Emergency Contraceptive Pills
– mechanisms of action

Kristina Gemzell Danielsson, MD, PhD
Karolinska University Hospital/ Karolinska Institutet
Stockholm, Sweden
Emergency Contraception (EC)

Any method used *after* an unprotected intercourse to prevent an unwanted pregnancy
the woman ought, in the moment during coitus when the man ejaculates his sperm, to hold her breath, draw her body back a little so that the semen cannot penetrate into the os uteri, then immediately get up and sit down with bent knees, and in this position, provoke sneezes. She should then wipe out the vagina carefully or drink cold water in addition”

Soranos of Ephesus 98-138 A.D
Methods for Emergency Contraception

Yuzpe - EE (100 µg) + LNG (0.5 mg) x 2 (12 h)

LNG - 1.5 mg single dose

UPA - 30 mg single dose

Mifepristone (RU486) - ≥ 10 mg, China

Cu-IUD
WHO multicentre trials on

Yuzpe vs LNG-EC, and LNG-EC vs. mifepristone

von Hertzen et al., 1998, 2002
Mechanisms of action

Possible targets

- Sperm transport and function
- Follicular development
- Ovulation
- Fertilization
- Embryo development and transport
- Endometrial receptivity and Implantation
- Corpus Luteum
Probability of conception in relation to the day of ovulation
Effects on the spermatozoa

- 90 s endocervix, 5 min Fallopian tube
- Progesterone triggers acrosome reaction of capacitated human spermatozoa in vitro (Fukui et al 2000)
- Effect in vitro: No effect of doses relevant for LNG-EC
  
  Yeung et al., 2002, Bahamondes et al., 2003
- Effect in vitro: No effect of doses relevant for UPA-EC
Effects of UPA on sperm DNA fragmentation in vitro

- A beneficial effect of low levels of oxidative stress on sperm-oocyte fusion previously described
- In EC relevant concentrations UPA counteracted the effect of induced oxidative stress and prevented DNA fragmentation.
- No effect on sperm vitality, lipid peroxidation or induced-AR
Levonorgestrel *in vivo*

LNG 3 to 10 h postcoital:
- Reduced no of sperms in uterine cavity (3h)
- Immobilisation of sperms (9h)
- Increased viscosity of cervical mucus (9h)
- Composition of the uterine fluid (10h)

Kesserü et al., 1974
Effects on follicular development and ovulation
Effects of levonorgestrel-EC pre- or post-ovulatory

- Fertile women
- Levonorgestrel 1.5 mg, pre- or post-ovulatory
- Control and treatment cycles
- Daily ultrasound examinations
- Endometrial biopsies on LH+6 to LH+8
- LH, estron- pregnanediol-glucuronide
Effects of LNG on follicular development and ovulation

- LNG-EC interrupts development of the dominant follicle if given before the onset of the LH peak
- Variable effects on follicular growth:
  - Delayed development
  - Inhibited growth
  - Unruptured follicle
- Ineffective if given after LH onset

Marions et al., 2002, Hapangama et al., 2001
Effects of UPA during the menstrual cycle

UPA 30 mg given in mid-follicular phase

- Inhibition or delay of folliculogenesis and steroidogenesis

UPA 30 mg given at LH onset or after LH has started to rise until the LH peak

- Inhibition of follicular rupture
- Progesterone Receptor-A is Essential for Follicular Rupture

Brahe et al., 2010, 2013
Kim J, Bagchi IC, Bagchi MK. Mol Hum Reprod. 2009 12:821-8
Cycles with no follicle rupture within 5 day after treatment (administered at a follicular diameter of ≥ 18 mm)

Brache et al., Contraception, 2013
Massai et al, Human Reproduction 2007;
Croxatto et al, Contraception 2004
In vivo model to study post-ovulatory effects

Levonorgestrel on LH+2

1.5 mg levonorgestrel
Rat embryo transport regulated by $E_2$ and $P$,

LNG given after ovulation did not prevent pregnancy.

Also in the monkey Cebus apella, LNG given after ovulation did not prevent the occurrence of pregnancy.
Effects on tubal contractility

- Progesterone regulates tubal transport in vitro; muscular contractions and cilia activity
- Cilia from the human fallopian tube beat slower after treatment with high doses of progesterone, reversed by mifepristone
- Dose dependent effect of LNG / mifepristone/UPA on muscular contractility in vitro
  
  Wånggren et al., 2008. Li et al., 2014

- Data from 136 studies on mifepristone or LNG - EC: 0.6 % and 1 %, of pregnancies, respectively were ectopic - not exceeding the rate in the general population.

  Cleland et al., 2010
LNG postovulatory Effects on the endometrium

- Endometrial development: No effect on endometrial histology
- No significant effect on markers of endometrial receptivity
- Same results with vaginal or repeat oral doses

Marions et al. 2001, Meng CX. et al., 2010

- Post-ovulatory LNG caused minimal changes in gene expression during the receptive period. Neither the magnitude nor the nature or direction of the changes endorses the hypothesis that LNG interferes with endometrial receptivity.

UPA and endometrial effects

- Previous studies – dose dependent effects
- Histological evaluation; endometrial dating and thickness
  Blithe et al., 2007; Huang et al., 2014; Williams et al., 2012
- Poor correlation with endometrial receptivity and fertility
  Coutifaris et al., 2004
- A very limited number of receptivity markers studied
  Stratton et al., 2000; Stratton et al., 2010
**In vitro model for Human embryo Implantation**

- The endometrial factor in human embryo implantation is difficult to study
- Ethical Approvals, Endometrial biopsies – Fertile human volunteers
- Human embryos – surplus embryos from donor couples undergoing IVF
- Construction of 3D endometrial cell culture system
- Immunohistochemical analysis for cell polarity and ‘markers of receptivity’

3D implantation model

endometrial biopsies (LH+4) -> culture insert
- epithelial cells
- stromal cells
- basement membrane extract
- stromal cells + collagen
- human blastocyst

Photo; Lennart Nilsson

Lalitkumar et al., 2007

Cytokeratin

Vimentin
Effects of mifepristone

Mifepristone interrupts or inhibits development of the dominant follicle depending on dose and cycle stage.

Following treatment in the follicular phase:- If ovulation occurs there is no adverse effect on the postovulatory endometrium.

Post ovulatory treatment results in a dose dependent effect on endometrial development and ”markers of receptivity”
Blastocyst attachment rate \textit{in vitro}

LNG

Mifepristone

![Graph image showing blastocyst attachment rates for different treatments.](image)

- **Control**
- **Mifepristone Treatment**
- **Levonorgestrel**

***P<0.01 compared with the control

Lalitkumar et al., Hum Reprod. 2007 Nov;22(11):3031-7
Low dose mifepristone - effect on implantation

Embryo attachment rate

control vs mife 0.05µM: p=0.0040
control vs mife 0.5µM: p=0.369
Human embryo attachment *in vitro*

UPA 200 ng/ml
UPA and endometrial effects

- There was no significant difference in the embryo attachment rate between UPA treated group vs. controls.
- 17 known receptivity genes studied;
- Only 2 genes, HBEGF (p=0.009) and IL6 (p=0.025) had a significant up-regulation and
- 4 genes, HAND2 (p=0.003), OPN (p=0.003), CALCR (p=0.016) and FGF2 (p=0.023) were down regulated.
Results:

- **Control**
- **UPA 200 ng/mL**

![Graph showing comparison between Control and UPA treatments.](image)
Effects on embryo development and pregnancy

- No direct effect on human embryos /implantation
- No effect of human pregnancies in vivo or the pregnancy outcome

  Lalitkumar et al., 2007, Meng et al., 2008, 2010, Zhang et al., 2009,
  Berger et al., 2015
Supportive clinical data
Clinical data; ECP pre-or post- ovulation

- Efficacy determined for cycles with EC before/after ovulation (day 0).
- Ovulation dated by hormonal (US) and ovarian parameters
- LNG EC; Novikova et al., 2007 pilot study, Noé et al., 2010
- UPSI during fertile days;
  LNG-EC before ovulation (days -5 to -1); 16 pregnancies expected and no pregnancy occurred (p<.0001).
- LNG-EC on the day of ovulation or thereafter, 8 pregnancies occurred and 8.7 were expected (p=1.00).
- UPA Li et al., 2016; 700 women. UPA effective as EC when administered before but not after ovulation which implied that any possible post-ovulatory mechanisms of UPA, if any, may not contribute to its action as EC.

Meta analysis
Most significant confounding factors effect on pregnancy risk

Confounding factors (1)

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<thead>
<tr>
<th></th>
<th>p-value</th>
<th>O.R</th>
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<tbody>
<tr>
<td>n = 3 445</td>
<td></td>
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<tr>
<td>Conception probability (2)</td>
<td>p &lt; 0.0001</td>
<td>4.4172</td>
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<tr>
<td>Further unprotected intercourse</td>
<td>p = 0.0002</td>
<td>4.638</td>
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Whatever the type of emergency contraception (UPA or LNG):

- 4.4 time higher risk of pregnancy in women having the highest conception probability
- 4.6 higher risk of pregnancy in case of further intercourse

Efficacy of EC methods

Pregnancies first month after EC
/1000 users

- LNG: 20
- UPA: 14
- Cu-IUD: 1


Emergency Contraception, K Gemzell Danielsson
Interactions

- The use of enzyme inducting drugs could affect the efficacy of UPA-EC and LNG-EC (reduced).
- Cu-IUD should always be the first choice!
- 3mg LNG could be considered (EMA)
- BUT women should be informed that the effectiveness of this regimen is unknown.
Interactions

• The efficacy of UPA-EC can be affected (reduced)

• By drugs which increase gastric pH.

• The efficacy of UPA-EC can be affected (reduced) by gestagens;
  
  • 7 days before and within
  
  • 5 days of UPA-EC.
EC Pills

Can the use of ECP be repeated in the same menstrual cycle?
EC Pills

- Levonorgestrel or ellaOne
- Should be repeated as needed
- Increased risk for irregular bleeding
- Less effective than regular contraception
- ECPs do not need to be taken more than once every 24 hours, if multiple acts of unprotected sex occurred within this timeframe.
EC Pills

• If UPA-EC has been used—LNG-EC should not be taken within the next 5 days!

• LNG-EC earlier in the cycle; LNG-EC can be repeated.

• If a woman has already taken LNG-EC; UPA-EC should not be taken in the following seven days.
Quick Start?
Start with hormonal contraception

Note the risk of a postponed ovulation in case of further UPSI

UPA
Wait 5 days before starting an hormonal method
Use barrier method until the hormonal method is effective; (5) + 7 days

LNG
Quickstart of an hormonal method is possible
Use barrier method until the hormonal method is effective; 7 days
Conclusions
Mechanism of action

- The contraceptive effect of LNG or UPA used for EC is due to impaired ovarian function
- UPA-EC is effective after LH has started to rise (until the LH peak)
- LNG or UPA in the doses used for EC have no significant effects on the endometrium
- LNG-EC or UPA in doses used for EC does not inhibit implantation in vitro and has no adverse effect on pregnancy