Ovarian stimulation

Didier Chardonnens
Infertility definition

Cumulative pregnancy rate (%)

Months
Fertility and age
Menken et al., 1986, Science, 233: 1389 - 1394

The graph shows the prevalence of infertility (%) across different age groups (15-19, 20-24, 25-29, 30-34, 35-39, 40-44 years). The prevalence increases with age, with the highest prevalence observed in the 40-44 age group.
Fertility and age
Trussel et al., 1985, Popul. Stud., 29: 269-286
Fertility and age


Relative fertility rates by age group in the Oxford Family Planning Association Contraceptive Study (N = 4104)
Fertility and life style factors

- Smoking
- Body weight
- Infectious disease
Fertility and smoking

The graph illustrates the relationship between cigarettes smoked per day and infertility risk odds ratio. The x-axis represents the number of cigarettes smoked per day (0, 1, 5, 10, 20), and the y-axis represents the infertility risk odds ratio. The data shows an increase in infertility risk odds ratio with an increase in the number of cigarettes smoked per day.
Fertility and body weight

Green et al., 1988, Fertil. Steril., 50:721 - 726

Percent of ideal body weight

Infertility relative risk

< 85 %  
85 - 120 % 
> 120 %
Changing a life style

- Stop smoking
- Diminish alcohol consumption
- Body weight back to normal
  - Diet counseling
  - Adapt physical activity
- Reduce stress
  - Psychological counseling
The axis

Hypothalamus

GnRH

Pituitary

FSH
LH

Ovary

E₂
Clomiphene citrate

Hypothalamus

GnRH

Pituitary

FSH

LH

Ovary

E2

Clomiphene

+ + +
Clomiphene citrate indications

- PCO
- Oligoanovulation
  - Progesterone positive test
Clomiphene citrate administration regimen

- **Dose**
  - 50-200 mg p.o. daily

- **Initiation**
  - D3-5 spontaneous or progesterone-induced cycle

- **Duration**
  - 5 days

- **Optional**
  - hCG at mid-cycle
Clomiphene citrate stimulation

- If 1 or 2 follicles with $\varnothing > 14$ mm
- Urinary LH 3 x/d
- 100 mg/d
- D3, D7, D10, ..., D
- US
- IUI or intercourse

Clomiphene citrate stimulation
Clomiphene citrate side effects

- vasomotor flashes (10%)
- poor cervical mucus (10%)
- multiple pregnancies (7%)
- abdominal distension (5.5%)
- nausea vomiting (2.2%)
- headaches (1.3%)
- visual disturbances
- teratogenic potential
Clomiphene citrate overall results

- Ovulatory rates
  - oligomenorrhea: 90%
  - secondary amenorrhea: 67%

- Pregnancy rates
  - overall: 40%
  - no other infertility factor: 80%
  - abortion: 20%

- Side effects: 13%
Clinical results (Gysler et al. 1982)

% of ovulatory patients who conceive

- Anovulatory
- Other
Gonadotropins

Hypothalamus

GnRH

Pituitary

FSH
LH

Ovary

E₂

Gonadotropins
**Gonadotropins indications**

- **Anovulatory patients**
  - Hypothalamic disorders
  - Pituitary failure
  - PCOS

- **Reproductive technology**

- **Poor candidates**
  - > 40 years old
  - Elevated D3 FSH

- **Contraindication**
  - Primary hypogonadism
Prognostic value of day 3 FSH levels in 758 patients undergoing an IVF cycle
Adapted from Scott et al. 1989, Fertil. Steril., 51 651 - 654

Basal day 3 FSH (mIU / mL)
Day 3 FSH levels: pregnancy rate and cancellation rate in 1478 IVF cycles
Adapted from Toner et al. 1991, Fertil and Steril., 55: 784 - 791
Gonadotropin stimulation

- hCG 5000-10000 UI
- if 1 or 2 follicles with ∅ > 16 mm:
  - 150 pg/ml < E2 > 450 pg/ml

- D3: US + E2
- D7: US + E2
- D?: US + E2
- D?: US + E2

- 75 - 150 UI/D
- ? UI/D

- IUI or intercourse

- Dx: 30 - 34 H
## Preparations

<table>
<thead>
<tr>
<th></th>
<th>FSH</th>
<th>LH</th>
<th>PRICE (SFr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG (Pergonal Humegon)</td>
<td>75</td>
<td>75</td>
<td>31</td>
</tr>
<tr>
<td>purified HMG (Metrodin HP)</td>
<td>75</td>
<td>&lt;0.1</td>
<td>63</td>
</tr>
<tr>
<td>recombinant FSH (Gonal F Puregon)</td>
<td>75</td>
<td>0</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>37.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Advantages for recombinant gonadotrophins in IVF

- Diminished total dose of gonadotrophins
- Diminished duration of treatment
- Higher number of mature oocytes retrieved
- Higher take home baby rate
  
  (OR 1.2  95% CI 1.1 -1.5)

Daya, Hum Reprod 1999, 14; 2207-2215
Gonadotropins overall results

- Ovulation: > 99%
- Pregnancy: 70%
- Multiple pregnancies: 10%
- Abortion: 28%
- Ovarian enlargement: 5%
- Hyperstimulation: < 0.1%
- Teratogenicity: none
Gonadotropins complications

Hyperstimulation
Multiple pregnancy

Wang et al 1980
PCO

↑ Volume ovarien

↑ Stroma ovarien

> 10 follicules Ø <10 mmsitués à la périphérie
(signe du collier de perles)
• Critères échographiques
• Infertilité 88 %
• Résistance à l’insuline 70 %
• Hirsutisme 62 %
• Troubles du cycle 50 %
• Obésité 38 %
• Acné 35 %
PCO versus PCOS

van Santbrink et al. 1997 Fertil Steril

Critères échographiques (66%)

Androgènes (36%)

LH (47%)
↑ nb follicules (58%)

↑ Stroma ovarien (45%)

↑ Volume ovarien (41%)

PCO
van Santbrink et al. 1997 Fertil Steril
Low dose step up regimen

[Diagram showing FSH levels with thresholds and window]

- Threshold
- Window
- 75 IU/D (15 days)
- 113 IU/D (7 days)
- 150 IU/D (7 days)
**Low dose step up regimen**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nb of cycles / patients</td>
<td>505 / 134</td>
</tr>
<tr>
<td>% ovulatory</td>
<td>73</td>
</tr>
<tr>
<td>% monovulatory</td>
<td>72</td>
</tr>
<tr>
<td>% non responders</td>
<td>5</td>
</tr>
<tr>
<td>% pregnancies</td>
<td>43</td>
</tr>
<tr>
<td>% multiple preg.</td>
<td>7</td>
</tr>
<tr>
<td>% miscarriages</td>
<td>30</td>
</tr>
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</table>
### Low dose step up regimen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean threshold dose (range)</td>
<td>95 IU (52-225)</td>
</tr>
<tr>
<td>Mean total dose (range)</td>
<td>18.5 amps (5 - 81)</td>
</tr>
<tr>
<td>Mean duration to hCG (range)</td>
<td>14.2 days (5 - 34)</td>
</tr>
<tr>
<td>Pregnancy rate per cycle</td>
<td>10 %</td>
</tr>
</tbody>
</table>
Stepdown regimen

- **Threshold**
- **Window**
- **hCG**

FSH levels:
- **D1**: 150 IU/d
- **D3**: 113 IU/d
- **Dx**: 75 IU/d
## Stepdown regimen

<table>
<thead>
<tr>
<th></th>
<th>Mizunuma et al. 1991</th>
<th>van Stanbrink et al. 1995</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nº cycles</td>
<td>17</td>
<td>234</td>
</tr>
<tr>
<td>Ovulatory rate</td>
<td>100</td>
<td>91</td>
</tr>
<tr>
<td>Conception rate</td>
<td>29</td>
<td>16</td>
</tr>
<tr>
<td>Multiple pregnancy rate</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Abortion rate</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Hyperstimulation rate</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>
GnRH agonists indications

- Pituitary downregulation
  - Ovarian stimulation (ultrashort, short and long protocol)
  - Endometriosis
  - Myomatous uterus
  - Hyperandrogenemia

- Ovarian stimulation
  - Pulsatile administration
Pulsatile GnRH

Hypothalamus

GnRH

Pituitary

FSH

LH

E2

Ovary
Pulsatile GnRH

- **Route**
  - Intravenous or subcutaneous

- **Dose**
  - theoretical 2-40 µg
  - practical 5 µg

- **Frequency**
  - 60 - 90 min

- **Duration**
  - optimal until menstruation or + pregnancy test
  - minimum until ovulation then luteal phase support
### Pulsatile GnRH in hypothalamic hypogonadism and PCOS

<table>
<thead>
<tr>
<th></th>
<th>Ovulation rate (%)</th>
<th>Pregnancy rate (%)</th>
<th>Pregnancy rate per ovulation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypogonadotrophic hypogonadism</strong></td>
<td>90</td>
<td>28.6</td>
<td>32</td>
</tr>
<tr>
<td><strong>PCOS</strong></td>
<td>50.7</td>
<td>14.6</td>
<td>28.7</td>
</tr>
</tbody>
</table>
Continuous GnRH

Hypothalamus

GnRH

Pituitary

Gonadotropins

Ovary

GnRH

FSH

LH

E₂
GnRH agonists continuous and ovulation induction

- Advantages
  - lower cancellation rate
  - more oocytes
  - no premature LH surge
GnRH agonists continuous and ovulation induction

- Disadvantages
  - More gonadotrophins needed
  - Ovarian cysts
  - Unwanted pregnancy exposure
Gonadotrophin stimulation with GnRH agonist

- **GnRH agonist 0.1 mg/D**
- **US + E₂**
- **10-15 days**
- **150 - 300 UI / D**
- **if 2 or more follicles with Ø > 18 mm**
- **1000 pg / ml < E₂ > 4000 pg /ml**
- **US + E₂**
- **US + E₂**
- **US + E₂**
- **hCG 5000-10000 UI**
- **OPU**
- **P, 3 x 100 mg /D**
- **D₁**
- **D₄**
- **D ?**
- **D ?**
- **D x**
- **Dx + 34 H**
### GnRH-agonists in IVF

*(Prospective studies long / short Protocol)*

<table>
<thead>
<tr>
<th></th>
<th>HMG (amp) Short</th>
<th>HMG (amp) Long</th>
<th>Embryos (n) Short</th>
<th>Embryos (n) Long</th>
<th>Preg rate (%) Short</th>
<th>Preg rate (%) Long</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hedon 88</strong></td>
<td>27.3</td>
<td>36.5</td>
<td>2.9</td>
<td>4</td>
<td>12.8</td>
<td>37.5</td>
</tr>
<tr>
<td><strong>Zorn 88</strong></td>
<td>20.5</td>
<td>39.5</td>
<td>1.8</td>
<td>2.3</td>
<td>25.3</td>
<td>26.6</td>
</tr>
<tr>
<td><strong>Remorgida 89</strong></td>
<td>23.7</td>
<td>31.7</td>
<td></td>
<td>34.7</td>
<td></td>
<td>36.4</td>
</tr>
<tr>
<td><strong>Ton 90</strong></td>
<td>24</td>
<td>27</td>
<td>1</td>
<td>3</td>
<td>16.6</td>
<td>25.7</td>
</tr>
<tr>
<td><strong>Tarlatzis</strong></td>
<td>27.9</td>
<td>37.7</td>
<td>4</td>
<td>6.3</td>
<td>19.4</td>
<td>25.8</td>
</tr>
</tbody>
</table>
## Incidence of OHSS

<table>
<thead>
<tr>
<th>Incidence Type</th>
<th>HMG %</th>
<th>Clomid %</th>
<th>Spontaneous %</th>
<th>TSH %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>3 - 23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3 - 16</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Risk factors for OHSS

- Gonadotrophin therapy
- Rapid E₂ rise
- PCO
- Younger age

Pregnancy
- Multiple gestation
- Molar pregnancy

Multiple small and intermediate follicle

hCG rise
Mediators of OHSS

- VEGF
- Renin angiotensin
OHSS pathophysiology

- hCG
- Ovarian VEGF
- Angiogenesis
- Hyperpermeability
**OHSS classification**

**Mild OHSS**
- grade 1: abdominal distention
- grade 2: nausea, vomiting or diarrhea, enlarged ovaries

**Moderate OHSS**
- grade 3: US evidence of ascites

**Severe OHSS**
- grade 4: clinical ascites
- grade 5: Hct > 45%, WBC > 15000, oliguria, creat clearance > 50 ml/min

**Critical OHSS**
- grade 6: Tense ascites, Hct > 55%, WBC > 25000, creat clearance < 50 ml/min, renal failure, thromboembolic phenomena, ARDS
Thromboembolic disease in OHSS

- Haemoconcentration
- High E₂ levels
Mild to moderate OHSS treatment

- Clinical assessment
  - daily abdominal diameter and weight
- Off work
  - home rest
Severe OHSS treatment

- Hospital admission
  - monitor input output
  - daily FBC, urea, creatinine, ultrasound
  - prophylactic anticoagulation
  - bed rest
**Critical OHSS treatment**

**Hemoconcentration / Ascites**
- Relative hemodilution
  - Hct < 45%
    - cristalloids
    - albumin
    - diuresis
    - recovery
  - Hct > 55%
    - cristalloids
    - albumin
    - paracentesis
    - renal failure, ARDS

**Tense ascites**
- Hct > 55%
  - cristalloids
  - albumin
  - paracentesis
  - Dopamine drip
  - impaired renal function

**TOP**
Treatment choices for ovulatory dysfunction

<table>
<thead>
<tr>
<th>Condition</th>
<th>CC</th>
<th>HMG/FSH</th>
<th>Pulsatile GnRH</th>
<th>Dopaminergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligoanovulation</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hypothalamic amenorrhea</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Hyper prolactinemia</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Pituitary insufficiency</td>
<td>-</td>
<td>+++</td>
<td>-</td>
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