

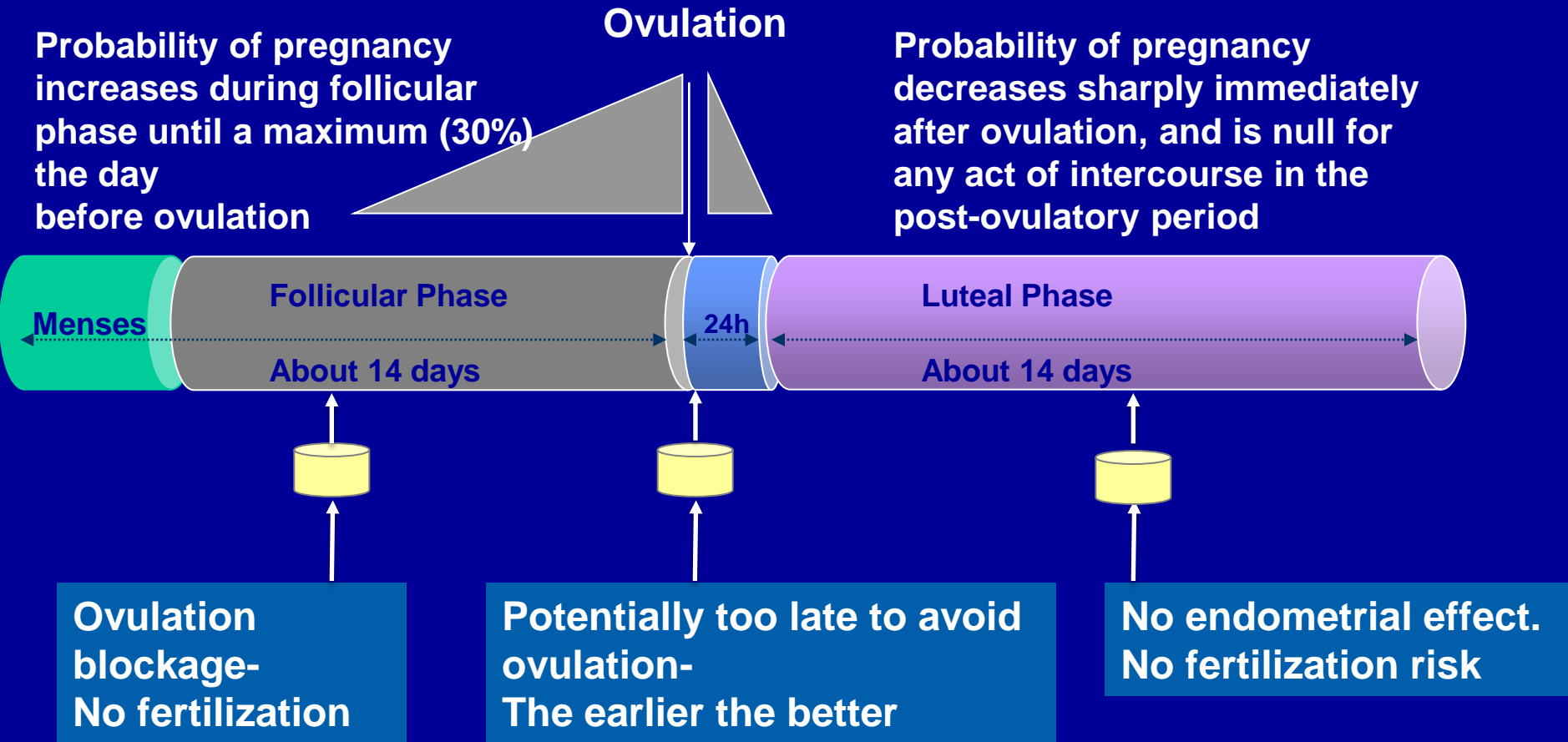
Emergency Contraception – mechanisms of action effects on the endometrium



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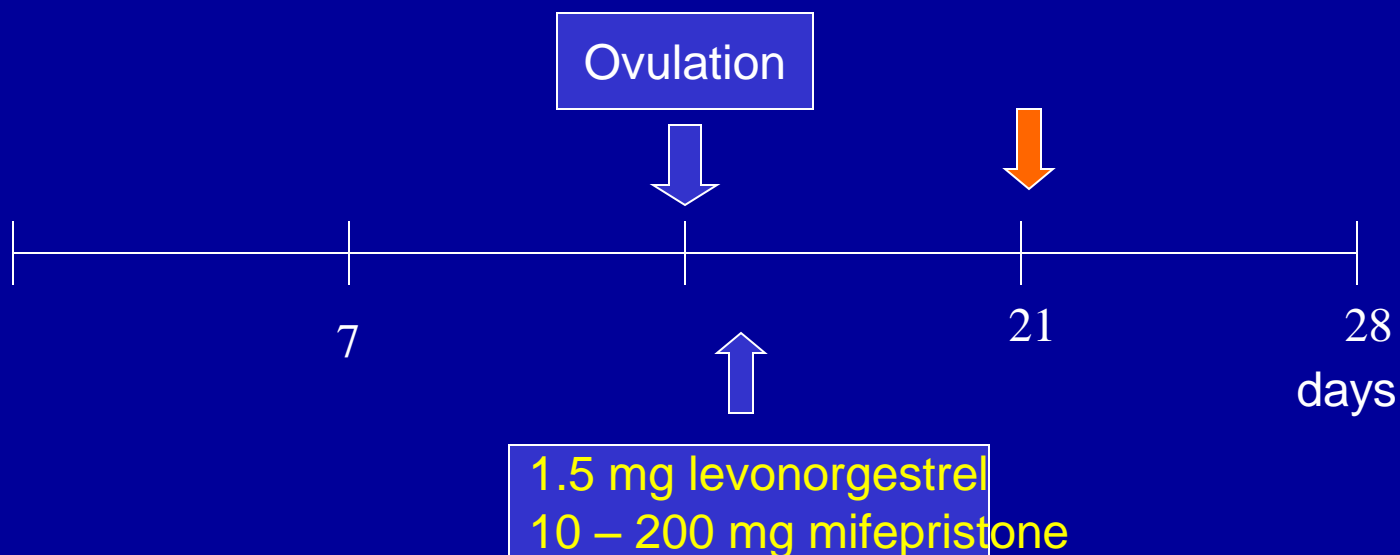
Emergency contraception Pills - - Mechanisms of Action



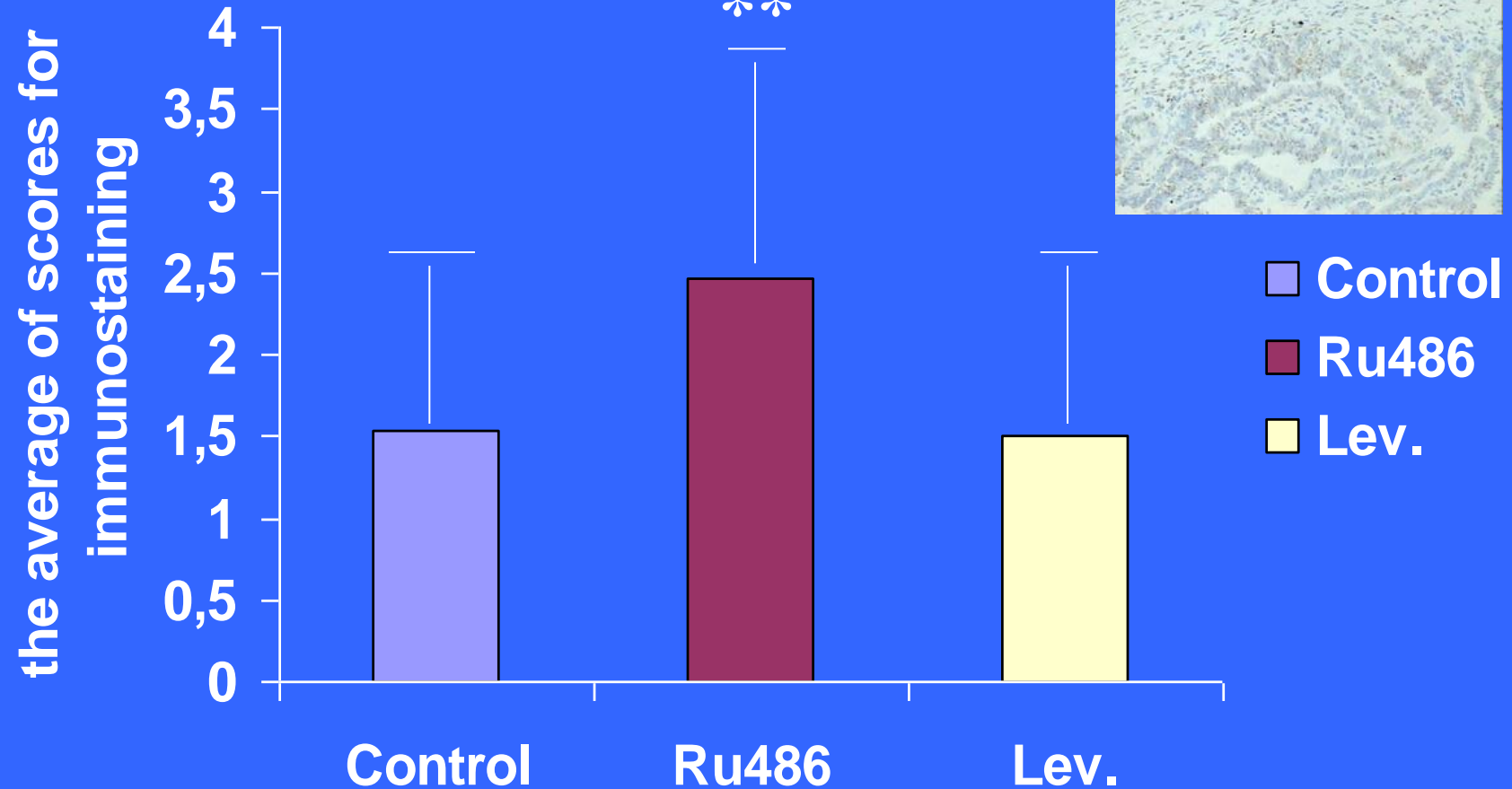
Croxatto et al., 2009

In vivo model to study endometrial effects

levonorgestrel / mifepristone on LH+2



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 (Wångren 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.

Vargas et al., J Mol Endocrinol. 2012 Jan 25;48(1):25-36.

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

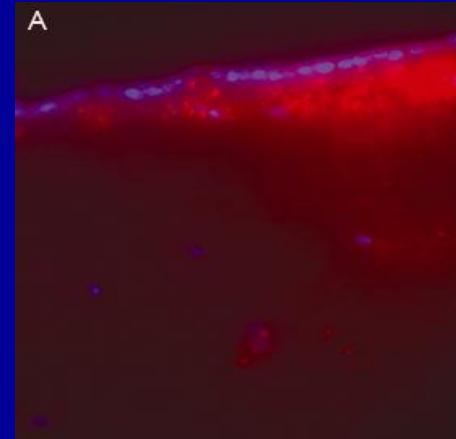
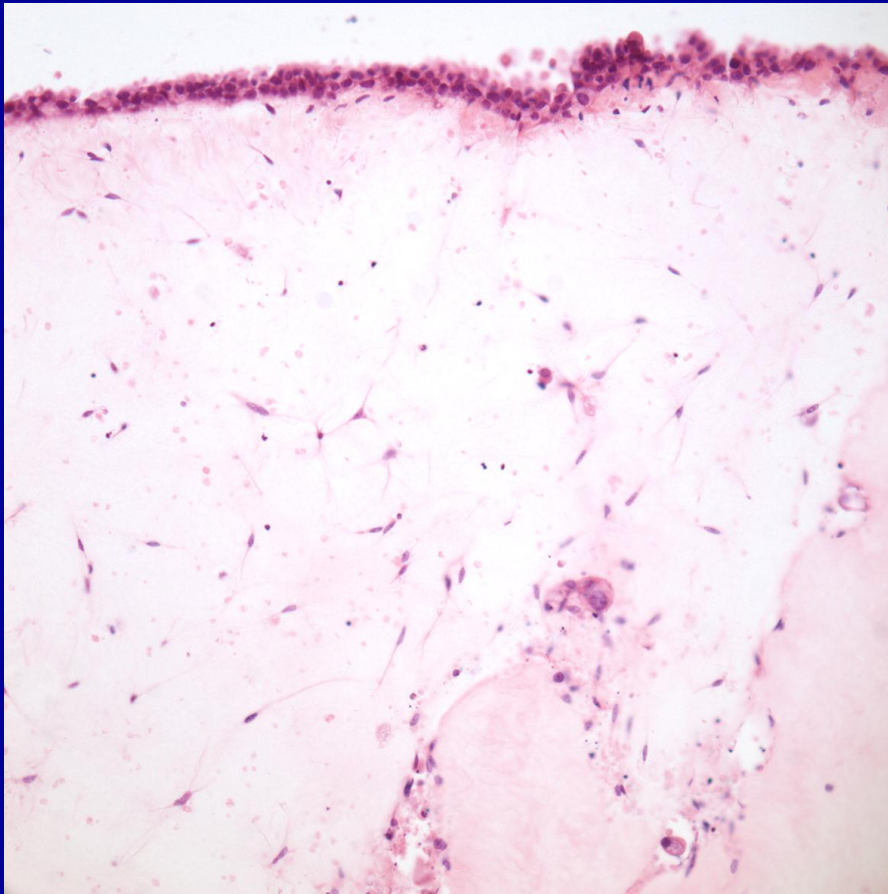
Brahe et al., 2010, Croxatto et al., Stratton et al., 2010

Cu-IUD

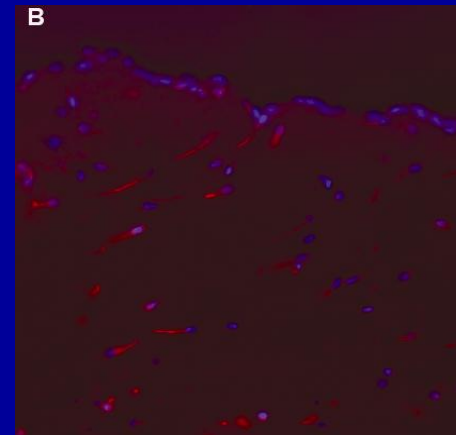
- Hippocrates mentioned copper as a metal with influence on fertility
- Main mechanism of action of Cu-IUD when used for regular contraception; Cu inhibit sperm migration and functions – prevention of fertilization
- Cu concentrations in the luminal fluids are toxic the gametes, decreases the rate of 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



Cytokeratin



Vimentin

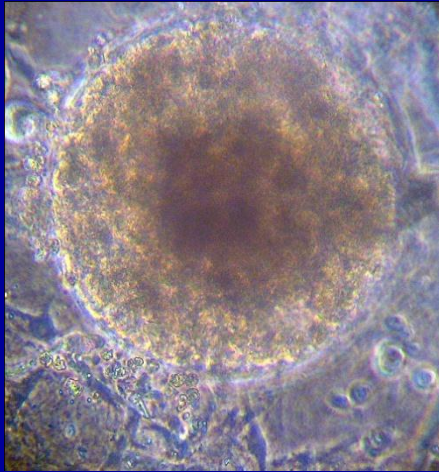
Human embryo attached to the culture



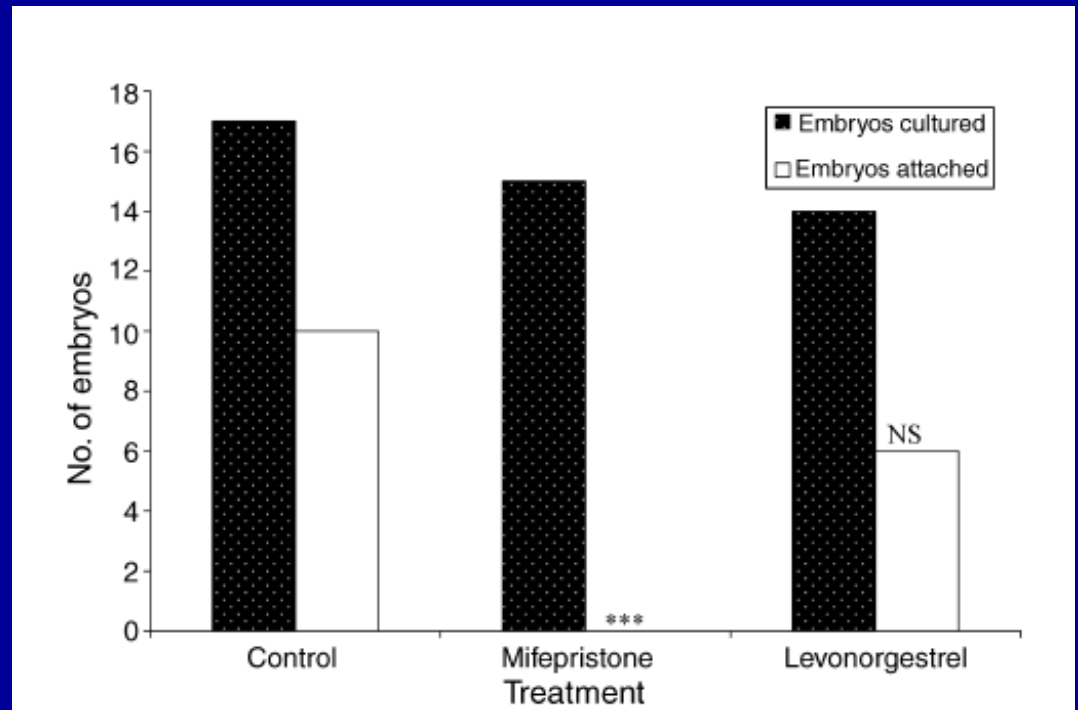
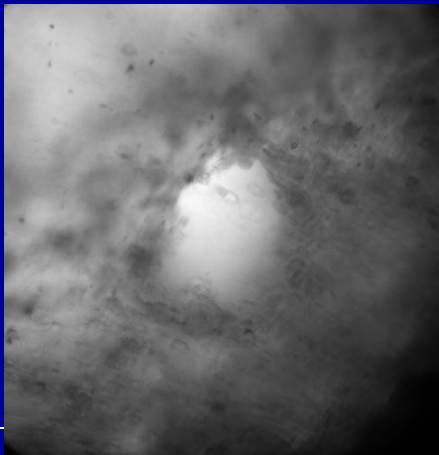
Foto: Lennart Nilsson

Blastocyst attachment rate *in vitro*

LNG



Mifepristone



***P<0.01 compared with the control

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

WHO Collaborating Centre for Research in Human Reproduction

Karolinska University Hospital/ Karolinska Institutet



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- Swedish research council

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