

South African National Essential Medicine List
Primary Health Care Medication Review Process
Component: Family planning

MEDICINE REVIEW:

1. Executive Summary

Date: 26 August 2020 (Update of August 2019 review)
Medicine (INN): Vaginal contraceptive ring with progesterone and estrogen
Medicine (ATC): G02BB01
Indication (ICD10 code): Contraception (Z30.0/Z30.4/Z30.8)
Patient population: Women of childbearing potential (WOCP)
Prevalence of condition: n/a - This is for prevention of pregnancy
Level of Care: Primary health care
Prescriber Level: Primary health care nurse prescriber
Current standard of Care: Oral contraception containing progesterone and estrogen
Efficacy estimates: (preferably NNT):
Motivator/reviewer name(s): GS Gebhardt
PTC affiliation: GS Gebhardt: Tygerberg Hospital, Western Cape; K Cohen: WC Provincial PTC

2. Name of author(s)/motivator(s):

Primary reviewer: Prof GS Gebhardt
Secondary reviewer: Prof K Cohen
Support: Ms TD Leong

3. Author affiliation and conflict of interest details:

- Prof GS Gebhardt: Stellenbosch University and Tygerberg Hospital, Adult Hospital Level Committee (2017-2020); No conflicts of interest to declare.
- Prof K Cohen: University of Cape Town: Division of Clinical Pharmacology, Department of Medicine; National Essential Medicines List Committee (2017-2020); No conflicts of interest to declare.
- Ms TD Leong: Essential Drugs Programme, National Department of Health; Secretariat to the Primary Health Care and Adult Hospital Level Expert Review Committees; No conflicts of interest to declare.

4. Introduction/ Background:

The currently available SAHPRA registered contraceptive vaginal ring is a polymeric vaginal ring containing 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol, which releases on average 0.12 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol. One ring is inserted in the vagina where it remains continuously for three weeks, followed by a one-week ring-free interval. The contra-indications are the same as for the oral contraceptive combination pill (COC). It has the advantage over intra-uterine devices of self-insertion; and a once a month schedule as compared to daily administration of the COC. It has to be stored refrigerated (2-8 degrees Celsius) but has a shelf life of 4 months after dispensing outside of a refrigerator (however, it must not be exposed to temperatures above 30 degrees, which could limit its distribution in rural areas).

A literature search was undertaken to evaluate the efficacy and tolerability (side-effects profile) and compliance of the combined contraceptive vaginal ring compared with combined oral hormonal contraceptives evidence. It is obvious that none of the studies would be able to reduce bias using blinding given the characteristics of the intervention (oral administration of a contraceptive or insertion of a vaginal ring).

PICO Question:

Population	Individuals of reproductive age
Intervention	Hormonal contraceptive vaginal ring containing progesterone and estrogen
Comparison	Oral contraception containing progesterone and estrogen
Outcomes	Efficacy – prevention of pregnancy Safety – weight gain, bleeding patterns, HIV acquisition, other adverse events

5. Methods:

a. Data sources: PubMed, ScienceDirect, EMBASE, Cochrane library

b. Search strategy A: Search details were ("contraceptive agents"[Pharmacological Action] OR "contraceptive devices"[MeSH Terms] OR ("contraceptive"[All Fields] AND "devices"[All Fields]) OR "contraceptive devices"[All Fields] OR "contraceptive"[All Fields] OR "contraceptive agents"[MeSH Terms] OR ("contraceptive"[All Fields] AND "agents"[All Fields]) OR "contraceptive agents"[All Fields]) AND ("vagina"[MeSH Terms] OR "vagina"[All Fields] OR "vaginal"[All Fields]) AND ring[All Fields] AND ("oestrogen"[All Fields] OR "estrogens"[Pharmacological Action] OR "estrogens"[MeSH Terms] OR "estrogens"[All Fields] OR "estrogen"[All Fields]) AND ("progesterone"[MeSH Terms] OR "progesterone"[All Fields])

91 Studies were retrieved, all articles excluded as content was not relevant to the PICO question.

Search strategy B (Cochrane Library): Vaginal ring in Title Abstract Keyword AND "contraception" in Title Abstract Keyword - in Cochrane Reviews (Word variations have been searched).

11 reviews retrieved, 9 excluded as not related to PICO question and 2 reviewed – Lopez et al, 2013; Krashin et al, 2015 (see below).

Additionally, GS hand-searched reference lists of identified articles for further citations of interest and for efficacy only studies designed with efficacy as the outcome/primary outcome were considered. Where individual studies were already included in systematic reviews, only results from the systematic reviews are given. Newer studies published after the systematic reviews are reviewed separately.

c. Evidence synthesis

Systematic reviews:

1. A systematic review in the Cochrane library (*Hormonal and intrauterine methods for contraception for women aged 25 years and younger* (1)) includes a single randomized, crossover trial comparing COC with the vaginal ring. This was only published as a conference abstract and the Cochrane reviewers obtained data directly from the author. There were 67 women in the COC (of which nine became pregnant) and 63 in the ring group (of which four became pregnant). The continuation rates were the same and there were no statistical differences.
2. A second Cochrane review deals with *Skin patch and vaginal ring versus combined oral contraceptives for contraception*.(2) There are 18 trials included (11 dealing with the combination vaginal ring) and was updated in 2013. The main findings are:

- a. Contraceptive effectiveness was not significantly different for the vaginal ring in comparison to COCs in the eight trials that reported on pregnancy.
 - b. Vaginitis was reported more frequently by the ring users (OR 2.48; 95% CI 1.39 to 4.43)
 - c. The ring users appeared more satisfied with their method than the COC users (MD 0.70; 95% CI 0.37 to 1.03).
 - d. Ring users had less acne (OR 0.18, 95% CI 0.06-0.54) than COC.
 - e. Emotional liability were less for ring users (OR 0.19, 95%CI 0.06-0.59) than COC.
 - f. Spotting and breakthrough bleeding were less common among ring users (OR 0.34 (95% CI 0.12 to 0.94)
 - g. No differences in any of the other aspects compared in the meta-analysis.
3. A 2017 systematic review with meta-analysis includes 14 randomised trials and assess the efficacy and tolerability (side-effects profile), and compliance of the combined contraceptive vaginal ring compared with combined oral hormonal contraceptives. (3) The study was conducted using the Cochrane risk of bias tool, the PRISMA statement is included as an appendix and they followed all the standards of the Cochrane collaboration. Due to the different routes of administration, a lack of blinding was not considered to be a reason to downgrade the quality of the study.

The main findings are:

- a. A trend to higher efficacy for the ring in preventing pregnancy (OR: 0.52 [95% CI: 0.26–1.04])
 - b. A significantly lower presence of nausea in ring users (OR: 0.66 [95% CI: 0.46–0.93]).
 - c. More women were compliant in the ring group (OR: 1.22 [95% CI: 1.12–1.32])
 - d. Fewer women reported breakthrough bleeding on the ring (OR: 0.68 [95% CI: 0.51–0.91])
4. There were no other systematic reviews identified that compared COC and rings as contraceptive methods. The randomised trials published after the 2017 systematic review will be discussed below.
- a. Efficacy and safety of the contraceptive vaginal ring compared with a combined oral contraceptive in Chinese women: a 1-year randomised trial (4). The ring (n=732) was compared with a monophasic COC (n=214) containing 30 µg EE and 3mg drospirenone. This was a phase III, open-label randomised trial in Chinese women. This study was industry sponsored. The Pearl index (PI) compared as follows: Vaginal ring PI 1.92; 95% CI 0.92 to 3.53 and COC group PI 3.12; 95% CI 1.01 to 7.29. There were no significant differences in side effect profiles.
 - b. A randomised trial in Rwanda comparing cyclical ring use to continuous ring use is not applicable to the current research question, but a qualitative analysis from this randomized trial showed that acceptability of the vaginal ring was high among study participants and represents a promising option that could contribute to lowering the unmet need for family planning in lower-middle income countries.(5)
6. **Conclusion:** In summary, the vaginal ring is as efficacious as the COC, with less side effects. It is a suitable alternative option for birth spacing. In terms of efficacy, there were 11 pregnancies reported amongst 1165 users of the ring (0.94%) and 22 pregnancies in 1241 COC users (1.77%). Most of the studies reported on women between 15-42 years of age. None of the studies reported on HIV acquisition.

The reported estimated first year pregnancy rate, measured in a cohort of USA women, was reported to be comparable between vaginal ring vs combined oral contraceptive users. (6)

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS																														
QUALITY OF EVIDENCE	<p>What is the overall confidence in the evidence of effectiveness?</p> <p>Confident Not confident Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	Systematic review of RCT and clinical trial data – see above																														
BENEFITS & HARMES	<p>Do the desirable effects outweigh the undesirable effects?</p> <p>Benefits outweigh harms Harms outweigh benefits Benefits = harms or Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	Benefits outweigh potential harms – see above																														
THERAPEUTIC INTERCHANGE	<p>Therapeutic alternatives available:</p> <p>Yes No</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/></p> <p>All other <i>available</i> contraceptive modalities, as women’s choice is a prerogative.</p> <p>List the members of the group: n/a</p>	Rationale for therapeutic alternatives included: Contraception choice is an option for all women.																														
VALUES & PREFERENCES / ACCEPTABILITY	<p>Is there important uncertainty or variability about how much people value the options?</p> <p>Minor Major Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p> <p>Is the option acceptable to key stakeholders?</p> <p>Yes No Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p>	Systematic review and narrative synthesis by Griffin et al (2019) ⁷ suggests that that most LMIC women users consider the contraceptive vaginal ring to be an acceptable contraceptive option and that familiarity increases with use. In addition, many of the women considered the vaginal ring delivery device acceptable for HIV prevention or other indications.																														
RESOURCE USE	<p>How large are the resource requirements?</p> <p>More intensive Less intensive Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p>	<p>Price of family planning agents/ month (28 days):</p> <table border="1"> <thead> <tr> <th>Family planning agent</th> <th>Pack size Price (ZAR)</th> <th>Price/ 28 days (ZAR)</th> </tr> </thead> <tbody> <tr> <td>Etonorgestrel 11.70mg/ethinyl estradiol 2.7mg vaginal contraceptive ring (100% of SEP*)</td> <td>170.11</td> <td>170.11</td> </tr> <tr> <td>Etonorgestrel 11.70mg/ethinyl estradiol 2.7mg vaginal contraceptive ring (60% of SEP*)</td> <td>102.07</td> <td>102.07</td> </tr> <tr> <td>Copper IUCD</td> <td>159,99**</td> <td>2,45</td> </tr> <tr> <td>Levonorgestrel/ethinyl estradiol, triphasic tablets</td> <td>6,28**</td> <td>6,28</td> </tr> <tr> <td>Levonorgestrel tablets</td> <td>3,03**</td> <td>3,03</td> </tr> <tr> <td>Levonorgestrel/ethinyl estradiol, monophasic tablets</td> <td>2,90**</td> <td>2,90</td> </tr> <tr> <td>Norethisterone enanthate injectionl</td> <td>24,01**</td> <td>12,01</td> </tr> <tr> <td>Etonogestrel implant</td> <td>224,58**</td> <td>5,74</td> </tr> <tr> <td>DMPA injection</td> <td>15,40**</td> <td>5,13</td> </tr> </tbody> </table> <p>* SEP database, March 2020, https://mpr.code4sa.org/ **Contract circulars RT283-2017, HP03-2017CHM/01</p> <p>Additional resources: n/a</p>	Family planning agent	Pack size Price (ZAR)	Price/ 28 days (ZAR)	Etonorgestrel 11.70mg/ethinyl estradiol 2.7mg vaginal contraceptive ring (100% of SEP*)	170.11	170.11	Etonorgestrel 11.70mg/ethinyl estradiol 2.7mg vaginal contraceptive ring (60% of SEP*)	102.07	102.07	Copper IUCD	159,99**	2,45	Levonorgestrel/ethinyl estradiol, triphasic tablets	6,28**	6,28	Levonorgestrel tablets	3,03**	3,03	Levonorgestrel/ethinyl estradiol, monophasic tablets	2,90**	2,90	Norethisterone enanthate injectionl	24,01**	12,01	Etonogestrel implant	224,58**	5,74	DMPA injection	15,40**	5,13
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EQUITY	<p>Would there be an impact on health inequity?</p> <p>Yes No Uncertain</p> <p><input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/></p>																															
FEASIBILITY	<p>Is the implementation of this recommendation feasible?</p> <p>Yes No Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>																															

Type of recommendation <input checked="" type="checkbox"/>	We recommend against the option and for the alternative <input type="checkbox"/>	We suggest not to use the option or to use the alternative <input type="checkbox"/>	We suggest using either the option or the alternative <input type="checkbox"/>	We suggest using the option <input type="checkbox"/>	We recommend the option <input type="checkbox"/>
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Recommendation: Based on the evidence reviewed, the Adult Hospital Level Committee recommends that the vaginal contraceptive ring be considered as an additional contraceptive option for women.

Rationale: The vaginal ring has been shown to be as efficacious as the COC, with less side effects. It is an ideal alternative option for birth spacing. However, acceptability amongst South African women is unknown, and this agent is currently cost prohibitive for inclusion on the EML.

Level of Evidence: I Systematic review, RCT of moderate quality

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

VEN status:

Vital	Essential	Necessary
<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

NEMLC MEETING OF 5 DECEMBER 2019:

NEMLC accepted the proposal as recommended by the Adult Hospital Level Committee, noting that the etonorgestrel 11.70mg/ethinyl estradiol 2.7mg vaginal contraceptive ring is currently unaffordable.

Monitoring and evaluation considerations

Research priorities

- Feasibility of self administration
- Long term safety profile
- Local acceptability study

References

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