Lebanese International Fertility Summit

2 – 3 October 2015
Hilton Beirut Habtoor Grand
Ovulation induction protocols
Clomiphene Citrate - FSH

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### Clomiphene Citrate

**Anti-œstrogenic effect ........ mainly**

<table>
<thead>
<tr>
<th>Target</th>
<th>Effect</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamus</td>
<td>-</td>
<td>GnRH</td>
</tr>
<tr>
<td>Hypophysis</td>
<td>+</td>
<td>LH</td>
</tr>
<tr>
<td>Ovaries</td>
<td>+</td>
<td>action FSH/aromatase</td>
</tr>
<tr>
<td>Cervical Mucus</td>
<td>-</td>
<td>Volume</td>
</tr>
<tr>
<td>Endometrium</td>
<td>-</td>
<td>Thickness Altered vascularisation</td>
</tr>
</tbody>
</table>
Clomiphene Citrate

**Action on ER & long half-life (5 d)**

- **GnRH frequency**
  - Pulsatility / Amplitude
- **Release of FSH & LH**
- **FSH**
- **E2**
- **Anti-estrogenic effect at hypothalamic level**
- **Risk of multi-follicular response**

- **CC**
- **ER**
- **day 5**
- **day 10**

- **No negative feed-back E2 on GnRH**
« Traditional » prescription of Clomiphene
(Anovulation type II OMS)

50 - 100 mg / d (According to BMI & Previous Hyperstimulation)

Prescription from d2 – d5 for 5 days

- Absence of ovulation : + 50 mg / d / cycle, max. 150 mg / d
- Ovulation without pregnancy : max 6 cycles

Risk of ovarian cancer
Survey of infertile women post-CC
(Rizzuto et al. Cochrane 2013; Trabert et al 2013)

Risk of endometrial cancer
Be careful in women treated before 30 yrs
(Brinton et al. 2013)
Monitoring of Clomiphene cycles (Anovulation Type II OMS)

US d14: optimal follicle size for hCG triggering?

ASRM 2003 Optimal: 25 mm
Palatnik et al. 2012 (50% anovulation)

Optimal size (23 – 28 mm) well correlated to endometrial thickness

In case of spontaneous LH surge: triggering with hCG (5000 IU)?

No significant advantage (Kosmas 2007)
No benefit for hCG triggering (George et al. Cochrane 2008 updated 2014)
## Monitoring of Clomiphene cycles

(Anovulation Type II OMS)

### Endometrial thickness: decreased (?)

**Change your prescription**

Takasaki et al. J Ov Res 2013

66 patients with endo < 8 mm after 50 mg/d D5-D9 (50 % anovulation)

<table>
<thead>
<tr>
<th></th>
<th>N = 66</th>
<th>CC 25 mg D5-D9</th>
<th>CC 50 mg D1-D5</th>
<th>CC 50 mg D5-D9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endo &gt; 8 mm</td>
<td>70%</td>
<td>90%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Endometrium (mm)</td>
<td>8.6 ± 1.5 *</td>
<td>9.4 ± 1.5 *</td>
<td>6.7 ± 1.8</td>
<td></td>
</tr>
</tbody>
</table>

**Specific effect of CC**

Reduce the starting dose – Start earlier (long half-life)

Need to be confirmed
Efficacy of Clomiphene citrate

(Anovulation type II OMS)

First intention treatment

- Ovulation rate
  60 à 80%
  OR 7,47 (3,24 - 17,23)
- Pregnancy rate
  15 à 25 % per cycle
  40 à 80 % after 6 cycles
  OR 5,77 (1,55 - 21,48)

Beck, Cochrane 2005
Efficacy of Clomiphene citrate

(Anovulation type II OMS)

- **Multiple pregnancy rate**: 6 à 10 % # 8%
  7 - 9 % twins; 0.3 - 0.5 % triplets
  0.3 % quadruplets; 0.13 % quintuplets

**Recommandations**: Serial US monitoring
  - Nice guidelines 2012
  - PCOS Australian alliance 2011

*No hCG triggering if more than 1« mature » follicle*

- **Miscarriage rate**: 15 à 20% NS
  PCOS: role of LH, luteal defect, endometrium?

- **Extra ut Pregnancy rate**: increase?
Resistance to CC
No ovulation with 150 mg/j

Failure of CC
No conception 6 ovulatory cycles

Resistance to CC
# 25%

Failure of CC
# 30%

Ovulation & conception
# 45%

Efficacy of Clomiphene citrate
(Anovulation type II OMS)
Predictive factors for CC resistance

- Hyperandrogenism: Testo / SHBG
- Ovarian volume (stroma)
- Amenorrhea
- BMI

Predictive factors for CC failure

- Age (oocyte quality)
- Amenorrhea

Clomiphene Citrate: Standard prescription

(Anovulation type II OMS)

No more than 6 cycles
6 - 12 months: How to simplify the scheme?
BMI & AMH: predictive factors for dose

**Partial resistance CC**

**PR** = 28% if BMI < 30  
16% if BMI > 35  
Legro 2007

**AMH: French study**

\[ AUC_{ROC} \text{ AMH} = 0.80 \ (95\% \ CI: 0.65-0.96, \ p<0.02). \]

Threshold for AMH
70 pmol/L (8 ng/ml)

Sensibility: 71%  
Specificity: 100%

AMH: Mahran 2013

If AMH < threshold  
Lower CC resistance  
Higher PR
Simplified scheme

WC > 90 cm

AMH > 70 pMol/L
Another strategy of prescription: The «stair-step»

Hurst et al Reprod Endo & Infertility 2009

Retrospective study: 31 PCOS

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comparison of stair-step protocol and traditional protocol for PCOS patients initially unresponsive to 50 mg clomiphene for 5 days</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stair-step protocol</th>
<th>Traditional protocol</th>
<th>Time to ovulation with both protocols</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CC 50 mg × 5 d</strong> (d 5-9)</td>
<td><strong>CC 50 mg × 5 d</strong> (d 5-9)</td>
<td>%</td>
</tr>
<tr>
<td><strong>Progesterone d 21</strong> (d 21)</td>
<td><strong>Progesterone d 21</strong> (d 21)</td>
<td></td>
</tr>
</tbody>
</table>

**No response:**
- CC 100 mg × 5 d (d 14-18)
- MPA 10 mg × 10 d (d 21-30), Menses (~d 34), then CC 100 mg × 5 d (d 38-42)

**U/S day 11-14** (d 14)

**U/S 1 wk after first U/S** (d 21)

**No response:**
- CC 150 mg × 5 d (d 21-25)
- MPA 10 mg × 10 d (d 55-64), Menses (~d 67), then CC 150 mg × 5 d (d 71-75)

**U/S 1 week after second U/S** (d 28)

**Progesterone ~14 d after last CC dose** (d 88)

Day of intervention from the first day of the first treatment cycle is shown in parentheses. CC, clomiphene citrate.


<table>
<thead>
<tr>
<th>Ovulation rate</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stair-step 100 mg</td>
<td>64 %</td>
</tr>
<tr>
<td>Traditional 100 mg</td>
<td>22 %</td>
</tr>
</tbody>
</table>
Conclusions

An « old » but effective treatment

✓ No expensive for type II OMS anovulation
✓ But risk of multiple pregnancy, cancers (?)
✓ US monitoring required (nb foll + endometrium)

The traditional scheme may be simplified: Take into account

- Predictive factors of response
- Simplified prescription (stair-step)
- Max 3-4 cycles (other causes of infertility ? Specifically when > 35 yrs)
FSH therapy for chronic anovulation

Objectives

- To get a singleton live birth

Cumulative pregnancy rate: 71%
(Eijkemans et al. 2003)

- To reduce the risk of high order multiple pregnancies
  ~ 2/3 of twins and ~ 1/2 of triplets from cycles without ART

Critical issue: the choice of stimulation regimen
« The FSH threshold and window » concepts

FSH threshold: level of FSH required to recruit the most sensitive follicle

FSH window: FSH levels decline in late follicular phase, closing the period of recruitment

« FSH requirement operates in a very narrow range (window) »
FSH step-up protocols

Principle: Stepwise increment of the initial FSH dose to carefully surpass the FSH threshold of the most sensitive follicle and limit the number of recruited follicles

3 parameters
- Starting dose
- Dose Increment
- Duration of the initial step
“Step up” Protocols: starting FSH dose

“Conventional dose protocol “

High (150 IU/d) FSH dose increased by 75 IU every 3-7 day

“Low dose protocol “

Low (37.5 - 75 IU/d) FSH dose increased by 100% every 7 days
### Comparative studies: starting dose

**Conventional dose (150 IU/d) vs low dose (75 IU/d)**

<table>
<thead>
<tr>
<th></th>
<th>Buvat et al. 1989</th>
<th>Brzyski et al. 1995</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional</td>
<td>Low dose</td>
</tr>
<tr>
<td></td>
<td>150 IU</td>
<td>75 IU</td>
</tr>
<tr>
<td>Patients</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>Cycles</td>
<td>21</td>
<td>44</td>
</tr>
<tr>
<td>Duration</td>
<td>10.6 ± 2.9</td>
<td>15.5 ± 5.8</td>
</tr>
<tr>
<td>FSH amp</td>
<td>22.1 ± 7.2</td>
<td>18.7 ± 9.1</td>
</tr>
<tr>
<td>Foll &gt; 10mm</td>
<td>3.7 ± 3.7</td>
<td>1.6 ± 0.9</td>
</tr>
<tr>
<td>Mono-foll (%)</td>
<td>9.5</td>
<td>59 *</td>
</tr>
</tbody>
</table>

**Low FSH dose: longer duration but reduction by 50% in follicle nb**
“Low dose Step up” Protocols : FSH increments

“ Modified Low dose protocol ”

Low (37.5 - 75 IU/d) FSH dose increased by 50 % every 7 days

- Starting dose
- Scan d 7
- Increase dose by 50%
- HCG 5000 IU
- Lead follicle > 16 mm
“Low dose Step-Up” : FSH increments

Starting dose : 50 IU - Increments by 50 or 100% after 7 days

Leader et al. 2006

<table>
<thead>
<tr>
<th></th>
<th>25IU (n=80)</th>
<th>50IU (n=78)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulation Rate</td>
<td>81.3 %</td>
<td>60.3 %</td>
<td>0.009</td>
</tr>
<tr>
<td>Monofollicular growth</td>
<td>41.3 %</td>
<td>21.8 %</td>
<td>0.010</td>
</tr>
<tr>
<td>Total FSH dose</td>
<td>887 IU</td>
<td>984 IU</td>
<td>0.013</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>14.0 d</td>
<td>13.4 d</td>
<td>NS</td>
</tr>
<tr>
<td>Cancellations</td>
<td>5.0 %</td>
<td>20.5 %</td>
<td>0.004</td>
</tr>
<tr>
<td>Ongoing pregnancy</td>
<td>20 %</td>
<td>12.8 %</td>
<td>NS</td>
</tr>
</tbody>
</table>

With 50% dose increment, monofollicular development is higher
### FSH therapy: «Low Dose Step-up» protocols

<table>
<thead>
<tr>
<th>Study</th>
<th>Ovul Cycle (%)</th>
<th>Uni-Ov / Ovul (%)</th>
<th>Uni-Ov / Cycle (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polson 1987</td>
<td>23/33 (70)</td>
<td>18/33 (78)</td>
<td>18/33 (78) (55)</td>
</tr>
<tr>
<td>Buvat 1989</td>
<td>33/44 (75)</td>
<td>26/44 (79)</td>
<td>26/44 (79) (59)</td>
</tr>
<tr>
<td>Sagle 1991</td>
<td>27/35 (77)</td>
<td>19/35 (70)</td>
<td>19/35 (70) (54)</td>
</tr>
<tr>
<td>Shoham 1991</td>
<td>9/9 (100)</td>
<td>6/9 (66)</td>
<td>6/9 (66) (66)</td>
</tr>
<tr>
<td>Hamilton-Fairley 1991</td>
<td>289/401 (72)</td>
<td>219/401 (76)</td>
<td>219/401 (76) (55)</td>
</tr>
<tr>
<td>Balasch 1996</td>
<td>419/534 (78)</td>
<td>198/534 (48)</td>
<td>198/534 (48) (37)</td>
</tr>
<tr>
<td>White 1996</td>
<td>305/429 (71)</td>
<td>256/429 (84)</td>
<td>256/429 (84) (59)</td>
</tr>
<tr>
<td>Loumaye 1996</td>
<td>333/513 (65)</td>
<td>279/513 (84)</td>
<td>279/513 (84) (54)</td>
</tr>
</tbody>
</table>

Even with careful step protocols, only half of ovulatory cycles are mono-follicular.
FSH therapy: “Chronic Low dose Step up” Protocol

“Chronic Low dose protocol“

Low (37.5 - 75 IU/d) FSH dose increased by 50% after 14 days

Starting dose

37.5 - 75 IU/d

14 days

Scan d 7

Scan d 14

Increase dose by 50%

HCG 5000 IU
lead foll > 16 mm

Scan d 21

Increase dose by 50%
# “Low dose Step-Up” Regimen

## Duration of the first step

Homburg et al. 1995 & Hedon et al. 1998

<table>
<thead>
<tr>
<th></th>
<th>Low dose (1st step : 7d)</th>
<th>C L D (1st step : 14 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cycles</td>
<td>Preg.</td>
</tr>
<tr>
<td>Homburg 1995</td>
<td>48</td>
<td>6</td>
</tr>
<tr>
<td>Hedon 1998</td>
<td>46</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>94</strong></td>
<td><strong>15 (16%)</strong></td>
</tr>
</tbody>
</table>

First step of 14 days: lower incidence of multiple pregnancies
Overall results with 75 IU for 14 days

Homburg

Table IV. Results of treatment of clomiphene-resistant patients with low dose, step-up FSH

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>841</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cycles</td>
<td>1556</td>
</tr>
<tr>
<td>Pregnancies (% patients)</td>
<td>320 (38%)</td>
</tr>
<tr>
<td>Fecundity/cycle</td>
<td>20%</td>
</tr>
<tr>
<td>Uni-ovulation</td>
<td>70%</td>
</tr>
<tr>
<td>OHSS</td>
<td>0.14%</td>
</tr>
<tr>
<td>Multiple pregnancies</td>
<td>5.7%</td>
</tr>
</tbody>
</table>

Updated from Homburg and Howles (1999).

A starting dose of 75 IU for 14 days has been demonstrated to be safe and effective in PCOS patients
Recommendations for « step-up » regimens

• Duration of first step: 14 days safer than 7 days
  • Dose increment: 50% is safer than 100%

« Chronic Low Dose: the safest step-up regimen »

• Starting dose: 37.5 to 75 IU / day according to patients’ characteristics
  objective: to achieve FSH threshold within 14 days and with no need for FSH dose increment
Predictors for ovarian response to FSH

**History**: Previous response to CC - failure or resistance

(Eijkemans et al, 2003 - Imani et al, 2002)

**Clinical**: Ovulatory Status, Age, BMI, Antral Follicular Count

(Dickey et al, 2001 - Homburg and Insler, 2002 - Imani et al 2002

**Baseline Hormone levels**: FSH, Testosterone, free-IGF-1, Insulin/glucose ratio, insulin resistance

(Imani et al, 2002 - Eijkemans et al, 2003
Mulders et al, 2003 - van Santbrink 2005)
“Step down” Protocols

“Step - down protocol“

Loading FSH dose (112.5-187.5 IU/d)
decreased by 37.5 IU every 3-5 d

Starting dose

Scan d 4-5
Foll > 9 mm
Decrease by 37.5 IU

Scan d 8
Decrease by 37.5 IU

HCG 5000 IU
lead foll > 16 mm

“Sequential protocol“

FSH threshold dose decreased by 50%
when leading follicle reaches 14 mm diam
### “Step up” versus “Step down” : randomized studies

<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Step-up</strong></td>
<td>Step-down</td>
<td></td>
</tr>
<tr>
<td>(19)</td>
<td>(18)</td>
<td></td>
</tr>
<tr>
<td>Median duration of treatment (day)</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Mono growth</td>
<td>56%</td>
<td>88%</td>
</tr>
<tr>
<td>Ovulation rate</td>
<td>84%</td>
<td>89%</td>
</tr>
</tbody>
</table>

### Reasons for discrepancies
- Patients characteristics: PCOS features
- Dose regimens: starting dose & adjustment

**In clinical practice, step up protocol is a preferred option**
Conclusions

Step protocols are effective but safety still questionable.

**First line regimen : CLD step-up regimen**
Second line regimen:  Step down regimen with an adjusted starting dose

**A decremental dose regimen for FSH administration** must be applied in patients at risk of overstimulation.

**Compliance to guidelines:** Individual adjustment of the starting dose according to patient’s characteristics (BMI - AFC - Hyperandrogenism)