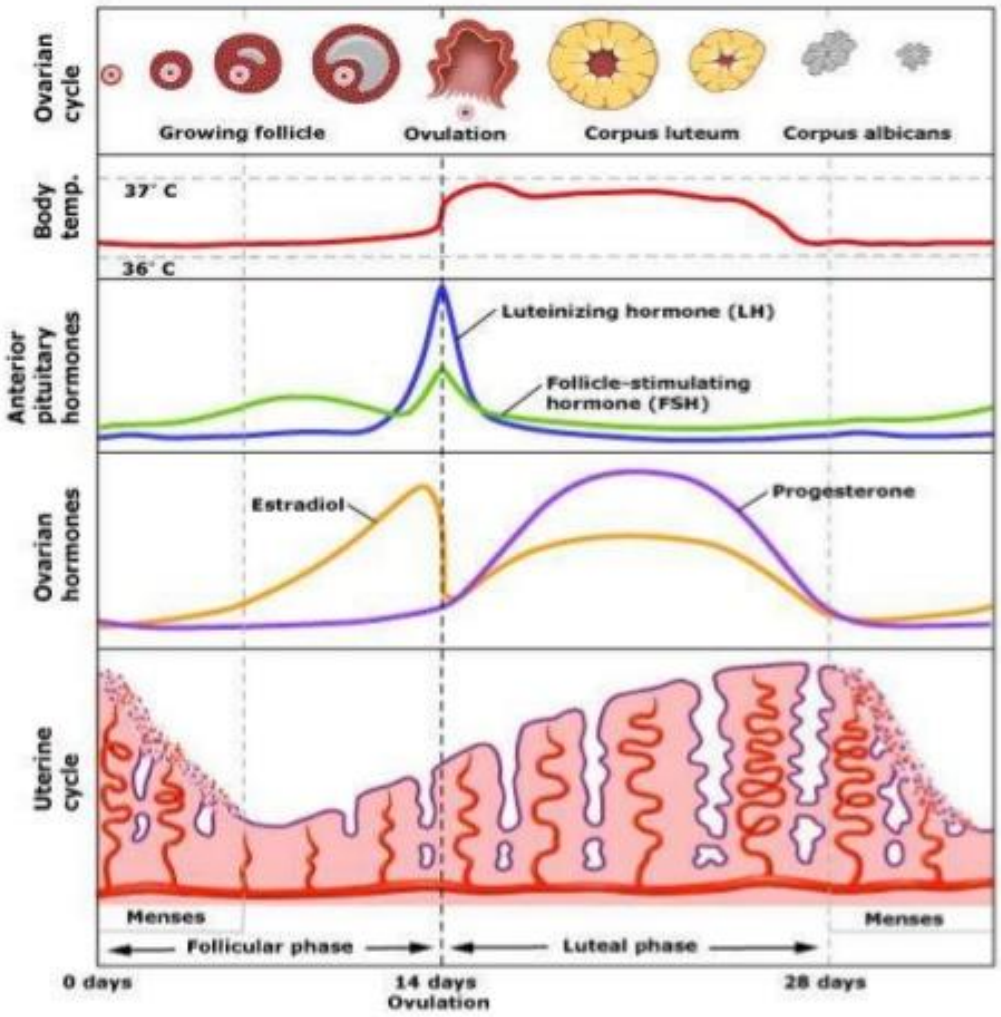
외래 **base** 에서 활용할 수 있는 기초적인 배란유도 및 초음파 검사법

Soo Jin Chae, M.D.

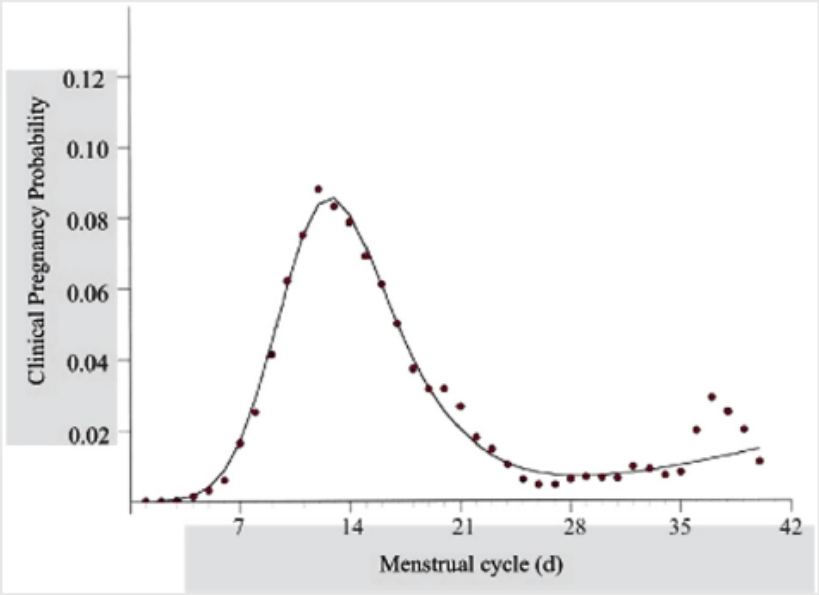
Maria Fertility Hospital

Menstruation



Natural fertility

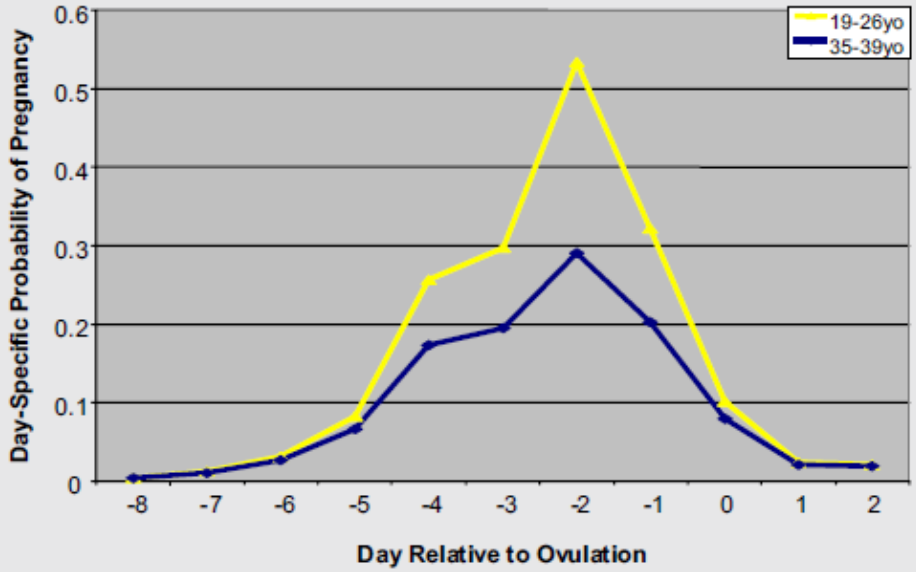
FIGURE 2



Probability of pregnancy with a single act of intercourse. Modified from Dunson et al. (14).

Practice Committee. Optimizing natural fertility. Fertil Steril 2013.

FIGURE 3



Probability of pregnancy by cycle day, involving recurrent intercourse, by age. Data from Stanford and Dunson 2007 (16).

Practice Committee. Optimizing natural fertility. Fertil Steril 2013.

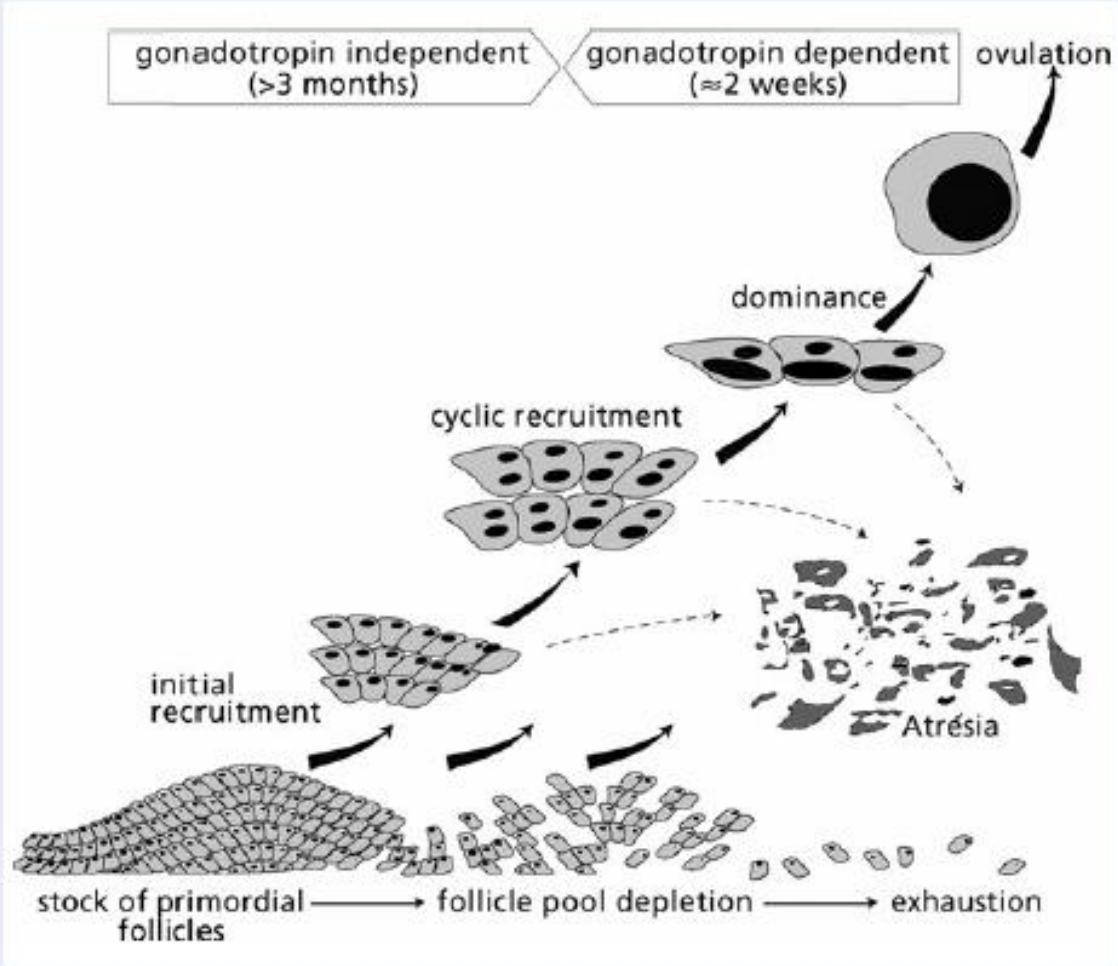


Figure 1 Schematic representation of life history of ovarian follicles: endowment and maintenance, initial recruitment, maturation, atresia or cyclic recruitment, ovulation, and exhaustion. Adapted from McGee and Hsueh (2000).

Verberg et al., 2009. Hum Reprod Update;15:13-29.

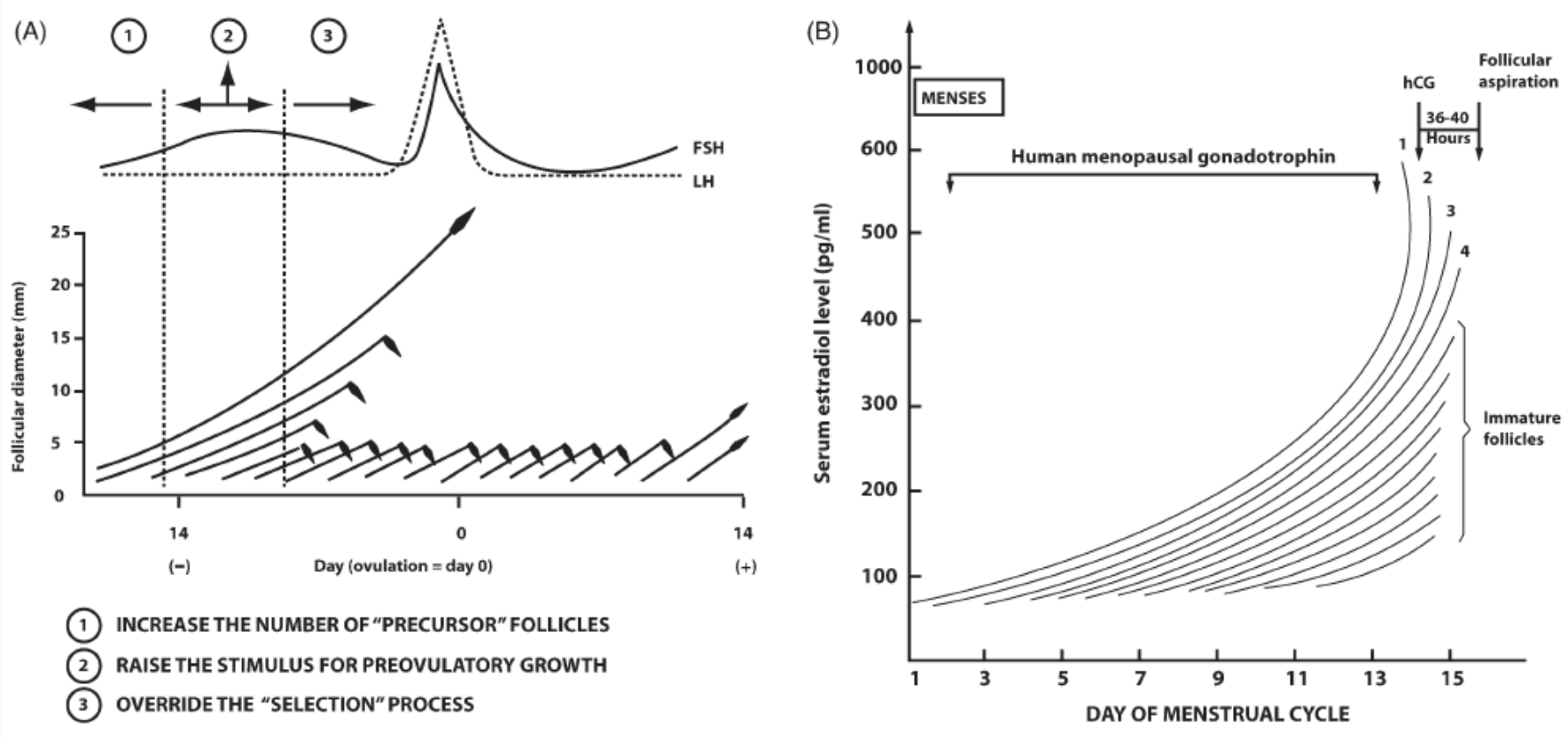


Figure 3 (A) Schematic representation of serum FSH levels and number and size of ovarian follicles during ovarian stimulation for IVF (Hillier *et al.*, 1985). (B) Schematic representation of the heterogeneous cohort of recruited and selected follicles in HMG-stimulated cycles for IVF (Oehninger and Hodgen, 1990).

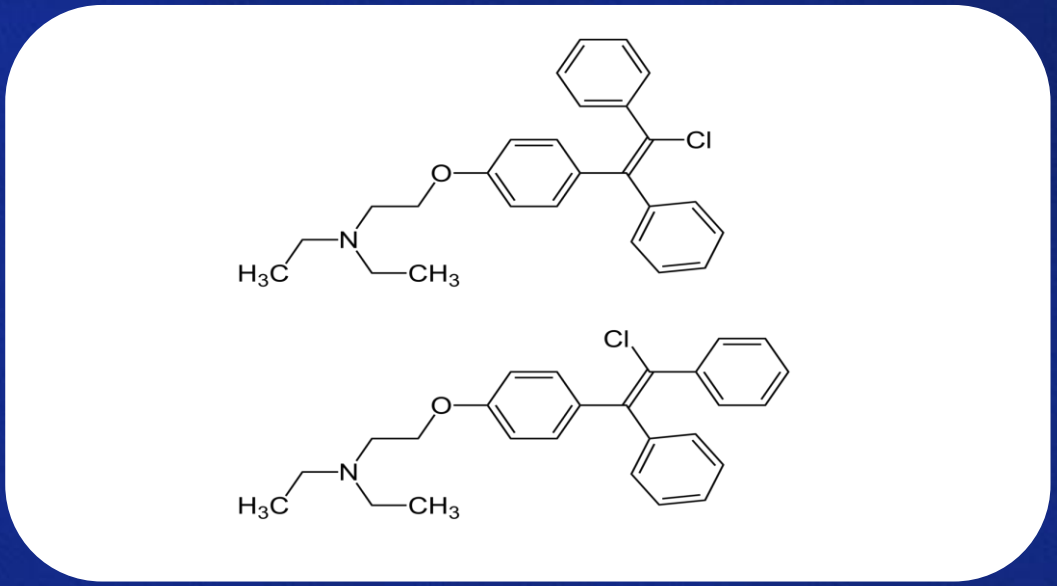
Verberg et al., 2009. Hum Reprod Update;15:13-29.

Ovulation induction

- Clomiphene citrate
- Letrozole
- Gonadotropin

Clomiphene citrate

- Synthetic nonsteriodal triphenylethylene derivative antiestrogen

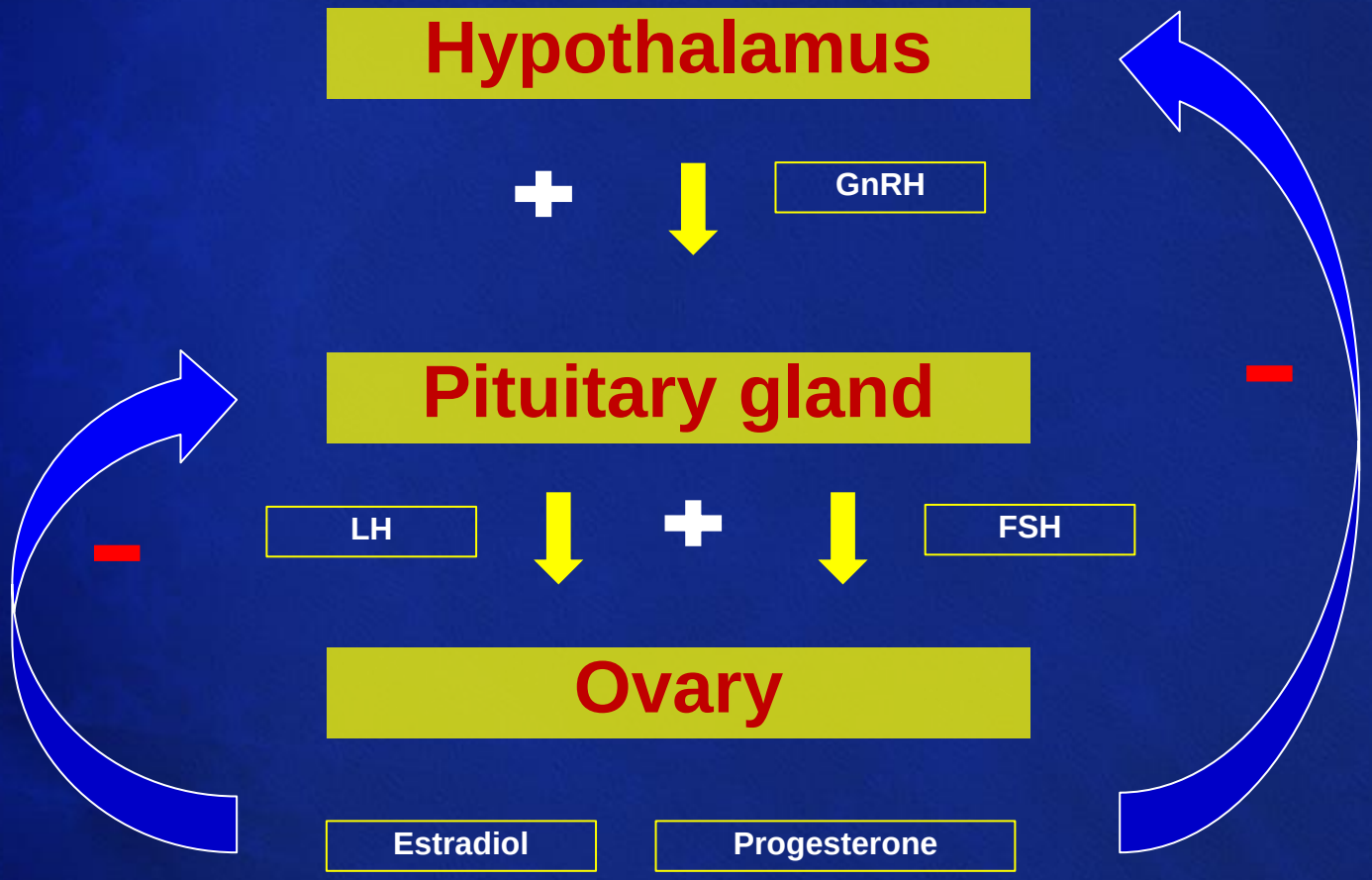


- Approved by the U.S. FDA in 1967
- Metabolism
  - Hepatic: 85% eliminated after 6days
  - Excretion: stool (42%) renal (8%)

Clomiphene citrate

- Enclomiphene vs Zuclomiphene> 3:2
- Enclomiphene
  - more potent
  - rapid rise and fall
- Zuclomiphene
  - clear more slowly

H-P-O axis


Hypothalamus
+
GnRH
Pituitary gland
LH
+
FSH
Ovary
Estradiol
Progesterone
-
-

Mode of action

- Bind to nuclear ER
- Deplete ER concentration by intefering with ER replenishment
- Actions at the hypothalamus level
- Reduced estrogen negative feedback trigger compensatory hypothalamic GnRH secretion and pituitary gonadotropin release

ASRM, 2013. Fertil Steril;10:341-8.

Mode of action

- Ovulatory cycle
  - Increase GnRH pulse frequency
- Anovulatory PCOS
  - Increase pulse amplitude

ASRM, 2013. Fertil Steril;10:341-8.

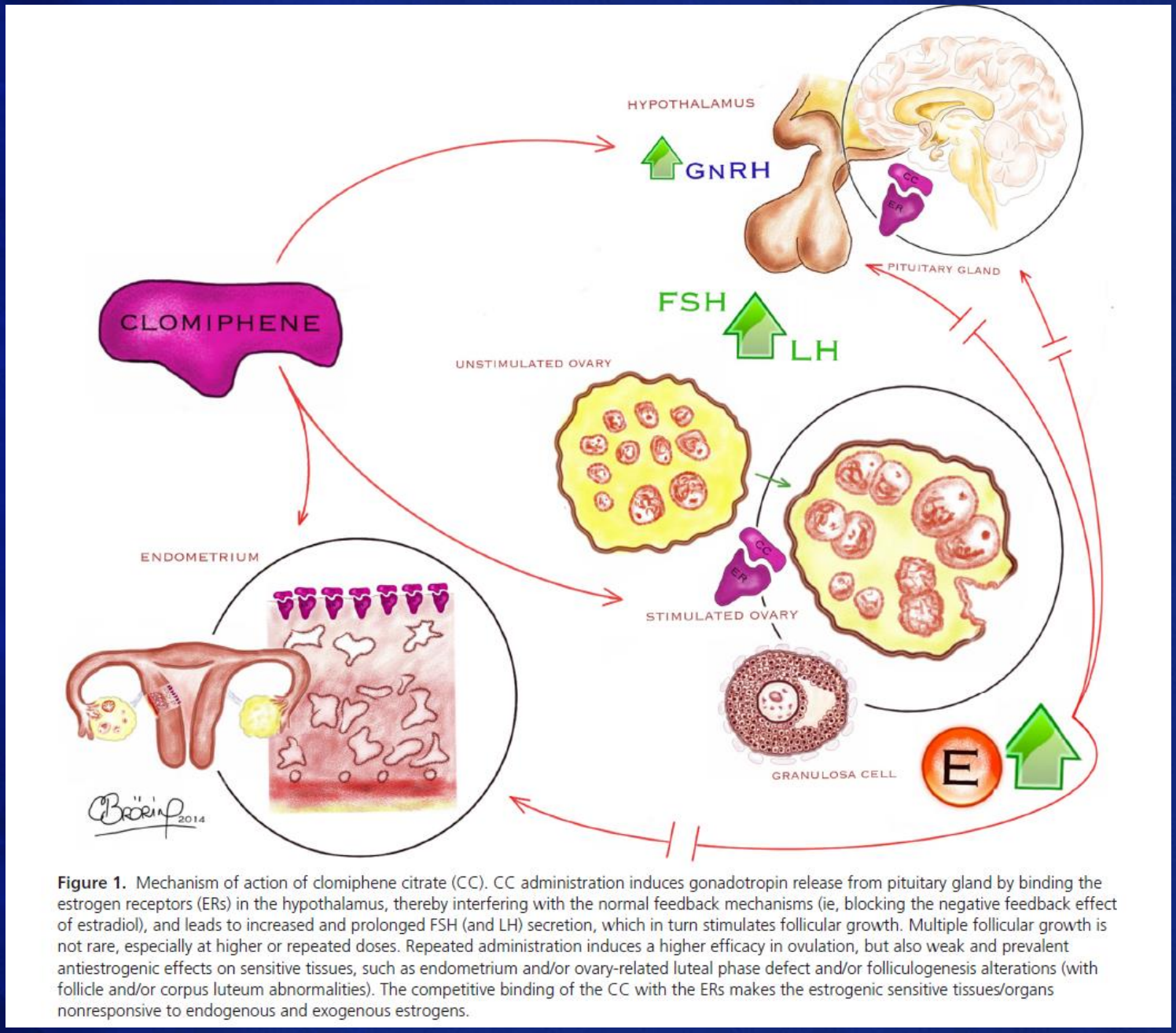


Figure 1. Mechanism of action of clomiphene citrate (CC). CC administration induces gonadotropin release from pituitary gland by binding the estrogen receptors (ERs) in the hypothalamus, thereby interfering with the normal feedback mechanisms (ie, blocking the negative feedback effect of estradiol), and leads to increased and prolonged FSH (and LH) secretion, which in turn stimulates follicular growth. Multiple follicular growth is not rare, especially at higher or repeated doses. Repeated administration induces a higher efficacy in ovulation, but also weak and prevalent antiestrogenic effects on sensitive tissues, such as endometrium and/or ovary-related luteal phase defect and/or folliculogenesis alterations (with follicle and/or corpus luteum abnormalities). The competitive binding of the CC with the ERs makes the estrogenic sensitive tissues/organs nonresponsive to endogenous and exogenous estrogens.

Palomba., 2015. J Clin Endocrinol Metab;100:1742-47.

Treatment regimens

- The 3rd to 5th day after the spontaneous or progestin-induced menses
- Ovulation rates, conception rates, and pregnancy outcome are same whether the starting on MCD#2-5
- Anovulatory women

Cumulative pregnancy rate	50mg/d	100mg/d	150mg/d
3months	50%	45%	33%
6months	62%	66%	38%

Imani et al., J Clin Endocrinol Metab, 1999

ASRM, 2013. Fertil Steril;10:341-8.

Treatment regimens

- 50mg daily for 5 consecutive days
- The effective dose: 50mg/d to 250mg/d

- Ovulation rate: 50mg (52%)

ASRM, 2013. Fertil Steril;10:341-8.

Treatment regimens

- Those who do not ovulate with 50 mg CC may ovulate at higher doses using a step-up regimen with doses escalating 50 mg with each anovulatory cycle
  - 22% with 100mg
  - 12% with 150mg
  - 7% with 200mg
  - 5% with 250mg

Gysler et al., Fertil Steril, 1982

ASRM, 2013. Fertil Steril;10:341-8.

Treatment regimens

- In obese, anovulatory women with at least 2 years of infertility, success rates generally are lower
- Live birth rate
  - 16% in women with BMI >35 kg/m2
  - 28% in women with BMI <30 kg/m2

Legro et al., NEJM 2007

- Pregnancy is most likely to occur in the first 3 to 6 cycles
- Therapy beyond 6 cycles is generally not recommended

ASRM, 2013. Fertil Steril;10:341-8.

Stair-step protocol

CC 50mg for 5days

↓

USG on days 11-14

↓ No dominant follicle is seen

CC 100mg for 5 days

↓

Repeat USG in 1 week

↓ No dominant follicle is seen

CC 150mg for 5days

↓

Repeat USG in 1 week

	Stair-step protocol	Traditional protocol
CC 100mg ovulation rate	64%	22%
Clinical pregnancy rate	13%	15%

Hust et al., Am J Obstet Gynecol 2009;200:510

Treatment regimens

- Inducing a menstrual bleed with progestins before CC in anovulatory cycle showed a lower conception and live birth rate than starting in the follicular phase remote from spontaneous or induced menses

  Diamond., Obstet Gynecol 2002

- In women treated with conventional CC step-up regimen
  - a overall cumulative pregnancy rate : 55%–73%

- Increasing age and duration of infertility a/w Tx failure

Side effects

- Vasomotor flushes 10%
- Mood swing
- Visual disturbance <2%
  - Blurred or double vision
  - Scotoma
  - Light sensitivity
  - Persist: optic neuropathy

ASRM, 2013. Fertil Steril;10:341-8.

Side effects

- Poor cervical mucus
- Reduced endometrial thickness
- Breast tenderness
- Pelvic discomfort
- Nausea
- Multiple pregnancy
- OHSS

ASRM, 2013. Fertil Steril;10:341-8.

CC + Metformin

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 8, 2007 VOL. 356 NO. 6

Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome

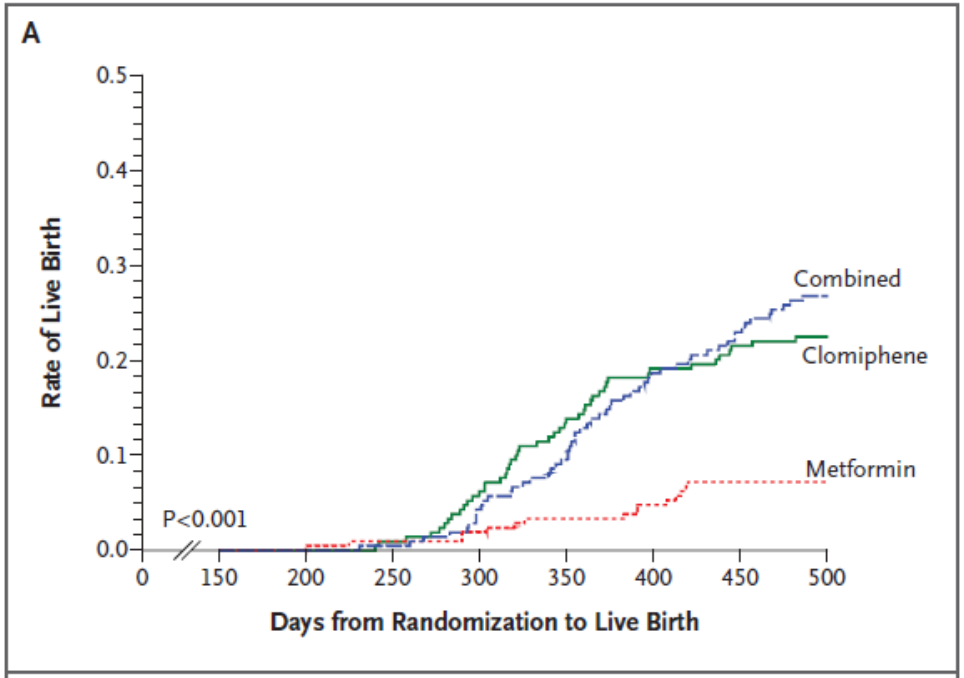
Richard S. Legro, M.D., Huiman X. Barnhart, Ph.D., William D. Schlaff, M.D., Bruce R. Carr, M.D., Michael P. Diamond, M.D., Sandra A. Carson, M.D., Michael P. Steinkampf, M.D., Christos Coutifaris, M.D., Ph.D., Peter G. McGovern, M.D., Nicholas A. Cataldo, M.D., Gabriella G. Gosman, M.D., John E. Nestler, M.D., Linda C. Giudice, M.D., Ph.D., Phyllis C. Leppert, M.D., Ph.D., and Evan R. Myers, M.D., M.P.H., for the Cooperative Multicenter Reproductive Medicine Network*

N Engl J Med 2007;356:551-66.

Table 2. Rates of Ovulation, Pregnancy, and Pregnancy Loss.*

N Engl J Med 2007;356:551-66.

Variable	Clomiphene Group (N=209)	Metformin Group (N=208)	Combination-Therapy Group (N=209)	Absolute Difference between Combination Therapy and Metformin	P Value	Absolute Difference between Combination Therapy and Clomiphene	P Value	Absolute Difference between Clomiphene and Metformin	P Value
	no./total no. (%)			*% (95% CI)*		*% (95% CI)*		*% (95% CI)*	
Ovulation	462/942 (49.0)	296/1019 (29.0)	582/964 (60.4)	31.4 (24.7 to 38.0)	<0.001	11.4 (4.2 to 18.4)	0.003	20.0 (9.1 to 30.9)	<0.001
Conception	62/209 (29.7)	25/208 (12.0)	80/209 (38.3)	26.3 (18.4 to 34.2)	<0.001	8.6 (–0.4 to 17.6)	0.06	17.7 (10.1 to 25.3)	<0.001
Pregnancy	50/209 (23.9)	18/208 (8.7)	65/209 (31.1)	22.4 (15.0 to 29.8)	<0.001	7.2 (–1.3 to 15.7)	0.10	15.2 (8.3 to 22.1)	<0.001
Singleton	47/50 (94.0)	18/18 (100.0)	63/65 (96.9)	–3.1 (–7.3 to 1.1)	0.96	2.9 (–4.9 to 10.7)	0.45	–6.0 (–12.6 to 0.6)	0.95
Twins	2/50 (4.0)	0	2/65 (3.1)	–3.1 (–10.1 to 16.3)	1.0	–0.9 (–9.8 to 8.0)	1.0	4.0 (–9.9 to 17.9)	1.0
Triplets	1/50 (2.0)	0	0	0 (–12.7 to 12.7)	1.0	–2.0 (–12.7 to 12.7)	1.0	2.0 (–11.5 to 15.5)	1.0
Other	0	0	0	0 (–12.7 to 12.7)	1.0	0 (–6.4 to 6.4)	1.0	0 (–13.0 to 13.0)	1.0
Live birth	47/209 (22.5)	15/208 (7.2)	56/209 (26.8)	19.6 (12.6 to 26.6)	<0.001	4.3 (–4.0 to 12.6)	0.31	15.3 (8.6 to 22.0)	<0.001



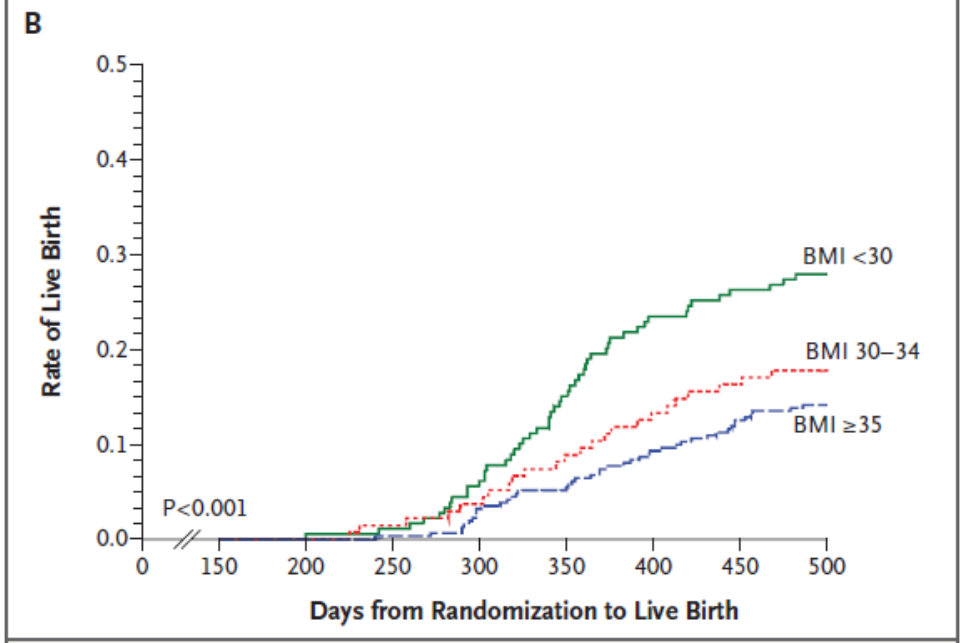


Figure 2. Kaplan–Meier Curves for Live Birth, According to Study Group (Panel A) and Body-Mass Index (BMI) (Panel B).

Clomiphene is superior to metformin in achieving live birth in women with PCOS

N Engl J Med 2007;356:551-66.

CC + Metformin

- For those women who fail to ovulate with CC, metformin has been advocated to improve ovulation and pregnancy rates in response to CC
  - Several small randomized, controlled studies

ASRM, 2013. Fertil Steril;10:341-8.

CC + Glucocorticoids

- CC 50 mg per day, increasing as needed to 150 mg
- CC plus dexamethasone 0.5 mg daily

	CC only	CC + Steriod	P
Ovulation	14/22 (63.6%)	23/23 (100%)	<0.05
Conception	8/14 (57.1%)	17/23 (78.9%)	<0.05

Daly et al., Fertil Steril, 1984:41:844-8.

CC + Gonadotropins

- Standard CC treatment regimen, followed by low-dose hMG or FSH (75–150 IU/day for 3 days)
- Transvaginal ultrasound examinations with or without serum estradiol assessment

MCD #2-5

Letrozole

- Aromatase inhibitor
- Block estrogen synthesis, directly affect hypothalamic–pituitary–ovarian function

- Potential advantages
  - more physiologic hormonal stimulation of the endometrium
  - lower multiple-pregnancy rate through single-follicle recruitment
  - fewer vasomotor and mood symptoms
  - more rapid clearance, reducing the chances of periconceptional exposure

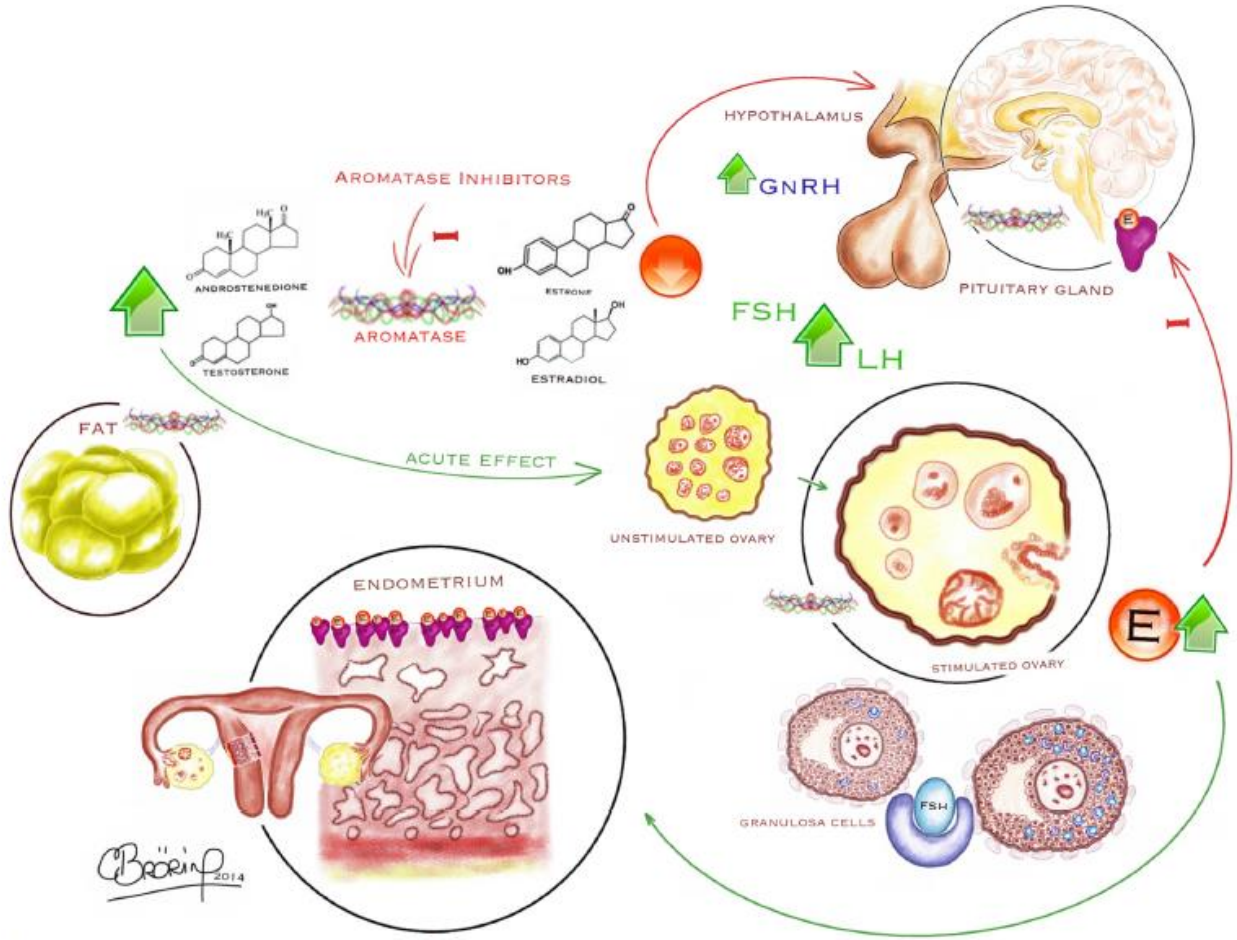


Figure 2. Mechanism of action of aromatase inhibitors (AIs). AIs exert an ovulation-inducing effect by inhibiting the aromatase, and ubiquitous (but mostly found in the granulosa cells, fat tissue, and placenta) cytochrome P450 enzyme complex. It is responsible for the androgen-to-estrogen conversion and, specifically for the conversion of C19 steroids [androgens, such as androstene-3,17-dione (A) and testosterone (T)] to C-I8 steroids (estrogens, such as estrone and estradiol, respectively) via the loss of the C-19 methyl group from the substrate and the formation of a benzoid A-ring (aromatization or 3-hydroxylation), that is the rate-limiting step in estrogen synthesis. AI administration induces an acute hypoestrogenic state that releases the hypothalamic-pituitary axis from estrogenic negative feedback, which in turn increases FSH secretion and ovarian follicle development. An effect of AIs on the CNS has been suggested. AIs increase serum LH, androstenedione (A), and testosterone (T) levels; the acute intraovarian increase in androgen levels acts on follicular growth, thereby increasing follicular sensitivity to FSH by amplification of FSH gene expression and/or stimulating insulin growth factor 1 (IGF-I), which may synergize with FSH. The normal negative-feedback of FSH with inhibin does not appear to be affected by AIs. In fact, under AI administration, no estrogen receptor (ER) antagonism (neither peripheral nor central) has been shown, and the physiologic protective mechanism for multiple ovulation and ovarian hyperstimulation syndrome (OHSS) should be preserved since as the dominant follicle grows and estrogen levels rise, normal suppression of FSH and atresia of the smaller growing follicles occurs. The suppression of the estrogen concentrations in the circulation and peripheral tissues can result in up-regulation of ERs in the endometrium, leading to rapid endometrial growth once estrogen secretion is restored.

Palomba., 2015. J Clin Endocrinol Metab;100:1742-47.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome

Richard S. Legro, M.D., Robert G. Brzyski, M.D., Ph.D., Michael P. Diamond, M.D., Christos Coutifaris, M.D., Ph.D., William D. Schlaff, M.D., Peter Casson, M.D., Gregory M. Christman, M.D., Hao Huang, M.D., M.P.H., Qingshang Yan, Ph.D., Ruben Alvero, M.D., Daniel J. Haisenleder, Ph.D., Kurt T. Barnhart, M.D., G. Wright Bates, M.D., Rebecca Usadi, M.D., Scott Lucidi, M.D., Valerie Baker, M.D., J.C. Trussell, M.D., Stephen A. Krawetz, Ph.D., Peter Snyder, M.D., Dana Ohl, M.D., Nanette Santoro, M.D., Esther Eisenberg, M.D., M.P.H., and Heping Zhang, Ph.D., for the NICHD Reproductive Medicine Network*

As compared with clomiphene, letrozole was associated with higher live-birth and ovulation rates among infertile women with the polycystic ovary syndrome

N Engl J Med 2014;371:119-29.

Table 2. Outcomes with Regard to Live Birth, Ovulation, Pregnancy, Pregnancy Loss, and Fecundity.*

Outcome	Clomiphene Group (N=376)	Letrozole Group (N=374)	Absolute Difference between Groups (95% CI)†	Rate Ratio in Letrozole Group (95% CI)	P Value‡
Primary outcome					
Live birth — no. (%)	72 (19.1)	103 (27.5)	8.4 (2.4 to 14.4)	1.44 (1.10 to 1.87)	0.007
Singleton live birth — no./total no. (%)	67/72 (93.1)	99/103 (96.1)	3.1 (–3.9 to 10.0)	1.03 (0.96 to 1.11)	0.49
Twin live birth — no./total no. (%)§	5/72 (6.9)	4/103 (3.9)	–3.0 (–10.0 to 3.9)	0.56 (0.16 to 2.01)	0.49
Birth weight					
No. of infants	71	102			
Mean weight — g	3229.9±715.3	3232.3±657.4	2.4 (–205.6 to 210.4)		0.83
Sex ratio at birth (boys:girls)	0.88 (36:41)	0.65 (42:65)		0.74 (0.41 to 1.33)¶	
Duration of pregnancy					
No. of women	72	101			
Mean duration — wk	38.0±3.6	38.4±2.7	0.4 (–0.6 to 1.4)		0.59

Table 2. Outcomes with Regard to Live Birth, Ovulation, Pregnancy, Pregnancy Loss, and Fecundity.*

Outcome	Clomiphene Group (N=376)	Letrozole Group (N=374)	Absolute Difference between Groups (95% CI)†	Rate Ratio in Letrozole Group (95% CI)	P Value‡
Secondary outcomes					
Pregnancy					
Conception — no. of women (%)	103 (27.4)	154 (41.2)	13.8 (7.1 to 20.5)	1.50 (1.23 to 1.84)	<0.001
Pregnancy — no. of women (%)	81 (21.5)	117 (31.3)	9.7 (3.5 to 16.0)	1.45 (1.14 to 1.85)	0.003
Twin pregnancy — no. of women/ total no. of pregnancies (%)	6/81 (7.4)	4/117 (3.4)	–4.0 (–10.6 to 2.6)	0.46 (0.13 to 1.58)	0.32
Time to pregnancy					
No. of women	90	145			
Mean time — days	85.9±48.8	90.4±44.4	4.5 (–8.0 to 17.0)		0.27
Pregnancy loss					
Pregnancy loss among women who conceived — no./total no. (%)	30/103 (29.1)	49/154 (31.8)	2.7 (–8.7 to 14.1)	1.09 (0.75 to 1.60)	0.65
Loss in first trimester — no./ total no. (%)	29/103 (28.2)	45/154 (29.2)	1.1 (–10.2 to 12.3)	1.04 (0.70 to 1.54)	0.85
Ovulation					
Women who ovulated — no. (%)	288 (76.6)	331 (88.5)	11.9 (6.5 to 17.3)	1.16 (1.08 to 1.24)	<0.001
No. of ovulations/total treatment cycles (%)	688/1425 (48.3)	834/1352 (61.7)	13.4 (9.7 to 17.1)	1.28 (1.19 to 1.37)	<0.001
Fecundity among women who ovulated — no./total no. (%)					
Conception	103/288 (35.8)	154/331 (46.5)	10.8 (3.1 to 18.5)	1.31 (1.07 to 1.58)	0.007
Singleton pregnancy	75/288 (26.0)	113/331 (34.1)	8.1 (0.9 to 15.3)	1.31 (1.03 to 1.58)	0.03
Singleton live birth	67/288 (23.3)	99/331 (29.9)	6.6 (–0.3 to 13.6)	1.29 (0.98 to 1.68)	0.06

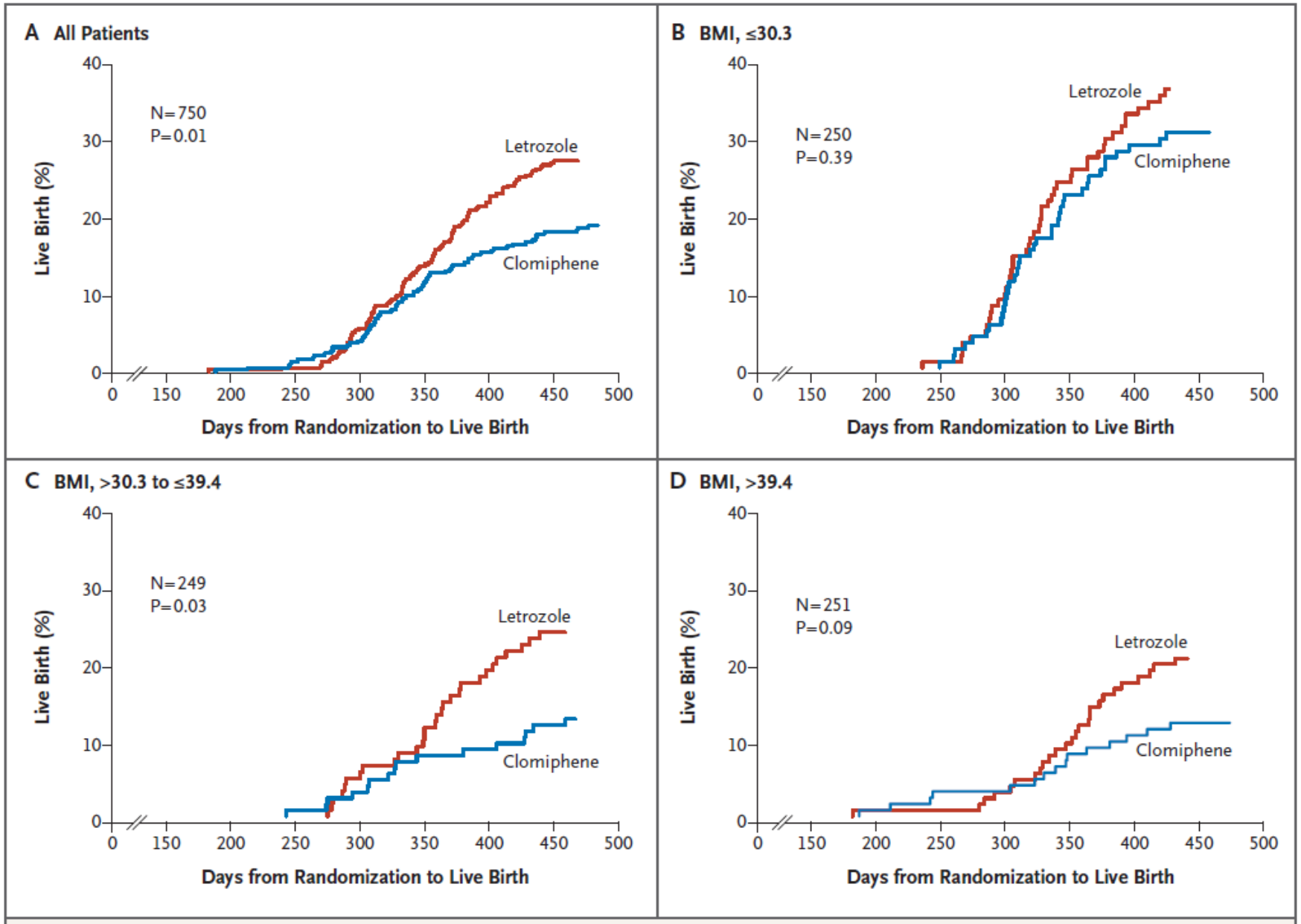


Figure 1. Kaplan–Meier Curves for Live Birth.

Live-birth rates are shown according to treatment group in Panel A and according to treatment group and maternal body-mass index (BMI, the weight in kilograms divided by the square of the height in meters), in thirds, in Panels B, C, and D.

Table 3. All Serious Adverse Events, plus Other Adverse Events with Significant Differences between the Treatment Groups.*

Event	Clomiphene Group	Letrozole Group
	no. of women/total no. (%)	
Event before conception in women who received a study drug		
Serious adverse event		
Ovarian torsion	1/355 (0.3)	0/359
Ruptured corpus luteum cyst	0/355	1/359 (0.3)
Hospitalization†	3/355 (0.8)	2/359 (0.6)
Other adverse event		
Hot flushes‡	117/355 (33.0)	73/359 (20.3)
Fatigue§	53/355 (14.9)	78/359 (21.7)
Dizziness§	27/355 (7.6)	44/359 (12.3)
Serious adverse event after conception in women who discontinued the study drug		
First trimester		
Ectopic pregnancy	3/94 (3.2)	4/149 (2.7)
Heterotopic pregnancy	1/94 (1.1)	0/149
Pregnancy of unknown location	1/94 (1.1)	1/149 (0.7)
Hospitalization¶	2/94 (2.1)	4/149 (2.7)
Second and third trimester		
Hospitalization for premature labor	0/94	2/149 (1.3)
Hospitalization for other reasons‖	2/94 (2.1)	7/149 (4.7)
Postpartum anemia requiring transfusion after delivery	0/94	1/149 (0.7)
Serious adverse event after 20 wk of pregnancy in fetus through neonatal period in infant		
Congenital anomaly**	1/66 (1.5)	4/102 (3.9)
Fetal death	1/66 (1.5)	1/102 (1.0)
Neonatal death	2/66 (3.0)	1/102 (1.0)

SPECIAL FEATURE

Controversy in Clinical Endocrinology

Aromatase Inhibitors for Ovulation Induction

Stefano Palomba

Unit of Reproductive Medicine, ASMN-IRCCS of Reggio Emilia, Italy

Letrozole is an effective drug for treating anovulatory infertile patients with PCOS, though it cannot yet be considered the first-line approach for these patients since further studies are needed to validate its better efficacy/safety over CC in other settings and to clarify its role in well-codified strategies and algorithms for ovulation induction

J Clin Endocrinol Metab, May 2015, 100(5):1742–1747

The NEW ENGLAND JOURNAL of MEDICINE

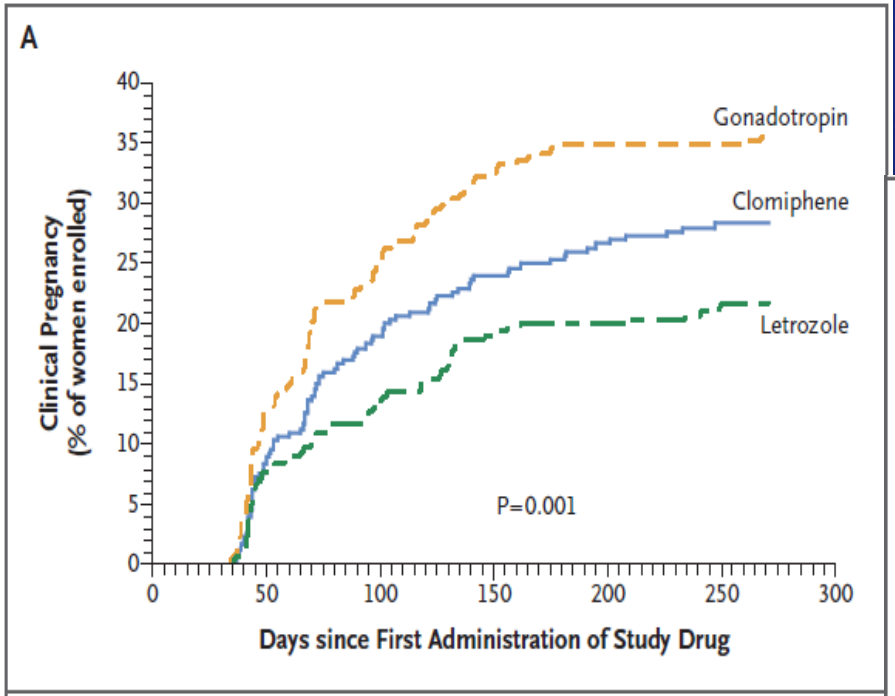
ORIGINAL ARTICLE

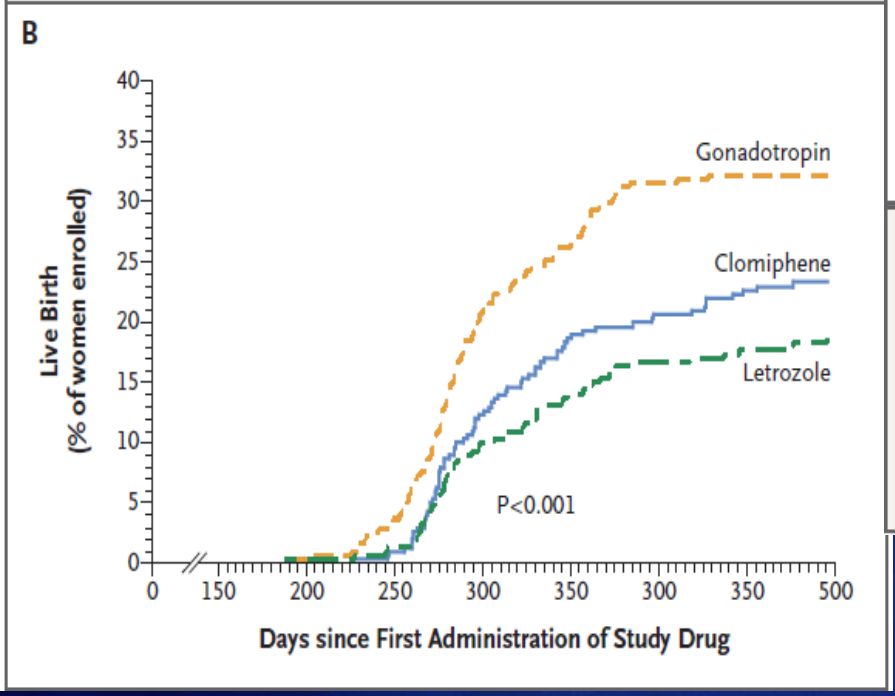
Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility

M.P. Diamond, R.S. Legro, C. Coutifaris, R. Alvero, R.D. Robinson, P. Casson, G.M. Christman, J. Ager, H. Huang, K.R. Hansen, V. Baker, R. Usadi, A. Seungdamrong, G.W. Bates, R.M. Rosen, D. Haisenleder, S.A. Krawetz, K. Barnhart, J.C. Trussell, D. Ohl, Y. Jin, N. Santoro, E. Eisenberg, and H. Zhang, for the NICHD Reproductive Medicine Network*

Ovarian stimulation with letrozole resulted in a significantly lower frequency of multiple gestation but also a lower frequency of live birth, as compared with gonadotropin but not as compared with clomiphene

N Engl J Med 2015;373:1230-40.





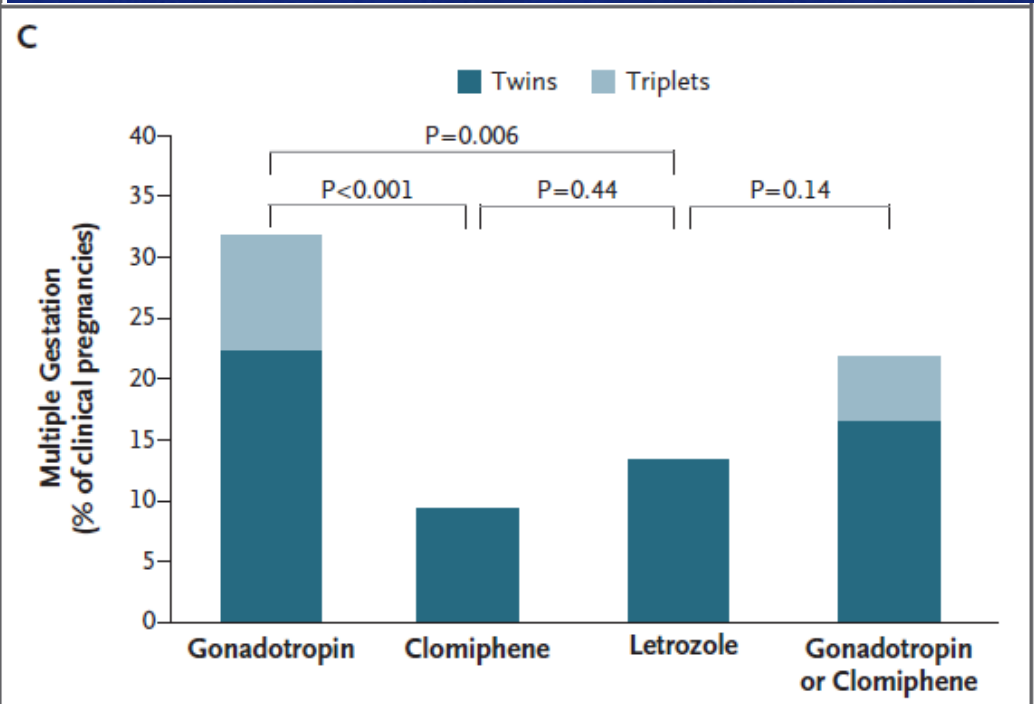


Figure 1. Pregnancy Rates in the Gonadotropin, Clomiphene, and Letrozole Groups.

Shown are rates of clinical pregnancy among all women enrolled in the study (Panel A), rates of live birth among all women enrolled (Panel B), and rates of multiple gestation among all clinical pregnancies (Panel C), according to the study treatment. In Panels A and B, the P value is for the comparison among the three treatment groups.

N Engl J Med 2015;373:1230-40.

Table 2. Rates of Clinical Pregnancy, Live Birth, and Pregnancy Loss.*

Variable	Gonadotropin (N=301)	Clomiphene (N=300)	Letrozole (N=299)	Gonadotropin or Clomiphene (N=601)	Absolute Difference			
					Clomiphene vs. Gonadotropin	Letrozole vs. Gonadotropin	Clomiphene vs. Letrozole	Gonadotropin or Clomiphene vs. Letrozole
	number/total number (percent)				*percent (95% confidence interval)*			
Clinical pregnancy among all women enrolled	107/301 (35.5)	85/300 (28.3)	67/299 (22.4)	192/601 (31.9)	−7.2 (−14.7 to 0.2)	−13.1 (−20.3 to −6.0)¶	5.9 (−1.0 to 12.9)	9.5 (3.5 to 15.6)§
Multiple gestations among clinical pregnancies	34/107 (31.8)	8/85 (9.4)	9/67 (13.4)	42/192 (21.9)	−22.4 (−33.2 to −11.6)¶	−18.3 (−30.4 to −6.3)§	−4.0 (−14.3 to 6.2)	8.4 (−1.6 to 18.5)
Live birth among all women enrolled†	97/301 (32.2)	70/300 (23.3)	56/299 (18.7)	167/601 (27.8)	−8.9 (−16.0 to −1.8)	−13.5 (−20.4 to −6.6)¶	4.6 (−1.9 to 11.1)	9.1 (3.4 to 14.8)§
Singleton live birth among all women enrolled	66/301 (21.9)	66/300 (22.0)	48/299 (16.1)	132/601 (22.0)	0.1 (−6.5 to 6.7)	−5.9 (−12.1 to 0.4)	6.0 (−0.3 to 12.2)	5.9 (0.6 to 11.2)
Twin live birth among all women enrolled	25/301 (8.3)	4/300 (1.3)	8/299 (2.7)	29/601 (4.8)	−7.0 (−10.4 to −3.6)¶	−5.6 (−9.2 to −2.0)§	−1.3 (−3.6 to 0.9)	2.2 (−0.4 to 4.7)
Triplet live birth among all women enrolled	6/301 (2.0)	0	0	6/601 (1.0)	−2.0 (−3.6 to −0.4)	−2.0 (−3.6 to −0.4)	0	1.0 (−0.1 to 2.0)
Multiple gestations among live births‡	31/97 (32.0)	4/70 (5.7)	8/56 (14.3)	35/167 (21.0)	−26.2 (−37.0 to −15.5)¶	−17.7 (−30.7 to −4.6)	−8.6 (−19.2 to 2.1)	6.7 (−4.4 to 17.7)
Gestations with ≥1 loss	51/140 (36.4)	31/106 (29.3)	26/85 (30.6)	82/246 (33.3)	−7.2 (−19.9 to 4.6)	−5.8 (−18.5 to 6.8)	−1.3 (−14.4 to 11.7)	2.8 (−8.7 to 14.2)
Loss in first trimester	48/140 (34.3)	28/106 (26.4)	25/85 (29.4)	76/246 (30.9)	−7.9 (−19.4 to 3.6)	−4.9 (−17.4 to 7.6)	−3.0 (−15.8 to 9.8)	1.5 (−9.8 to 12.8)
Loss in second or third trimester	3/140 (2.1)	3/106 (2.8)	1/85 (1.2)	6/246 (2.4)	0.7 (−3.3 to 4.7)	−1.0 (−4.3 to 2.4)	1.7 (−2.3 to 5.6)	1.3 (−1.7 to 4.3)

N Engl J Med 2015;373:1230-40.

Monitoring

- Serial transvaginal ultrasound
- The size and number of developing follicles
- Presumptive evidence of ovulation
  - progressive follicular growth
  - sudden collapse of the preovulatory follicle
  - increase in cul-de-sac fluid volume
- Luteinization
  - loss of clearly defined follicular margins
  - appearance of internal echoes

De Crespigny et al., Am J Obstet Gynecol 1981

What is the optimal follicular size before triggering ovulation in intrauterine insemination cycles with clomiphene citrate or letrozole? An analysis of 988 cycles

Anna Palatnik, M.D.,[a] Estil Strawn, M.D.,[a] Aniko Szabo, Ph.D.,[b] and Paul Robb, M.D.[a]

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The optimal size of the leading follicle in ovulation induction with CC and letrozole is similar for both drugs and is closely related to the endometrial thickness

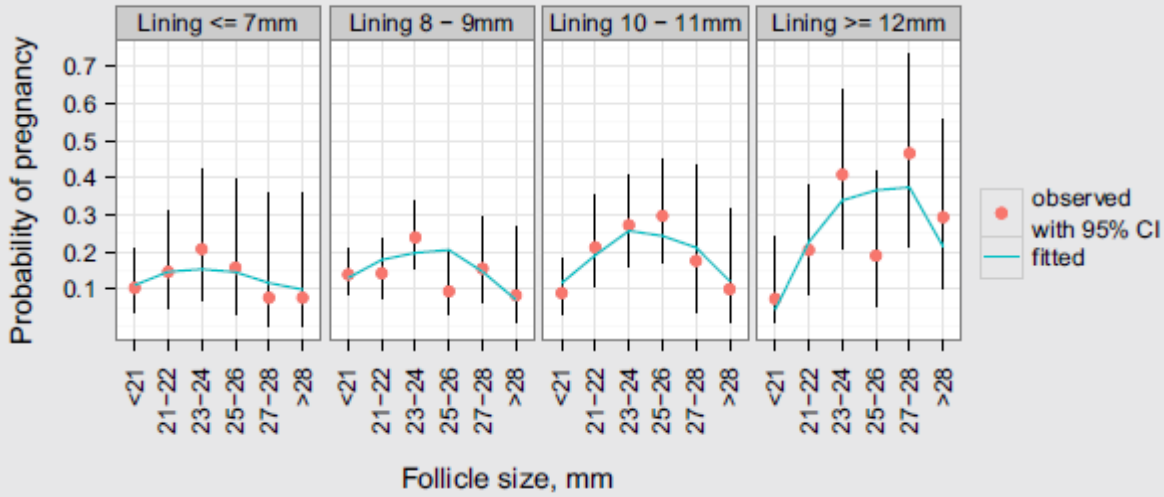
Palatnik et al., 2012. Fertil Steril;97:1089-94.

TABLE 1

Descriptive statistics of the study population by cycle type.

	N	CC (n = 777)	Letrozole (n = 211)	Combined (N = 988)	*P* value
Pregnancy	988	16% (125)	23% (48)	18% (173)	.024[a]
Age	988	31/34/37[c]	29/32/36[c]	30/34/37[c]	<.001[b]
Postprocessing TMSC (millions)	985	12.0/28.0/59.0[c]	17.0/38.5/79.8[c]	13.0/30.0/64.0[c]	<.001[b]
Leading follicle (mm)	988	20/23/26[c]	19/22/24[c]	20/23/25[c]	<.001[b]
Second follicle present	988	87% (675)	64% (135)	82% (810)	<.001[b]
Endometrial lining (mm)	988	7.4/8.5/10.0[c]	7.6/8.7/10.1[c]	7.5/8.6/10.1[c]	.325[b]
Primary diagnosis	988				<.001[a]
Unexplained		56% (432)	31% (65)	50% (497)	
Anovulation		14% (111)	50% (105)	22% (216)	
Male factor		9% (71)	9% (18)	9% (89)	
Endometriosis		6% (47)	5% (10)	6% (57)	
Tubal factor		6% (45)	2% (4)	5% (49)	
Advanced maternal age		5% (40)	1% (3)	4% (43)	
PCOS		2% (16)	3% (6)	2% (22)	
Recurrent miscarriages		2% (15)	0 (0)	2% (15)	

FIGURE 1



The probability of pregnancy by the size of the leading follicle and the endometrial lining thickness. *Points* represent observed proportions with 95% binomial confidence intervals; *lines* connect the average model-based predicted values for each patient in the given follicle size/endometrial thickness group, thus it is adjusted for the observed age, cycle type, and diagnostic group distribution.

Palatnik. Optimal follicular size before hCG. Fertil Steril 2012.

TABLE 2

Parameters of the parabolic relationship between leading follicle size, endometrial thickness, and probability of pregnancy, adjusted for age and primary diagnosis.

Parameter	Estimate	95% CI	*P* value
OR for pregnancy rates at optimal follicle size			
Thicker endometrial lining (mm)	1.14	1.05–1.24	.002
Letrozole vs. CC	1.8	1.05–2.9	.03
OR for pregnancy rates 2 mm away from the optimal follicle size			
Increase in 1 mm in endometrial lining	0.99	0.98–0.99	.005
Letrozole vs. CC	0.90	0.83–0.99	.030
Optimal diameter (mm)			
Value when endometrial lining = 9 mm, CC	24 mm	22.4–25.5 mm	
Increase of 1 mm in endometrial lining	+0.5 mm	0.2–0.9 mm	.003
Letrozole vs. CC	+0.8 mm	−1.1–2.7 mm	.44
Value when endometrial lining = 9 mm, letrozole	24.7 mm	23.5–25.9 mm	

Note: CC = clomiphene citrate; CI = confidence interval; OR = odds ratio.

Palatnik. Optimal follicular size before hCG. Fertil Steril 2012.

TABLE 3

Observed pregnancy rates by endometrial lining thickness and size of leading follicle.

	Leading follicle size													
	≤20 mm		21–22 mm		23–24 mm		25–26 mm		27–28 mm		≥29 mm		Total	
Lining	n	%	n	%	n	%	n	%	n	%	n	%	n	%
≤7 mm	58	10	34	15	24	21	19	16	13	8	13	8	161	13
8–9 mm	136	14	84	14	96	24	53	9	45	16	24	8	438	16
10–11 mm	67	9	47	21	55	27	47	30	17	18	20	10	253	20
≥12 mm	27	7	34	21	22	41	21	19	15	47	17	29	136	25
Total	288	11	199	17	197	26	140	19	90	20	74	14	988	18

Palatnik. Optimal follicular size before hCG. Fertil Steril 2012.

Conclusion

- Individual ovulation induction
- Pt oriented ovulation induction
- Clomiphene
- Gonadotropin

Thank you for attention !!