OVULATORY DYSFUNCTION
1. PROLONGED FOLLICULAR RIPENING
2. EXCESS ANDROGENS IN FOLLICLE
3. PREMATURE LH SURGE
4. ABSENT OR INADEQUATE LH SURGE
### Treatment Options

<table>
<thead>
<tr>
<th>Option 1</th>
<th>Option 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypogonadism</td>
<td>Bromocriptine</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>HMG or GNRH</td>
</tr>
<tr>
<td>Glioma</td>
<td>Clomiphene</td>
</tr>
<tr>
<td>Ovarian failure</td>
<td>Clomiphene</td>
</tr>
<tr>
<td>Polyovarian disease</td>
<td>Clomiphene</td>
</tr>
</tbody>
</table>

*MG = human menopausal gonadotropin, hCG = human chorionic gonadotropin, GNRH = gonadotropin-releasing hormone

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### Clomiphene Citrate: Patient Selection/Contraindications

**Good response**
- In patients with:
  - Anovulation
  - Adequate endogenous estrogen

**Poor response**
- FSH >80 mIU/mL
- Low estrogen levels (failure to respond to progesterone challenge)

**Contraindicated**
- Pregnancy
- Uncontrolled thyroid/renal dysfunction
- Ovarian hyperstimulation syndrome
- Liver disease/history of liver dysfunction
- Abnormal uterine bleeding
- Ovarian cysts/ovarian abnormalities (not PCOS)

PCOS = polycystic ovary syndrome

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### Pharmacodynamics of Clomiphene Citrate

- Direct & Indirect Actions
- Hypothalamic-pituitary axis dysregulation
- Pituitary gland
- Hypothalamus -gonadotropin releasing hormone
- Pituitary increases release of gonadotropins
- Ovaries respond with increased estrogen levels
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

<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBT</td>
<td>Determines approximate time of ovulation, duration of luteal phase; convenient; inexpensive</td>
<td>Does not confirm adequate luteal phase function</td>
</tr>
<tr>
<td>LH surge kits</td>
<td>Determine approximate time of ovulation; convenient</td>
<td>False-negative results are not uncommon</td>
</tr>
<tr>
<td>Serum progesterone</td>
<td>No-office visits; reproducible</td>
<td>Single assessment may not reflect luteal phase accurately</td>
</tr>
<tr>
<td>Endometrial biopsy</td>
<td>Evaluates luteal phase; confirms completion of luteal phase differentiation</td>
<td>Expensive; uncomfortable; inconvenient</td>
</tr>
</tbody>
</table>
FERTILITY TREATMENT
Initial
Climophene Citrate
1. 50 mg X 5 days (start 2-4 days of cycle)
2. Maximum dose 150 mg/d
3. 75-90% ovulation
4. 22% conception rate/cycle
5. 66% cumulative -- 6 cycles
6. 8 ovulatory cycles

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 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Letrozole (n = 32)</th>
<th>CC (n = 33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulation</td>
<td>28/32</td>
<td>29/32</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>19/32</td>
<td>18/32</td>
<td>&gt;0.05*</td>
</tr>
<tr>
<td>Iamplification</td>
<td>13/32</td>
<td>13/32</td>
<td>&gt;0.05*</td>
</tr>
<tr>
<td>Ovulation among</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>activated patients</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* *X² = 4.01, df=1.*
* *X² = 3.66, df=1.*
* *X² = 0.66, df=1.*

* *X² = 4.01, df=1.*

* *X² = 3.66, df=1.*

* *X² = 0.66, df=1.*

* *X² = 4.01, df=1.*


---

**NIH – Reproductive Medicine Network**

Legro, et al., NEJM, 2007

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Clomiphene 208</th>
<th>Metformin 208</th>
<th>Combination 208</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovulation</td>
<td>49*</td>
<td>29</td>
<td>60**</td>
</tr>
<tr>
<td>Conception</td>
<td>30*</td>
<td>12</td>
<td>38*</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>24*</td>
<td>9</td>
<td>31*</td>
</tr>
<tr>
<td>Live birth</td>
<td>23*</td>
<td>7</td>
<td>27*</td>
</tr>
<tr>
<td>Multiple</td>
<td>6</td>
<td>0</td>
<td>3*</td>
</tr>
</tbody>
</table>

* *p < 0.05 combination vs. clomiphene

---

**RMN – PPCOS Trial**

Conclusions:

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

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.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Merismin group</th>
<th>Placebo group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of women who ovulated/no. of women</td>
<td>9/12</td>
<td>4/15</td>
<td>.02</td>
</tr>
<tr>
<td>No. of women who ovulated (%)</td>
<td>(75%)</td>
<td>(27%)</td>
<td></td>
</tr>
<tr>
<td>No. of women who conceived/no. of women</td>
<td>6/11</td>
<td>1/14</td>
<td>.02</td>
</tr>
<tr>
<td>No. of women who conceived (%)</td>
<td>(55%)</td>
<td>(7%)</td>
<td></td>
</tr>
</tbody>
</table>

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

Ovarian Drilling

- > 6 holes/ovary
- Reduction of ovarian 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

- Urinary Derived
  - u-Menopausal Gonadotropins (hMG)
    - Repronex®
    - Menopur™
  - Bravelle™

- Recombinant
  - u-hFSH
  - r-hFSH
    - Follistim®
    - AQ Cartridge
    - Gonal-f®
    - RF®
  - r-hLH
    - Luveris®

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

Ovulation Induction vs. Controlled Ovarian Hyperstimulation

<table>
<thead>
<tr>
<th></th>
<th>OI</th>
<th>COH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Eggs</td>
<td>Limited number</td>
<td>Non-physiologic number</td>
</tr>
<tr>
<td>Stimulated &amp; Released</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fertilization</td>
<td>In vivo</td>
<td>In Vitro</td>
</tr>
<tr>
<td>Risk of Multiple</td>
<td>Dependant upon number of eggs</td>
<td>Dependant upon number of embryos</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>released</td>
<td>returned to uterus</td>
</tr>
</tbody>
</table>

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)
Congenital Malformations After Gonadotropin Therapy

- Minor
- Major

General Population vs. Fetal

Ovarian Hyperstimulation Syndrome

- Mild, moderate, or severe
- Unknown etiology
- Frequency is proportional to estradiol concentrations
- Withholding hCG (Profasi®) when E₂ exceeds 1,500 pg/mL minimizes the risk

Ovarian Hyperstimulation - Mild

- 20-30% of Pergonal® cycles
- Ovarian enlargement ≤ 5 cm
- Bloating
- ≤ 5 lb weight gain

- Observation
- Nonnarcotic analgesics
- No strenuous physical activity