Combined hormonal contraceptives CHC Session IV

Vaginal Ring CVR – Transdermal Patch CTP

Advanced slide kit complementing the WHO training tool www.fptraining.org

Update April 2022 Frans Roumen, Gabriele Merki

CHC Session IV

Vaginal Ring CVR – Transdermal Patch CTP

Unless expressly stated otherwise, all information given in this CHC session concerns

- the **vaginal ring with EE/ENG - Nuvaring®** and
- the **transdermal patch with EE/NGMN - Evra®**

Alternatives and new developments are discussed at the end of this session

Contents

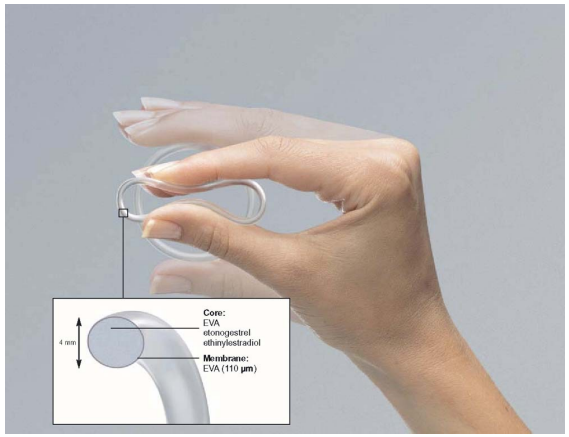
To enable teachers to understand and explain:

- Description and formulation; Mode of use
- Pharmacokinetics; Regimen of use
- Similarities ring, patch and pill; Advantages ring and patch > pill
- Contraceptive failure rates
- Dosing errors; Extended use
- Concurrent use
- Cycle control; Acceptability; Compliance; Side effects compared with pill
- Device-related problems; Acceptability ring vs patch
- Venous and arterial thromboembolism
- Counselling

Description and formulation

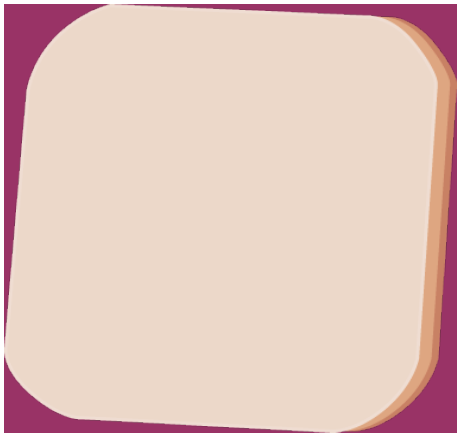
Vaginal ring

- Flexible, soft, latex-free ring, 54 mm in diameter, 4 mm in cross-section
- Contains 2.7 mg EE and 11.7 mg ENG (etonogestrel)



Transdermal patch

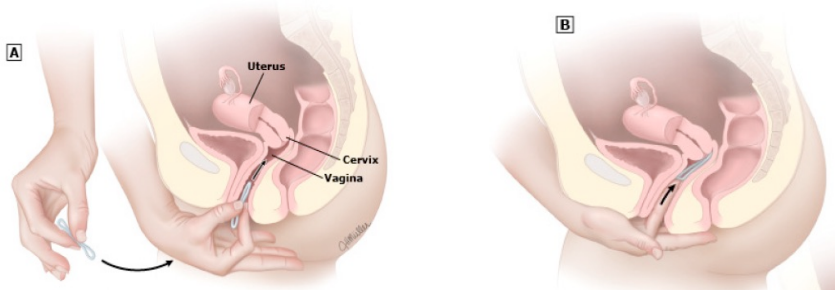
- Matrix system, 20 cm^2, 3 layers
- Middle layer contains 0.60 mg EE and 6 mg NGMN (norelgestromin) (in EU)



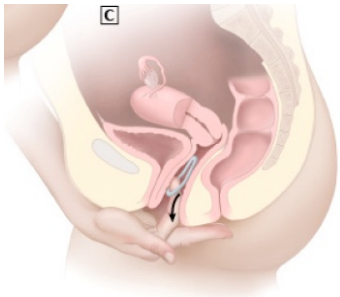
Mode of use

Vaginal ring

- The ring is inserted into the vagina as high as possible



The ring can be removed by hooking a finger in it



Transdermal patch

- Clean, dry, intact healthy skin
- Not on the breast
- Each time different site
- No lotions or occlusive dressings

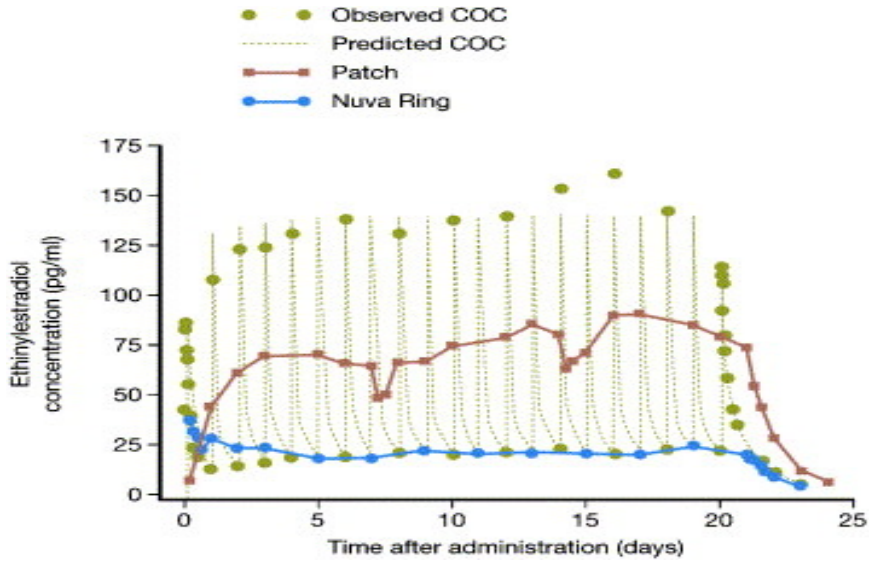
Pharmacokinetics

Vaginal ring

- Daily release 15 µg EE and 120 µg ENG
- Systemic EE exposure low (3.4x lower than with patch) (2.1x lower than with 30 µg pill)

Transdermal patch

- Daily release 35 µg EE and 200 µg NGMN
- Overall EE concentration ≈ 50 µg EE pill



Ref 1-5, Graph Ref 2

Regimen of use

Vaginal ring

- Start cycle day 1-5
- 3 weeks in, 1 week out
- Omitting hormone-free week is possible
- Extended use may result in unscheduled bleeding

Transdermal patch

- Start cycle day 1-5
- Once a week for 3 weeks, 1 week out
- Switch of 'patch change day' advised in patch-free week only
- Omitting hormone-free week not advised
- Extended use may result in headache, nausea, mastodynia, thrombosis (due to incremental EE levels)

Many properties of ring, patch and pill are essentially the same

- Combined hormonal method
- Systemic working mechanism
- Medical eligibility criteria (WHO)
- Recommendations for postpartum use (breastfeeding and non-breastfeeding)
- Effectiveness
- Non-contraceptive benefits and risks
- General contraindications
- Metabolic effects
- Recommendations for initiation, switching and need for back-up method
- Quick return of ovulation
- Follow-up rules

Advantages of ring and patch over the pill

- No enzymatic degradation in the gastrointestinal tract
- No first-pass hepatic metabolism
- Lower hormone doses needed (ring only, patch is higher)
- No daily peak and troughs of plasma hormone levels
- No need for daily self-administration
- No daily user compliance
- No difficulty swallowing pills

Contraceptive failure rates

Method	% of women experiencing an unintended pregnancy within first year	
	Typical use	Perfect use
No method	85	85
Spermicides	28	18
Condom male	18	2
Diaphragm	12	6
Combined pill	9	0.3
Evra Patch	9	0.3
NuvaRing	9	0.3
Progestin –only pill	9	0.3
Depo-Provera	6	0.2
Implanon	0.05	0.05
IUD Copper T380Ag*	0.3	0.3
IUD Mirena (LNG)*	0.2	0.2
Female sterilisation	0.5	0.5
Male sterilisation	0.15	0.1
*Source I.Sivin, Contraception 1990,; Vol.42NO 4.; adapted from Trussel Contraception 2011		

➢ Patch is less effective in women with body weight ≥90 kg!

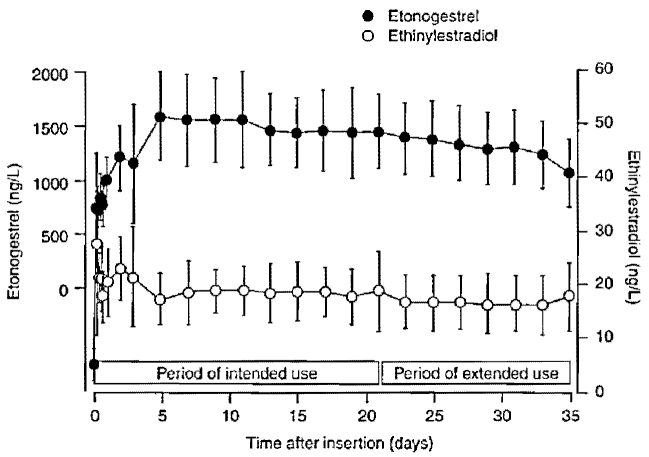
Recommendations for dosing errors ring and patch

- In case of extension of the ring- or patch-free week
- Or in case of unscheduled removal of the ring or detachment of the patch, you should:
  - apply a new device as soon as possible
  - keep the originally scheduled day for ring removal or patch change
  - If the error duration is ≤48 h: no additional contraception is needed
  - If the error duration is >48 h:
    - ✓ Apply 7 days additional contraception
    - ✓ And if unprotected sex took place
      - During previous 5 days in hormone-free interval:
        - ➢ Consider emergency contraception
      - On any day in week 1:
        - ➢ Consider emergency contraception
      - On any day in week 3:
        - ➢ Omit the ring- or patch-free week

Ref 1

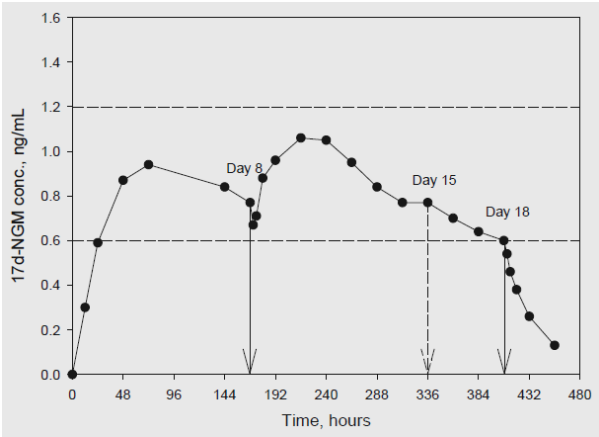
Rules for forgotten removal are different between ring and patch

Vaginal ring



- Up to 35 days: no additional contraception is needed
  - <28 days, ring-free week is possible
  - 28-35 days: no ring-free week possible

Transdermal patch



- Up to 2 days: no additional contraception is needed
- >2 days
  - Additional contraception is needed or avoid sex for 7 days, eventually Emergency Contraception
  - Keep same ‘patch change day’

Ref 1-4

Interactions with spermicide, tampons and drugs

(see also TTT-Tool on drug interactions)

Vaginal ring

- EE and ENG levels not altered by
  - Spermicide (nonoxynol-9)
  - Tampons
  - Antibiotics (amoxicillin, doxycyclin)
- EE and ENG levels increased by
  - Miconazole
- Lamotrigine levels
  - decreased

Transdermal patch

- EE and NGMN levels not altered by
  - Tetracycline
- Lamotrigine levels
  - decreased

Cycle control as compared with a 30µg EE pill

Vaginal ring

- Equivalent or superior
  - Less frequent spotting and breakthrough bleeding, especially in the first few months of use
  - Prolonged or frequent bleeding is less likely
  - Early or late withdrawal bleeding is less likely
  - Improved cycle control after switching from pill or patch
  - Superior cycle control in women with dysfunctional uterine bleeding

Transdermal patch

- Equivalent or inferior
  - Unscheduled bleeding common in first two cycles
  - After two cycles, similar pattern spotting and breakthrough bleeding
  - At six months, unscheduled bleeding declines and remains stable

Acceptability compared with pill

Vaginal ring

- In 4 studies satisfaction was higher than with the pill (OR 1.50: 95% CI 1.01-2.24)
- In 1 RCT satisfaction was comparable with the pill: 84% vs. 87% (30EE/3mgDRSP pill)
- Improvement of some aspects of psychosexual function (sexual fantasy, sexual interest, complicity, intercourse frequency) was reported in several RCTs, but decreased libido in another RCT

Transdermal patch

- In 1 RCT satisfaction was higher than with the pill (**20**EE/**150**NGMN patch vs. 20EE/150DSG pill) (OR 1.35: CI 1.09-1.68)

Higher acceptability ‘ring vs. patch’ in 1 RCT

- Continuation during 3 cycles
  - per protocol population: 94.6% vs. 88.2%, p=.03
  - Intention-to-treat population: 91.6% vs. 83.7%, p=.03
- Reasons for discontinuation
  - Ring: discomfort, adverse effects
  - Patch: adverse effects, skin irritation, problems with adherence
- Plan to continue method after 3 cycles: 71.0% vs. 26.5%, p<.001
- Adverse effects:
  - Ring: frequent vaginal discharge, bothersome with sex to user or partners
  - Patch: longer periods, increased dysmenorrhea, frequent nausea, frequent mood swings, frequent skin rash
- Device-related problems ‘at least once during any 3 week use period’
  - Ring was ‘expelled’ 20.4% vs. patch ‘fell off’ 46.0%, p<.001
- Satisfaction: 78% vs. 39%, p<.001

Ref 1

Compliance compared with pill

Vaginal ring

- Results in several non-randomized studies:
  - Adherence: 80%-90%
  - Discontinuation rate: 28%-35% within one year
  - Side effects as reason for discontinuation: 11%-30%
- Different results in randomised controlled trials:
  - in one RCT ring users less likely to discontinue (12% vs 22%)
  - no difference in another RCT
  - in a RCT using „quick start“: ring users less likely to discontinue (11% vs 16%)

Transdermal patch

- In 2 adequate and well-controlled comparative trials:
  - Adherence superior to the pill: 89% vs 79% (OR 2.05; CI 1.83-2.29)
  - Discontinuation rate higher (58% vs pill 47%) (OR 1.59; CI 1.26-2.00)
  - Side effects as reason for discontinuation higher (OR 2.28; CI 1.61-3.25)

Side effects compared with the pill

Vaginal ring	Transdermal patch

Systemic side effects are generally similar
No differences in headache or weight gain

Vaginal ring

- Breast tenderness and nausea less frequent
- Less acne compared with EE/LNG pill

Transdermal patch

- Breast tenderness (first two cycles), nausea, vomiting, and dysmenorrhea more frequent
- Less moodiness

Device-related problems

Vaginal ring

- Local vaginal symptoms
  - Vaginitis
  - Vaginal wetness
  - Vaginal discharge (17%)
  - No increased bacterial vaginosis
- Device related events including foreign body sensation, coital problems and expulsion
  - Europe 4.1%, 4.7%, 6.6%,
- Expulsion rates are quite different
  - Switzerland 1.7%
  - The Netherlands 6.0% (negative relation with ease of insertion)
  - USA 9% - 20%
  - Africa 14%
  - ➢ Advice: counsel women to check for the presence of the ring after coitus, a strenuous effort (e.g. at defaecation), or tampon removal
- During intercourse
  - 13%-16% of women chose to remove the ring
  - ➢ Advice: reinsert the ring within 3 hours

Transdermal patch

- Mild-to-moderate application site reactions
  - Skin reactions 14%-20%
  - Reason to stop treatment 2.6%
- Replacement of patch needed for
  - Complete detachment 1.8%
  - Partial detachment 2.9%

Same VTE risk for ring and patch

Risk of developing a blood clot (VTE) in a year in 10.000 women	
Women not using CHC pill / patch / ring	About 2 / 10.000
Women using a CHC containing ethinylestradiol/ levonorgestrel, norethisterone, norgestimate	About 5-8.9 / 10.000
Women using a CHC containing ethinylestradiol/ drospirenone, gestoden, desogestrel	About 9-12 / 10.000
Women using a CHC containing estradiol/nomegestrolacetate*	About 4.8 / 10.000
Women using a CHC containing estradiolvalerate/dienogest	About 7.7 / 10.000
Women using a CHC containing estetrol/drospirenone	Not yet known

Arterial thromboembolism

Vaginal ring

- No significant difference compared with two types of pills
  - 2.2 vs. 2.8 (2.5 resp.)/10.000 woman-years

Transdermal patch

- No significant difference compared with NGM pills
  - 13.6 vs. 11.3/100.000 woman-years

Microbial adhesion during vaginal ring use

- Vaginal rings may be important for protection of the vaginal microbiota during ring use. This is most likely attributed to the action of the estrogen on the vaginal flora.
- The status of the woman's vaginal microbiota and the formation or deposition of biomass on vaginal rings are inter-related.
- In one study (Ref 5), the adherence of C. albicans, as well as that of L. acidophilus when co-cultured with C. albicans, was lower with the Ornibel vaginal ring compared with NuvaRing.
- As SEM studies demonstrated no significant differences in measured surface roughness between unused Ornibel® and NuvaRing® devices, the difference in vinyl acetate content in the EVA polymer rate-controlling outer membranes of these rings (NuvaRing® 9% vs. Ornibel® 28%) is the more likely explanation for the differences in microbial adhesion.

Alternatives (or in development)

Vaginal ring

- Generics of Nuvaring
- EE/ENG ring (Ornibel®) (bioequivalent to Nuvaring in terms of efficacy, safety, tolerability and acceptability, but the new polymer composition is associated with more stability and gradual hormonal release during the first day of use, particularly for EE)
- E_2/ENG rings (in development)
- E_2/NOMAC rings (in development)
- EE/SA (segesterone acetate) ring (Annovera®) (approved by the FDA for women with BMI < 29 kg/m^2 and now available in the U.S.)

Transdermal patch

- EE/LNG patch (Twirla®) (2.3-mg EE and 2.6-mg levonorgestrel, approved by the FDA for women with BMI <30 kg/m^2, providing a steady-state EE level equal to that with 30-µg EE containing oral pills)
- EE/GSD patch (in development)

Ref 1-6

Counselling aspects

Vaginal ring

- Highly effective, reversible, non-coitally-dependent method of contraception
- Use only in case of no contraindications to estrogen or progestins
- Good candidates are women with pill aversion, frequently forgetting pill, with gastrointestinal problems, and adolescents with their irregular lives

Contraindications:

- Genital problems such as pelvic organ prolapse or genital touch taboo

Advantages:

- Lower estrogen exposure
- Better cycle control
- Extended regimen possible

Transdermal patch

- Highly effective, reversible, non-coitally-dependent method of contraception
- Use only in case of no contraindications to estrogen or progestins
- Good candidates are women with pill aversion, frequently forgetting pill, with gastrointestinal problems, and adolescents with their irregular lives

Contraindications:

- Dermatological problems
- Overweight women
- Diabetic women

Disadvantage:

- Extended regimen not advised

Ref 1, 2