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Blurring the lines

Setting the scene. What the science tells us

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UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development
and Research Training in Human Reproduction, WHO, Geneva

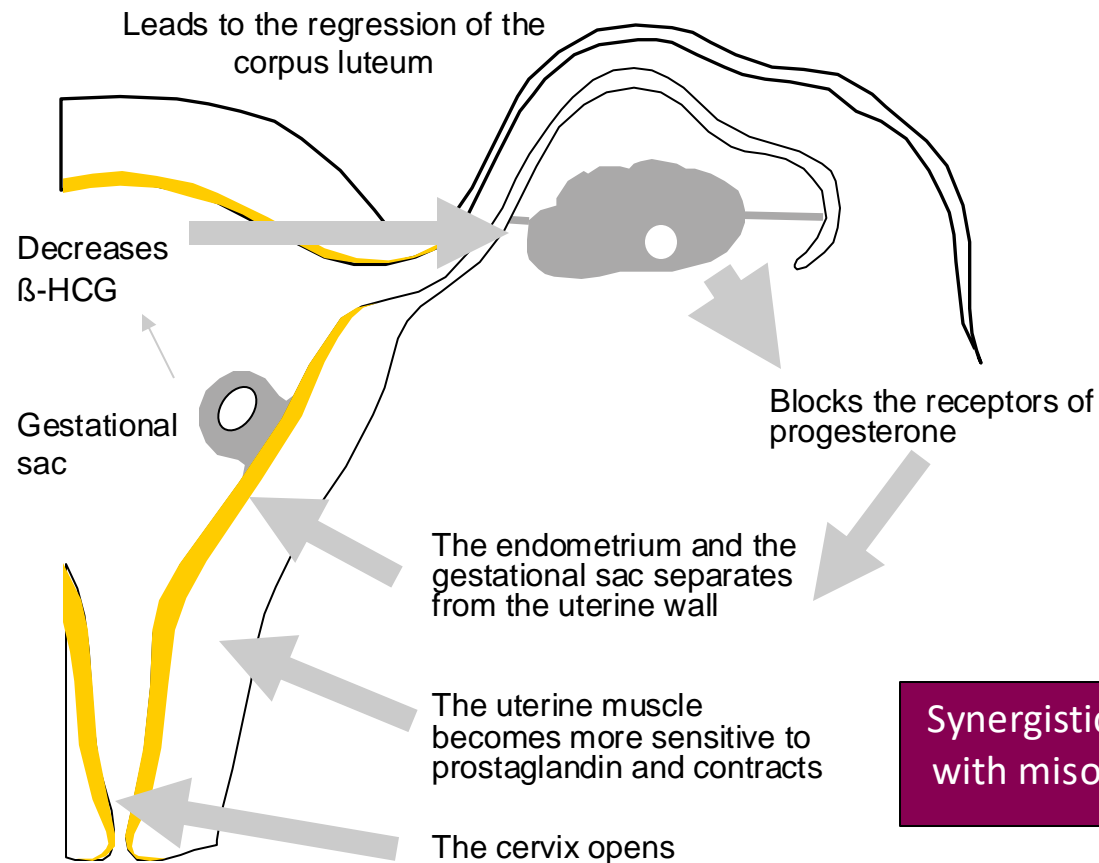
Disclosures;

Gemzell-Danielsson ad hoc advisory board and/or invited speaker for Organon
(MSD), Bayer, Exelgyn, Actavis, Gedeon Richter, Mithra, Exeltis, Ferring, Natural
Cycles, MedinCell, Cirql, Medicine360, Obseva, and HRA-Pharma



Reproductive Health Research
From bench - to bed - to the hands of women
to improve women's health

Mode of action of mifepristone

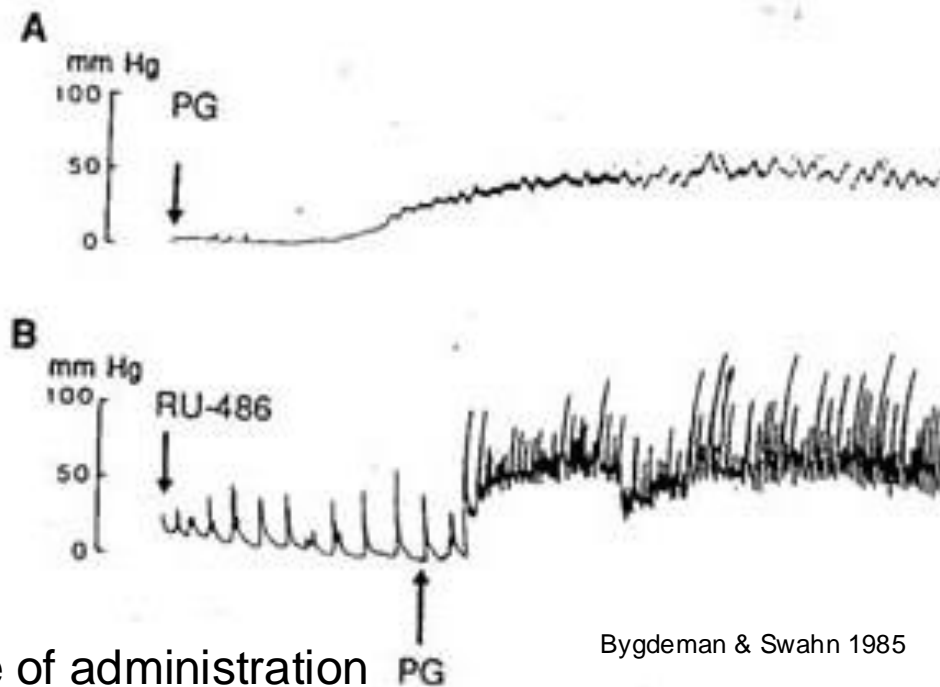


Development of medical abortion

- 70ies, Prostaglandin analogues (PG) discovered by prof Sune Bergström and his team at KI, Awarded the Nobel Price in 1982
- Induced uterine contractions and cervical ripening;
- Shown to act in synergy with progesterone receptor modulator;
- Mifepristone (RU486) E Bauleu, Fr

→ Medical abortion (1988)

- Optimal mifepristone dose
- Optimal prostaglandin- type, dose, route of administration
- Gestational length vs efficacy
- Acceptability

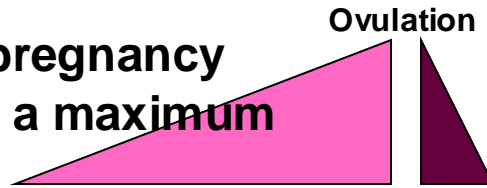


Bygdeman & Swahn 1985

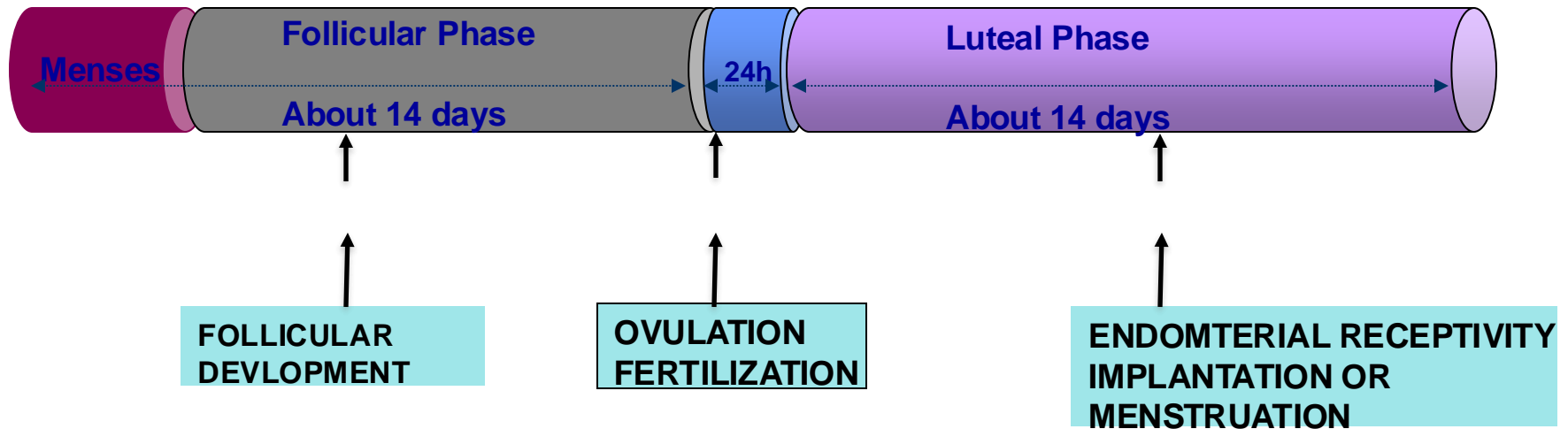
Bygdeman M, Gemzell Danielsson K, Marions L:
JAMWA 55: 3: 195-6, 2000.

Reproductive physiology —Points for inter(action)

Probability of pregnancy increases until a maximum (30%) LH+0



Sharp decline immediately post ovulation, to 0% for any act of intercourse



Effects on the non-pregnant uterus

- Effects on the cervix?
- Effects on follicular development after selection of the dominant follicle
- Delays or inhibits ovulation
- Complex effects on the endometrium
- Affects PR expression in the Fallopian tube

PRMs for contraceptive use:

- Inhibition of Ovulation
- Endometrial Contraception
- Emergency Contraception
- "Menstrual induction"
- Combination with progestins

Endometrial Contraception

ONCE-A-MONTH TREATMENT WITH 200MG MIFEPRISTONE ON DAY LH+2 AS A CONTRACEPTIVE METHOD

Number of cycles with an intercourse from 3 days before to 1 day after ovulation

<u>Treatment</u>	<u>No. of cycles</u>	<u>No. of pregnancies</u>	<u>Probability of pregnancy</u>
Mifepristone	124	1	0.008
None*	72	35	0.486

*Unprotected intercourse during the time period 3 days before to 1 day after mucus peak day (from WHO multicentre study, Fertil Steril 40:773,1993)

Clinical studies

PRMs

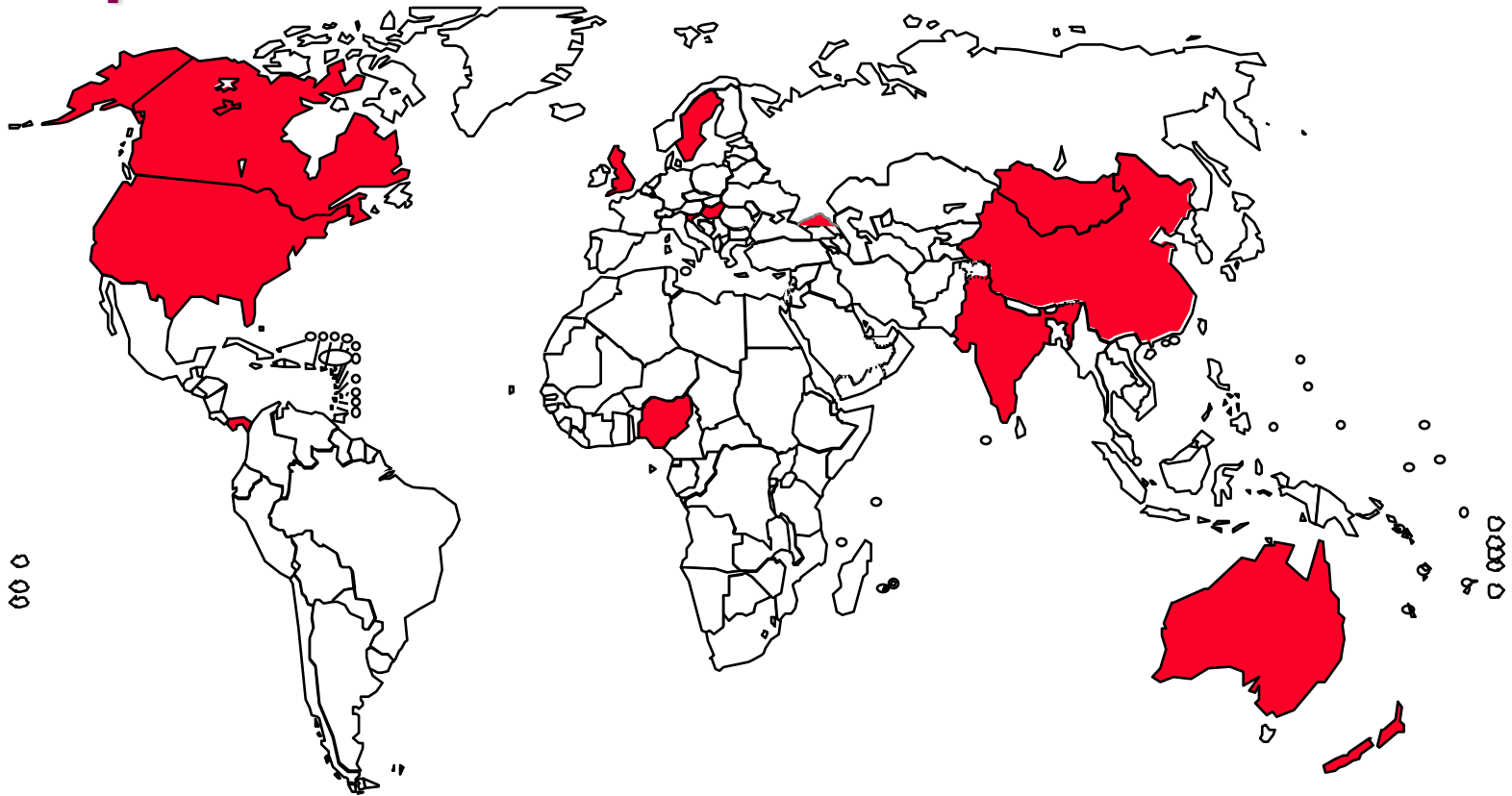
- "Once-a-month" pill
- Once-a-week/day
- EC
- "Menstrual induction/regulation"
mifepristone + misoprostol

Pills
IUDs
Ring

Endometrial contraception



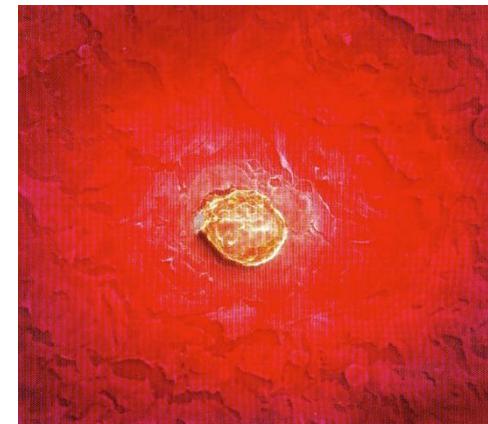
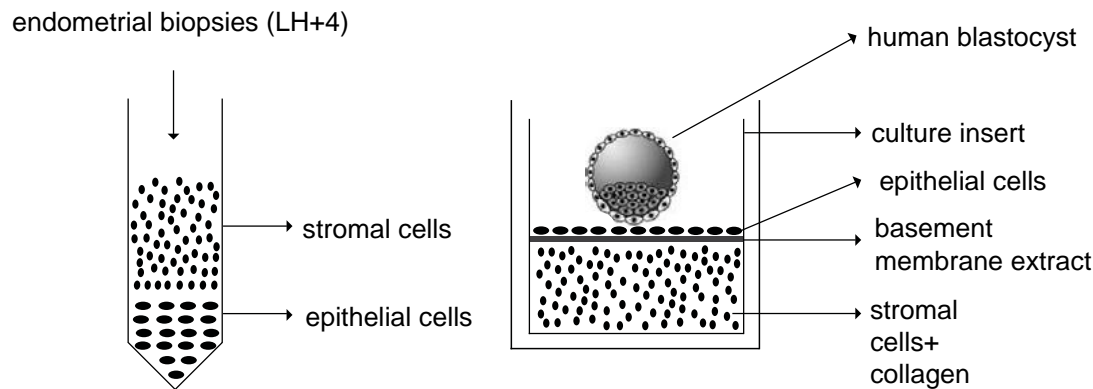
WHO multicentre trials on Yuzpe vs LNG-EC, and LNG-EC mifepristone



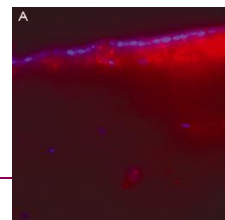
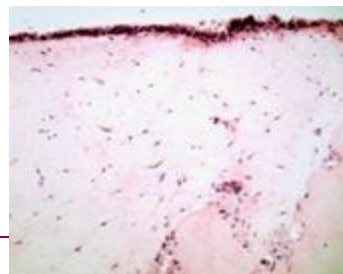
In vitro model for Human embryo Implantation

- 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’

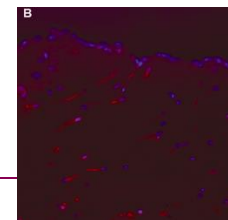
3D implantation model



Photo; Lennart Nilsson

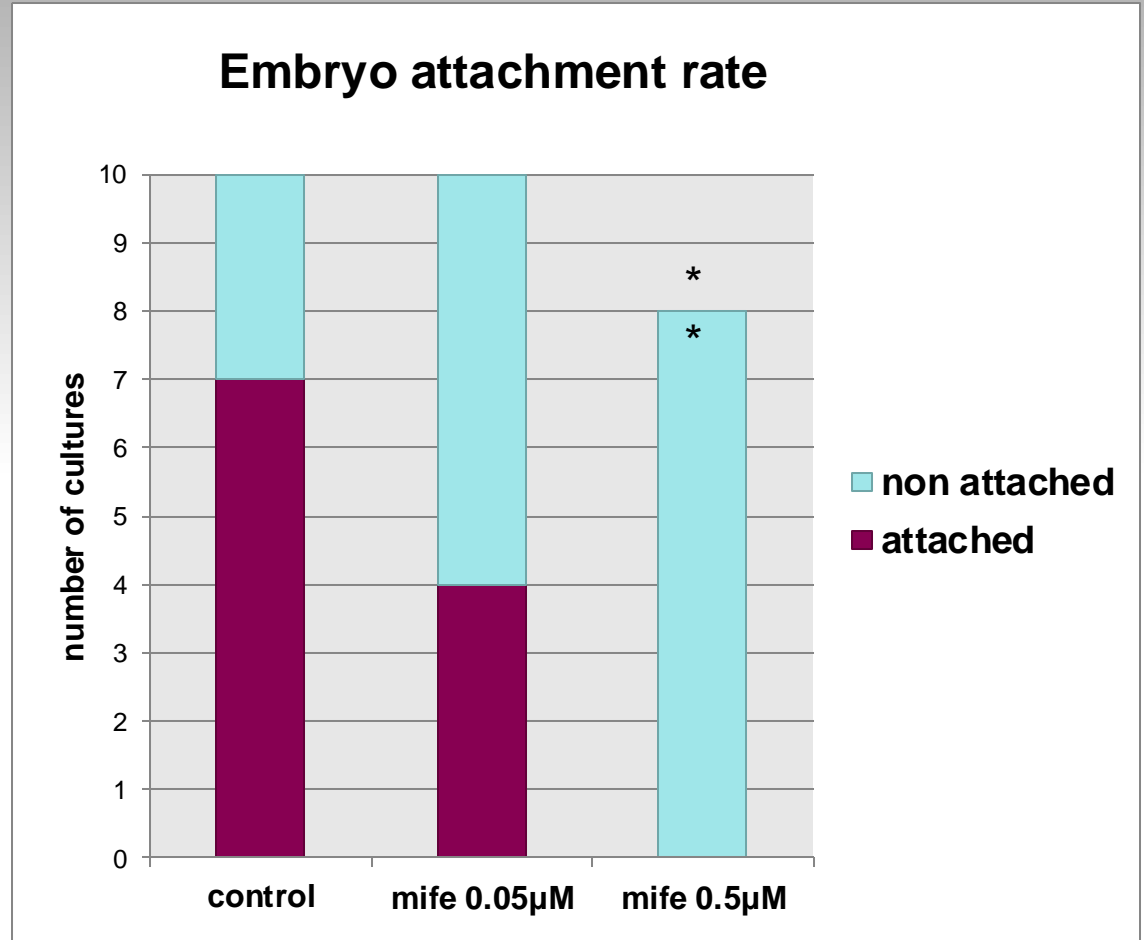
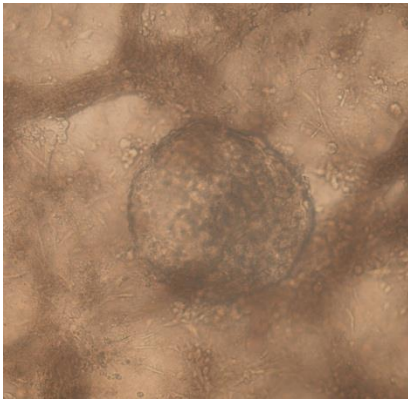


Cytokeratin



Vimentin

Low dose mifepristone - effect on implantation



control vs mife 0.05µM: $p=0.0040$
control vs mife 0.5µM: $p=0.369$

Piroxicam and levonorgestrel co-treatment for emergency contraception: a randomised double-blind controlled trial

Dr. Raymond H.W. Li, Dept Obstetrics and Gynaecology,
The University of Hong Kong

Results: **piroxicam**, a long-acting COX inhibitor, co-treatment with LNG-EC, improved the contraceptive efficacy.



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HKU Med School of Clinical Medicine
Department of Obstetrics
& Gynaecology
香港大學婦產科學系



Results – primary efficacy outcome

	Piroxicam group (n=418)	Placebo group (n=418)	p-value
Pregnancy rate, n (%)			
Observed	1 (0.24%)	7 (1.67%)	
Expected^a	19.019 (4.55%)	19.061 (4.56%)	
Proportion of pregnancies prevented^b	94.7%	63.3%	<0.0001*

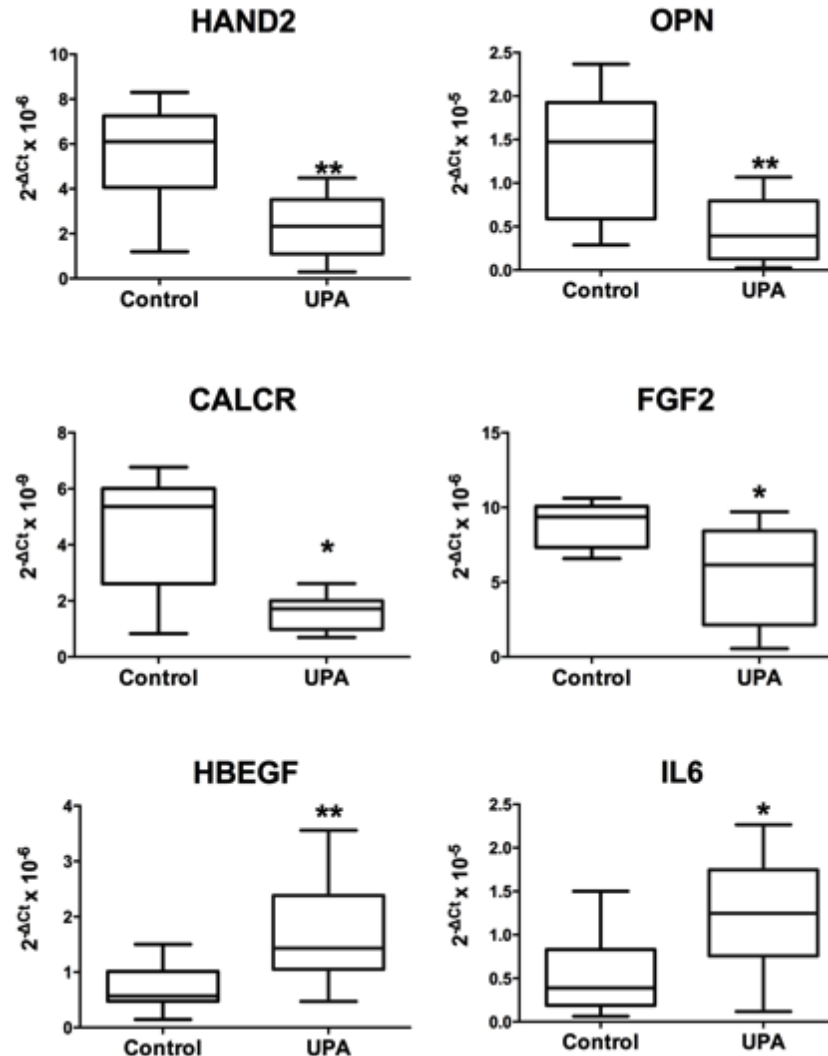
^a Calculated based on the model by Trussell et al. (2003)

^b Calculated by the formula: (Expected pregnancies – observed pregnancies) / expected pregnancies

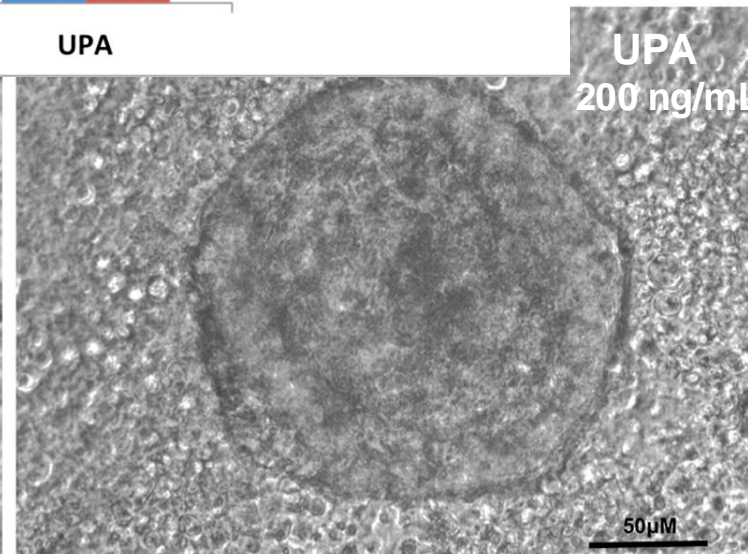
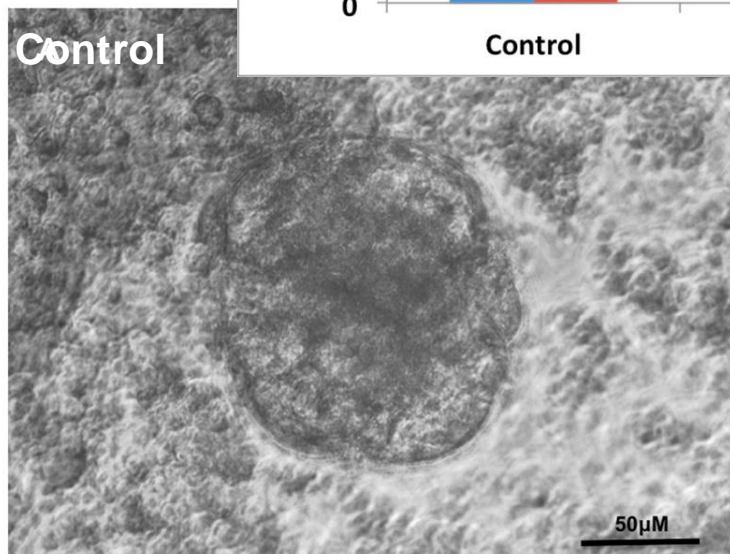
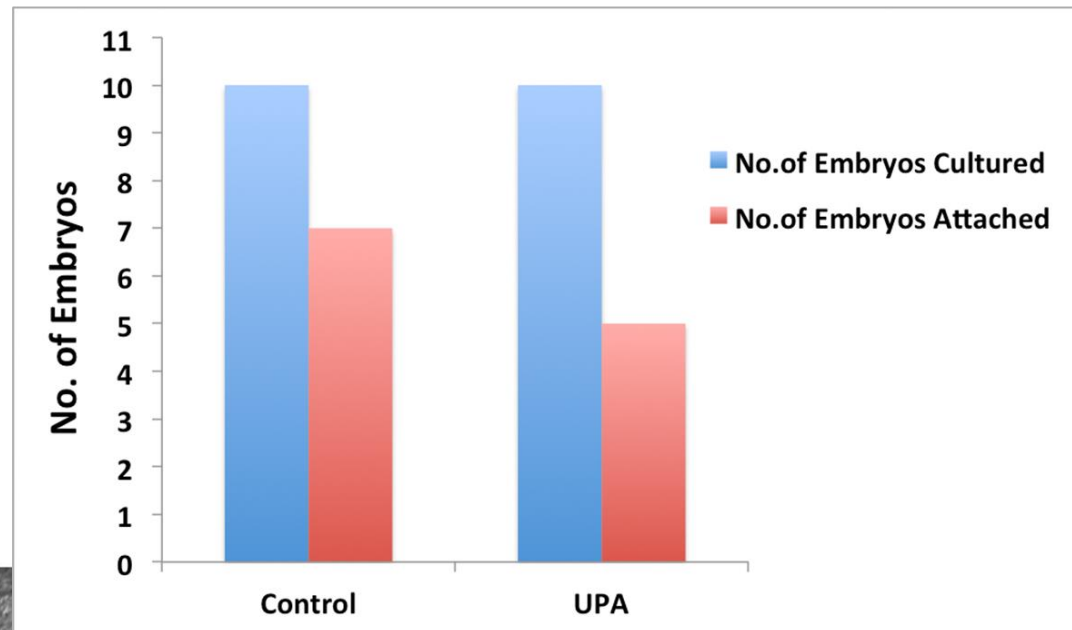
* Statistically significant (χ^2 test)

Effects of UPA-EC on endometrial receptivity

Significant change in the expression of endometrial receptivity markers



..but no functional effect



Effects of mifepristone- Summary

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"

- No direct effect on human embryos

Lalitkumar et al., 2007, Meng et al., 2008, 2010, Zhang et al.,2009,

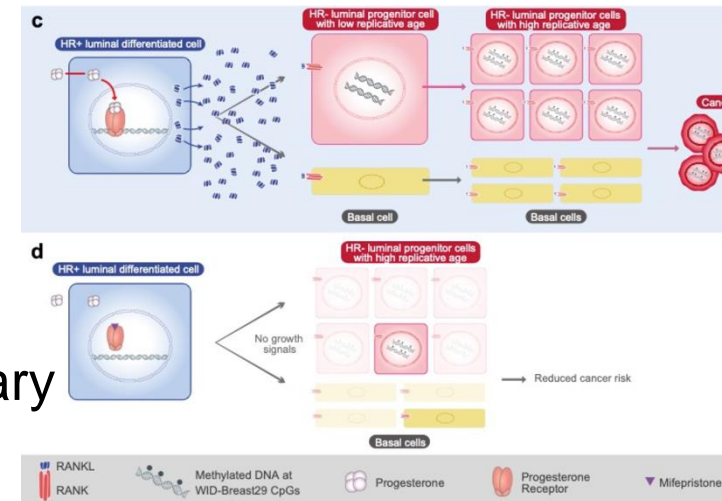
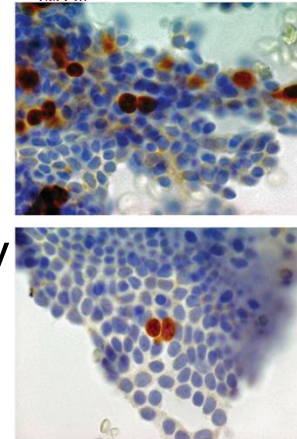
Berger et al., 2015

Prospective multi-center single arm open label study of efficacy, safety and acceptability of long-term weekly oral Mifepristone 50 mg as contraceptive

Drug Product:	Mifepristone tablets 50 mg
Protocol Number:	2019001_mife 50
Study Phase:	III
Study Sponsor:	Women on Waves Karolinska Institutet

”Added health benefits”

- In vitro Mife, breast cancer cells - apoptotic effect
- Mife: partial response in metastatic breast cancer
Benagiano et al 2008
- In BRCA1/p53 deficient mice: Mife prevents mammary development
Poole 2006
- Reduction in Ki67 in epithelial cells
Engman 2008
- Higher P throughout the menstrual cycle of BRCA1/2 mutation carriers,
- LP cells with elevated replicative age are more prone to malignant transformation. Mife reduced mitotic age and proportion of LP cells in normal breast and in 64% BRCA1/2 mut. carriers.
- Mife reduced TP53 mutation frequency.
Bartlett et al. Genome Medicine 2022, 29;23(1):142.
Barrett et al., Nat Commun. 2022 Feb 1;13(1):449.



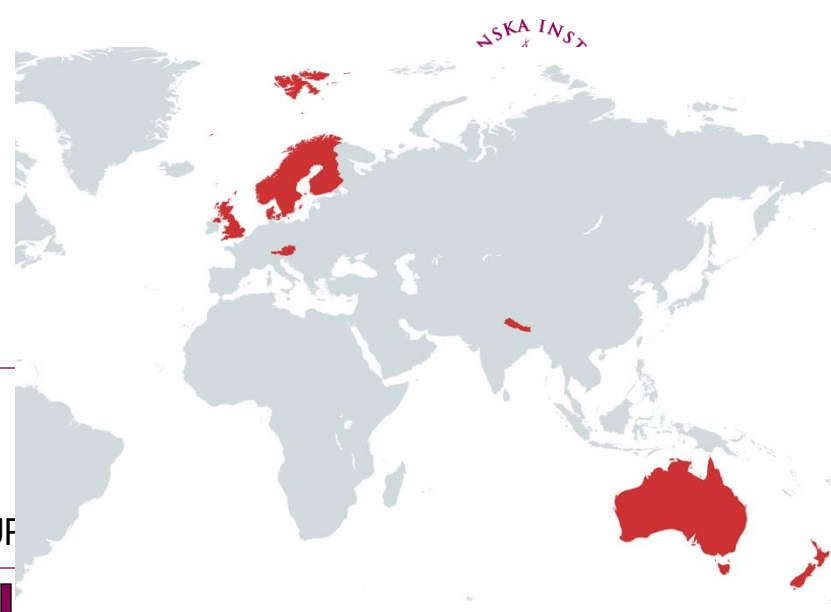
Conclusions: These data support Mife for primary prevention of poor-prognostic breast cancers

Contraception; regular vs occasional administration

- Once-a-month 200mg mifepristone + 0.4 mg misoprostol po 48h later before or on the day of menstruation,
- Conclusion; not effective enough to be used for menstrual regulation.

- “Late EC” >5 days after a single or several UPSI
- 100 mg mifepristone 48h later 0.4 mg misoprostol po, in the luteal phase of the cycle. u-hCG negative.
- 25 women (2.7%) became pregnant.
- -→could provide an option for preventing unwanted pregnancies in women who are late for EC.

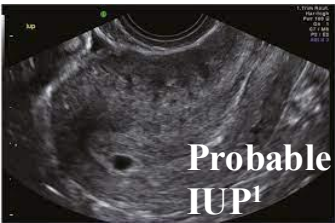
VEMA RCT – multicentre, multinational



Population:
1500 women
<= 6+0 LMP
US: Non-confirmed IUF

Intervention: VEMA
Immediate start of medical abortion
Baseline s-hCG
Day 7: S-hCG for assessment of treatment

Control: Delayed treatment
Day 7: Renewed ultrasound
Start medical abortion when confirmed IUP
U-hCG 2-3 weeks post abortion for assessment of treatment



Outcome: Complete abortion –
No ongoing pregnancy or need for surgical intervention

Mifepristone and Letrozole versus Methotrexate as treatment for Ectopic pregnancy – a randomized controlled non-inferiority trial (MILE)

Towards Contraception.....

Conclusions

- Room to expand access to SPRMs (mifepristone)
- Holds the potential to be developed for contraceptive use
- Also holds the potential for development on other non contraceptive indications
- More data needed re PAEC and long term endometrial effects
- Potential protective effect on the breast
- The same treatment at the same time of the menstrual cycle /pregnancy- if we call it Contraception it is ok BUT if we call it abortion.....

Potential for a contraceptive continuum



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Thank you!