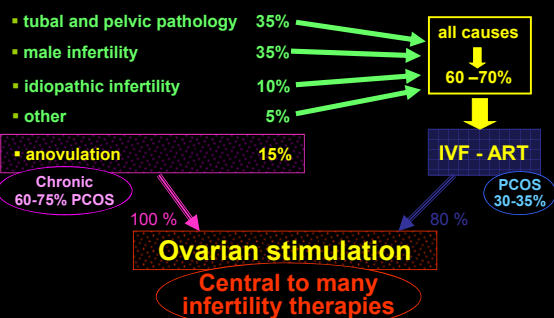


What role of clomiphene citrate in the mild stimulation cycle?

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Causes of infertility- when ovarian stimulation is used



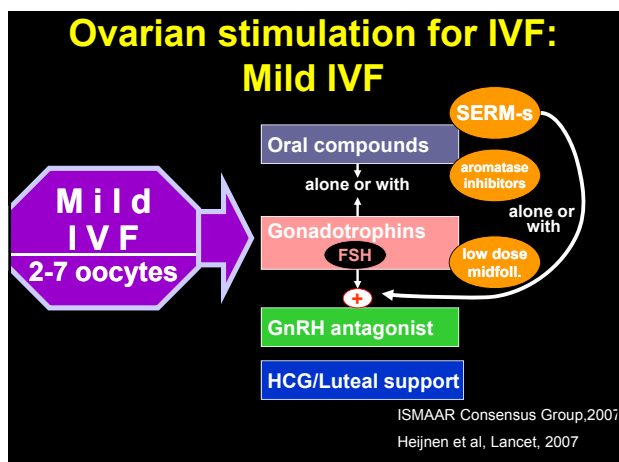
Ovarian stimulation for IVF/ART: Rotterdam ISMAAR Consensus Group

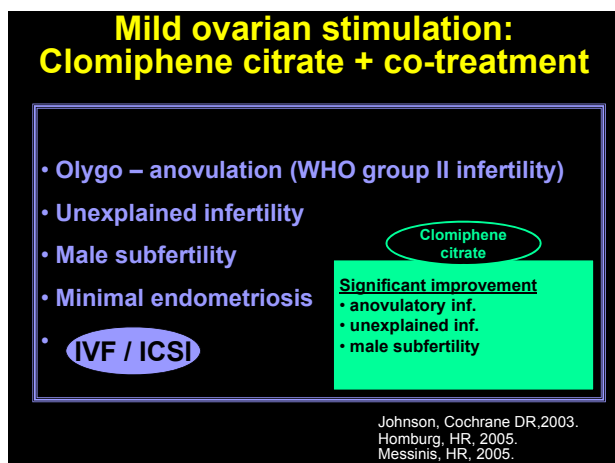
Terminology

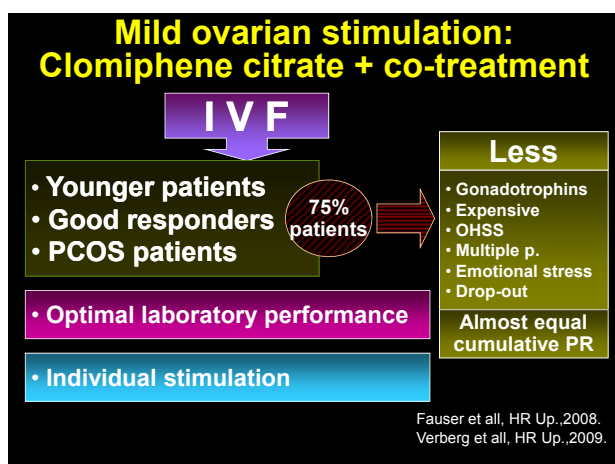
- Natural cycle IVF
- Modified natural IVF
- Mild IVF
- Conventional IVF

- Reduce patient distress
- Lower the cost of IVF
- Lower OHSS and multiple births risk
- Improve oocyte and endometrial quality

Pelinch et al, HR, 2006
Heijnen et al, Lancet, 2007
Nargund et al, HR, 2007







Clomiphene citrate (mixture of 2 stereoisomers)
Triphenylethylene derivative

Enclomiphene
short HL/potent

Zuclomiphene
long HL 1 month

- **Blocks hypothalamic ER and signals a lack of circulating estrogens**
 - Rise of endogenous **FSH** and **LH** 30-50%
 - Rise of **IGF**
- Mild stimulation of antral follicles cohort
- Normal estrogen production needed
- Improvement of CL function
- Peripheral antiestrogenic effects

Greenblatt et al, AJOG, 1961.
Yen: Human Reprod, 2005.
Homburg, HR, 2005.
Messinis, HR, 2005.

Clomiphene citrate: Dose – positive effects

Starting day 2/3/4/5 of the m.c. (th. duration 5 days)
→ dose not influence the results (Wu, F.St.,1989)

Dose → 50 to 150 mg / d

- 50 mg – 52% ovulations
- 100 mg – 22% ovulations
- 150 mg – 12% ovulations
- 200 mg – 7% ovulations

Ovulation 60-80%

Extended regimen - until final maturation
→ Enclomiphene prevents premature LH surge

Pregnancy rate → 30-50%
→ cumulative 6 cycles – 70%
→ 6 cycles - reevaluation

PR 40%
% with 50mg/d

Homburg,HR,2005
Messinis,HR,2005
Teramoto,RBM,2007

Clomiphene citrate: Negative outcome and side effects

Peripheral antiestrogen

- ↓ cervical mucus – 15%
- ↓ endometrium – 17%
- ↓ tubal function

Failure to ovulate / low PR

- obesity, IR, hyperandrogenism, age
- high LH

Multiple pregnancies 8-13% **OHSS** - rare

Spontaneous abortions 15-22% **Ectopic p.** - 0,5-4,5%

Borderline serous ovarian tm.

Ovarian cysts
Hot flushes
Mood swings
Nausea
Visual disf.
Mastodynia
2-10%

Rosing et al,NEJM,1994
Dickey et al, HR,1997
Imani et al, FS,2002
Homburg, HR,2005

Ovarian stimulation with clomiphene citrate: co-treatment I

• Human chorionic gonadotrophin (HCG)

→ obligate in ART

• Corticosteroids

→ Dexamethasone 0,5 mg/d

→ Prednisolone 7,5 mg/d

• Metformin

→ older women (>28 yrs)

→ visceraally obese patients (BMI>35)

→ Moll 2005

• Oral hormonal contraception pretreatment

→ with cyproterone acetat

→ with drospirenone

→ with dienogest

• PCOS

• Hyperandrogenism

• IR

Ovarian stimulation with clomiphene citrate: co-treatment II

• GnRH antagonists

- Cetrorelix 0,25 mg/d

- Ganirelix 0,25 mg/d

• Follitropin (FSH)

- low dose (75-225 IU)

- midfollicular phase → because $\uparrow E_2$ / \downarrow FSH

- every or every other day

• Lutropin (LH)

- rLH (Luveris)

• GnRH agonists

- final oocyte maturation trigger / instead of HCG

- 300 µg nasal spray

Clomiphene citrate: and IUI

- unexplained infertility
- male subfertility
- minimal endometriosis

• No difference CC/rFSH

• CC first line stimulation drug

NICE, 2004
Dankert et al, HR, 2007
Pennings and Ombelet, HR, 2007

Unexplained infertility: Pregnancy rate in one cycle

- Expectant → 1,3%
- Clomiphene citrate → 5,6% (CC/No th. OR 2,5)
- Clomiphene c.+IUI → 8,3% (1 pregnancy – 15-20 cycles)
- Clomiphene c.+FSH+IUI → 10-20%

Yen: Human Reproduction, 2005.
Messinis, HR, 2005.
Boroso et al, FS, 2008.
Devey et al, FS, 2008.

Clomiphene citrate: and IUI in 4100 cycles

Age	Pregnancy rate/cycle	Cumulative PR
< 35 y	11,5%	24,2%
35-37 y	9,2%	18,5%
38-40 y	7,3%	15,1%
41-42 y	4,3%	7,4%
> 42 y	1,0%	1,8%

Dovey et al, FS, 2008

Mild ovarian stimulation: Clomiphene versus Letrozole with low dose FSH (75 IU)

Unexplained infertility ⇒ IUI

	Clomiphene+FSH	Letrozole+FSH
No follicles	1,9	2,1
Peak E ₂ (pg/ml)	1207	914*
Day of HCG	12,4	12,1
Endometrium (mm)	7,3	9,5*
Pregnancy rate	20%	23,8%

Barroso et al, FS, 2006

Unexplained infertility: ovarian stimulation and IUI

	Clomiphene citrate	Letrozole
Age	28,3	29,1
BMI	26,1	26,6
Endometrium	9,2 mm	9,3 mm
E ₂	410 pg/ml	289 pg/ml*
Pregnancy	18%	19,0%
Miscarriage	16,2%	14,4%

Radawski et al. ES, 2008

Ovarian stimulation for IUI: unexplained infertility

- Metaanalysis – 5 studies, 273 patients
- Clomiphene citrate (+FSH) versus Letrozole (+FSH)

	Letrozole (+FSH)	Clomiphene (+FSH)
Mean no Follicles	1,3	1,8
Endometrium (mm)	9,1	8,1
Miscarriage	0	4
Ectopic	2	0
Multiple p.	0	1
Live birth	comparable	OR 0,87

Polyzos et al, CME Rev.A, 2008

Ovarian stimulation for IUI: Clomiphene citrate versus low dose FSH

- Unexplained infertility / male subfertility
- 4 cycles cumulative pregnancy rate
- Less than 3 follicles

	Clomiphene (100 mg/d)	r FSH (75 IU/d)
Drop out	22,5%	11,9%*
Pregnancy (cycle)	10%	8,7%
Cumulative PR	38%	34,3%
Spontaneous abort.	26%	21,7%
Multiple pregnancies	7,4%	4,3%
OHSS	0	0

Dankert et al. HB, 2007

Mild ovarian stimulation for IVF: Predictors of PR with single embryo transfer (SET)

FSH from 5 th day	ongoing pregnancy /SET=28%	
	odds ratio	correlation with PR
• Body mass index (BMI)	0,89	-
• Total amount of FSH	0,92	
• Number of oocytes	0,93	
• Top-quality embryo	2,18	+
no correlation with PR		
• Age		
• History of previous pregnancy		

Verberg, et al. FS 2008

Verberg, et al. FS 2008

Ovarian stimulation for IVF: Reduction of aneuploidy

- Comparison Mild and Conventional IVF protocol
- Same age and basal characteristics
- Embryo biopsy and FISH screening

	Conventional	Mild (FSH+GnRHa)
oocytes	12,1	8,2*
embryo (patient)	6,5	3,9*
Embryo (normal morphology)	35%	51%
Chromosomal abnormal E	63%	45%
Abnormal and mosaic E	73%	55%
Chromosomal normal E (No)	1,8	1,8

Reduced interference with ovarian physiology → sufficient number of chromosomally normal embryos

Baart et al. HR 2007

Minimal stimulation with clomiphene citrate for IVF: oral contraception pretreatment

Oral contraception 35-42 d
Clomiphene citrate + HCG

- 64 aspirations
- No LH surge
- Mature oocytes 3,2
- Embryos / ET 2,5
- Clinical pregnancy 32,8%
- Multiple pregnancy 14,3%

Branigan and Estes, FS 2000

Ovarian stimulation for IVF: Mild versus standard protocol

RCT - 294 cycles

- Clomiphene citrate + rFSH + rLH (alternate days)
- GnRH ag (long p.) + rFSH
- all patients – OC pretreatment and Prednisolon

	CC+rFSH/LH	Standard
Cancelled cycles	16,9%	15,7%
Oocytes	7,7	8,7*
Embryos – ET	2,1	2,1
OHSS	3%	10%*
Endometrium (mm)	13,5	13,4
Pregnancy / OPU	42,2%	34,7%

• Mild stimulation → ½ dose FSH compared to standard p.

Weigert et al, FS 2002

Mild ovarian stimulation for IVF: Same chance for pregnancy (1 year treatment)

	Mild	Standard
Embryos	2,8	3,8*
Cumulative cont. pregnancy	43,4%	44,7%
Multiple pregnancies	0,5%	13,1%*
OHSS (med/ser)	1,4%	3,7%*
Total cost (1y)	8300 Euro	10700 Euro

Heijnen et al, Lancet 2007

Minimal ovarian stimulation for IVF: Clomiphene citrate with FSH

- 44.300 cycles
- Extended clomiphene citrate 50 mg from 3rd day till maturation
- From day 8 – event. FSH/or HMG 150 IU every other day
- Final maturation triggered → 300 µg GnRHa spray

⇒ Enclomiphene → suppression luteinization

	Mean
Estradiol	850 pg/ml
HMG/FSH dose	257 IU
OPU	83,3%
Oocytes	2,2
Embryos	1,49
Live births (total)	11,1%
- 27-35 y of age	23-28,1%
Misscarriages	3,4%

- OC pretreatment → improved No oocytes and embryos
- Patients < 38 y → 2,5 cycles → 53% live births (≈ 5000 EURO)

Teramoto, RBM 2007

Mild ovarian stimulation for IVF: a meta-analysis

Mild IVF \Rightarrow midfollicular FSH+GnRH antagonist

592 cycles

Reduced number of oocytes **6/9**
 Optimal implantation rate (IR)
 - mild IVF 5 oocytes (31%)
 - standard IVF 10 oocytes (29%)

Modest number of oocytes – optimal IR

Verberg et al, HR Upd., 2009

Mild ovarian stimulation: Clomiphene citrate for IVF

Summary

Women $\leq 35y$

	Mean	
Cancelled cycles	10,8%	4,9-16,9%
Oocytes	5,4	1,9-8,2
Embryos (patient)	2,7	
Pregnancy (OPU)	27,9%	11,4-42,2%
Misscariages	11,1%	3,4-18,6%
Multiple pregnancies	9,4%	

Pregnancy rate in IVF: Natural versus Clomiphene c. cycles

Natural cycles for IVF – 20 studies meta-analysis (1800 cycles)

\Rightarrow started cycle 7,2%
 \Rightarrow ET 16%

PR

Clomiphene / CC + gonadotrophins (40.000 cycles)

\Rightarrow ET 20,5%

PR

H \rightarrow First IVF Pregn. – Natural cycle
 \rightarrow Further 4 Pregn. – CC
 \rightarrow Conventional protocols

Kenny, BJOG, 1995
 Cochrane Database, 2003

Cost-effectiveness: Mild and standard IVF

- Mild IVF (1 y) • 2500 EURO
- Pregnancy (live birth) • 5000 EURO

Standard strategy

- ⇒ expensive stimulation
- ⇒ multiple pregnancies
- ⇒ antenatal care
- ⇒ cesarian section
- ⇒ postpartum care

Polindar et al, HR, 2008

ZAGREB, YUGOSLAVIA
Initial Results of the in Vitro
Fertilization Program: January 31–June
15, 1983

- 152 patients – beginning of 1983
- Clomiphene citrate (100-150 mg/d)
 - ↳ LHSIR (serum LH 4 times/d)
 - ↳ Hcg

	LHSIR	HCG
Cancelled cycles - negative OPU	22,3%	27,8%
Laparoscopic OPU pos.	57	58
Oocytes No (mean)	1,3	1,7
Fertilization	54,2%	59,4%
ET / patients	30	33
Pregnancy	3	2
Spontaneous ab.	1	1
Clinical pregnancy / ET	3 (4,8%)	

Drobnjak Grizelj Šimunić I IVE 1984

Ovulation stimulation with clomiphene citrate / HMG: pregnancies after IVF

- 153 patients – 33,5y / infertility 11,4y (1984/85 y)
- Clomiphene citrate from day 3 (100-150 mg)
- From 8th day m.c. HMG (Pergonal) 150 IU/HCG 5000 IU
- Mean HMG 7,6 amp/570 IU

N= 153	Result
Cancelled cycles	10,6%
Laparoscopic OPU positive	124 (83,2%)
Oocytes No/patient	4,1 (57% mature)
ET	113 (91,1%)
Embryos / ET	2,9 (2 to 6 cells)
Clinical pregnancy/ET	11 (9,7%)
Twins	1 (9,1%)
Spontaneous abortion	2 (18,2%)

Grizelj, Puharić, Šimunić, Diab.Cro, 1985.

Ovulation stimulation for IVF: Clomiphene citrate/FSH mild protocol (I)

- 86 patients → < 38 y (mean 32,5 y) → 2007/08
- Clomiphene citrate + FSH 75-150 IU (mean 606 IU) 8 amps
- Cetrotide 0,25 mg – 4-5 days (76% patients)
- Urine LH testing

	Result
Cancelled cycles	9 (10,4%)
OPU	77 (89,5%)
Oocytes (patient)	6,8
Embryos (mean)	3,4
Top quality E	98 (37,1%)
ET	68 (88,3%)

Šimunić, Tomić, Dmitrović, in press, 2009

Ovulation stimulation for IVF: Clomiphene citrate/FSH mild protocol (II)

Clinical pregnancies	Result
ET / patients	68
Pregnancy / started cycle	33,7%
Pregnancy / OPU	37,6%
Pregnancy / ET	42,6%
Live birth / OPU	25,9%
Spontaneous ab.	11,7%
Multiple pregnancies	13,8%

⇒ Results comparable to standard IVF

Šimunić, Tomić, Dmitrović, in press, 2009

Ovarian stimulation for IVF: Mild protocol in women ≥ 39 y

- 38 patients 39 – 42 years of age (mean 40,7y) ⇒ 2007/2008.
- CC + FSH (975 IU – 13 amps) + Cetrotide

N=38	Results
Cancelled cycles	9 (23,7%)
OPU	29 (76,3%)
Oocytes (mean)	3,6
Embryos (mean)	1,9
Top quality E	7 patients (24,1%)
ET	22 patients (75,8%)
Pregnancy/OPU/ started	4 (13,8%) / (10,5%)
Pregnancy/ET	18,2%
Spontaneous abortion	25%

Šimunić and Dmitrović, in press

Mild ovarian stimulation with CC:**CONCLUSIONS**

- Clomiphene citrate still has important role in mild ovarian stimulation protocols for ART
- Clomiphene citrate with co-treatment
 - less oocytes but better quality
 - less embryos but higher % of top quality embryos
 - comparable cumulative pregnancy rates
- Benefits of CC in mild protocol
 - less gonadotrophin administration (↓ total cost)
 - less OHSS, miscarriages, multiple P
- Comparable cancellation and ongoing PR to conventional protocols
- CC mild protocol - less physical and psychological burden
