PCOS
First line ovulation induction

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The health economic impact of PCOS in the USA has been estimated at up to $1.77 billion (Azziz 2005).

UK: 16-22 million £ for diagnosis and treatment per year (Hum Reprod 2000).
<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>PCO</td>
<td>70-80%</td>
</tr>
<tr>
<td>Hirsutismus</td>
<td>30-80%</td>
</tr>
<tr>
<td>Obesity</td>
<td>20-60%</td>
</tr>
<tr>
<td><strong>Anovulation</strong></td>
<td><strong>80-90%</strong></td>
</tr>
<tr>
<td>Oligo/amenorrhea</td>
<td>50-70%</td>
</tr>
<tr>
<td>Acne</td>
<td>15-20%</td>
</tr>
<tr>
<td>Androgenic alopecia</td>
<td>5-10%</td>
</tr>
</tbody>
</table>
What are the expectations from ovulation induction?
Aim

- Ovulatory cycle ended with singleton pregnancy
- Low abortion rate
. First line medications

. Second line options
1. Weight loss: If BMI > 30 kg/m²
2. Clomiphene citrate (CC)
3. CC + corticosteroids if DHEAS > 2ug/ml
4. CC + Metformin
5. Low dose FSH injection
6. Low dose FSH injection + Metformin
7. Ovarian drilling

(ACOG, 2002)
PCOS obesity: 35-50% 

Central Obesity
Negative effects of obesity

Early menarch
Oligo-amenorrhea
High risk of Abortion
Lower ART chance
Pregnancy complications

Pasquali et al., Human Rep 2003
Weight loss

► Improve ovulatory function
► Regular menses
► Elevate SHBG concentrations
► Lower free testosterone levels
► Improve lipids
► Improve insulin sensitivity

From Hoeger et al. Best Pract Res Clin Endocrinol Metab 2006; 20:293
Trials of dietary intervention and impact on key features in overweight/obese women with PCOS

Studies (not controlled) (n = 20):

Patients: 319
Duration: 1-7 months

Major findings:

- Weight loss: all
- Decreased testosterone (or FAI): 11/20
- Improvement in menses: 10/20
- Improvement in ovulation (no pregnancies included): 1/20
- Occurrence of spontaneous conception: 7/20
- Improved hirsutism: 3/20
- Increased SHBG: 7/20
- Improved insulin resistance or insulin (fasting, OGTT): 12/20
- Anti-Mullerian hormone (AMH) 1/1* (no change)

General comment: heterogeneity in the pts response (particularly on androgens, menses, ovulation)

Weight loss is cheap, non-complicating method

For anovulatory PCOS obes patients may be the **FIRST LINE** therapy

*Homburg R 2003*
Clomiphene citrate

► Since 1962
  ▪ minimal adverse effects
  ▪ triphenylethylene derivative
► dihydrogen citrate salt
  (clomiphene citrate)
► Two stereoisomer: zu-clomiphene (38 %) and en-clomiphene (62 %)
Primary indication: oligoovulatory or anovulatory infertility

normogonadotropic, normoprolactinemic, euthyroid women (WHO group 2)
Pharmacology

- Selective estrogen receptor modulator
- Competitive inhibition of estrogen for binding to estrogen receptors
► **En-clomiphene** faster elimination

► **Zu-clomiphene** **longer**

► **Zu-clomiphene** higher estrogenic effect than **en-clomiphene**
Oral dose elimination

- 50% in five days,
- Radioactive labelled CC has been showed as long as to six months in faeces
Mechanism

► Hypophysis: Increased sensitivity to GnRH

► Ovary: stimulation for follicle growth up secondary to FSH, LH increase

► Uterus, cervix, vagina: anti-estrogenic,

► Cervical mucus: negative effects with 100 mg
Estrogen agonistic effects if estrogen is low,

Stimulation of LH receptors in granulosa cells with FSH

Direct effect to the aromatase activity
CC ADMINISTRATION

- For 5 days
- Onset on days 2-5
- No difference between different days of onset
- Starting dose 50 mg/day per os
CC: Monitoring the treatment

- No consensus
- Progesterone assay
- Ultrasound
- Estradiol assay
- Basal body temperature chart
**CC vs PLACEBO**

4 studies (cross-over)
- CC increased ovulation (OR: 6.8) (3 studies) and pregnancy rate (OR: 3.41) (2 studies)
  
  (Hughes et al., 2000 Cochrane Database Syst. Rev. (2): CD000056)

3 RCTs
- CC increased pregnancy rate (OR 5.8, 95% CI 1.6 to 21.5)
  
  (Beck et al., 2005 Cochrane Database Syst. Rev. (1): CD002249)
### Table I. Results of treatment with clomiphene citrate: a collection of published data

<table>
<thead>
<tr>
<th></th>
<th>No of patients</th>
<th>Ovulation</th>
<th>Pregnancy</th>
<th>Abortion</th>
<th>Live birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGregor et al. (1968)</td>
<td>4098</td>
<td>2869</td>
<td>1393</td>
<td>279</td>
<td>1114</td>
</tr>
<tr>
<td>Garcia et al. (1977)</td>
<td>159</td>
<td>130</td>
<td>64</td>
<td>16</td>
<td>48</td>
</tr>
<tr>
<td>Gysler et al. (1982)</td>
<td>428</td>
<td>364</td>
<td>184</td>
<td>24</td>
<td>160</td>
</tr>
<tr>
<td>Hammond (1984)</td>
<td>159</td>
<td>137</td>
<td>67</td>
<td>10</td>
<td>57</td>
</tr>
<tr>
<td>Kousta et al. (1997)</td>
<td>128</td>
<td>113</td>
<td>55</td>
<td>13</td>
<td>42</td>
</tr>
<tr>
<td>Messinis and Milingos (1998)</td>
<td>55</td>
<td>51</td>
<td>35</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td>Imani et al. (2002)</td>
<td>259</td>
<td>194</td>
<td>111</td>
<td>11</td>
<td>98</td>
</tr>
<tr>
<td><strong>Total (% of patients)</strong></td>
<td><strong>5268 (100)</strong></td>
<td><strong>3858 (73)</strong></td>
<td><strong>1909 (36)</strong></td>
<td><strong>357</strong></td>
<td><strong>1550 (29)</strong></td>
</tr>
</tbody>
</table>

### Table II. Outcome of pregnancy following treatment with clomiphene citrate

<table>
<thead>
<tr>
<th></th>
<th>Pregnancies</th>
<th>Abortion</th>
<th>Live births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total data from Table 1</td>
<td>1909</td>
<td>357</td>
<td>1550</td>
</tr>
<tr>
<td>Ahlgren et al. (1976)</td>
<td>159</td>
<td>18</td>
<td>141</td>
</tr>
<tr>
<td>Adashi et al. (1979)</td>
<td>86</td>
<td>23</td>
<td>62</td>
</tr>
<tr>
<td>Correy et al. (1982)</td>
<td>156</td>
<td>16</td>
<td>140</td>
</tr>
<tr>
<td>Dickey et al. (1996)</td>
<td>1744</td>
<td>413</td>
<td>1331</td>
</tr>
<tr>
<td><strong>Total (% of pregnancies)</strong></td>
<td><strong>4054 (100)</strong></td>
<td><strong>827 (20.4)</strong></td>
<td><strong>3224 (79.5)</strong></td>
</tr>
</tbody>
</table>
Effective dose

► Most of the pregnancies occurs in the first 6 ovulatory cycles

► Approx 50% occurs with the dose of 50 mg/day

► Other 25% occurs with 100 mg/day
Schematic representation of the algorithm used currently for dose adjustment in the treatment of infertile women with clomiphene.

- **50 mg**
  - No Ovulation
  - Ovulation
- **100 mg**
  - No Ovulation
  - Ovulation
- **150 mg**
  - No Ovulation
  - Ovulation
- **200 mg**
  - No Ovulation
  - Ovulation
- **250 mg**
  - No Ovulation
  - Ovulation

**Continuation of Therapy (6-12 months)**

**Pregnancy**

**Switch to Alternative Treatment**

OVULATION INDUCTION WITH CLOMIPHENE

- Response (ovulation - conception)
- Response (ovulation - no conception)
  CLOMIPHENE FAILURE

- No response (no ovulation)
  CLOMIPHENE RESISTANCE
Factors effecting the pregnancy rates with CC

- baseline free androgen index (FAI),
- baseline proinsulin level,
- body mass index (BMI)
- duration of attempting conception

(Rausch et al., 2009)
Chances of live birth in CC ovulation induction

FIGURE 2

Nomogram designed to predict chances for live birth in clomiphene citrate induction of ovulation. Note the two different steps. (Imani et al., Fertil Steril 2002;77:91–7. Used with permission.)

Required screening information
- Amenorrhea or oligomenorrhea
- BMI (kg/m²)
- FAI (T x 100/SHBG)
- Age (y)

Chance of ovulation (%)

<table>
<thead>
<tr>
<th>FAI</th>
<th>BMI</th>
<th>Chance of a live birth (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Amenorrhea</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>15</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>25</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>30</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>35</td>
<td>35</td>
<td>40</td>
</tr>
</tbody>
</table>

The predictive value of circulating anti-Müllerian hormone in women with polycystic ovarian syndrome receiving clomiphene citrate: a prospective observational study
Mahran et al. UK Clin Endocrinol Metab. 2013 Oct;98(10):4170-5

Serum AMH concentrations were significantly (P < .001) lower in responders (achieving ovulation) vs nonresponders (mean ± SEM, 2.5 ± 0.1 vs 5.8 ± 0.7 ng/mL, respectively).

Similarly, serum AMH concentrations were significantly (P = .046) lower in pregnant (3.0 ± 0.4 ng/mL) vs nonpregnant patients (4.4 ± 0.5 ng/mL).

Ovulation and pregnancy rates were significantly higher (97%, P < .001, and 46%, P = .034) in patients with low AMH (<3.4 ng/mL) vs women with AMH 3.4 ng/mL or greater (48% and 19%).

CONCLUSION
PCOS women with high circulating AMH (≥ 3.4 ng/mL) seem to be resistant to CC and may require a higher starting dose
Consensus on infertility treatment related to polycystic ovary syndrome

The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group* March 2–3, 2007, Thessaloniki, Greece

- Clomiphene citrate remains the treatment of first choice for induction of ovulation in most anovulatory women with PCOS.
- Selection of patients for CC treatment should take into account body weight/BMI, female age, and the presence of other infertility factors.
- The starting dose of CC should be 50 mg/day (for 5 days), and the recommended maximum dose is 150 mg/day.
- Results of large trials suggest monitoring by ultrasound or progesterone is not mandatory to ensure good outcome.
- Life-table analysis of the largest and most reliable studies indicates a conception rate of up to 22% per cycle in women ovulating while on CC.
- Further studies should demonstrate efficacy and safety of aromatase inhibitors.
Ovulation inducing drugs and ovarian cancer risk: results from an extended follow-up of a large United States infertility cohort
Trabert B et al. Fertil Steril 2013 Dec 100(6)

- 9825 women treated between 1965 and 1988 follow up through 2010
  No association of cancer risk ever use of CC
- Women who used CC and remained nulligravid did demonstrate much risk RR 3.63
- Remains to be determined
CC FAILURE
Can we improve?

- Patients selection
- Combinations of clomiphene with other drugs
- Second line treatment
Higher doses (up to 250 mg)
Extended treatment (~ 20 days)
Combinations with other drugs
Alternatives as first line?

- Insulin sensitizers (Metformin)
- Aromatase inhibitors (Letrozole)
- Laparoscopic ovarian drilling (LOD)
- Low-dose FSH
**METFORMIN vs CC**

First line

626 women with PCOS

<table>
<thead>
<tr>
<th></th>
<th>Conception rate</th>
<th>Live-birth rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>39.5%</td>
<td>47/209 (22.5%)</td>
</tr>
<tr>
<td>CC + M</td>
<td>46.0%</td>
<td>56/209 (26.8%)</td>
</tr>
<tr>
<td>M</td>
<td>21.7%**</td>
<td>5/208 (7.2%)*</td>
</tr>
</tbody>
</table>

*P<0.001  
**P=0.002

Legro et al., 2007  
*N. Engl. J. Med. 356, 551-66*
### Analysis 3.1. Comparison 3 Metformin versus clomiphene citrate, Outcome 1 Live birth.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>metformin</th>
<th>clomiphene</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Fixed, 95% CI</td>
<td></td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>1 Patients with BMI &lt; 30kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palomba 2005</td>
<td>26/50</td>
<td>9/50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>50</strong></td>
<td><strong>50</strong></td>
<td></td>
<td><strong>8.0 %</strong></td>
<td><strong>4.94 [1.99, 12.26]</strong></td>
</tr>
<tr>
<td>Total events: 26 (metformin), 9 (clomiphene)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 3.44 (P = 0.00059)</td>
<td></td>
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</tr>
<tr>
<td>2 Patients with BMI &gt; 30kg/m²</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Legro 2007</td>
<td>15/208</td>
<td>47/209</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zain 2008</td>
<td>4/42</td>
<td>7/41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>250</strong></td>
<td><strong>250</strong></td>
<td></td>
<td><strong>92.0 %</strong></td>
<td><strong>0.30 [0.17, 0.52]</strong></td>
</tr>
<tr>
<td>Total events: 19 (metformin), 54 (clomiphene)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.76, df = 1 (P = 0.38); I² = 0.0%</td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 4.25 (P = 0.000021)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>300</strong></td>
<td><strong>300</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.67 [0.44, 1.02]</strong></td>
</tr>
<tr>
<td>Total events: 45 (metformin), 63 (clomiphene)</td>
<td></td>
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</tr>
<tr>
<td>Heterogeneity: Chi² = 27.12, df = 2 (P&lt;0.00001); I² = 93%</td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 1.87 (P = 0.061)</td>
<td></td>
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</tbody>
</table>

From Tang et al. Cochrane Library 2010
CC+Metformin
First-line (Dutch study)

► CC+M vs CC+P (228 PCOS women) No difference in:

- Ovulations (64% vs 72%)
- Ongoing pregnancies (40% vs 46%)
- Miscarriages (12% vs 11%)

Moll et al., 2006. BMJ 332, 1485
**CC+Metformin**

**Systematic review**

- **CC is still first choice therapy**
- **In CC-resistant women, CC+M is the preferred treatment before moving to LOD or FSH**

*Moll et al., 2007*  
*Hum. Reprod. Update 13, 527-537*
LETRAZOLE IN PCOS
Meta-analysis

► 4 RCTs

Letrozole vs CC

- Ovulation (OR 1.17, 95% CI 0.66 to 2.09)
- Pregnancy/cycle (OR 1.47, CI 0.73 to 2.96)
- Pregnancy/patient (OR 1.37, CI 0.70 to 2.71)

Requena et al., 2008
Hum. Reprod. Update 14, 571-82
Aromatase inhibitors for subfertility treatment in women with PCOS
Franik S, Kremer JAM, Nelen WLDM, Farquhar C

Cochrane summaries, 24 February 2014

Over the last ten years clinical trials have reached differing conclusions as to whether the AI letrozole is at least as effective for treating subfertility as the most commonly used treatment, clomiphene citrate.

26 randomised controlled trials (RCT) with 5560 women

Letrozole appears to improve live birth and pregnancy rates compared to clomiphene citrate.

However the quality of this evidence was low and findings should be regarded with some caution.
Conclusion

Weight loss, exercise, and lifestyle modifications should be the first-line option for these women.

► Clomiphene citrate has been proven effective in ovulation induction for women with PCOS and should be considered the first-line therapy.

► Patients should be informed that there is an increased risk of multiple pregnancy with ovulation induction using clomiphene citrate.