Oral Contraception and the HPG Axis

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Division of Endocrinology
The Growth of the World Population

Raleig, Hum Repro Update 1999
Table 17-1. Fertility Control Methods: Failure Rates and Continuation of Use (United States Data)

<table>
<thead>
<tr>
<th>Method</th>
<th>Perfect use</th>
<th>Typical</th>
<th>Estimates 1995, † Reversible Methods</th>
<th>Continuation after First Year of Use* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chance</td>
<td>85</td>
<td>85</td>
<td>85</td>
<td>?</td>
</tr>
<tr>
<td>Sterilization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.1</td>
<td>0.2</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>Female</td>
<td>0.2</td>
<td>0.4</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>Surgical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemical (quainacrine)‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women &lt;35 y</td>
<td>13.0</td>
<td></td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Women ≥35 y</td>
<td>7.0</td>
<td></td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Hormonal contraception, emergency contraception, and contraception</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination pill</td>
<td>0.1</td>
<td>5.0</td>
<td></td>
<td>8.0</td>
</tr>
<tr>
<td>Progestagen-only pill</td>
<td>0.5</td>
<td>5.0</td>
<td></td>
<td>2.0</td>
</tr>
<tr>
<td>Norplant</td>
<td>0.05</td>
<td>0.05</td>
<td></td>
<td>3.0</td>
</tr>
<tr>
<td>Depo-Provera</td>
<td>0.3</td>
<td>0.3</td>
<td></td>
<td>3.0</td>
</tr>
<tr>
<td>Emergency contraception—hormonal contraception</td>
<td>0.1</td>
<td>3.0</td>
<td></td>
<td>ND</td>
</tr>
<tr>
<td>Contraception—pharmacologic abortion</td>
<td>1.0–5.0 (up to 7 wk)</td>
<td>9.0 (&gt; 7 wk)</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Intravaginal devices (IUDs)
- IUD-progestrone T: 1.5, 2.0
- IUD-levonorgestrel 20: 0.1, 0.1
- IUD-11 380 (copper): 0.6, 0.8

Barrier methods
- Condom
  - Male: 3.0, 14.0
  - Female: 5.0, 21.0
- Diaphragm: 6.0, 20.0
- Cervical cap
  - Parous women: 26.0, 40.0
  - Nulliparous women: 9.0, 20.0
- Sponge
  - Parous women: 20.0, 40.0
  - Nulliparous women: 9.0, 20.0

Spermicides: 6.0, 26.0
Withdrawal: 4.0, 19.0
Periodic abstinence$: 9.0, 19.0

Calendar: 3.0, 21.0
Ovulation method: 2.0, 21.0
Postcoital method: 1.0, 21.0
Symptothermal method: 2.0, 21.0

Lactational amenorrhea provides an effective but temporary method of contraception
Landmarks in the Development of Oral Contraceptive Methods

1940: first inhibition of ovulation by estrogens and progestagens

Sturgis SH and Albright R. Mechanism of estrin therapy in the relief of dysmenorrhea.
Endocrinology 26:68.

1952: synthesis of norethisterone, orally active progestagen more potent (10x) than natural progesterone

Djerassi et al. 17alpha-Ethynyl-19-nortestosterone.
American Chemical Society Meeting, abstract18J.
Development of norethindrone from testosterone. Splitting off the C-19 radical from the testosterone molecule changes this androgen to a progestagen. Attachment of the ethinyl group to C-17 enhances the progestagenic activity of the compound and makes it orally active.
Landmarks in the Development of Oral Contraceptive Methods

1953: John Rock and Gregory Pincus test oral progesterone \textit{(norethynodrel, G.D. Searle)}


The Pill was born
Currently Available, « Low Dose » Formulations

Monophasic

- EE 35 µg – norgestinate 250 µg
- EE 30 µg – levonorgestrel 150 µg
- EE 30 µg – gestodene 75 µg
- EE 20 µg – norethisterone acetate 1000 µg
- EE 20 µg – desogestrel 150 µg

Cilest
Microgynon 30
Minulet
Loestrin 20
Mercilon

Bi-/Tri-phasic

- EE 35 µg – norethisterone 500/750/1000 µg
- EE 30/40/30 µg – levonorgestrel 50/75/125 µg
- EE 30/40/30 µg – gestodene 50/70/100 µg

TriNovum
Logynon
Tri-Minulet

EE: 17α-ethinylestradiol
The multifaceted nature of the steroid molecule is illustrated by its capacity to bind to several different receptors and activate them to various degrees.
Ovarian Function During Hormonal Contraception

Combined oral contraceptives exert a range of effects on the reproductive tract, resulting in the inhibition of ovulation.

- Estrogens and progestogens inhibit LH secretion
  - no preovulatory LH surge
- Estrogens suppress FSH
  - no follicular development
Follicular-like structures were observed in 9/51 patients

Table 2. Characteristics of the cycles with follicular development

<table>
<thead>
<tr>
<th>Pill</th>
<th>Pts.</th>
<th>Cycle</th>
<th>No. pill</th>
<th>Follicular diameter (mm)</th>
<th>Endometrial thickness (mm)</th>
<th>E2 (pg/ml)</th>
<th>Prog (ng/ml)</th>
<th>FSH (UI/L)</th>
<th>LH (UI/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triphasic pill</td>
<td>S.S.</td>
<td>3rd</td>
<td>7</td>
<td>11</td>
<td>6</td>
<td>24</td>
<td>0.2</td>
<td>4.4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>F.P.</td>
<td>4th</td>
<td>10</td>
<td>13</td>
<td>9</td>
<td>&lt;5</td>
<td>&lt;0.2</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>S.S.</td>
<td>6th</td>
<td>7</td>
<td>19</td>
<td>6</td>
<td>&lt;5</td>
<td>&lt;0.2</td>
<td>7.7</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>M.M.</td>
<td>6th</td>
<td>10</td>
<td>11</td>
<td>3</td>
<td>29</td>
<td>0.3</td>
<td>3.6</td>
<td>1</td>
</tr>
<tr>
<td>20 mg EE + 75 mg gestodene</td>
<td>A.G.</td>
<td>3rd</td>
<td>11</td>
<td>12</td>
<td>8</td>
<td>&lt;5</td>
<td>&lt;0.2</td>
<td>0.7</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td></td>
<td>R.S.</td>
<td>4th</td>
<td>12</td>
<td>13</td>
<td>4</td>
<td>12</td>
<td>0.3</td>
<td>2.9</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>A.G.</td>
<td>8th</td>
<td>11</td>
<td>12</td>
<td>8</td>
<td>&lt;5</td>
<td>&lt;0.2</td>
<td>1.8</td>
<td>2</td>
</tr>
<tr>
<td>20 mg EE + 150 mg DSG</td>
<td>M.G.</td>
<td>4th</td>
<td>17</td>
<td>17</td>
<td>4</td>
<td>15</td>
<td>0.5</td>
<td>4.5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>S.B.</td>
<td>6th</td>
<td>10</td>
<td>13</td>
<td>7</td>
<td>&lt;5</td>
<td>0.3</td>
<td>3.5</td>
<td>1</td>
</tr>
</tbody>
</table>

*Including 35 mg ethinyl estradiol (EE) and 50 mg desogestrel (DSG) in the first seven tablets, 30 mg EE and 100 mg DSG in tablets 8 to 14, and 30 mg EE and 150 mg DSG in tablets 15 to 21.

Crosignani et al, Contraception 1996
Aim: to evaluate pituitary-ovarian recovery in the pill-free interval during use of three low-dose combined oral contraceptives

Subjects: 44 healthy volunteers, aged 18-39 years

Main outcome: evidence of ovulation and ovarian activity
Results:

• No ovulations were observed
• FSH levels were higher in the 30 µg EE group
• Follicle diameters were significantly smaller in the 30 µg EE group
• Dominant follicles (>10 mm) were observed at the end of the pill-free period in both 20 µg groups, but not in the 30 µg group

Van Heusden and Fauser, Contraception 1999
Conclusion

The EE content, rather than the progestin content, determines the extent of residual ovarian activity at the beginning of the pill-free interval

Van Heusden and Fauser, Contraception 1999
Combined Oral Contraceptive Agents

Two recent studies using pills containing 20 µg EE and 100 mg levonorgestrel:

- Follicles >10 mm seen in majority of cycles
- Spontaneous ovulation in 1.7 – 2.7% of cycles

Coney and Del Conte, Am J Obst Gynecol 1999
Jain et al, Contraception 2000
Combined Oral Contraceptive Agents

Large follicles (>12 mm) can be found during treatment with combined OC.

Because of the low LH concentrations, these follicles secrete very little estradiol.

However, they may continue to produce inhibin and hence can be called *functional*. 
20 µg of EE probably represents the minimum that will reliably suppress folliculogenesis

The ESHRE Capri Workshop Group, 2001
Aim: to compare ovulation inhibition and ovarian activity with 21-day and 24-day regimen of combined oral low-dose contraceptive (60 µg gestodene and 15 µg EE)

Subjects: 58 healthy volunteers, aged 18-35 years

Main outcome: evidence of ovulation and ovarian activity
Ovarian activity over three consecutive cycles

Sullivan et al, Fertil Steril 1999
Follicular growth over three consecutive cycles

Sullivan et al, Fertil Steril 1999
Results:

- No ovulation in the 24-d regimen vs 1/75 cycles in the 21-d regimen
- No luteinized, unruptured follicle in the 24-d regimen vs 6/75 cycles (8%) in the 21-d regimen

The 24-d cycle strategy may be useful for maintaining effective ovulation inhibition at ultra-low doses of contraceptive steroids

Sullivan et al, Fertil Steril 1999
Progestogen-Only Pills

FSH secretion is very little or not affected by progestagens
Progestogen-Only Pills

FSH secretion is very little or not affected by progestagens.

Follicular development continues during administration of progestogen-only pills and in some (0.3 mg norethisterone, 0.075 mg levonorgestrel), ovulation can occur.
Progestogen-Only Pills

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Follicular development continues during administration of progestogen-only pills and in some (0.3 mg norethisterone, 0.075 mg levonorgestrel), ovulation can occur.

The contraceptive effect is probably dependent on the effect of continuous gestogen on cervical mucous and endometrium
Oral Contraceptive Agents
Non-Reproductive Benefits

Decreased incidence of endometrial and ovarian carcinomas
Oral Contraceptive Agents
Non-Reproductive Benefits

Uterine leiomyomas
Endometriosis
Bone mineral density

Management of hyperandrogenism
Oral Contraceptive Agents

Adverse Events

Most common adverse events:
• Breakthrough bleeding
• Amenorrhea
• Headache, nausea, breast tension, mood change, weight gain

Cardiovascular events:
• Venous thromboembolism
• Stroke (not increased in non-smokers, with low estrogen pills)
• Myocardial infarcts
Oral Contraceptive Agents
Polycystic Ovary Syndrome

Two considerations:

• Effect on the ovaries and ovarian hormone secretion

• Effect on accompanying metabolic conditions
Polycystic Ovary Syndrome: Ovarian Effects of OC

In PCOS, ovaries are enlarged and full of small, immature follicles 2 – 8 mm (cysts).

Upon treatment with OC, cysts become smaller and ovarian volume decreases.

- Reduction in ovarian testosterone secretion
- Increase in SHBG

Additional advantage of cyproterone acetate