Mifepristone and Levonorgestrel

Research on Mechanism of Action of Emergency Contraception
Ideal Emergency Contraception

- Effective and safe
- No side-effects
- No cycle disturbance
- Easy to administer
- Easily accessible
- Reasonable length-interval since intercourse
- Cheap
Established Methods of Emergency Contraceptives

- High dose estrogen (1963)
- Estrogen-progestogen combination:
  - Yuzpe regimen (1972)
- Intrauterine contraceptive devices (IUD’s) (1976)
- Danazol (1982)
- Progestogens (1970)
  - *Levonorgestrel*
- Antiprogestogens
  - *Mifepristone (1979)*
April, 1995: Bellagio

Consensus Statement on Emergency Contraception

- Women and providers are uninformed about methods
- Few products are marketed for emergency contraception
- Service providers are too often reluctant to provide this method

Proposed Recommendation

- Antiprogestogens are promising compounds, and deserve top medical research priority
- ...
**Mechanism of action of currently used methods**

- All emergency contraceptives currently in use act before implantation

- Prevention of
  - Ovulation
  - Fertilization
  - Implantation
Timing of Treatment - “Morning After Pill”?  

**Risk of conception**
- High between 5 days before and 1 day after ovulation, and highest the 2 days prior to ovulation.

**Problem:**
- Variability of ovulation
- Ignorance of individual cycle

**Proposal:**
- Treatment as soon as it is practicable after unprotected coitus
## Problem: Timing

<table>
<thead>
<tr>
<th>Day in relation to ovulation</th>
<th>No. of cycles with intercourse only on this day</th>
<th>No. of pregnancies</th>
<th>Single-day conception rate</th>
<th>Estimated conception rate $\pm$ SE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5</td>
<td>12</td>
<td>1</td>
<td>0.08</td>
<td>0.10$\pm$ 0.08</td>
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<tr>
<td>-4</td>
<td>24</td>
<td>4</td>
<td>0.17</td>
<td>0.16$\pm$ 0.06</td>
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<tr>
<td>-3</td>
<td>13</td>
<td>1</td>
<td>0.08</td>
<td>0.14$\pm$ 0.08</td>
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<tr>
<td>-2</td>
<td>28</td>
<td>10</td>
<td>0.36</td>
<td>0.34$\pm$ 0.07</td>
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<tr>
<td>-1</td>
<td>38</td>
<td>13</td>
<td>0.34</td>
<td>0.31$\pm$ 0.06</td>
</tr>
<tr>
<td>Day of ovulation</td>
<td>14</td>
<td>5</td>
<td>0.36</td>
<td>0.33$\pm$ 0.09</td>
</tr>
<tr>
<td>Total</td>
<td>129</td>
<td>35</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Probability of conception based on 129 menstrual cycles in which sexual intercourse occurred on only one day during the six-day interval ending with the day of ovulation, by Wilcox et al., 1982-1985.
Different drug models

- **Drug A**: follicular phase / preovulatory phase
  - Blocks oocyte maturation and ovulation

- **Drug B**: early fertile period
  - Provides fertilization rather than ovulation

- **Drug C**: late fertile period / around or shortly after ovulation
  - Intercepts events after fertilization (embryo, endometrium)
Different drug models

Timing in the menstrual cycle when emergency contraceptive compounds would be effective.
Timing: What the doctor should ask

- First day of last period
- Length of cycle
- First episode of unprotected intercourse
- Attempts at contraception
Mifepristone (RU 486)

- **1979** discovered by pharmaceutical company Roussel-Uclaf (France):
- Synthetic steroid with high affinity to glucocorticoid and progesterone receptor
- **Class:** Antiprogestogens
- Approved for early abortion in combination with prostaglandin in few countries
- Progesterone inhibition is achieved through Progesterone receptor blockers
Mechanism of Action and Effects of Mifepristone

**Ovulation**
- Single 5 mg dose: retarded the growth of the leading follicle (14 mm) for up to 36 hours
- Higher doses can cause regression and initiation of a new cycle

**Fertilisation**
- In vitro: 100 mg oral 35 hours before recovering the oocyte → no effect on fertilization
- In vitro: High doses can slow sperm movement
Mechanism of Action and Effects of Mifepristone

- Development and transport of embryos:
  - Animal-test: accelerated embryo transport through the fallopian tubes with loss of the embryo from the uterus before implantation

- Endometrial maturation:
  - 200 mg on the 2nd day after LH peak → delay of endometrial development for at least 6 hours but with possible extension of luteal phase with prolonged cycle length
Levonorgestrel

- Synthetic Steroid
- Class: Progestogens
  - Used as regular oral contraception
- 1970 studies for regular postcoital use
  - Insuitable because of high incidence of cycle disturbance
- Emergency Contraception
  - In several countries marketed for occasional contraception in packs containing 0.75 mg tablets
  - Cycle disturbance are of less issue because only used occasionally
Mechanism of action of Levonorgestrel

- **Affects:**
  - Follicle growth
  - Development of corpus luteum

- **Ovulation**
  - 1.6 mg on day 10 of cycle → suppressed midcycle LH peak (no ovulation)
  - Daily dose of 0.75 mg for 4 days →
    - **before ovulation:** increased duration of follicular phase
    - **around ovulation:** blocked or didn’t influence ovulation, or deficient luteal function was observed
    - **after ovulation:** no effect on cycle length, no endometrial changes
Regular Postcoital Contraception

Peripheral effects:

- Alteration in cervical mucus with consequent prevention of sperm migration (Study with d-Norgestrel)
Comparative Research Studies

Levonorgestrel versus Yuzpe regimen (1998)

- Double-blind randomized controlled trial
- Levonorgestrel: 0.75 mg repeated 12 h later
- Yuzpe regimen: ethinylestradiol 100 µg plus Levonorgestrel 0.5 mg repeated 12 h later

Findings:
- Levonorgestrel better tolerated, higher efficacy (pregnancy rates: Lev: 1.1%, Yuzpe: 3.2%)
- For both methods: clustering of observed pregnancies around predicted ovulation
- Timing of the treatment: inversely related to time since intercourse
- Delay of next menstruation not observed
Levonorgestrel versus Yuzpe regimen

Observed and expected numbers of pregnancies by timing of coitus
Comparative Research Studies

- Mifepristone compared with high-dose estrogen and progestogen (1992)
  - Randomized, controlled trial
  - 100 µg of ethinylestradiol and 1 mg of norgestrel, repeated 12 hours later
  - 600 mg mifepristone

- Findings:
  - Mifepristone: no pregnancy, fewer side-effects, good compliance because of single dose
  - Disadvantage: delay of onset of next menstruation
Comparative research studies

Three single doses of mifepristone (1997)

- Randomized controlled trial
- 600 mg, 50 mg, 10 mg mifepristone within 120 hours

Findings:
- Similar pregnancy rate among the three groups (1.2%, 1.3% and 1.3%)
- Lower doses were associated with no major side effects and less disturbance of the menstrual cycle
- Administration in the preovulatory phase: delays or blocks ovulation
Comparative Research studies

- Mifepristone and two regimen of levonorgestrel (1998)
  - Multicenter, single-blind, randomized controlled trial
  - Mifepristone 10 mg
  - Levonorgestrel: two doses of 0.75 mg at 12 hours interval
  - Levonorgestrel in one dose of 1.5 mg
  - Administered up to 120 hours after intercourse

- Expected study-outcome
  - Mifepristone may be the drug of choice, with properties close to the ideal emergency contraceptive.
Conclusion

- Mifepristone and levonorgestrel are approaches to improved methods in emergency contraception

- Open questions on mechanism of action remain

- Mifepristone may be the better choice in future