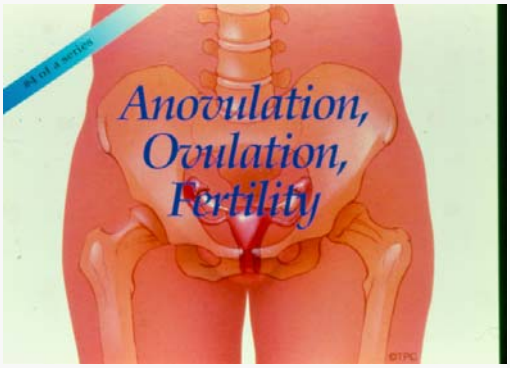


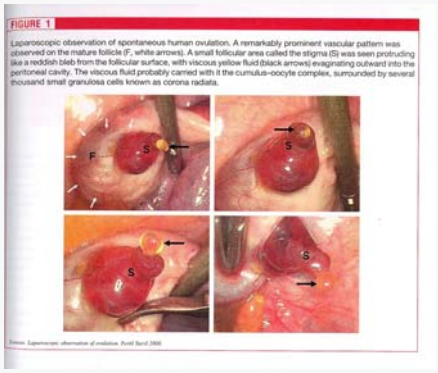
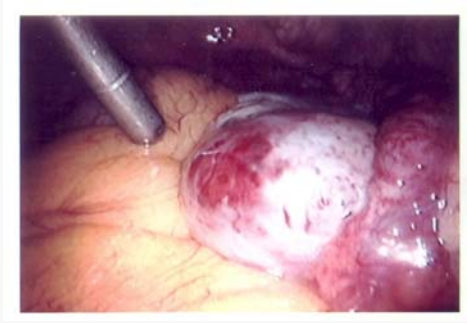
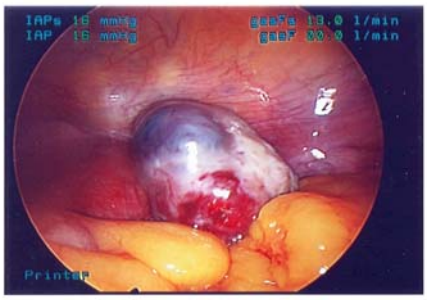
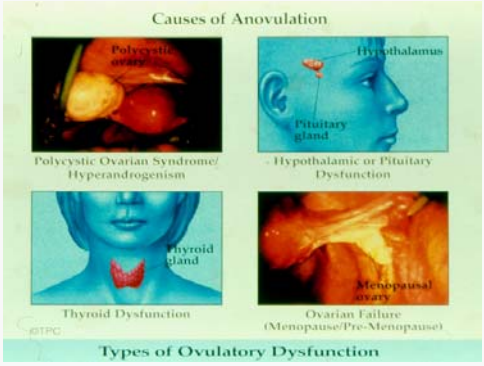


FIGURE 1

Laparoscopic observation of spontaneous human ovulation. A remarkably prominent vascular pattern was observed on the mature follicle (F, white arrows). A small follicular area called the stigma (S) was seen protruding like a reddish bleb from the follicular surface, with viscous yellow fluid (black arrows) evaginating outward into the peritoneal cavity. The viscous fluid probably carried with it the cumulus–oocyte complex, surrounded by several thousand small granulosa cells known as corona radiata.







OVULATORY DYSFUNCTION

1. PROLONGED FOLLICULAR RIPENING
2. EXCESS ANDROGENS IN FOLLICLE
3. PREMATURE LH SURGE
4. ABSENT OR INADEQUATE LH SURGE

Treatment Options

	Option 1	Option 2
Hyperprolactinemia	Bromocriptine	Repeat in 3 months
Hypothalamic hypogonadism	hMG +hCG* or GnRH	
Oligo-ovulation	Clomiphene	hMG or FSH and hCG*
Premature ovarian failure	Estrogen replacement	Donor oocyte program*
Polycystic ovarian disease	Clomiphene	FSH + hCG*

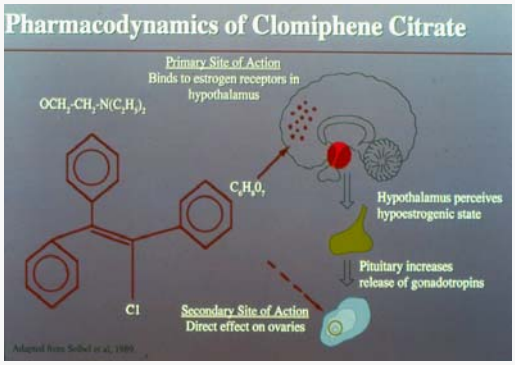
*Referral may be appropriate
hMG = human menopausal gonadotropin; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; GnRH = gonadotropin-releasing hormone
Adapted from Lynskey et al, 1991.

Clomiphene Citrate: Patient Selection/Contraindications

Good response	In patients with: Anovulation Adequate endogenous estrogen
Poor response	FSH ≥40 mIU/mL Low estrogen levels (failure to respond to progesterone challenge)
Contraindicated	Pregnancy Uncontrolled thyroid/adrenal dysfunction Organic intracranial lesion Liver disease/history of liver dysfunction Abnormal uterine bleeding Ovarian cysts/enlargement (not PCOD)

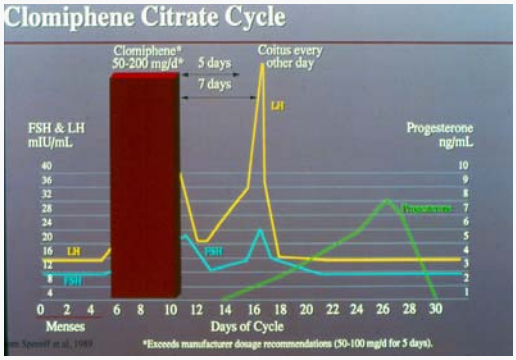
PCOD = polycystic ovarian disease

Pharmacodynamics of Clomiphene Citrate



Adapted from Seibel et al, 1989

Clomiphene Citrate Cycle

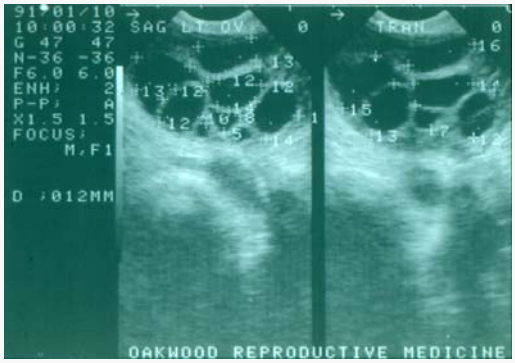


Serophene® (clomiphene citrate tablets, USP) 50 mg Therapy General Guidelines

Treatment Onset:	Therapy may be started at any time if the patient has had no recent uterine bleeding.
Initial Dosage:	50 mg per day for 5 days
Dosage Increments:	50 mg at a time
Maximal Dosage:	100 mg per day for 5 days

Clomiphene Citrate: Monitoring Techniques

	Advantages	Disadvantages
BBT	Determines approximate time of ovulation, duration of luteal phase; convenient; inexpensive	Does not confirm adequate luteal phase function
LH surge kits	Determine approximate time of ovulation; convenient	False-negative results are not uncommon
Serum progesterone	No office visits; reproducible	Single assessment may not reflect luteal phase accurately
Endometrial biopsy	Evaluates luteal phase; confirms correction of luteal phase dysfunction	Expensive; uncomfortable; inconvenient



Assessment Of The Female Genital Tract

Postcoital test	Quality of cervical mucus
	Sperm–mucus interaction
Hysterosalpingogram	Uterine abnormalities
	Patency of fallopian tubes
Laparoscopy	Endometriosis
	Pelvic adhesions

Clomiphene Citrate Ovulation And Pregnancy Rates *

	Ovulation Rate (%)	Pregnancy Rate (%)
Bishop, et al	72.4	45.0
Figueroa Casas, et al	68.2	33.4
Greenblatt	70.0	35.0
Insler, et al	62.6	33.6
Kase	80.0	50.0
Kistner	70.0	40.0
Lamb	78.0	60.0
MacGregor, et al	70.0	31.0
Pollack, et al	68.7	34.7
Roland, et al	69.0	48.0
Vande Wiele	70.0	30.0

* Asch RH, Greenblatt RB, The Journal of Reproductive Medicine 1976; 17:179.

Serophene® (clomiphene citrate tablets, USP) 50 mg

Side Effects

1. Ovarian enlargement	13–14%
2. Vasomotor flushes	10–11%
3. Abdominal discomfort	05–08%
4. Breast tenderness	02–03%
5. Nausea, vomiting	01–02%
6. Nervousness, insomnia	01–02%
7. Visual symptoms	01–02%
8. Headache	01–02%

Precautions

1. Diagnosis prior to Clomiphene Citrate therapy
2. Ovarian overstimulation during treatment with Clomiphene Citrate
3. Multiple pregnancy

Clomiphene Citrate Dose Effects

Dose (mg)	Ovulation Rate (%)	Conception Rate (%)
50	52.1	52.8
100	21.9	20.7
150	12.3	9.8
200	6.9	8.8
250	4.9	6.2

GYSLER et al., FERTIL STERIL 37:161, 1982

Clomiphene Citrate Related Conceptions

Effect Of Duration Of Treatment

Ovulatory Cycle	Cumulative Conception (%)
1	51.8
2	76.7
3	84.5
4	91.2
5	95.4
≥6	100.0

GYSLER et al., FERTIL STERIL 37:161, 1982

FERTILITY TREATMENT
Initial

Clomiphene Citrate

1. 50 mg X 5 days (start 2-5 days of cycle)
2. Maximum dose 150 mg/d
3. 75-80% ovulate
4. 22% conception rate/cycle
   55% cumulative – 6 cycles
5. 6 ovulatory cycles

Fertil Steril 89:505, 2008

LETROZOLE (Femara)

Aromatase inhibitor of androgens

Half-life – 45 hours

2.5 mg. – 7.5 mg. daily x five days

NOT approved for ovulation induction

Fewer side effects, more expensive

TABLE 2

Response to treatment.

	Letrozole (n = 32)		CC (n = 32)		
Parameters	Mean ± SD	Range	Mean ± SD	Range	*P* value
Follicular development by day 16 (mm)	18.84 ± 3.17	14–23	16.19 ± 3.47	12–22	<.001
Serum E_2 on day of hCG (pg/mL)	444.03 ± 85.42	310–650	817.75 ± 280.70	55–1,232	<.001
Endometrial development by day 16 (mm)	10.37 ± 1.2	8–12	9.03 ± 0.89	7–14	<.001
Serum P on day 21 (ng/mL)	19.09 ± 10.47	3–37	13.90 ± 12	2–35	<.05

Bayar, Comparison of efficacy of aromatase inhibitor. Fertil Steril 2009.

TABLE 4

Outcome of ovulation induction.

Parameters	Letrozole (n = 32) No.	%	CC (n = 32) No.	%	*P* value
Ovulation	20/32	62.50	12/32	37.50	<.05[a]
Pregnancy	13/32	40.62	6/32	18.75	>.05[b]
Pregnancy among ovulatory patients	13/20	65	6/12	50	>.05[c]

[a] $\chi^2 = 4$, df-1.
[b] $\chi^2 = 3.66$, df-1.
[c] $\chi^2 = 0.694$ df-1.

Begum. Comparison of efficacy of aromatase inhibitor. Fertil Steril 2009.

NIH – Reproductive Medicine Network
Legro, et al., NEJM, 2007

%	Clomiphene 209	Metformin 208	Combination 209
Ovulation	49*	29	60**
Conception	30*	12	38*
Pregnancy	24*	9	31*
Live birth	23*	7	27*
Multiple	6	0	3*

*P <.001
**P <.001 combination vs. clomiphene

RMN – PPCOS Trial

Conclusions

(1) CC is superior to Metformin in achieving live births in women with PCOS (multiple birth – risk)

(2) Ovulation should not be used as a surrogate for pregnancy in infertility trials.

TABLE 2

Ovulatory and pregnancy outcomes in response to clomiphene citrate.

Outcome	Metformin group	Placebo group	*P* value
No. of women who ovulated/total no. of women	9/12	4/15	.02
No. of women who ovulated (%)	(75)	(27)	
No. of women who conceived/total no. of women	6/11	1/14	.02
No. of women who conceived (%)	(55)	(7)	

Note: One patient each in the metformin and placebo groups who ovulated failed to complete the study protocol and was not included in the pregnancy rate analysis.

Vandermolen. Metformin use in clomiphene resistance. Fertil Steril 2001.

Therapeutic Options

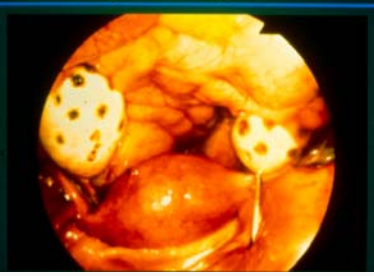
Ovarian Wedge Resection (prior to 1966)

Total number of PCO cases – 1,079

Result	Usable No. of Cases	Frequency (%) Mean	Range
Regular cycle	447	80	6-93
Pregnancy	640	63	13-83
Decreased hirsutism	205	16	0-18

Therapeutic Options

Laparoscopic Cautery



Ovarian Drilling

- > 4-8 holes/ovary
- Reduction of intraovarian androgen production
- Reduction of testosterone level by 40-50%
- Pregnancy rates of 60-80% at 2 years

Serophene® (clomiphene citrate tablets, USP) 50 mg Resistance

Subtypes

I. "Ovulation Failure"

II. "Conception Failure"

Human Menopausal Gonadotropin (hMG) Therapy: Indications

- Anovulation (hypothalamic-pituitary failure or dysfunction)
- Multiple follicular recruitment for IVF
- Male hypogonadotropic hypogonadism

IVF = in vitro fertilization

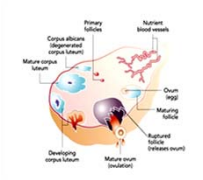
CONTRAINDICATIONS TO HMG/FSH THERAPY

- 1. OVARIAN FAILURE
- 2. OVERT THYROID OR ADRENAL DYSFUNCTION
- 3. PITUITARY MACROADENOMA
- 4. OVARIAN ENLARGEMENT NOT DUE TO PCO

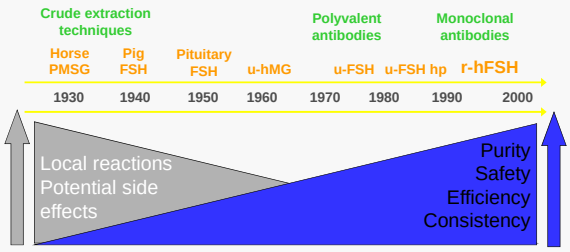
Ovulation Induction vs. Controlled Ovarian Hyperstimulation

- Goal is to stimulate ovaries
  - induce follicle development
  - egg maturation and release

Both use various hormones and hormone analogs

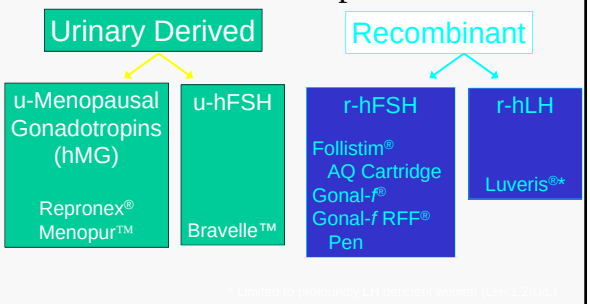


Technology & Product Timeline: Gonadotropins



Adapted from Lunenfeld. RBM Online 2002;4(suppl 1):11

Gonadotropins



* Limited to profoundly LH deficient women (LH<1.2IU/L)

Ovulation Induction vs. Controlled Ovarian Hyperstimulation

	OI	**COH**
Number of Eggs Stimulated & Released	Limited number	Non-physiologic number
Fertilization	*In vivo*	*In Vitro*
Risk of Multiple Pregnancy	Dependant upon number of eggs released	Dependant upon number of embryos returned to uterus

Ovarian Stimulation Protocols

- Clomiphene Citrate with or without gonadotropins
- Gonadotropins alone
- Down-regulation with GnRH agonists plus gonadotropins
- GnRH antagonist suppression plus gonadotropins
- Flare protocols with GnRH agonists

FSH-Containing Products

- Direct ovarian stimulation
- Source material may be urinary or recombinant (genetically engineered)

Urinary-Derived hFSH Products

Source material:

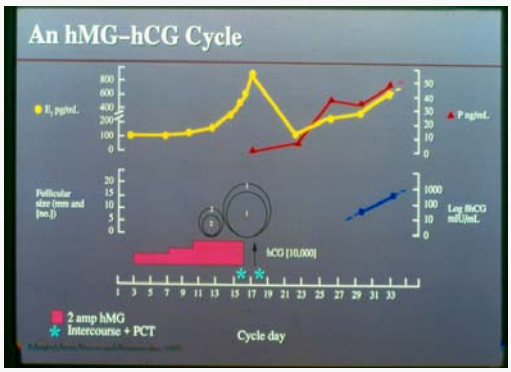
- Urine of post-menopausal women

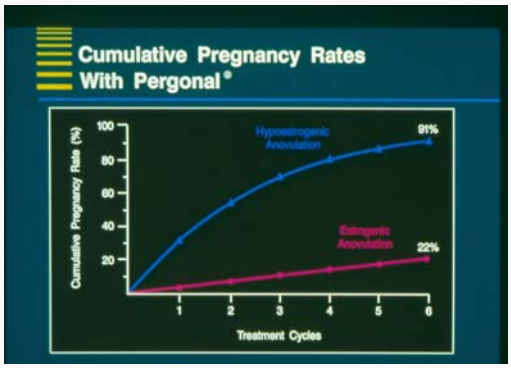
- u-hFSH: Bravelle®
  - 75 IU FSH; up to 2% LH
- u-hMG: Repronex® and Menopur™
  - 75 IU FSH; 75 IU LH

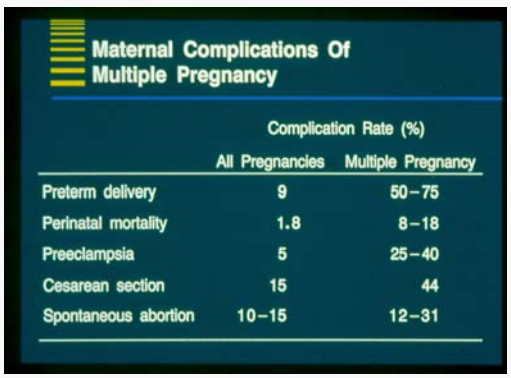
Recombinant hFSH Products

Recombinant DNA Technology provides for:

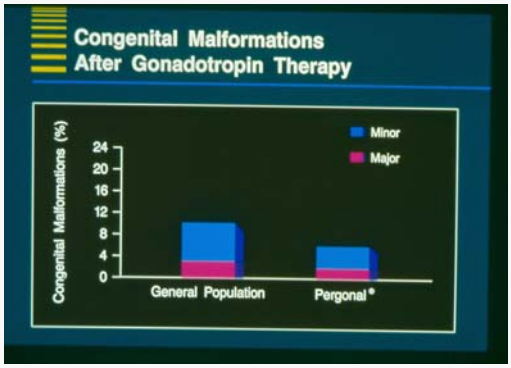
- Increased product purity – No LH activity – FSH is the primary hormone responsible for follicular recruitment and development
- Provided in improved delivery devices
  - PreFilled, ready-to-use Pen (Gonal-f RFF®)
  - Cartridge Pen (Follistim® AQ Cartridge)

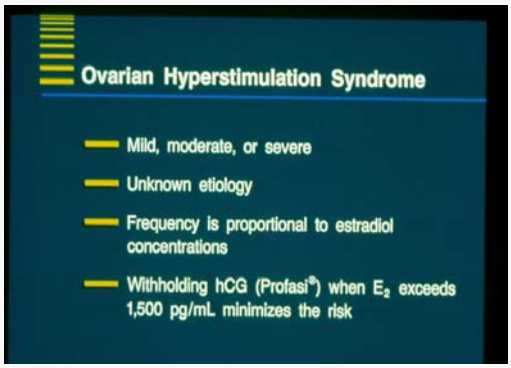


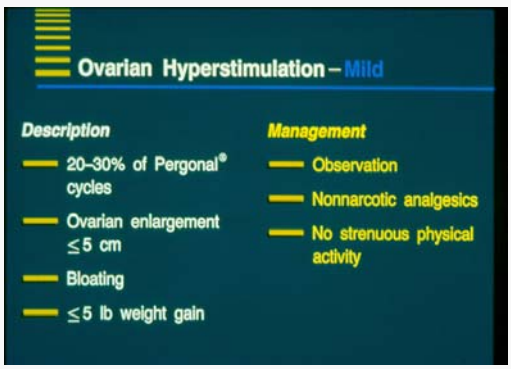




	Complication Rate (%)	
	All Pregnancies	Multiple Pregnancy
Preterm delivery	9	50–75
Perinatal mortality	1.8	8–18
Preeclampsia	5	25–40
Cesarean section	15	44
Spontaneous abortion	10–15	12–31


Congenital Malformations
After Gonadotropin Therapy
Congenital Malformations (%)
24
20
16
12
8
4
0
Minor
Major
General Population
Pergonal®


Ovarian Hyperstimulation Syndrome
Mild, moderate, or severe
Unknown etiology
Frequency is proportional to estradiol concentrations
Withholding hCG (Profasi®) when E_2 exceeds 1,500 pg/mL minimizes the risk


Ovarian Hyperstimulation – Mild
Description
20–30% of Pergonal® cycles
Ovarian enlargement ≤5 cm
Bloating
≤5 lb weight gain
Management
Observation
Nonnarcotic analgesics
No strenuous physical activity

Ovarian Hyperstimulation – Moderate

Description

- 1–3% of Pergonal® cycles
- Ovarian enlargement to 5–12 cm
- Slight abdominal distension
- Nausea and vomiting
- 5–10 lb weight gain

Management

- Bed rest
- Measure hemoglobin and serum electrolytes
- Monitor ovarian size

Ovarian Hyperstimulation – Severe

Description

- < 2% of Pergonal® cycles
- Ovarian enlargement > 12 cm
- Nausea and vomiting
- Ascites and pleural effusion
- > 10 lb weight gain
- Hemoconcentration
- Rupture of ovarian cysts and hemoperitoneum are possible

Table . Pregnancy rates and the rates of pregnancy loss (chemical pregnancy, miscarriage, and total pregnancy loss) associated with various ovarian stimulation treatments

Treatment	All started cycles	All positive pregnancy test n (%)	Chemical pregnancy n (% from positive pregnancy test)	Miscarriage n (% from positive pregnancy test)	Total pregnancy loss n (% from positive pregnancy test)
CC	994	80 (8.0)	10 (12.5)	15 (18.8)	25 (31.3)
Gonadotropins alone	671	110 (16.4)	15 (13.6)	12 (10.9)	27 (24.6)
Letrozole (2.5 mg/d)	167	33 (19.8)	6 (18.2)	4 (12.1)	10 (30.3)
Letrozole (5.0 mg/d)	432	70 (16.2)	9 (12.8)	4 (5.7)	13 (18.2)
CC + gonadotropins	205	33 (16.1)	4 (12.1)	3 (9.1)	7 (21.2)
Letrozole + gonadotropins	153	30 (19.6)	2 (6.7)	6 (20.0)	8 (26.7)
Spontaneous (no ovarian stimulation)	423	38 (9.0)	4 (10.5)	7 (18.4)	11 (29.0)
All cycles	3045	394 (12.9)	50 (12.7)	51 (12.9)	101 (25.6)

Mitwaky, Amer. J. OB. GYN., 2005

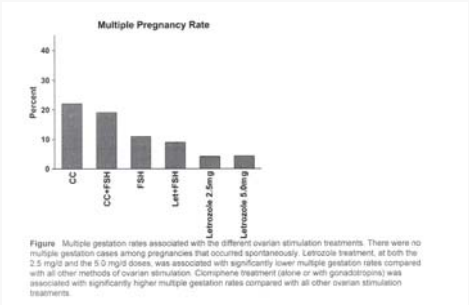


Figure. Multiple gestation rates associated with the different ovarian stimulation treatments. There were no multiple gestation cases among pregnancies that occurred spontaneously. Letrozole treatment, at both the 2.5 mg/d and the 5.0 mg/d doses, was associated with significantly lower multiple gestation rates compared with all other methods of ovarian stimulation. Clomiphene treatment (alone or with gonadotropins) was associated with significantly higher multiple gestation rates compared with all other ovarian stimulation treatments.