Common protocols in intra-uterine insemination cycles

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Ovulation induction with intra-uterine insemination

- Ovulation induction with intrauterine insemination (OI/IUI) is the first-line treatment for couples with;

  - unexplained infertility,
  - minimal and mild endometriosis,
  - co-existing male factor

Ovulation induction with intrauterine insemination

- OI/IUI are combined in order to increase fecundability
- Ovulation induction: monofollicular
- Mild ovarian hyperstimulation (MOH)/Controlled ovarian stimulation (COS): 2-3 dominant follicles

Common protocols in IUI cycles

I) Oral drugs:

- Anti-estrogens (Clomiphene citrate, tamoxifen)
- Aromatase inhibitors (Letrozol, anastrazol))

II) Injectable (gonadotropins) drugs:

- Human menopausal gonadotropins (HMG),
- Purified or recombinant follicle-stimulating hormone (hpFSH, rFSH)

Common protocols in IUI cycles

- The advantages of oral drugs over gonadotropins for OI;
  - Oral administration
  - Low cost
  - Less need for cycle monitoring
  - Low incidence of multiple pregnancies and OHSS

Clomiphene Citrate

- Since the 1960s, clomiphene citrate (CC) is used for ovulation induction
- Non-steroidal triphenylethylene derivate
- Selective estrogen receptor modulator (SERM)
- Estrogen agonist and antagonist properties
- Acts purely as an anti-estrogen

Clomiphene Citrate

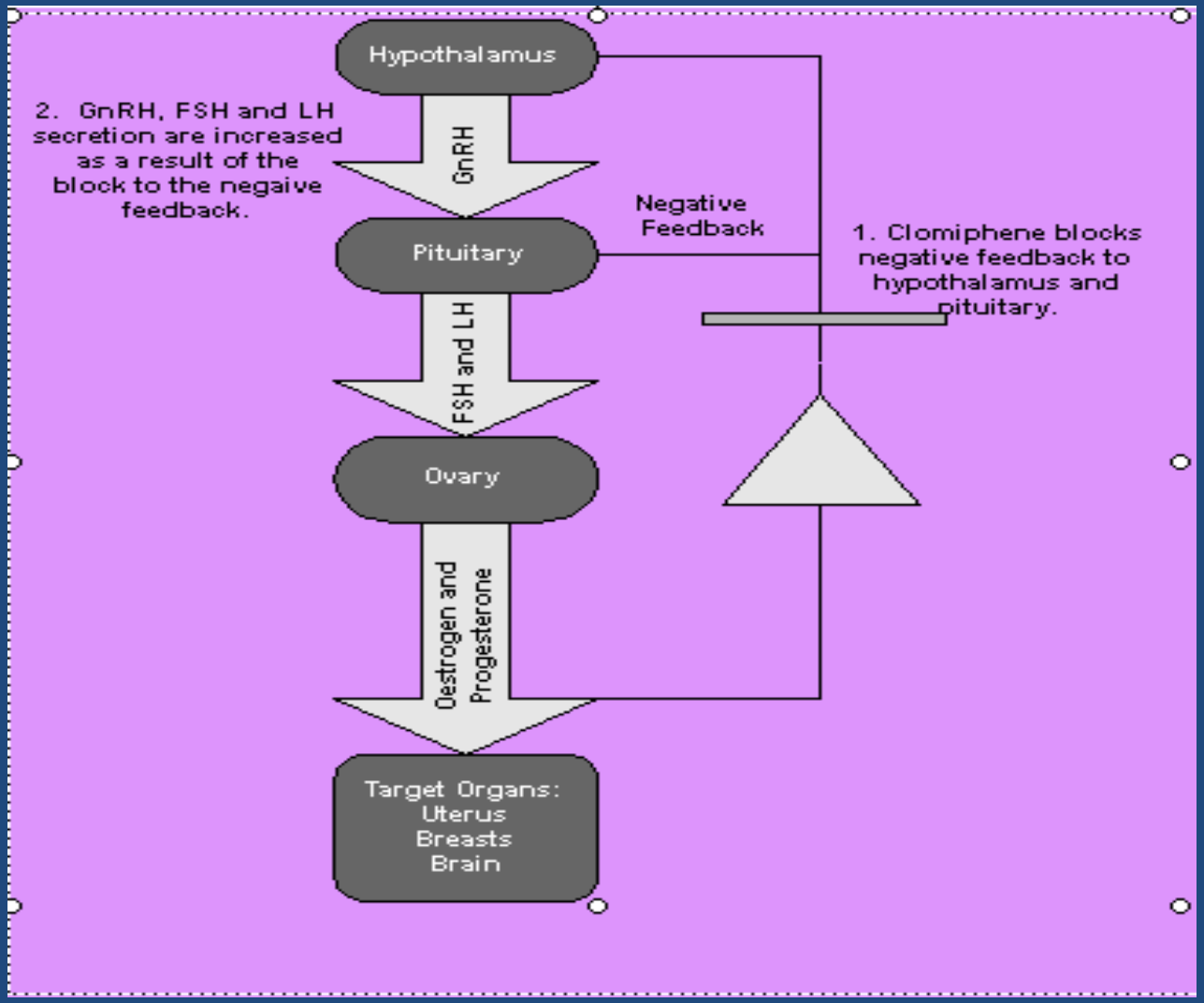
- **Enclomiphene** → anti-estrogenic, the half-life of enclomiphene is relatively short (62%)

- **Zuclomiphene** → mildly estrogenic, cleared much more slowly (38%)

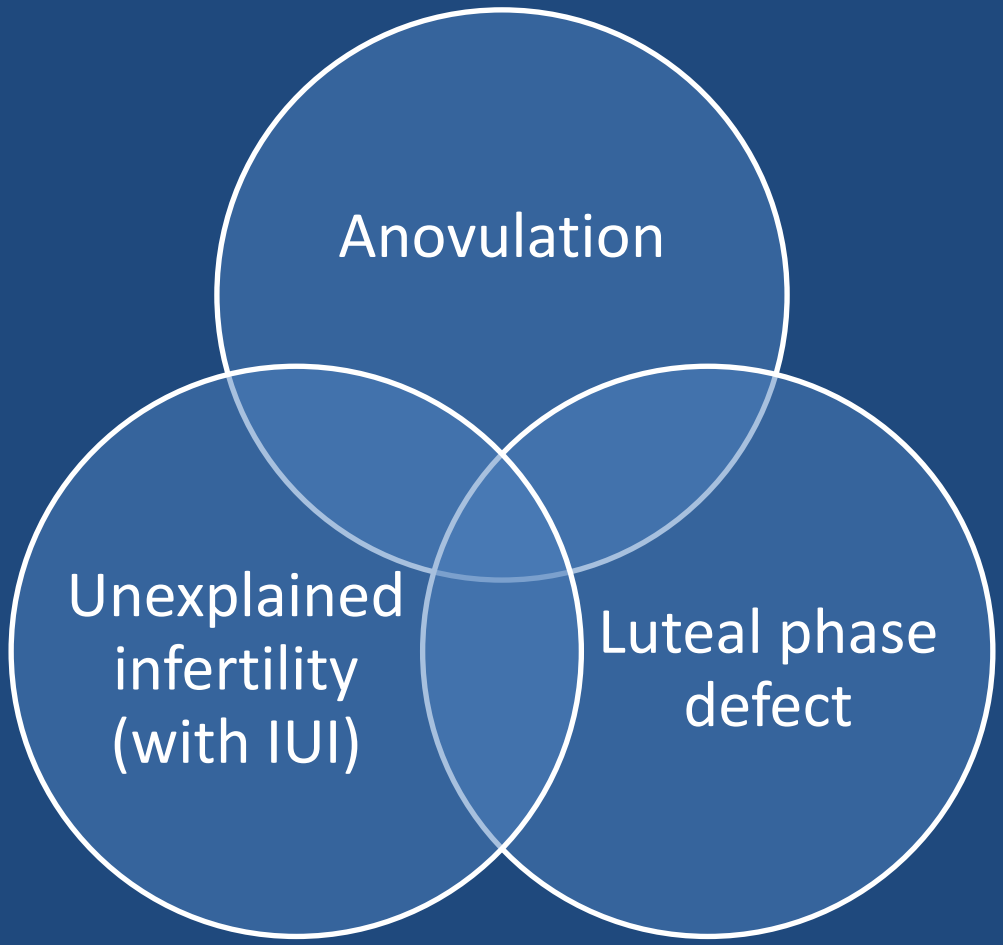
Clomiphene Citrate

- Stimulating the normal endocrine mechanisms
- Structural similarity to estrogen
- Binds to estrogen receptors (extended interval)
- At the hypothalamic level, depletes receptor concentration (receptor recycling↓)
- prevents accurate interpretation of circulating estrogen levels
- GnRH, FSH, LH ↑

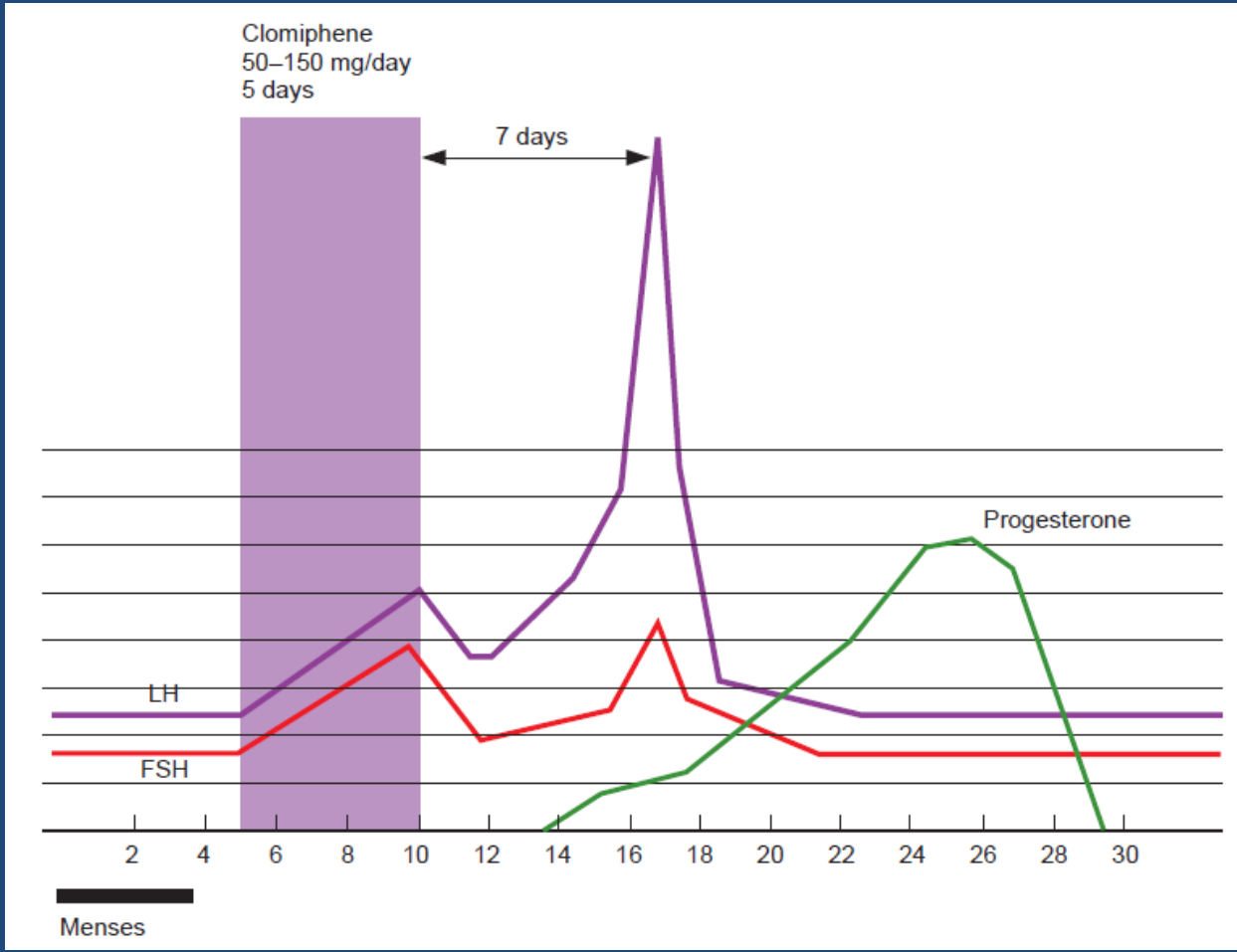
Clomiphene Citrate



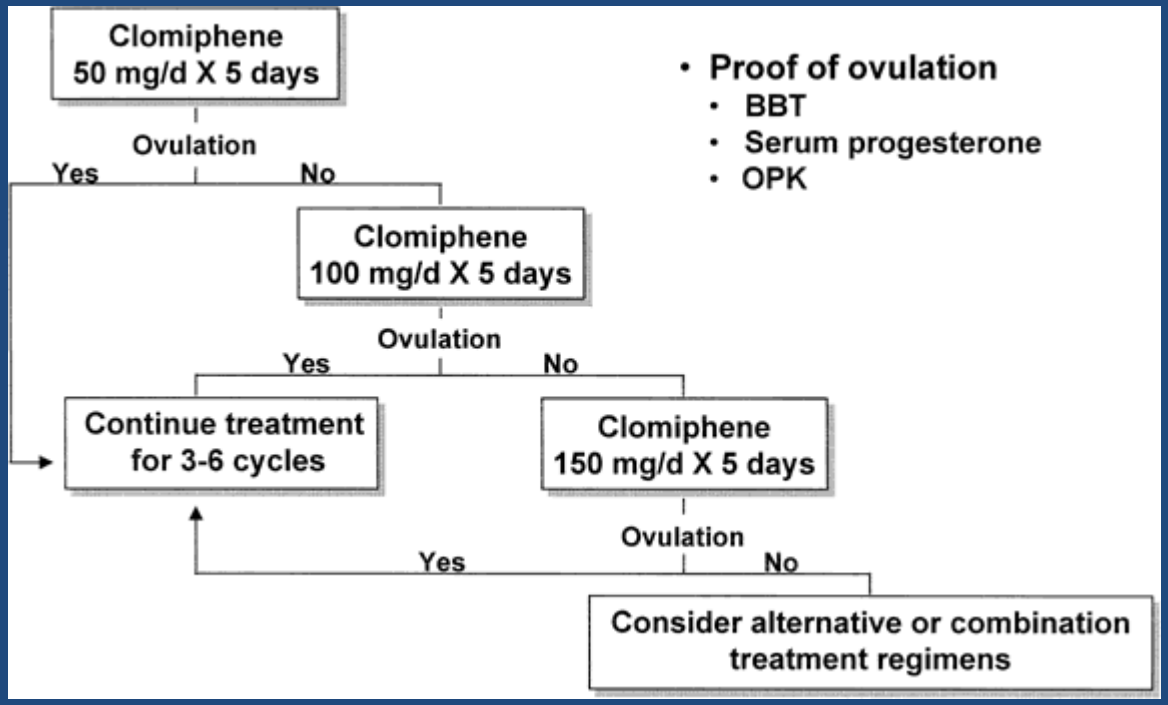
Clomiphene Citrate



Clomiphene Citrate (CC)



Clomiphene Citrate



Clomiphene Citrate

Effectiveness:

Anovulatory infertil women

The ovulation rate: 70–85% (age, BMI, hyperandrogenemia)

The pregnancy rate: 36%

The live-birth rate : 29%

3-6 cycles (clomiphene-induced ovulatory cycles)

Clomiphene Citrate

Effectiveness:

in patients with unexplained infertility;

CC plus timed intercourse: 5.6% PR per cycle

CC plus intrauterine insemination (CC/IUI): 8.3% PR per cycle

Clomiphene Citrate

- Longer half-life (45 h)
- Anti-estrogenic effect
- Endometrial thinning
- Poor cervical mucus
- Resistance 15-40 %

Clomiphene Citrate

- **Clomiphene resistant;** If women do not respond to the 50-mg dose, then incremental dose of 50 mg up to 150 mg are given before the patients is labelled as clomiphene resistant

- **Clomiphene failure**; one or more follicles emerge and grow, ovulation +, pregnancy (-)

Common protocols in IUI cycles

Clomiphene- resistant anovulatory women (15-40%):

- Long term (8 days), high dose (200-250 mg/dl)
- Clomiphene and metformin
- Clomiphene and glucocorticoids
- Pretreatment with oral contraceptive
- Aromatase inh
- Gonadotropins

Addition of metformin

- Improved ovulation in women with insulin resistance and hyperandrogenism associated with PCOS who were resistant to CC
- Metformin was associated with improved clinical pregnancy but there was no evidence that metformin improves live birth rates
- Metformin is not currently licensed for use in the management of PCOS

Cochrane Database Syst Rev. 2012 May

Metformin combined with CC

Cochrane Database Syst Rev. 2012 May

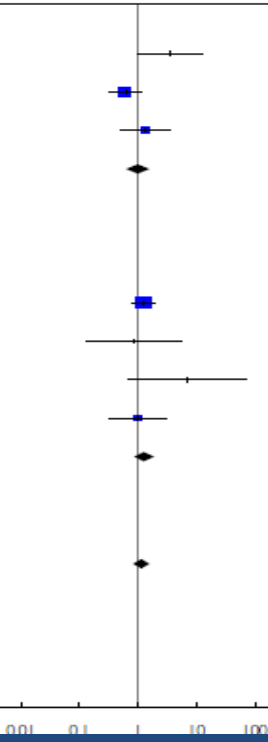
Analysis 2.1. Comparison 2 Metformin combined with ovulation induction agent clomifene versus clomifene alone, Outcome 1 Live birth rate.

Review: Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility

Comparison: 2 Metformin combined with ovulation induction agent clomifene versus clomifene alone

Outcome: 1 Live birth rate

Study or subgroup	Met + clomifene n/N	clomifene n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Participants with BMI < 30kg/m2 or ≤32kg/m2					
Boudhraa 2010	11/32	4/31		3.4 %	3.54 [0.98, 12.70]
Moll 2006	21/111	31/114		31.8 %	0.62 [0.33, 1.17]
PCOSMIC 2010 (1)	15/35	13/36		9.4 %	1.33 [0.51, 3.45]
Subtotal (95% CI)	**178**	**181**		**44.7 %**	**1.00 [0.62, 1.59]**
Total events: 47 (Met + clomifene), 48 (clomifene)					
Heterogeneity: $Chi^2 = 6.23$, df = 2 (P = 0.04); I^2 =68%					
Test for overall effect: Z = 0.02 (P = 0.99)					
2 Participants with BMI ≥ 30kg/m^2					
Legro 2007	56/209	47/209		44.2 %	1.26 [0.81, 1.97]
Sahin 2004	3/11	3/10		2.9 %	0.88 [0.13, 5.82]
Vandermolen 2001	4/12	1/15		0.8 %	7.00 [0.66, 73.93]
Zain 2009	7/41	7/41		7.5 %	1.00 [0.32, 3.16]
Subtotal (95% CI)	**273**	**275**		**55.3 %**	**1.28 [0.86, 1.91]**
Total events: 70 (Met + clomifene), 58 (clomifene)					
Heterogeneity: $Chi^2 = 2.33$, df = 3 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 1.24 (P = 0.22)					
Total (95% CI)	**451**	**456**		**100.0 %**	**1.16 [0.85, 1.56]**
Total events: 117 (Met + clomifene), 106 (clomifene)					
Heterogeneity: $Chi^2 = 9.23$, df = 6 (P = 0.16); I^2 =35%					
Test for overall effect: Z = 0.94 (P = 0.35)					
Test for subgroup differences: $Chi^2 = 0.66$, df = 1 (P = 0.42), I^2 =0.0%					



Addition of dexamethasone

Clomiphene- resistant anovulatory women:

- DHEAS levels are > 180ug/dL
- Suppressing adrenal androgen,
- Negates the antiestrogen effect of CC on endometrium
- Ovulation 80 %, pregnancy 40 %

Parsanezhad ME et al. Fertil Steril. 2002

Clomiphene failure

Antiestrogenic effect !!!

- Early administration (day 1-5)
- Addition of estrogen (2mg oral /vaginal)
- Tamoxifen
- Aromatase inh
- Gonadotropins

Time of initiation of clomiphene citrate and pregnancy rate in polycystic ovarian syndrome

International Journal of Gynecology and Obstetrics (2006) 93, 44–48

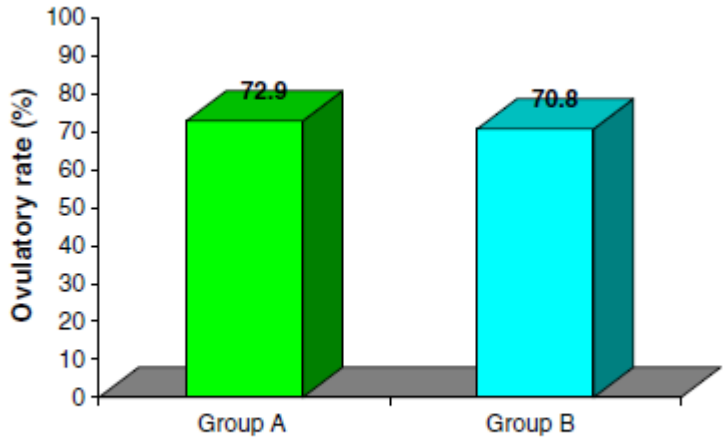


Figure 3 The ovulatory rate in two groups.

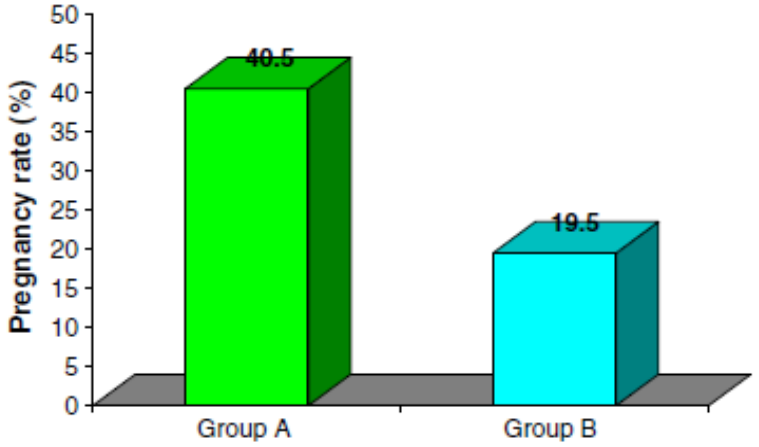


Figure 4 The pregnancy rate in two groups.

Clomiphene Citrate

Side effects

- hot flushes,
- breast discomfort,
- abdominal distension,
- nausea and vomiting,
- sleeplessness,
- headache,
- mood swings,
- dizziness and hair loss.
- Visual symptoms (visual blurring or spots)

Clomiphene Citrate

- Multiple pregnancy (7-10%)
- Congenital anomalies (2.3%)
- Miscarriage (%16-20)
- OHSS (uncommon)
- Ovarian cancer (no causal relationship)

Tamoxifen (TMX)

- Triphenylethylene derivative with a structure similar to CC,
- TMX → only the z-isomer, similar to zuclomiphene
- Occupying the estrogen receptors in the hypothalamus,
- GnRH pulse frequency ↑

Tamoxifen

- 20–40 mg daily,
- Cycle day 3 for 5 days
- Tamoxifen is used ‘‘off label’’ to replace CC

Tamoxifen seems as effective as clomiphene at increasing ovulation rates, pregnancy rates and live birth rates in anovulatory women (moderate-quality evidence)

Steiner, A.Z et al, Human Reproduction 2005

Brown J et al, Cochrane Database Syst Rev. 2009

CC and TMX-induced ovulation

- Luteal phase, serum progesteron and estradiol levels ↑
- During the fisrt trimester of CC pregnancies; serum progesteron level is 200-300 % higher and serum estradiol level is 66 % higher than in sponteneous pregnancies
- There is less need for supplemental progesteron support in CC than in gonadotropin pregnancies

Aromatase inhibitors

Letrozol (Femara)/ Anastrozol (Arimidex);

- A third generation aromatase inhibitors used for treatment of estrogen-positive breast cancer
- Reversible/selective aromatase inhibitor
- Prevents androgen-to-estrogens conversion
    - ovarian follicles
    - peripheral tissues
    - beyin

Aromatase inhibitors

Blocks the conversion of androgens to estrogens

- Serum ve lokal estrojen ↓
- GnRH secretion ↑ ,
- Pituitary FSH and LH production ↑,
- Monofollicular growth and ovulation

Intraovarian androgens ↑

- intraovarian androgens ↑ (FSH res, IGF-I ↑)
- Follicular sensitivity to FSH ↑

Letrozol

- Alternative first-line treatment for ovulation induction in selected groups of infertile patients,
  - PCOS (resistans, failure)
  - Unexplained infertility,
  - Endometriosis
  - Estrogen dependent cancer
  - Coagulation defect

Letrozol

- Not associated with adverse antiestrogen effects
- Monofollicular (< 5% multiple pregnancy)
- Mid-luteal-phase serum progesterone ↓ (compared to CC cycles)

Meta-analysis of letrozole versus clomiphene citrate in polycystic ovary syndrome

Donghong He, Fengyan Jiang *

Study or Subgroup	LE Events	LE Total	CC Events	CC Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Atay 2006	5	51	11	55	8.4%	0.49 [0.18, 1.31]
Aygen 2007	2	5	1	5	0,8%	2,00 [0,26, 15,62]
Badawy 2009	82	218	94	220	73.9%	0.88 [0.70, 1.11]
Bayar 2006	9	40	7	40	5.5%	1.29 [0.53, 3.12]
Dehbashi 2009	13	50	7	50	5.5%	1.86 [0.81, 4.26]
Zeinalzadeh 2010	10	50	8	57	5.9%	1.43 [0.61, 3.33]
Total (95% CI)		**414**		**427**	**100.0%**	**0.97 [0.79, 1.18]**
Total events	121		128			

Heterogeneity: Chi² = 6.51, df = 5 (*P* = 0.26); I² = 23%

Test for overall effect: Z = 0.34 (*P* = 0.73)

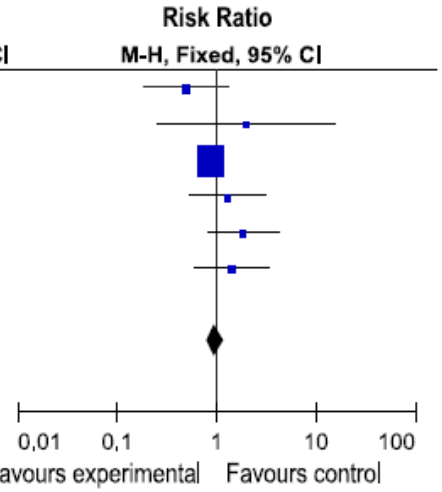


Figure 3 Forest plot of pregnancy rate associated with comparison of letrozole (LE) with clomiphene citrate (CC). CI=confidence intervals; M–H=Mantel-Haenszal.

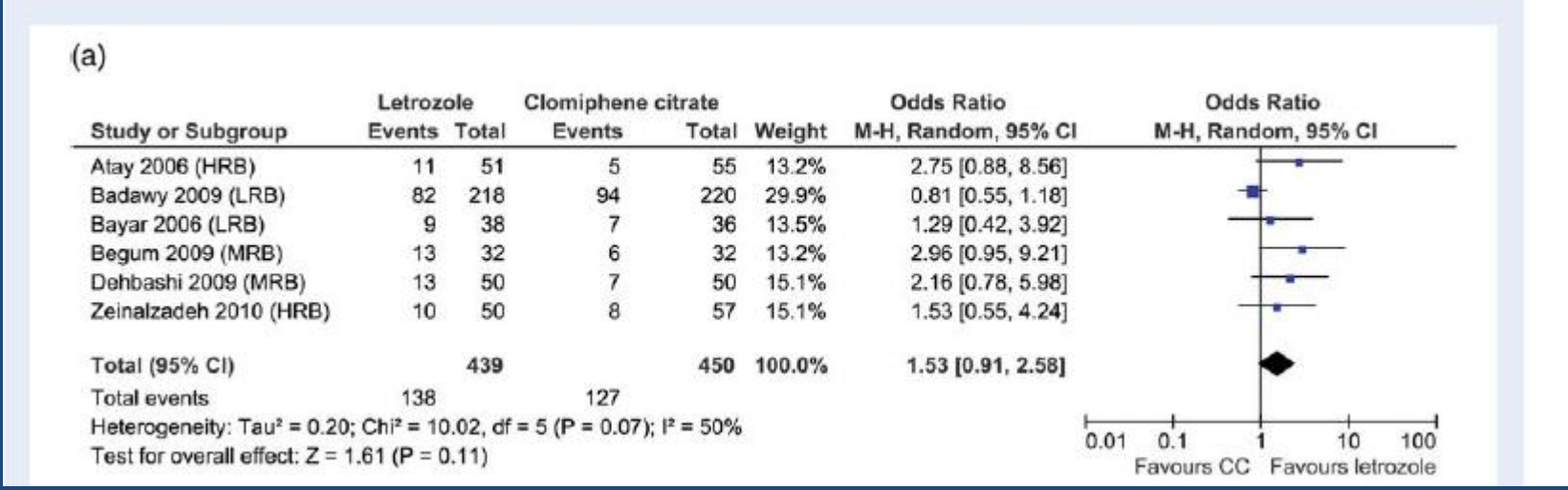
Reproductive BioMedicine Online (2011) **23**, 91–96

LET versus CC

- Pregnancy rate
- Miscarriage rate
- Live birth rate
- Multiple pregnancy rate
- no statistical difference beetwen LET and CC

Misso ML et al, Aromatase inhibitors for PCOS: a systematic review and meta-analysis. Hum Reprod Update 2012

LET versus CC/pregnancy rate



(a)

Study or Subgroup	Letrozole Events	Letrozole Total	Clomiphene citrate Events	Clomiphene citrate Total	Weight	Odds Ratio M-H, Random, 95% CI
Atay 2006 (HRB)	11	51	5	55	13.2%	2.75 [0.88, 8.56]
Badawy 2009 (LRB)	82	218	94	220	29.9%	0.81 [0.55, 1.18]
Bayar 2006 (LRB)	9	38	7	36	13.5%	1.29 [0.42, 3.92]
Begum 2009 (MRB)	13	32	6	32	13.2%	2.96 [0.95, 9.21]
Dehbashi 2009 (MRB)	13	50	7	50	15.1%	2.16 [0.78, 5.98]
Zeinalzadeh 2010 (HRB)	10	50	8	57	15.1%	1.53 [0.55, 4.24]
Total (95% CI)		**439**		**450**	**100.0%**	**1.53 [0.91, 2.58]**
Total events	138		127			

Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 10.02$, df = 5 (P = 0.07); $I^2 = 50\%$

Test for overall effect: Z = 1.61 (P = 0.11)

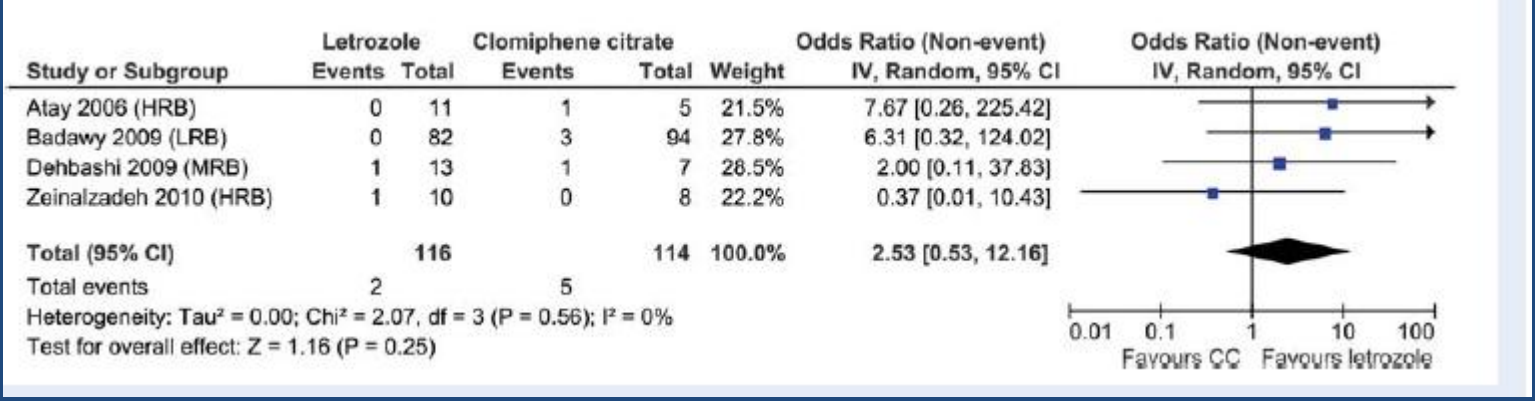
Odds Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Favours CC Favours letrozole

Misso ML et al, Aromatase inhibitors for PCOS: a systematic review and meta-analysis. Hum Reprod Update 2012

LET versus CC/live birth rate

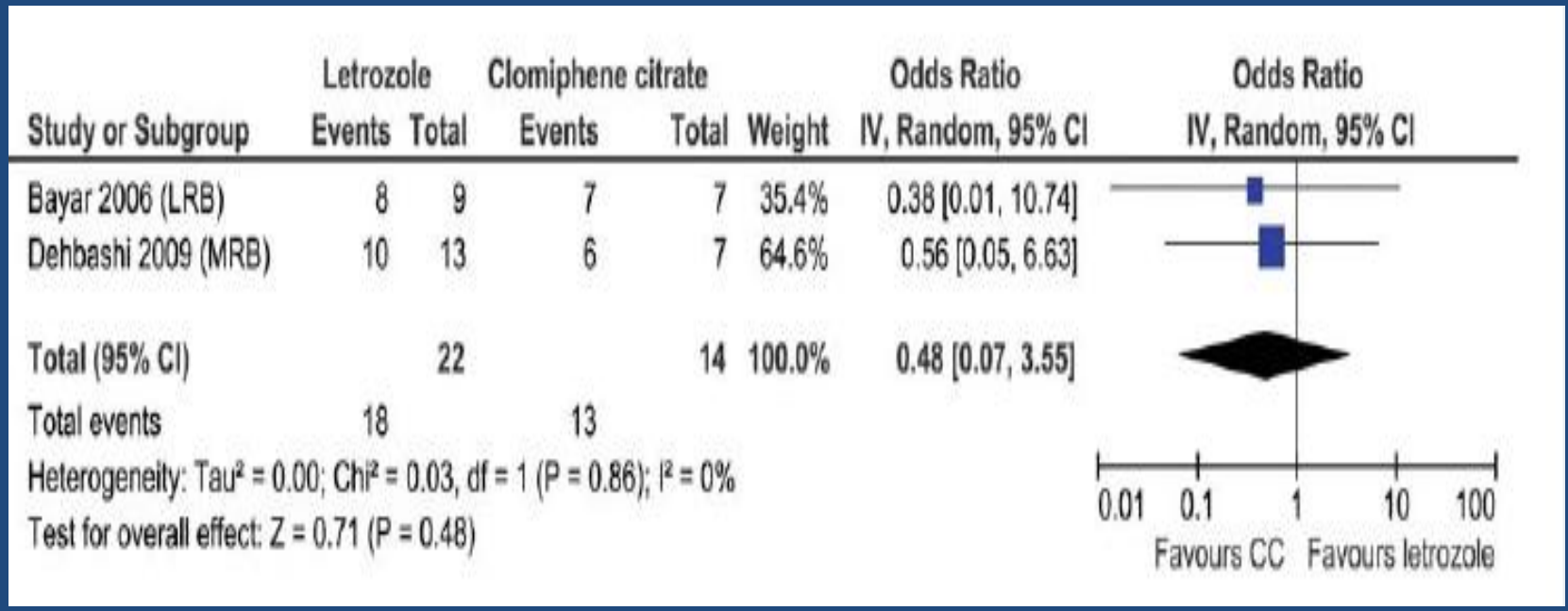


Study or Subgroup	Letrozole Events	Letrozole Total	Clomiphene citrate Events	Clomiphene citrate Total	Weight	Odds Ratio (Non-event) IV, Random, 95% CI
Atay 2006 (HRB)	0	11	1	5	21.5%	7.67 [0.26, 225.42]
Badawy 2009 (LRB)	0	82	3	94	27.8%	6.31 [0.32, 124.02]
Dehbashi 2009 (MRB)	1	13	1	7	28.5%	2.00 [0.11, 37.83]
Zeinalzadeh 2010 (HRB)	1	10	0	8	22.2%	0.37 [0.01, 10.43]
Total (95% CI)		**116**		**114**	**100.0%**	**2.53 [0.53, 12.16]**
Total events	2		5			

Heterogeneity: Tau² = 0.00; Chi² = 2.07, df = 3 (P = 0.56); I² = 0%

Test for overall effect: Z = 1.16 (P = 0.25)

LET versus CC/multiple pregnancy



Clomiphene citrate or aromatase inhibitors for superovulation in women with unexplained infertility undergoing intrauterine insemination: a prospective randomized trial

TABLE 2

Outcome in letrozole and clomiphene citrate (CC) groups.

	Letrozole group (n = 205)	CC group (n = 207)	t	*P* value
Total number of follicles >18 mm	1.6 ± 0.41	3.1 ± 0.36	4.4	.045[a]
Pretreatment endometrial thickness	4.7 ± 0.4	4.4 ± 0.6	1.41	.52
Endometrial thickness at hCG (mm)	9.3 ± 0.4	9.2 ± 0.6	2.40	.08[a]
Serum E_2 (pg/mL)	289.1 ± 64.2	410 ± 81.2	3.12	.021[a]
Serum progesterone (ng/mL)	8.2 ± 0.9	11.4 ± 1.1	6.30	.023[a]
Days to hCG injection (days)	12.1 ± 1.38	10.5 ± 2.52	4.90	.080
Pregnancy/cycle	76/400 (19.0%)	74/404 (18.3%)	1.88	.78
Pregnancy/patient	76/205 (37.07%)	74/207 (35.7%)	2.3	.31
Miscarriage/patient	11 (14.4%)	12 (16.2%)	1.53	.42

[a] Statistically significant difference: $P < .05$.

Badawy. CC and letrozole for IUI. Fertil Steril 2009.

Gonadotropins

Indications:

- Hypogonadotropic anovulation (WHO Group I, unifollicular),
- Clomiphene-resistant, failure (WHO Group II, unifollicular),
- Unexplained infertility (COH/IUI)

Gonadotropins versus anti-estrogens

Cantineau AE, et al. Cochrane Database 2007 (level 1a)

Analysis 1.2. Comparison 1 anti-estrogens versus gonadotrophins, Outcome 2 pregnancy rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 1 anti-estrogens versus gonadotrophins

Outcome: 2 pregnancy rate per couple

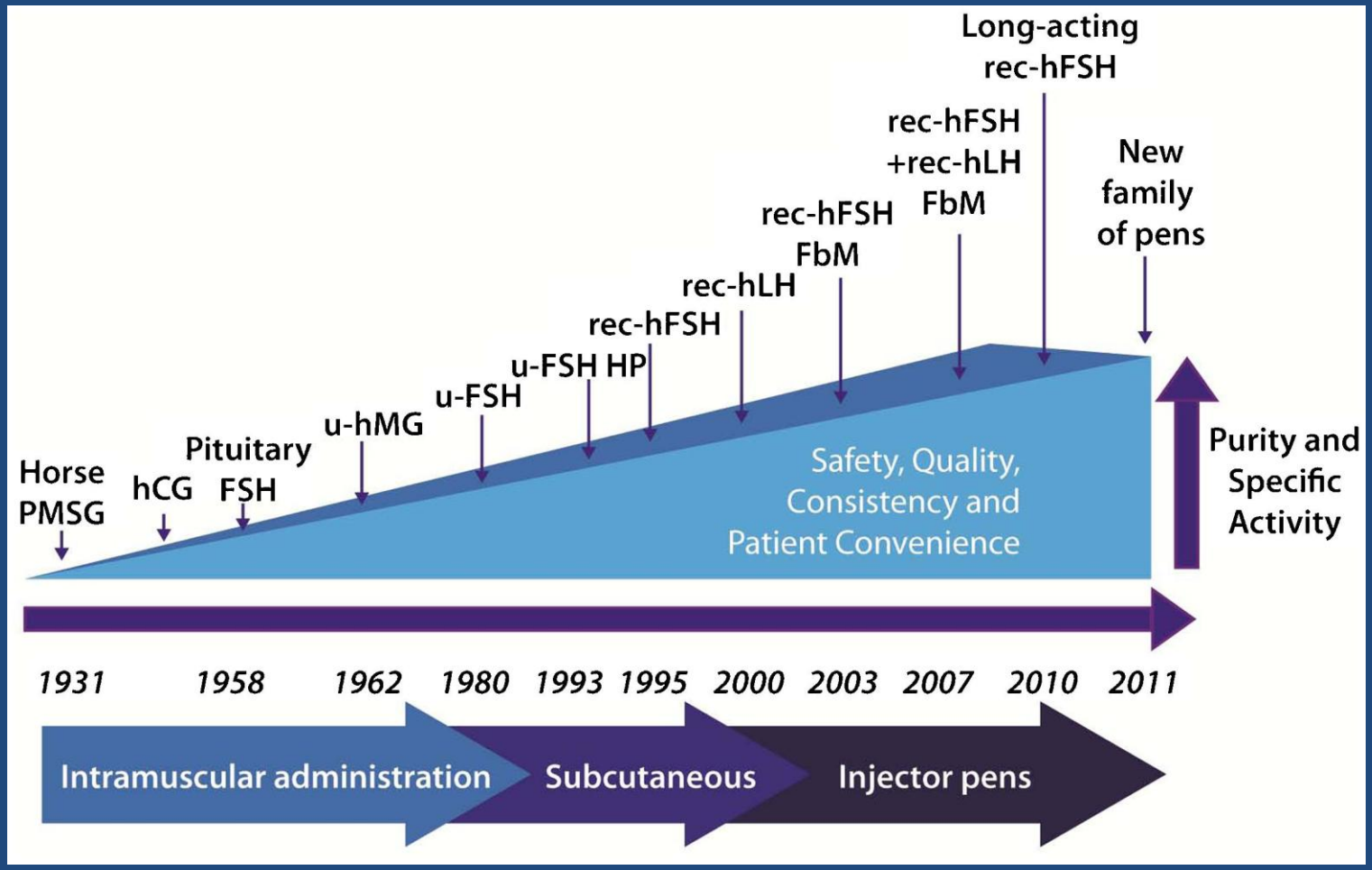
Study or subgroup	Gonadotrophins n/N	Anti-estrogens n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Balasch 1994	12/50	4/50		8.9 %	3.63 [1.08, 12.18]
Dankert 2006	17/67	19/71		40.2 %	0.93 [0.43, 1.99]
Ecochard 2000	3/29	6/29		15.7 %	0.44 [0.10, 1.97]
Kamel 1995	4/28	2/26		5.2 %	2.00 [0.33, 11.97]
Karlstrom 1993	3/15	1/17		2.2 %	4.00 [0.37, 43.38]
Karlstrom 1998	8/40	4/34		10.1 %	1.88 [0.51, 6.88]
Matorras 2002	30/49	16/51		17.7 %	3.45 [1.51, 7.88]
Total (95% CI)	**278**	**278**		**100.0 %**	**1.76 [1.16, 2.66]**

Total events: 77 (Gonadotrophins), 52 (Anti-estrogens)
Heterogeneity: $Chi^2 = 10.40$, $df = 6$ ($P = 0.11$); $I^2 = 42\%$
Test for overall effect: $Z = 2.68$ ($P = 0.0074$)
Test for subgroup differences: Not applicable

Gonadotropins

- Human menopausal gonadotropins (HMG),
- Purified or recombinant follicle-stimulating hormone (hpFSH, rFSH)
- A recombinant form of human LH
- Urinary hCG/rec hCG

Gonadotropins



Gonadotropins

Advantages of recombinant products;

- higher batch-to-batch consistency,
- high purity, avoiding injection of potentially allergenic
- proteins, the likelihood of reducing the risk of infectious particles
- rendering the production independent of urine collection and the elimination of drugs co-extracted from urine

Gonadotropins

Table 2. Different gonadotrophin preparations

Preparation	Source of FSH	FSH activity (IU/ ampoule)	LH activity (IU/ ampoule)	Non-FSH urinary proteins
HMG	Urine	75	75	95%
Urinary FSH	Urine	75	< 0.7	95%
Urinary FSH – high purity	Urine	75	< 0.001	< 1%
Recombinant FSH	Chinese hamster ovary	50, 75, 100, 150, 200	None	None

FSH = follicle-stimulating hormone; HMG = human menopausal gonadotrophin.

Gonadotrophins

- hMG versus r-FSH
- u-FSH versus r-FSH
- 43 trial, 3957 women

Cantineau AE, Cohlen BJ, Heineman MJ. Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility. Cochrane Database Syst Rev. 2007

Gonadotropins

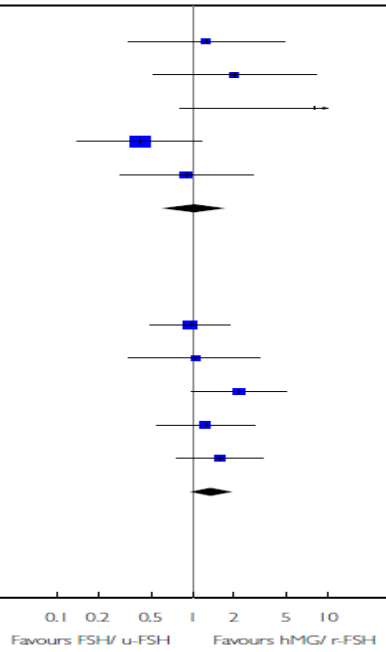
Analysis 5.2. Comparison 5 different types of gonadotrophins, Outcome 2 pregnancy rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 5 different types of gonadotrophins

Outcome: 2 pregnancy rate per couple

Study or subgroup	hMG (or r-FSH) n/N	FSH (or u-FSH) n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 A). hMG versus FSH					
Filicori 2001	6/25	5/25		14.7 %	1.26 [0.33, 4.84]
Filicori 2003	7/25	4/25		11.1 %	2.04 [0.51, 8.12]
Gerli 1993	5/15	1/17		2.4 %	8.00 [0.81, 78.83]
Gurgan 2004	5/40	21/81		47.0 %	0.41 [0.14, 1.18]
Gurgan II 2004	5/40	11/80		24.8 %	0.90 [0.29, 2.78]
Subtotal (95% CI)	**145**	**228**		**100.0 %**	**1.02 [0.59, 1.75]**
Total events: 28 (hMG (or r-FSH)), 42 (FSH (or u-FSH))					
Heterogeneity: $Chi^2 = 7.10$, df = 4 (P = 0.13); I^2 =44%					
Test for overall effect: Z = 0.07 (P = 0.94)					
2 B). r-FSH versus u-FSH					
Gerli 2004	23/88	22/82		32.1 %	0.97 [0.49, 1.91]
Gerli 2004 (II)	9/35	8/32		11.8 %	1.04 [0.34, 3.13]
Gurgan 2004	21/81	11/80		15.6 %	2.20 [0.98, 4.92]
Matorras 2000	26/45	24/46		19.1 %	1.25 [0.55, 2.87]
Pares 2002	28/55	24/61		21.3 %	1.60 [0.76, 3.34]
Subtotal (95% CI)	**304**	**301**		**100.0 %**	**1.36 [0.95, 1.94]**
Total events: 107 (hMG (or r-FSH)), 89 (FSH (or u-FSH))					
Heterogeneity: $Chi^2 = 2.78$, df = 4 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 1.68 (P = 0.093)					



Step-up protocol

- Aim; To define the effective threshold of response
- WHO Group I, WHO Group II (unifollicular)
- A low daily dose (75 IU daily)
- After 4 to 7 days of stimulation; TV-USG, a serum estradiol level
- The dose of gonadotropins may be maintained or increased, as indicated (7-12 days)
- The lead follicle reaches 16–18 mm, hCG is administered
- Ovulation generally may be expected to occur approximately 36–48 hours later

Low slow protocol

Low dose step-up (PCOS); > 85 % monofollicular

- Starting dose: 37.5–75 IU/day (hMG/rFSH) given for 7-14 days
- Step up (by 37.5 IU), ıf no follicles ≥ 10 mm after 7 days
- Step up every 7 days until dominant follicle appear
- Average stimulation duration 28-35 days

Step-down protocol

Day 3 : Start FSH 150-250 IU x 5 days

Day 8 : US every 2-4 days

Foll>9mm :

Decrease by 37.5 IU every 3 days until 75 IU

Maintain 75 IU until hCG injection

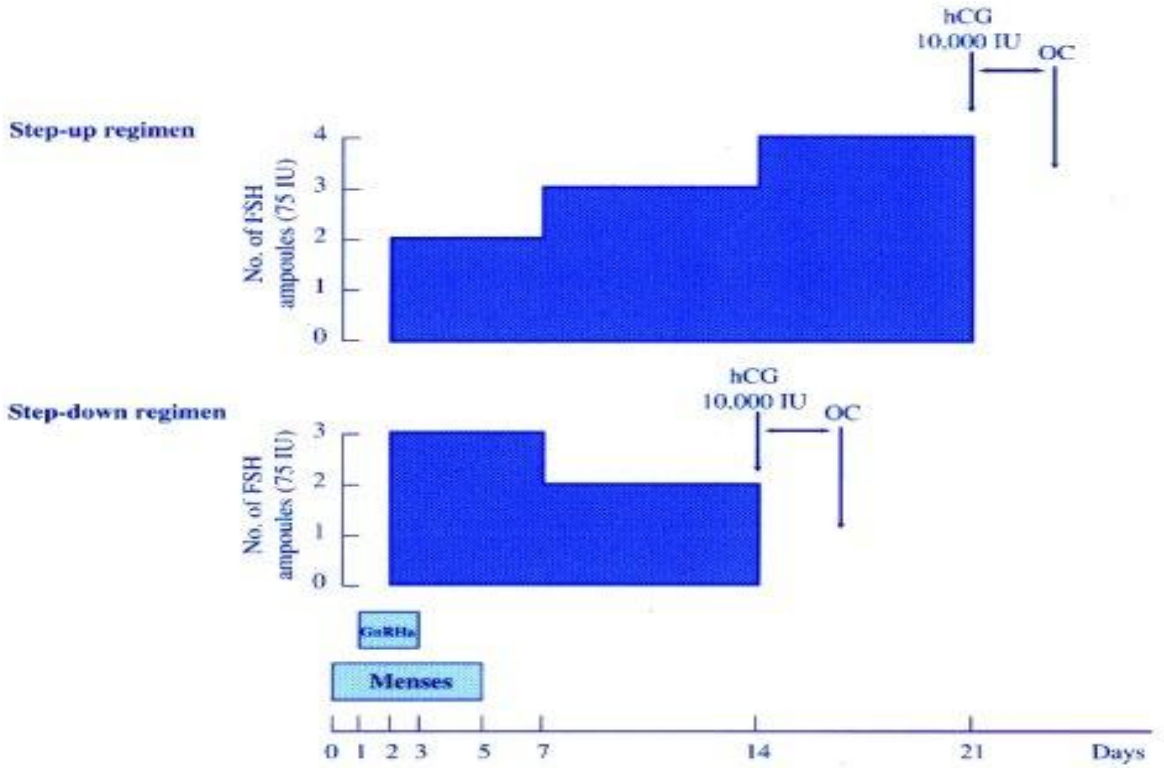
Foll<9mm :

Increase by 37.5 IU, maintain for 10 days

Then recheck US.

If follicle 9mm or less, cancel cycle.

Gonadotrophins



FSH = follicle-stimulating hormone; GnRHa = gonadotrophin-releasing hormone agonist; hCG = human chorionic gonadotrophin; OC = oocyte collection.

Modified protocol

- Step up and step down protocol can be combined,
- Starting doses (37.5/75 IU/day) gradually increased
- ≥ 10 mm follicul is seen by USG, the doses of gonadotropins ↓

.

Sequential protocol

- Clomiphene and gonadotropins;
- 50–100 mg daily CC (5 days),
- followed by low dose FSH/hMG (75 IU daily) beginning on the last day of clomiphene therapy or the next day
- Treatment is monitored and individualized thereafter as in standard gonadotropin-stimulated cycles

The prevalence and influence of luteinizing hormone surges in stimulated cycles combined with intrauterine insemination during a prospective cohort study

TABLE 2

Results

	Total group (n = 66)	CC group (n = 33)	FSH group (n = 33)
Total no. completed treatment cycles	210	105	105
Pregnancies			
Total	20 (9.5%)	10 (9.5%)	10 (9.5%)
Spontaneous	4 (1.9%)	2 (1.9%)	2 (1.9%)
Ongoing	4	2	2
Miscarriage	0	0	0
Treatment-dependent	16 (7.6%)	8 (7.6%)	8 (7.6%)
Ongoing	12 (5.7%)	6 (5.7%)	6 (5.7%)
Miscarriage	4 (1.9%)	2 (1.9%)	2 (1.9%)
No. cycles with LH measurements	153	76	77
No. pregnancies/cycles with an LH surge	2/55 (3.6%)	1/23 (4.3%)	1/32 (3.1%)
No. pregnancies/cycles without an LH surge	9/98 (9.2%)	4/53 (7.5%)	5/45 (11.1%)
No. pregnancies/cycles with no LH determination	5/57 (8.8%)	3/29 (10.3%)	2/28 (7.1%)

Cantineau. LH surges in stimulated cycles with IUI. Fertil Steril 2007.

Adjuvant GnRH agonist therapy

- ***combined treatment with a GnRH agonist and exogenous gonadotropins;***

  Elevated endogenous LH levels (PCOS);

  - predispose to premature luteinization during exogenous gonadotropin stimulation

  - a contributing factor in the higher incidence of spontaneous miscarriage

  - GnRH agonist; endogenous LH levels ↓, premature luteinization ↓

Tulppala M et al, *Hum Reprod 8:7640, 1993*

Manzi DL et al, *Fertil Steril 63:866, 1995*

Adjuvant GnRH agonist in OI/IUI

Analysis 6.2. Comparison 6 gonadotrophins alone versus gonadotrophins with GnRH agonist, Outcome 2 pregnancy rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 6 gonadotrophins alone versus gonadotrophins with GnRH agonist

Outcome: 2 pregnancy rate per couple

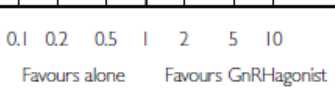
Study or subgroup	Gonadotrophins alone n/N	gonadotrophins+GnRHanta n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Carrera 2002	9/30	5/30		14.9 %	2.14 [0.62, 7.39]
Carrera 2002 (II)	8/30	5/30		15.6 %	1.82 [0.52, 6.38]
Pattuelli 1996	27/104	16/100		51.3 %	1.84 [0.92, 3.68]
Sengoku 1994	7/46	5/45		18.2 %	1.44 [0.42, 4.91]
Total (95% CI)	**210**	**205**		**100.0 %**	**1.81 [1.10, 2.97]**

Total events: 51 (Gonadotrophins alone), 31 (gonadotrophins+GnRHanta)

Heterogeneity: $Chi^2 = 0.21$, df = 3 (P = 0.98); $I^2 = 0.0\%$

Test for overall effect: Z = 2.34 (P = 0.019)

Test for subgroup differences: Not applicable



GnRH- antagonist in OI/IUI

Analysis 7.2. Comparison 7 gonadotrophins alone versus gonadotrophins with GnRH antagonist, Outcome 2 pregnancy rate per couple.

Review: Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility

Comparison: 7 gonadotrophins alone versus gonadotrophins with GnRH antagonist

Outcome: 2 pregnancy rate per couple

Study or subgroup	gonadotrophins+antag n/N	gonadotrophins alone n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Gomez 2005	15/39	7/41		24.2 %	3.04 [1.07, 8.57]
Lambalk 2006	13/93	12/85		62.2 %	0.99 [0.42, 2.30]
Ragni 2001	3/19	3/22		13.5 %	1.19 [0.21, 6.72]
Total (95% CI)	**151**	**148**		**100.0 %**	**1.51 [0.83, 2.76]**

Total events: 31 (gonadotrophins+antag), 22 (gonadotrophins alone)

Heterogeneity: $Chi^2 = 2.77$, $df = 2$ ($P = 0.25$); $I^2 = 28\%$

Test for overall effect: $Z = 1.34$ ($P = 0.18$)

Test for subgroup differences: Not applicable

LH in OI/IUI cycles

- Hypo-hypo (LH levels <1.2 IU/L)
- ≥35 years
- Poor responders
- PCOS previous excessive response

- hMG/ rec LH supplementation from stimulation day D1,
- Latter stages of follicular development, the number of developing follicles ↓

Loumaye E, et al, *Hum Reprod 18:314, 2003.*

LH supplementation in OI/IUI

Actions of LH in larger and smaller follicles different;

- promote larger follicle growth
- regression of smaller follicles (OHSS ↓)
- intrafollicular androgen ↑

Filicori M et al, Modulation of folliculogenesis and steroidogenesis in women by graded menotrophin administration, *Hum Reprod 17:2009, 2002.*

Monitoring Gonadotropin Therapy

- TV-USG, serum estradiol measurements
- Gonadotropins are administered in the evening (5:00 and 8:00 p.m.)
- Serum estradiol measurements are obtained early in the morning
- Estradiol levels rise at a constant exponential pace, doubling approximately every 2–3 days
- Serum estradiol level ≥ 180-250 pg/mL per mature follicle,
- uhCG (5,000 or 10,000 IU) or rhCG 250 mg if the lead follicle is at least 16 mm and estradiol concentration is consistent with the number of follicles

Optimal follicular size?

19- 30 mm (mean 25 mm) in CC cycles

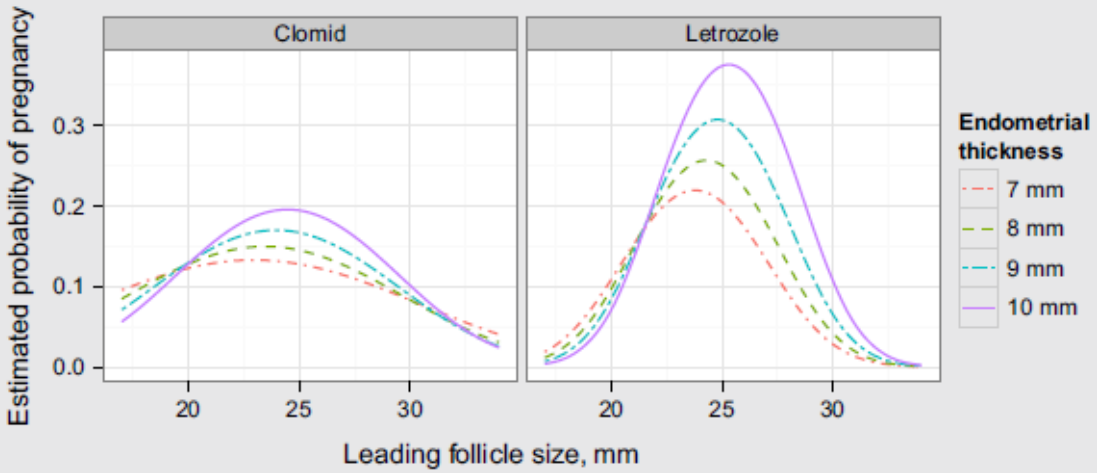
23 to 28 mm range in letrozol cycles

≥ 16 mm in gonadotropin cycles;

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]

SUPPLEMENTAL FIGURE 1



The estimated effect of the leading follicle size on the probability of pregnancy depending on endometrial thickness and cycle type. The figure is adjusted for other covariates via logistic regression. Reference levels (mean for continuous and mode for discrete variables): age = 34 years; primary diagnosis = unexplained.

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

Monitoring Gonadotropin Therapy

- hCG generally should not be administered;
  > 3 dominant follicules (≥14 mm),
  > 5 follicules exist > 10-11 mm follicules

Andersen AN, et alHum Reprod. 2006

Steures P et al, Reprod Biomed Online. 2007

Optimal timing of IUI

- At least one follicle ≥ 18 mm
- 24 or 36 h after hCG injection
- IUI 36 h after hCG has marginally better pregnancy rates than 24 h
- Premature administration of hCG acts like a premature LH surge and may result in follicular atresia

Progesterone luteal support after ovulation induction and intrauterine insemination: a systematic review and meta-analysis

Micah J. Hill, D.O.,[a] Brian W. Whitcomb, Ph.D.,[b] Terrence D. Lewis, M.D.,[c] Mae Wu, D.O.,[c] Nancy Terry,[d] Alan H. DeCherney, M.D.,[a] Eric D. Levens, M.D.,[e] and Anthony M. Propst, M.D.[c]

TABLE 2

Primary pregnancy outcomes in the five included randomized controlled trials reported on a per cycle basis.

Study	Group	Patients (n)	Cycles (n)	Positive hCG	*P* value	Clinical pregnancy	*P* value	Live birth	*P* value
Erdem et al. 2009 (6)	P	109	223	25.1%	.002	21.2%	.028	17.4%	.016
	Control	105	204	13.7%		12.7%		9.3%	
Kyrou et al. 2010 (8)	P	243	243	NR	NR	7.3%[a]	NS	NR	NR
	Control	225	225	NR		8.7%[a]		NR	
Ebrahami et al. 2010 (5)	P	98	252	13.5%	NS	11.5%	NS	7.5%	NS
	Control	102	259	11.2%		10.0%		5.7%	
Maher 2011 (7)	P	37[b]	132	37.1%	.004	29.5%	.07	18.9%	< .001
	Control	34[b]	126	20.6%		19.8%		5.5%	
Agha-Hosseini et al. 2012 (4)	P	148	148	29.0%	NS	24.3%	.02	NR	NR
	Control	142	142	21.8%		14.1%		NR	

Note: NR = not reported; NS = not significant.
[a] Values reported as ongoing pregnancy (intrauterine fetal cardiac activity after 12 weeks gestation).
[b] Other studies reporting gestational sac on ultrasound.

Hill. Progesterone luteal support for IUIs. Fertil Steril 2013.

Progesterone luteal support after ovulation induction and intrauterine insemination: a systematic review and meta-analysis

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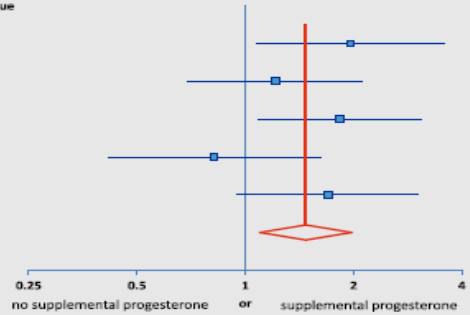
FIGURE 1

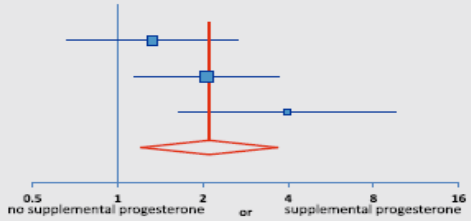
A Clinical Pregnancy

Author	Sample size	Measure (CI)	Weight	*P* value
Agha-Hosseini	290	1.96 (1.07; 3.59)	18.91	.03
Ebrahimi	511	1.21 (0.69; 2.11)	21.52	.5
Erdem	427	1.83 (1.08; 3.08)	23.7	.02
Kyrou	452	0.82 (0.41; 1.62)	15.48	.57
Maher	258	1.69 (0.95; 3.01)	20.4	.07
Synthesis	1938	1.47 (1.1; 1.98)	100	.01



B Live Birth

Author	Sample size	Measure (CI)	Weight	*P* value
Ebrahimi	511	1.33 (0.66; 2.67)	33.79	.43
Erdem	427	2.06 (1.15; 3.7)	40.36	.02
Maher	258	3.97 (1.65; 9.56)	25.85	0
Synthesis	1196	2.11 (1.21; 3.67)	100	.01



Forrest plot of (A) clinical pregnancy and (B) live birth. CI = confidence interval.

Hill. Progesterone luteal support for IUIs. Fertil Steril 2013.

Common protocols in IUI cycles

- Individualize the ovarian stimulation protocol
- CC, first line treatment agent for OI (3 ovulatory cycles)
- Gonadotropins , the most effective drugs when IUI is combined with OI
- Low dose daily, step-up protocol are advised when using gonadotropins
-
- GnRH-a, no proven advantage in OI/IUI cycles
- GnRH- antg, promising but needs definitive answers ??
- LH supplementation has a role in selected patients