The contraceptive continuum

Kristina Gemzell Danielsson, MD, PhD
Karolinska University Hospital/ Karolinska Institutet
Stockholm, Sweden
WHO Collaborating Centre for Research in Human Reproduction
Karolinska Universitetssjukhuset / Karolinska Institutet


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Reproductive Health Research
From bench - to bed - to the hands of women to improve women’s health
Effective contraceptive methods and safe abortion are prerequisite for Reproductive Health.

"Sexual and reproductive health and rights constitute fundamental human rights, form a vital aspect of the women’s empowerment and are a key to the achievement of gender equality"
Who decides over fertility?

There is no tool for development more effective than empowerment of women.

(Kofi Annan)
Main cause of MM - key interventions

Lancet 2016

Complications of abortion
- Family planning
- Safe abortion services
- Post abortion care

Indirect causes
- Iron folate supplements
- Malaria intermittent treatment
- Insecticide-treated nets
- Anti-retrovirals

Haemorrhage
- Uterotonic
- Blood transfusion
- Balloon tamponade
- Surgery
- NASG

Sepsis & other maternal infections
- Tetanus toxoid
- Clean delivery
- Antibiotics
- WASH

Other maternal disorders
- Caesarean-section
- Other emergency obstetric care

Obstructed labour
- Caesarean-section

Hypertensive disorders
- Early identification & timely delivery
- Magnesium sulphate
- Calcium
- Aspirin
- Anti-hypertensive
- Caesarean-section

Is there a need for new contraceptive methods?

Globally 225 million women lack access to effective and acceptable contraception.

>40% of all pregnancies are unplanned.

50% Results in an induced abortion.
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

Menses

Follicular Phase

About 14 days

24h

Luteal Phase

About 14 days

FOLLICULAR DEVELOPMENT

OVULATION FERTILIZATION

ENDOMTERIAL RECEPTIVITY IMPLANTATION OR MENSTRUATION

Emergency Contraception. K Gemzell Danielsson
Mifepristone
Effects during the cycle and in pregnancy

- Contragestion
- Contraception
- Follicular phase
- Pregnancy Interruption
- Labour Induction
- Adjuvant to late Pregnancy termination
Selective progesterone receptor modulators (SPRM) for contraception and contragestion

- Emergency Contraception → ”Regular/ on demand contraception”
  - Inhibition of Ovulation, → Endometrial Contraception---> ”Menstrual induction” – ”contragestion” → VEMA, medical abortion

RU-486 (Mifepristone)  Ulipristal acetate (Esmya®)  J-867 (Asoprisnil)

ZK98299 (Onapristone)  Telapristone acetate (Proellex®)

SPRM: Selective Progesterone Receptor Modulator
UPA: Ulipristal acetate
WHO multicentre trials on Yuzpe vs LNG-EC, and LNG-EC mifepristone

UPA - 30 mg single dose (ellaOne)
Mifepristone (RU486) - ≥ 10 mg, China
Endometriereceptivitet

Progesteron - ett nyckelhormon för fertilitet
Effects of ECP on the endometrium

endometrial biopsies (LH+4)

stromal cells
epithelial cells

human blastocyst
culture insert
epithelial cells
basement membrane extract
stromal cells + collagen

No. of Embryos Cultured
No. of Embryos Attached

Berger C, et al..Hum Reprod. 2015 Apr;30(4):800-11
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".
Endometrial Contraception

Once-a-month Pill shown to be a highly effective contraceptive method,

200mg mifepristone

P4, E2 normal plasma levels

Ovulation

21 days

28 days

Gemzell-Danielsson et al., Lancet 1992, Hum Reprod 1993
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
Inhibition of ovulation
SPRM – daily oral administration

- Mifepristone continuous low dose
- Disruption of the follicle maturation, inhibition of ovulation
- Non-secretory endometrium
- Amenorrhea
- Well tolerated
- Highly effective contraceptive method (RCT 2 and 5 mg mifepristone/d 120d).

Brown et al., JCEM 2002

UPA. –similar effects

Chabbert-Buffet et al., JCEM 2007
Diagram of CDB-2914 Ring

Vaginal ring dimensions

Cross-sectional view of vaginal ring. The shaded areas are micronized CDB-2914 in silicone matrix.
Once-a-week mifepristone

- Double-blind, RCT with weekly doses of 25 or 50 mg of mifepristone in three centers in China.
- Each study cycle defined as 28 days.
- Outcome measures efficacy, changes of menstrual pattern, side effects.
- No pregnancy (76 women/ 456 cycles)

Pei K, Xiao B, et al., Contraception 2007
Contragestion

- Treatment at/ just before expected time of menstruation
- Induction of abortion in pregnant women with very early pregnancy or
- Induction of menstruation

Swahn et al., Hum Reprod 1999,
CL Li, et al., Hum Reprod, 30:12 ;2794–2801, 2015
VEMA, very early medical abortion

VEMA failure (ie ongoing pregnancy or incomplete abortion)

- NOT more likely in women with no confirmed intrauterine gestation (IUG) vs. confirmed IUG, gestations ≤ 49 days
- Significantly lower rate of treatment for incomplete abortion
- Findings support that VEMA is effective and safe

Recommendation

Avoid unnecessary delay!
Offer medical termination accordingly

Bizjak et al., 2017
I need an abortion

Using telemedicine for termination of pregnancy with mifepristone and misoprostol in settings where there is no access to safe services

RJ Gomperts, a K Jelinska, b S Davies, c K Gemzell-Danielsson, d G Kleiverda e

aWomen on Waves, Amsterdam, the Netherlands b Women’s Wallet, Amsterdam, the Netherlands c Women on Web, Minneapolis, MN, USA d Department of Woman and Child Health, Karolinska Institutet, Stockholm, Sweden e Department of Obstetrics and Gynaecology, Hevikkienhuis, Almere, the Netherlands

Correspondence: RJ Gomperts, Women on Waves, PO Box 15683, 1001 ND, Amsterdam, the Netherlands. Email gomperts@womenonwaves.org

I had an abortion
Contragestion; 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.
Summary

- The unmet need in contraception remains high
- Today many women are reluctant to use any of the existing contraceptive methods due to side effects or fear of experiencing such effects.
- **New options should be explored to allow women and men all possible options for controlling and preserving their reproductive health and lives.**
- To achieve this we need translational research incl basic research
- Link research to policy, and base policy on evidence
- Room to expand access to SPRMs
WHO Collaborating Centre for Research in
Human Reproduction
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- Research Group on Post-Ovulatory Methods for Fertility Regulation,
  UNDP/UNFPA/WHO/World Bank Special Programme of Research,
  Development and Research Training in Human Reproduction, WHO, Geneva
- ICCR Population Council, Regine Sitruk-Ware
- Swedish research council
- www.muvs.org

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