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

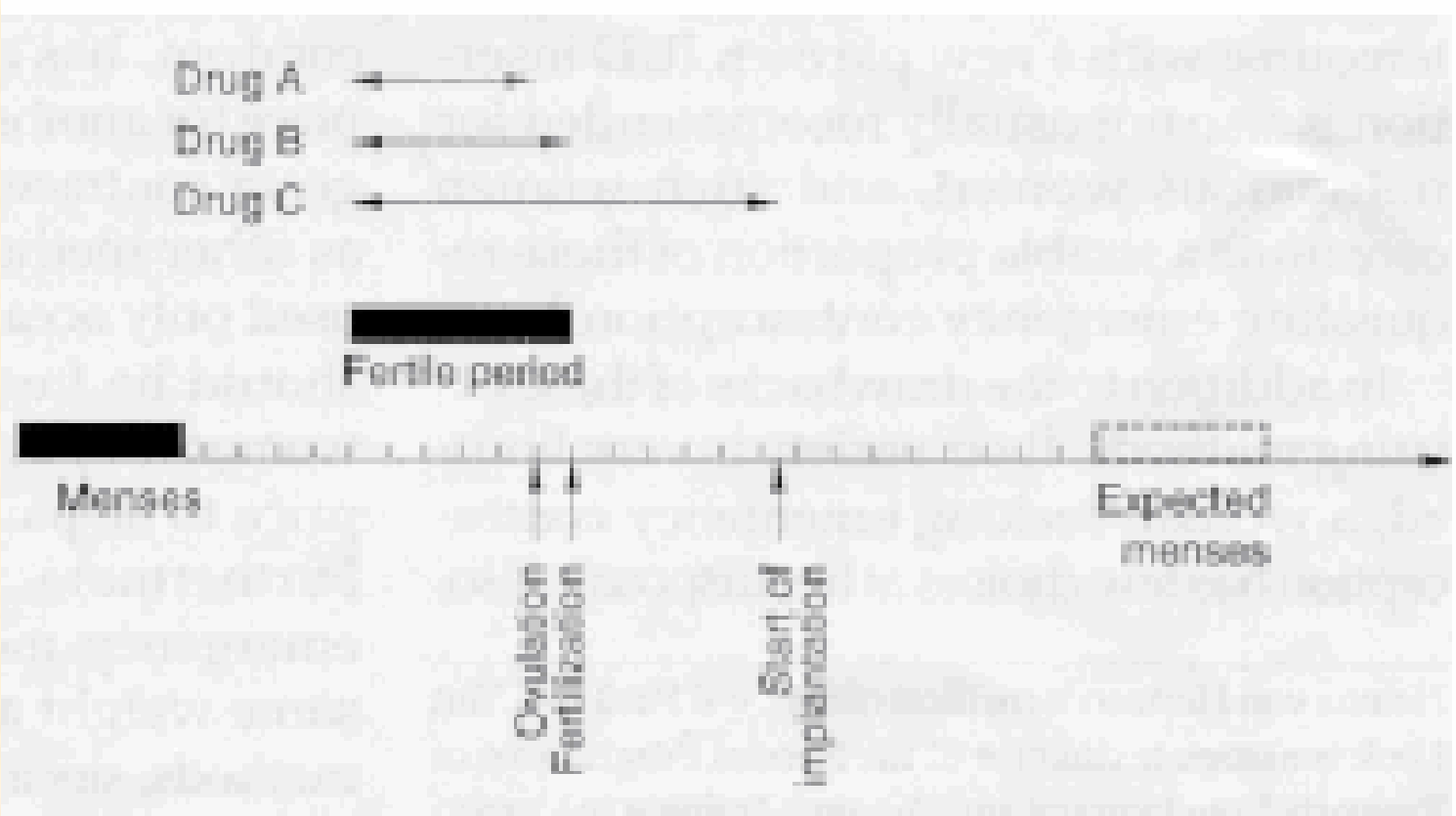
Day in relation to ovulation	No. of cycles with intercourse only on this day	No. of pregnancies	Single-day conception rate	Estimated conception rate ☝ SE*
-5	12	1	0.08	0.10☝ 0.08
-4	24	4	0.17	0.16☝ 0.06
-3	13	1	0.08	0.14☝ 0.08
-2	28	10	0.36	0.34☝ 0.07
-1	38	13	0.34	0.31☝ 0.06
Day of ovulation	14	5	0.36	0.33☝ 0.09
Total	129	35		

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 prostaglandins 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)

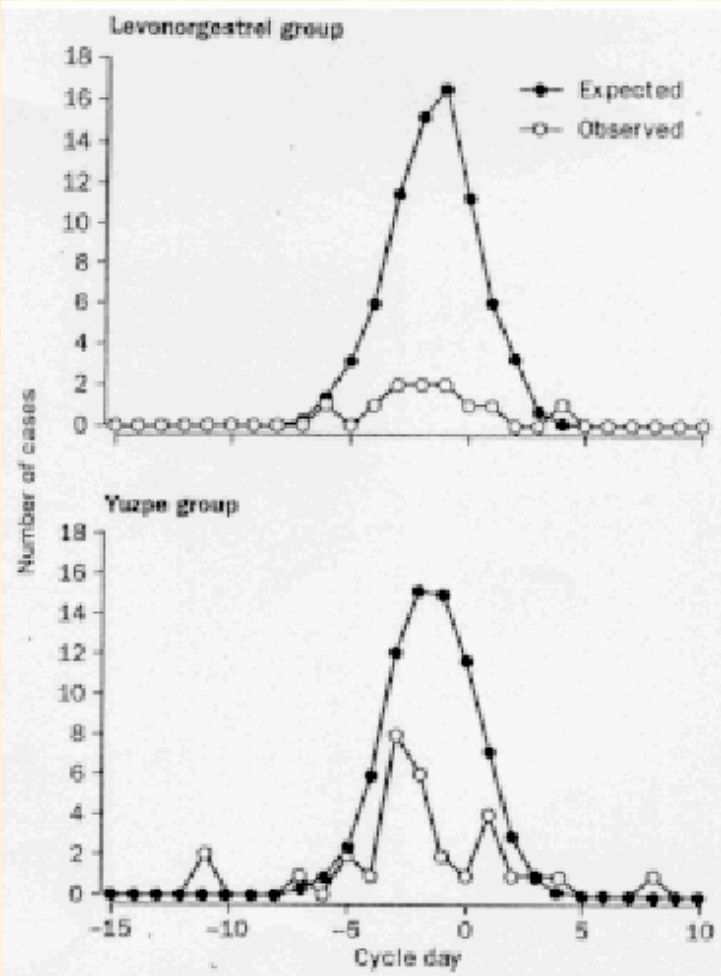
Levonorgestrel versus Yuzpe regimen (1998)

- 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% and1.3%)
    - 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