



Vision for Contraceptive Research and Development: 100th meeting ICCR

Contraceptive Vaginal Rings

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Overview

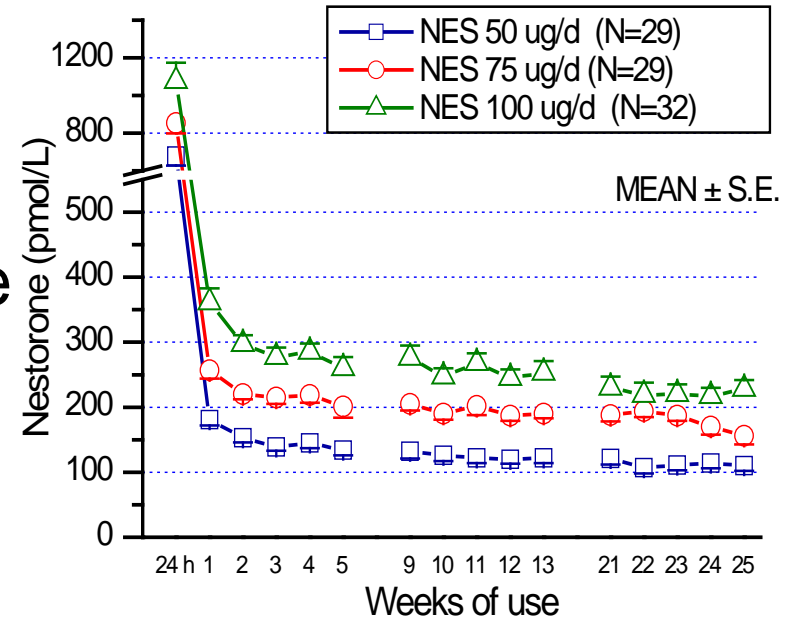
- Concepts for development of CVR
- History of development
- Contraceptive vaginal rings in advanced development
 - ✓ NES/EE one-year ring
- Contraceptive vaginal rings launched
 - ✓ Nuvaring®
 - ✓ Progering®
- Future Developments

Vaginal rings: rationale for development

- Development of steroid releasing systems, which allow a slow constant rate diffusion through polymers.
- Capability of the vaginal epithelium to absorb hormonal steroids into the systemic circulation.
- Ability to use orally inactive steroids
- Need for long acting method that is user controlled-non provider dependent.

Contraceptive Rings PK

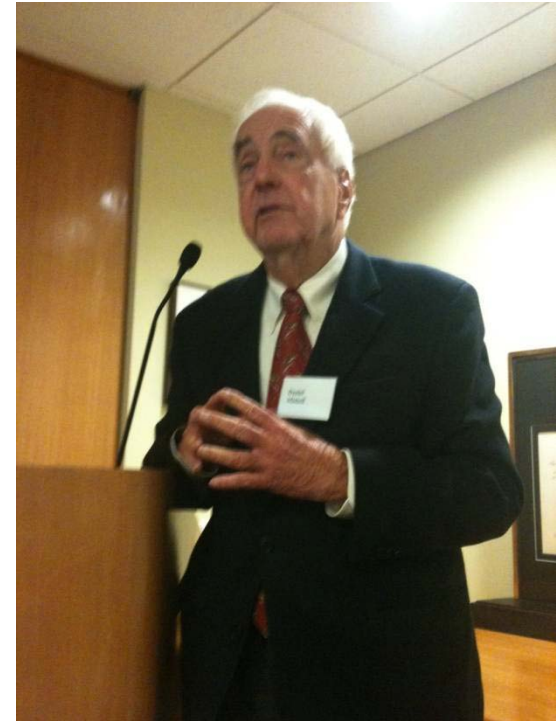
- Constant drug release resulting in steady blood levels of the minimum dose required.
- Increased bioavailability
 - lower doses and lower systemic exposure
 - achieving the same pharmacodynamic effect



Brache V. et al, 2001

History of development of CVR

- First clinical trial of contraceptive rings published by Dr. Dan Mishell in 1970.
 - *Mishell DR, Lumkin ME. Contraceptive effect of varying dosages of progestogen in silastic vaginal rings. Fertil Steril 1970; 21: 99-103.*



History of development of CVR

- International Committee for Contraception Research of the Population Council tested several ring prototypes
 - Progestin-only
 - Progesterone
 - Nestorone
 - Combined progestin with EE or E2
 - LNG/E2
 - NETAc/EE
 - NES/EE

History of development of CVR

- World Health Organization/HRP (1970's)

Levonorgestrel (20 mcg/day) progestin-only ring

One year discontinuation rates

- Pregnancy 4.5 %
- Menstrual problems 17.2 %

- Organon (1990's) NuvaRing

- ENG (etonogestrel 120 mcg) +
- EE (ethinyl-estradiol 15 mcg)

Progesterone Vaginal Ring: Progering® for breastfeeding women



- Initial trial conducted in Santiago, Chile by Croxatto and Diaz (1980's).
- Developed and manufactured in Chile with collaboration from the Population Council (Laboratorios Andromaco)
 - Diameter 56mm/9mm cross-section
 - Delivers 10mg/day over 3 months
 - Serum levels of 10-20 nmol/L
 - Approved in Chile, Peru, Ecuador, Bolivia, Guatemala, DR, Panama

Contraception during lactation

- Progesterone is a natural steroid
- Short-half life and extensively degraded after ingestion
- Low amount of progesterone excreted in milk is unlikely to affect the infant.
- Prolongs lactational amenorrhea

ICCR Multicenter Study in lactating women

Asia (5), Latin America (5), North Africa (1), USA (1)

	PVR	IUD
N of Women	802	734
Women-Years	431	533
Pregnancy Rate	1.5%	0.5%
Continuation Rate 6m	52.5	74.8
Continuation Rate 12m	23.5	34.5

Sivin I et al Contraception 1997

Phase III Clinical Trial Plan

Collaboration ICMR/Pop Council

- Primary objective: Confirm contraceptive efficacy and compare it to that of the CopperT 380A IUD in 20 centers in India (750 women in each arm)
- Secondary: Child development, safety, bleeding pattern, duration of lactational amenorrhea, acceptability (in both urban & rural settings)
 - GCP training in all centers
 - Plans for technology transfer

NES Vaginal Contraceptive Rings

ICCR/Population Council studies

- Advantages of Nestorone
 - 19-nor-progesterone derivative
 - No androgenic or estrogenic activity
 - Potent progestin-active at low doses
 - No effect on lipoproteins
 - Orally inactive-excellent for lactating women

Nestorone® vaginal rings

Antiovulatory effect

Dose delivered µg/d	50	75	100
% with luteal activity (P>10 nmol/L)	2.5	2.6	1.2

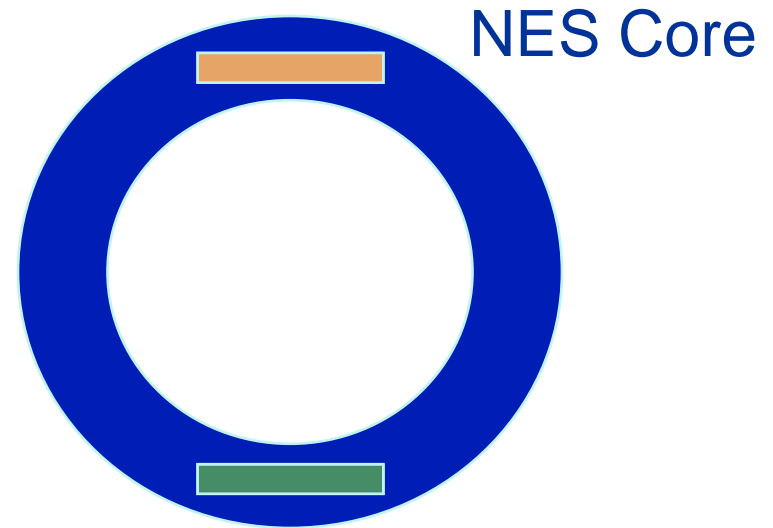
- Excellent inhibition of luteal activity
- Low pregnancy rate 0.0-2.1% in 6 months
- Bleeding irregularities

(Brache V et al Contraception 2001)

Combined contraceptive rings: progestins with estrogen

- Increases the contraceptive efficacy of the progestin by a synergistic effect on ovulation inhibition
- Good menstrual cycle control with regular withdrawal bleeding patterns.
- Maintains the endometrial development, and prevents breakthrough bleeding

Nestorone[®] / Ethinyl Estradiol 1-Year Ring (NES 150µg / EE 15 µg CVR)



13 cycles

3 weeks on followed by 1 week off

Developed by the Population Council

Sponsored by USAID, NICHD, WHO

8.4 mm (3/8") in cross section

58 mm (2 1/4") in diameter

NES/EE One-Year Vaginal Ring (pre-registration stage)

- Major milestone: two Phase III completed
 - 300A supported by NICHD
 - 15 NIH CCTN sites in the US
 - 300B- supported by USAID & WHO
 - 12 study sites
 - 3 in LA (Brazil, Chile, Dominican Republic)
 - 3 in Europe (Finland, Hungary, Sweden)
 - 1 in Australia
 - 5 in US (Bronx, Columbus, Chicago, Los Angeles, San Francisco)



The NES/EE CVR appears as an effective, convenient, easily-used new contraceptive method.

- Effective for one year
- User satisfaction high
- Medical risks & side effects similar to current combined hormonal contraceptives
- Same contraindications as COC's
- Expect to submit NDA in early 2014, in collaboration with licensing partner, Watson Pharmaceuticals.

NuvaRing[®] (Developed by Organon)

- Approved for contraceptive use by the FDA in October 2001
- Outer diameter: 54 mm
- Cross section: 4 mm
- Releases:
 - 15 ug/d EE
 - 120 ug/d ENG (etonogestrel)
- Ovulation inhibition: 98-99%
- Duration: 1 month (3 wk in/1 wk out)



NuvaRing: Contraceptive efficacy

Study	Method (n)	Pearl Index	95% CI
Roumen, 2001	NuvaRing (n=1145)	0.65	0.24-1.41
Dieben, 2002	NuvaRing (n= 1177)	1.75	0.98–2.89
Oddsson, 2005	NuvaRing (n = 512)	1.23	0.40–2.86
	150LNG/30EE COC (n = 518)	1.19	0.39–2.79
Ahrendt, 2006	NuvaRing (n=499)	0.25	0.01-1.36
	3DRSP/30EE (n=484)	0.99	0.27-2.53

NuvaRing clinical performance

- Excellent bleeding patterns (2.6-6.4% irregular bleeding)
- Higher incidence of vulvovaginal complaints and ring-related events (expulsions)
- Blood pressure: no significant change from baseline
- Minimal body weight increase: < 1 kg
- No change in bone mineral density

Roumen 2008, 2001, Dieben 2002

NuvaRing

- Adverse events: comparable between NuvaRing and COC
 - Headache 6.3-7.2
 - Breast tenderness 3.1-4.2
 - Nausea 0.8-2.7
- Similar compliance as COC
- Same potential adverse events as combined oral contraceptives



The future: next generation rings

- UPA-CVR (estrogen-free; PRM)
- NES/E2 rings
- Dual protection: microbicide and contraceptive

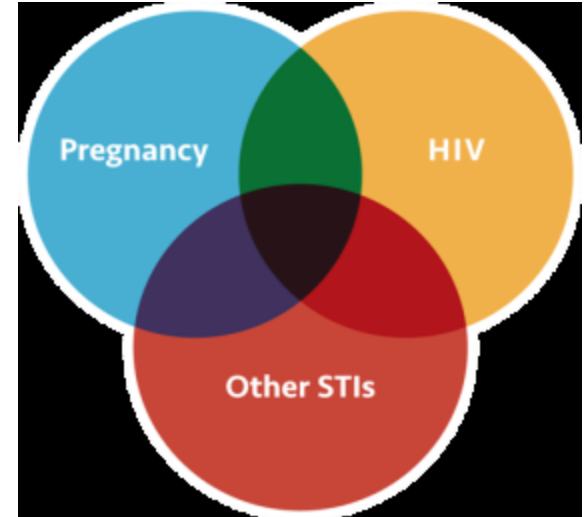
Next generation rings: NES/E2

- Target a safer contraceptive ring with “natural” estradiol combined with NES as a potent inhibitor of ovulation
- Potential for low risk of thrombosis
- NES 200 µg/d to block ovulation
- Use estradiol (and not EE) add-back therapy to prevent hypoestrogenism
- Continuous use for better compliance
- Phase IIa in collaboration CCTN of NICHD to start 2012

Multipurpose Prevention Technologies MPT

A woman at risk of unintended pregnancy due to unprotected intercourse is also at risk for HIV/STI/RTI

- Prevent unintended pregnancy
- Protect against HIV, & other STIs



USAID-supported MPT development activities, I: *Sustained-Release Combination Intravaginal Rings (IVRs)*

❖ **90-day Tenofovir + LNG IVR** (CONRAD)

- Combines the hormonal contraceptive LNG with the ARV tenofovir (TFV) in a polyurethane IVR.
- TFV is the only ARV shown thus far to be effective in preventing HIV (39%) and HSV-2 (51%).
- Clinical studies of TFV+LNG ring to begin 2012.



❖ **60-day Dapivirine + Contraceptive IVR** (IPM)

- Combines a hormonal contraceptive (tbd) with dapivirine in a vaginal ring (material tbd).
- Formulation work is underway.
- The current dapivirine-only ring will begin Phase III efficacy testing for HIV prevention in mid-2012.

Sustained Release Devices: Intravaginal Rings (IVRs), #2

- **MZL Combination IVR (Population Council)**
- **Combines**
 - MIV-150 (antiretroviral)
 - Zinc Acetate (antiviral agent with activity against HIV and HSV-2)
 - LNG (contraceptive).
- EVA or polyurethane ring material.
- Coitally independent; safe for sustained use.
- Continuous protection for more than 30 days.





Contraceptive Rings: Advantages

- Effectiveness
- Long-acting: constant low steroid release
- User-controlled, non provider-dependent
- Ease of use, no daily intake of a pill
- Non-coital related
- Good cycle control
- Expands contraceptive options

Contraceptive Rings

Unique opportunity

- Use of same technology and same route of administration for dual protection
- No longer would we have to say:
 - *This product does not protect against the transmission of sexually transmitted infections (STIs) including HIV, the virus that causes AID). Male latex condoms are considered the most effective means of protecting against STIs...*

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