Emergency Contraception – mechanisms of action effects on the endometrium

Kristina Gemzell Danielsson, MD, PhD
Karolinska University Hospital/ Karolinska Institutet
Stockholm, Sweden
Emergency contraception Pills -
- Mechanisms of Action

Probability of pregnancy increases during follicular phase until a maximum (30%) the day before ovulation.

Probability of pregnancy decreases sharply immediately after ovulation, and is null for any act of intercourse in the post-ovulatory period.

- Ovulation blockage - No fertilization
- Potentially too late to avoid ovulation - The earlier the better
- No endometrial effect. No fertilization risk

Croxatto et al., 2009
In vivo model to study endometrial effects

levonorgestrel / mifepristone on LH+2

1.5 mg levonorgestrel
10 – 200 mg mifepristone
Expression of PR in the Fallopian tube

No effect on PR levels following treatment with LNG

Significant increase after 200 mg mifepristone

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 on muscular contractility in vitro
  
  41,42 (Wånggren et al.,2008)

- 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 (0.75 mg x 4 p.o., or 1.5 mg p.v)

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.

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"
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**
- Inhibition of follicular rupture

**UPA 30 mg: given in early-luteal phase**
- No endometrial effects

Brahe et al., 2010, Croxatto et al., Stratton et al., 2010

Emergency Contraception. K Gemzell Danielsson
Cu-IUD

- Hippocrates mentioned copper as a metal with influence on fertility
- Main mechanism of action of Cu-IUD when used for regular contraception; Cu inhibit sperm migration and functions – prevention of fertilization
- Cu concentrations in the luminal fluids are toxic the gametes, decreases the rate of fertilization and the chances of survival of any embryo that may be formed, before it reaches the uterus
- In addition: Cu influence on the endometrium and foreign body reaction

Ortiz & Croxatto 2007
In vitro 3D endometrial cell culture

Emergency Contraception. K Gemzell Danielsson
Human embryo attached to the culture

Foto: Lennart Nilsson

Emergency Contraception. K Gemzell Danielsson
Blastocyst attachment rate \textit{in vitro}

LNG

Mifepristone

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure}
\caption{Graph showing the blastocyst attachment rates for different treatments.}
\end{figure}

\textbf{Statistical Analysis:}

**P<0.01 compared with the control**

\textit{Lalitkumar et al., Hum Reprod. 2007 Nov;22(11):3031-7}
LNG-EC effects on embryo development and pregnancy

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

Lalitkumar et al., 2007, Meng et al., 2008, 2010, Cheng et al., 2009
Conclusions
Mechanism of action

• The contraceptive effect of LNG, mifepristone or UPA used for EC is due to impaired ovarian function
• LNG, mifepristone or UPA in the doses used for EC have no effect on the endometrium
• LNG-EC does not inhibit implantation *in vitro* and has no adverse effect on pregnancy
• Cu IUD is the most effective EC. Acts via prevention of fertilization. "Back up" effect on the endometrium/uterine fluid