Legro et al, NEJM 2014

Conclusion of Study

- Letrozole is superior to Clomiphene
  - Cumulative live birth rate (trend consistent for all BMI tertiles)
  - Ovulation rates

Legro et al, NEJM 2014

Conclusion

- Letrozole should be considered as first line treatment for anovulatory infertility in PCOS

Legro et al, NEJM 2014

Cochrane Review 2018

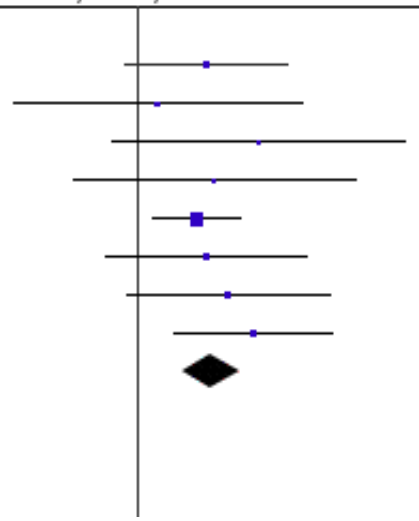
- Live birth rates higher with letrozole (with or without adjuncts) compared to clomiphene citrate (with our without adjuncts) followed by timed intercourse
- 2954 participants; 13 studies
- OR 1.68 (95% CI 1.42 to 1.99)
- Number needed to treat for an additional pregnany (NNTB) = 10
- Moderate-quality evidence

CC vs Letrozole

Study or Subgroup	Aromatase inhibitor Events	Total	Other agents for OI Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 AIs versus clomiphene citrate						
Amer 2017 (1)	39	80	28	79	6.9%	1.73 [0.92, 3.27]
Bayar 2006 (2)	8	40	7	40	2.7%	1.18 [0.38, 3.63]
Begum 2009 (3)	12	32	6	32	1.8%	2.60 [0.83, 8.13]
Dehbashi 2009 (4)	10	50	6	50	2.3%	1.83 [0.61, 5.50]
Legro 2014 (5)	103	374	72	376	24.9%	1.60 [1.14, 2.26]
Liu 2017 (6)	21	67	14	67	4.6%	1.73 [0.79, 3.78]
Ray 2012 (7)	20	69	13	78	4.1%	2.04 [0.93, 4.50]
Roy 2012 (8)	39	104	21	108	6.2%	2.49 [1.34, 4.62]
Subtotal (95% CI)		**816**		**830**	**53.4%**	**1.79 [1.42, 2.25]**
Total events	252		167			

Heterogeneity: $Chi^2 = 2.53$, $df = 7$ ($P = 0.92$); $I^2 = 0\%$

Test for overall effect: $Z = 5.01$ ($P < 0.00001$)



Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome (Review)
Cochrane Database of Systematic Reviews, 2018

Cochrane Review 2018

- Multiple pregnancy rate 1.7% with CC vs 1.3% with letrozole
- OR 0.69 (95% CI 0.41 to 1.16)
- 3579 participants; 17 studies
- High quality evidence

Summary

- Letrozole more effective than CC for ovulation induction in PCOS
- Higher pregnancy and live birth rates
- May be effective for CC failures
- Low risk of multiple pregnancy when used alone
- Short half-life
- No anti-estrogenic or estrogenic effects

Safety of Aromatase Inhibitors?

Multicenter Canadian Study

- 5 fertility clinics in Canada with experience with both letrozole and CC
- 911 babies born
- 514 babies following letrozole or letrozole plus FSH
- 397 babies following CC or CC plus FSH
- Congenital abnormalities recorded

Tulandi et al. Fertil Steril Jun 2006; 85(6): 1761–1765

Letrozole vs CC

	Letrozole	Letrozole + FSH	CC	CC + FSH
Newborns	252	262	293	104
Birth weight (grams)	3287 ± 616	3248 ± 639	3159 ± 609	3323 ± 365
Twins	12 (4.8%)	23 (8.8%)	15 (5.1%)	6 (5.8%)
Triplets	1	1	1 (fetal reduction to twins)	1
Age of mother (years)	33.1 ± 5.3	32.4±5.4	32.9 ± 4.5	33.9 ± 4.9

Tulandi et al. Fertil Steril Jun 2006; 85(6): 1761–1765

Congenital Malformations and Chromosomal Abnormalities

- Overall malformation rate
  - 14 of 514 newborns with letrozole (2.4%)
  - 19 of 397 newborns with CC (4.8%)

- Major malformation rate
  - letrozole 1.2 % (6/514)
  - CC 3.0% (12/397)

Tulandi et al. Fertil Steril Jun 2006; 85(6): 1761–1765

Cardiac Anomalies

- Letrozole group

  1/514 (0.2%)

- CC group

  7/397 (1.8%)

P = 0.02

Tulandi et al. Fertil Steril Jun 2006; 85: 1761–1765

Conclusion

- Letrozole use for ovulation induction is not associated with an increased risk of birth defects when compared to CC
- CC may be associated with an increased risk of cardiac anomalies

Meta-analysis ASRM 2019

- Total 4613 babies reported from 44 studies with the use of letrozole
- 94 (2.04%) babies were born with congenital malformations
- 21 (0.46%) babies were born with major congenital malformations
- Not different from natural conceptions

Pundir et al, ASRM O-69, Oct 14, 2019

AIs as First Line Treatment

- Similar efficacy to CC for ovulation induction
- Appear to be efficacious in CC failures
- No adverse ER effects
- Short half life and no accumulation from cycle to cycle
- Low multiple pregnancy rate in PCOS
- Reduced need for monitoring
- Newer data indicates AIs are safe with no adverse fetal effects when used for ovulation