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Review article

Safety of the progesterone-releasing vaginal ring (PVR) among lactating women: A systematic review☆

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Abstract

Context: Lactation causes a delay in ovulation in the postpartum period, and therefore a delay in the resumption of menses. However, return to fertility is variable in the postpartum period and is contingent upon numerous factors. The postpartum period is therefore a critical time to initiate effective contraception in order to support the numerous beneficial health outcomes of optimal pregnancy spacing. Breastfeeding women have an unmet need for highly effective birth control methods that do not interfere with lactation and that are safe for their infants. The progesterone-releasing vaginal ring (PVR) releases a natural progesterone that suppresses ovulation and is specifically designed for breastfeeding women in the first postpartum year.

Objective: To review the published peer-reviewed literature regarding the safety and effectiveness of the PVR used for contraception among lactating women, as well as the safety for their infants. Results of this review informed the decisions of the Guideline Development Group to include recommendations on contraceptive eligibility for the PVR within the *World Health Organization Medical Eligibility Criteria for Contraceptive Use, 5th Edition*.

Methods: We searched the PubMed, Popline, and LILACS bibliographic databases for articles published in any language from database inception through October 1, 2014. We reviewed the literature for evidence regarding the safety of the PVR among breastfeeding women using the method, as well as for their infants. The US Preventive Services Task Force system was applied to assess the quality of the evidence.

Results: Seven articles met our criteria for inclusion in this review. All studies were of a prospective cohort design. All studies consistently showed that use of the PVR among breastfeeding women compares favorably to other methods of contraception with regard to effectiveness, does not compromise a woman's breastfeeding performance, and does not adversely affect infant growth during the first year postpartum.

Conclusion: The PVR is a safe and highly effective method of contraception for use among breastfeeding women. It should be offered to women who plan to breastfeed in the context of postpartum contraceptive counseling.

Keywords: Progesterone vaginal ring; Lactation; Breastfeeding; Contraception

1. Introduction

Worldwide, postpartum women represent a large proportion of women who have an unmet need for family planning services. Failure to meet the contraceptive needs of these women results in adverse outcomes for women, their infants, and their families. Recognizing the imperative to reach women in the postpartum period, the 2012 London Summit on Family Planning included a prioritization on expanding services and methods to this vulnerable population [1,2].

Lactational amenorrhea (LAM) is one method of contraception available to those women who choose to breastfeed. In addition to a host of well-documented maternal and child health benefits, LAM is approximately 98% effective in preventing pregnancy, provided that women adhere to three criteria: (1) menstruation has not resumed, (2) the infant is fully or nearly fully breastfeeding, and (3) the infant is less than 6 months of age [3]. While this method is safe and effective, LAM offers only short-term protection against unplanned pregnancy. At any time a

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woman no longer meets criteria or no longer wishes to rely on LAM for contraception, transition to other effective methods is key to preventing unintended pregnancy during the postpartum period. Many women discontinue fully breastfeeding before 6 weeks postpartum and will be at risk for rapid repeat pregnancy [4], even though the majority of women do not wish to conceive again during their first postpartum year [5]. In addition, multinational survey data from developing countries reveal that breastfeeding and/or postpartum amenorrhea are cited as a primary reasons for not using a contraceptive method [6]. Therefore, it is critical to provide women with options for early initiation of contraception in the postpartum period to prevent unplanned and rapid repeat pregnancies.

The progesterone-releasing vaginal ring (PVR) is a contraceptive device that was specifically designed for use among breastfeeding women in order to expand the method mix for this population. Safety and efficacy trials have been carried out in Latin America where it is approved and currently in use in nine countries [7]. The device is manufactured in Chile under the trade name "Progering®". The silicone-elastomer ring has a cross-sectional diameter of 8.4 mm, has an overall diameter of 58 mm, and contains micronized progesterone (P) that is released at an average rate of 10 mg/day over a 90-day period. The ring is designed for 6 months continuous use for women breastfeeding at least four times per day, with infrequent removal approved for 2 h maximum. The non-oral delivery system of the PVR allows for a sustained release of micronized P at levels sufficient to inhibit ovulation and extend the period of lactational amenorrhea [7,8]. During proper use, an average plasma concentration of 20 nmol/L is achieved, which is similar to that detected in the average luteal phase among normally ovulating women. The critical P threshold required to inhibit ovulation during breastfeeding is 10 nmol/L [9]. In a phase 2 clinical trial that assessed extending use of the PVR to 4 months, mean P levels decreased from 17±1 to 14±1 nmol/L (mean± S.E.), still within the range to inhibit ovulation [10]. With regard to infant exposure to P via the breast milk of mothers who use the PVR, ingestion of 600 mL of breast milk per day will expose infants to approximately 4.2 mcg of P [11,12]. This amount is well below the recommended maximum intake of 150 mcg/day as per the European Medicines Agency [13]. In addition, P is rapidly degraded after ingestion and has a very short half-life of 3–90 min, thus conferring additional reassurance of lack of exposure to exogenous hormones for infants whose mothers use the PVR [13].

The World Health Organization (WHO) convened meetings of its Guideline Development Group (GDG) during March 9–12, 2014 and September 24–25, 2014. The purpose of these meetings was to review and, where appropriate, revise specific evidence-based recommendations included in the *WHO Medical Eligibility Criteria (MEC) for Contraceptive Use*. The GDG consisted of 62 participants from 25 countries including experts in international family planning and HIV, clinicians, epidemiologists, researchers, program managers, policymakers, guideline methodologists, reproductive biologists, and pharmacologists. In order to consider eligibility for inclusion of the PVR in the fifth edition of the MEC guidelines, we conducted this systematic review of the evidence regarding the safety and efficacy of the PVR for use among breastfeeding women.

2. Methods

We searched the PubMed, Popline, and LILACS bibliographic databases for articles published in peer-reviewed journals in any language from database inception through October 1, 2014 for evidence reporting data addressing the safety of PVR use among breastfeeding women. The following search terms were applied: "Progesterone"[Mesh] AND "Contraceptive Devices, Female"[Mesh] for PubMed; Progesterone, vaginal rings, safety for Popline; and anillo vaginal, Progestina, and Progesterona for LILACS. In addition, a search of the International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/) was performed to identify completed and ongoing trials investigating the safety of PVRs for women who are breastfeeding. Reference lists from articles identified by the search, as well as key review articles, were hand-searched to identify additional articles.

2.1. Study selection

We reviewed titles as well as abstracts to identify primary reports of studies investigating the safety of PVR use among breastfeeding women of any age or parity. Specifically, we sought to answer the following key question: Among breastfeeding women and their infants, does the use of the PVR, compared with non-use of progestogen-only contraceptive methods, affect maternal health, breastfeeding performance, and infant health? Articles reporting outcomes related to safety, breastfeeding performance (e.g. duration of lactation, continuation, supplementation), infant health (e.g. growth, development, or adverse health events), as well as contraceptive effectiveness were selected for inclusion in this review. In addition, studies reporting on these outcomes among women using the PVR with medical conditions or characteristics currently included in the MEC were of interest. Unpublished studies, conference presentations, review articles, commentaries, and dissertations were excluded. Articles addressing combined estrogen–progestogen vaginal rings or dosing patterns that differed from the current 3-month PVR labeling instructions were excluded.

2.2. Study quality assessment

The quality of each individual piece of evidence was assessed using the United States Prevention Task Force grading system [14]. Evaluation criteria included the following: type of study design; sample size and representativeness; maintenance of comparable groups; extent of loss to follow-up; completeness of outcome measurement; and adjustment for confounders.

2.3. Data synthesis

Two authors (MG and SC) participated in summarizing and systematically assessing the evidence through the use of standard abstract forms [15]. Results from the seven articles included in this review are presented in Table 1. We did not compute summary measures of associations due to heterogeneity across study designs, study populations, outcome measures collected, and attrition rates within groups across the studies.

3. Results

Our search strategy identified 679 articles. Following a review of titles and abstracts, or a full article when necessary, seven articles satisfied the review inclusion criteria [16–22]. Studies were excluded primarily because either breastfeeding women were not included in the study populations or the investigations focused on progestogen-only contraceptive methods but did not address PVRs.

All seven studies applied a prospective cohort design; no randomized controlled trials were identified. Each study enrolled healthy, fully breastfeeding volunteers between the ages of 18 and 38 years who delivered healthy singletons. Contraception initiation ranged from 5 to 9 weeks postpartum. Follow-up of women and their infants varied; three studies followed them through 12 months post-initiation of the chosen contraceptive method [18,20,21], three studies followed them through 12 months postpartum [16,17,19], and one study followed them through 12 months after weaning [22]. Four studies presented comparisons on outcomes between women who self-selected to use either the PVR or the copper-containing intrauterine device (Cu-IUD) [16,18,20,21]. The remaining three studies compared PVR users with women who elected to use the Cu-IUD, the six-rod levonorgestrel subdermal implant (LNG implant), LAM, or progestogen-only pills (POPs) [17,19,22]. Four of the seven studies were conducted in public sector clinics in Latin America [16,19,21,22].

All seven studies reported on pregnancy outcomes, infant weight gain, and method discontinuation/continuation. Six studies examined lactation performance and occurrence of side effects and/or adverse events such as device expulsion. Four studies investigated bleeding patterns. One study specifically assessed measures of bone metabolism and bone density during breastfeeding and 6–12 months after weaning. With respect to the various conditions or characteristics published within the MEC, all seven studies reported evidence for the condition, “breastfeeding”, and one study provided evidence on measures of bone health for the age subcategory of 18–35 years.

3.1. Contraceptive effectiveness

Two studies reported no pregnancies during 12 months of follow-up among women who chose to use either the PVR or Cu-IUD [20,21]. Similarly, another study reported no pregnancies among PVR or Cu-IUD users at 12 months; however, 50 pregnancies occurred among women in this study who elected other contraceptive methods (2 among POP users and 48 among users who initially elected LAM, respectively) [19]. The remaining four studies observed one pregnancy in the PVR group compared with none observed among either Cu-IUD users [16,18,22] or LNG implant users [22]. Two studies recorded pregnancy rates at 12 months among PVR volunteers of 1.5/100 [18] and 3.5/100 [22]. One pregnancy was observed during 739 woman-months of exposure in one of the studies [16] and 1007 woman-months of exposure in another study [17].

3.2. Breastfeeding performance

Among six studies evaluating the effect of PVR use on various measures of breastfeeding performance in comparison with women using nonhormonal contraception or other types of progestogen-only contraception (depending upon the particular study design), no significant differences were reported. Three studies examined duration of lactation among Chilean women using the following: the PVR, Cu-IUD, or LNG implant [22]; PVR, Cu-IUD, POPs, and LAM [18]; and PVR and Cu-IUD [16]. No significant differences in lactation duration were recorded in any of these studies. Similarly, two studies found no difference in the proportion of women who were fully breastfeeding at either 6 months postpartum among PVR, Cu-IUD, or LNG implant users [22] or 14 months post-recruitment among PVR and Cu-IUD users [21]. Two studies examined whether differences in the number of breastfeeding episodes occurred among PVR users compared with women using other contraceptive methods. In general, no significant differences were noted at 12 months follow-up between PVR and Cu-IUD users enrolled in a large multicountry study; however, PVR users reported a slightly higher number of breastfeeding episodes per day compared with Cu-IUD users at 183 days postpartum (8.3 vs. 7.9, respectively; $p<.05$) [18]. The other study that assessed the number of breastfeeding episodes did not show any significant differences between PVR and Cu-IUD users at 14 months postpartum [21]. Lastly, no differences on the introduction of supplementary foods were observed among women using the PVR or Cu-IUD in a study conducted in Egypt [17].

3.3. Infant health

All seven studies included in this review monitored infant weight gain during study follow-up. Weight gain, either absolute or average, did not differ among infants whose mothers used the PVR compared with infants whose mothers used nonhormonal contraceptives or other progestogen-only methods across three studies conducted in Chilean health centers [16,21,22]. Moreover, no statistically significant differences in infant weight gain were observed among PVR users compared with women using a Cu-IUD [17,19,20], an

Table 1
Evidence for the progesterone-releasing vaginal ring.

Author year, source of support, location	Study design	Outcome measures	Results	Strengths/weaknesses	Quality
Diaz S, 1999 Population Council Chile	Prospective cohort study LNG implant (*N*=36) PVR (*N*=36) Cu-IUD (*N*=57) Initiated 57±3 days postpartum Lactating, 18–35 years, normal vaginal delivery of healthy singleton 38–40 weeks Bone evaluation at 1, 6, 12 months postpartum and 6 (PVR), 12 (LNG implant, Cu-IUD) months after weaning	Pregnancy Lactation performance: duration Infant health: weight Bone density (dual-energy X-ray absorptiometry) Biochemical measures of endocrine function and nutritional status	One pregnancy in PVR group (1/28), no pregnancies in Cu-IUD (0/48), or LNG implant (0/24) groups. Significant differences in mean months of LAM between PVR and LNG implant vs. Cu-IUD (12, 12, and 7 months, respectively). No difference in mean infant weight at months 1, 6, and 12 months; % fully breastfeeding at 6 months. No difference in any bone density measures after contraceptive initiation; lumbar spine significantly lower at 1 month postpartum in all groups vs. nonbreastfeeding women ($p<.05$), no difference after weaning. Biochemical values similar across three groups; borderline significant difference in parathyroid hormone between LNG implant vs. PVR and Cu-IUD ($p=.047$). Bone metabolism did not differ between groups, except alkaline phosphatases were lower in PVR vs. Cu-IUD at 6 months.	Strengths: Detailed clinical and biochemical measures collected Weaknesses: Few measures of infant health Limited information on method use 16% loss to follow-up Small sample size PVR group 78% (*N*=22) using other methods at postweaning bone density measurement.	II-2, fair
Massai R, 1999 USAID Chile	Prospective cohort; pharmacokinetic study and clinical trial PVR (*N*=285) Cu-IUD (*N*=262) Initiated 5–9 weeks postpartum Follow-up at 1, 3, 6, 9, 12 months postmethod initiation, until weaning, or use of 4 rings Lactating, 18–38 years, normal vaginal delivery of healthy singleton 38–40 weeks	Pregnancy Lactation performance: nursing frequency Infant health: weight Adverse events: colposcopic vaginal epithelium evaluation: PVR=45, Cu-IUD=54. Method continuation	No pregnancies observed over 2320 women-months exposure (PVR); 2183 women-months exposure (Cu-IUD). No differences between groups for % fully breastfeeding or number of breastfeeding episodes at 14 months. LAM mean duration: PVR=361±9 days vs. Cu-IUD=198±8 days ($p<.01$). No significant differences in monthly infant weight or mean weight increases between groups. Vaginal complaints, urinary discomfort, urinary infections higher in PVR group ($p=.005$); low abdominal pain and menstrual problems higher in Cu-IUD group ($p<.01$); cervical intraepithelial neoplasia stage 1 (HPV) in 3 PVR users. Minor vaginal alterations in 8/45 PVR users and 2/54 Cu-IUD users. PVR: vaginal abrasions (*n*=2); one women	Strengths: Low loss to follow-up (3%), nondifferential by method Weaknesses: Timing of initiation of method varied among volunteers Self-reported bleeding, nursing outcomes Differential continuation rates, differential loss to follow-up within groups Mean weight significantly higher among PVR users compared with Cu-IUD users (62.6±9 kg vs. 60.2±8 kg)	II-2, fair

			with small asymptomatic abrasion, one women had extended area abrasion that regressed with ring removal and normal after 3 months; 6 women had minor abrasions. Cu-IUD: one woman with hyperemia at 6 months, one woman with petechiae at study discontinuation Continuation significantly lower in PVR group at 3, 6 months (86.7% vs. 95%, 66.8% vs. 78.5%), p=.001; NS at 9 months. Reasons for discontinuation: method use problems (26.8% PVR vs. 2.3% Cu-IUD), p=.001; loss to follow-up (5.2% PVR vs. 16.2% Cu-IUD), p=.0004; personal (10.1% PVR vs. 2.2% Cu-IUD), (p=.004)		
Chen JH, 1998 Population Council China	Prospective cohort study PVR (*N*=100) Cu-IUD (*N*=97) Initiated 29–64 days postpartum Follow-up at 1, 3, 6, 9, 12 months postmethod initiation (clinic or home) Lactating, 18–35 years, normal delivery of healthy singleton 38–40 weeks	Pregnancy Infant health: weight Method continuation Adverse events	Pregnancy: none in Cu-IUD or PVR groups at 12 months. No difference in infant weight gain between groups. Discontinuation: PVR=65.4/100 women/years, *N*=54; Cu-IUD=2.3/100 women-years, *N*=2. Reasons for discontinuation PVR: menstrual problems *N*=3; vaginal problems (increased discharge or vaginitis) *N*=10; expulsion *N*=7; ring out ≥48 h *N*=12; unpleasant ring use *N*=13; other medical reasons *N*=5. Complaints higher at all follow-up visits among PVR vs. Cu-IUD users; significantly higher at 1, 3, 6 months. Mean B/S episodes and B/S days: significantly lower for PVR vs. Cu-IUD for all follow-up periods (p≤.001). Irregular bleeding significantly lower for PVR vs. Cu-IUD at 1, 3 months; NS for later periods. More than 75% PVR reporting amenorrhea during study period, significantly higher than Cu-IUD at all visits (p≤.01).	Strengths: Clear definition and analysis of bleeding and spotting patterns Weaknesses: Self-reported bleeding Significant differences in baseline characteristics between methods: PVR users slightly more educated; more PVR users had cesarean section. Few measures of infant health High and differential method discontinuation (PVR=54%, Cu-IUD=2.3%). Limited 12 months data/limited explanation: PVR=31%; Cu-IUD=60%	II-2, poor
Diaz S, 1997 WHO, CONRAD, Population Council Chile (same protocol as Sivin 1997)	Prospective cohort study "treated" LNG implant (*N*=120) PVR (*N*=187) POP (*N*=117) Cu-IUD (*N*=122)	Pregnancy Lactation performance: duration Infant health: weight Method continuation Adverse events	Pregnancies: number of pregnancies/months of exposure POP 2/1023 PVR 0/1339 Cu-IUD 0/1410 LNG implant 0/1410	Strengths: Relatively low loss to follow-up: PVR=7%, POP=9%, LNG implant=1%, Cu-IUD= 10%, LAM=0% Weaknesses: Self-reported bleeding	II-2, poor

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Table 1 (*continued*)

Author year, source of support, location	Study design	Outcome measures	Results	Strengths/weaknesses	Quality
	LAM "untreated" (*N*= 236) Initiated 57±3 days postpartum Lactating, 18–35 years, normal vaginal delivery of healthy singleton 38–40 weeks Follow-up days 7–10, 20, 30 postpartum; days 15, 30 after initiation; monthly through 12 months postpartum		LAM "untreated" 48/1363 (1 before first episode of bleeding) Duration of lactation: mean NS across groups. Infant weight increase: NS differences across groups. Reasons for discontinuation: Weaning: POP=64%, PVR=80% Bleeding: LNG implant=2%, other methods=0% Bleeding, spotting greater in "treated" vs. "untreated" group within first 30 days of initiation. LAM significantly longer in POP, PVR, LNG implant compared with Cu-IUD and "untreated" (controlled for age, parity) and PVR significantly greater than POP, LNG implant.	Several significant differences in baseline characteristics between methods: Cu-IUD users older; lactation users lower parity, lower BMI, lower weight. Difficult to determine if some of the study population is reported elsewhere (i.e. Diaz 1999). High attrition in POP, PVR groups: protocol stipulated stopping at weaning vs. LNG implant, Cu-IUD. Few measures of infant health reported. PVR use problems resulted in discontinuation (*N*=23); not an issue for other groups.	
Sivin I, 1997 USAID, UNFPA, Population Council Multicenter study (9 clinics) Egypt, USA, Chile, Singapore, China, Sri Lanka (same protocol as Diaz 1997)	Prospective cohort study PVR (*N*=802) Cu-IUD (*N*=734) Initiation 4–9 weeks postpartum Follow-up 1, 3, 6, 9, 12 months postmethod initiation	Pregnancy Lactation performance: number of episodes Infant health: weight Method continuation Adverse events	Pregnancy rate at 12 months: 1.5/100 PVR vs. 0.5/100 Cu-IUD. Mean number breastfeeding episodes: NS between method groups at 61, 91, 274 and 365 days. Slightly higher for PVR group at 183 days ($p<.05$). No difference in infant weight during year, but significantly higher at 12 months in Cu-IUD group ($p=.02$) Discontinuation: significantly higher for bleeding in PVR group at 6, 12 months $p<.001$. Overall rates at 6 and 12 months: PVR=52.5, 23.5; Cu-IUD=74.8, 34.5, respectively. Bleeding: significantly higher amenorrhea in PVR group at 1, 6, 9, 12 months ($p<.001$). Vaginal complaints (i.e. feeling the ring): higher in PVR ($p<.001$) Abnormal vaginal findings: (i.e. vaginal discharge, nonspecific vaginitis, yeast) higher in Cu-IUD group ($p<.01$). Expulsion: PVR=6%; 8.1/100 termination rate. Cu-IUD=0.8% at 6 months, 3.7% at 12 months; 5.6/100 termination rate.	Strengths: Multiple study locations Large sample size Low loss to follow-up: PVR=4.4%, Cu-IUD=5.7% Weaknesses: Most baseline characteristics were similar between groups. PVR significantly lower parity; Cu-IUD higher maternal weight ($p<.05$) and higher percentage of vaginal deliveries ($p<.01$). Difference in continuation rates Large interstudy center differences	II-2, fair

			Study termination for weaning/infant health higher in Cu-IUD group: 58% vs. 51% in PVR group ($p<.05$).		
Shaaban M, 1991 WHO, Population Council, Rockefeller Foundation Egypt	Prospective cohort study PVR (*N*=103) Cu-IUD T380A (*N*=83) Initiated 5–7 weeks postpartum Follow-up at 12 months postpartum	Pregnancy Lactation performance: Time to introduction of supplementary foods Infant health: weight Method continuation	Pregnancy: 1/1007 woman-months in PVR group, 0/958 woman-months in Cu-IUD group. No difference between groups. No differences in infant weight or health Continuation rates at one year: PVR=66.6%, Cu-IUD=85.5% No data on population characteristics	Weaknesses: Baseline characteristics of study population not presented Differential continuation rates Low loss to follow-up: PVR=4%, Cu-IUD=0%. Study methodology not adequately described	II-2, poor
Diaz S, 1985 WHO, Population Council, USAID, Rockefeller Foundation, Andrew W Mellon Foundation, George J Hecht Funds, The Ford Foundation UNFPA Chile	Prospective cohort study PVR (*N*=128) Cu-IUD (*N*=127) Placebo injection (*N*= unknown) Initiated 60±5 days postpartum Lactating, 18–35 years, normal vaginal delivery of healthy singleton 38–40 weeks Follow-up at 12 months postpartum (monthly visits to 6, every 2 months up to 12 months)	Baseline characteristics Pregnancy Lactation performance: duration Infant health: weight Method continuation	No significant differences in baseline characteristics. Pregnancies (woman-months): PVR=1/739, Cu-IUD=0, placebo=19/677. No significant differences; exclusively breastfeeding at 6 months=57% vs. 58%, at 12 months=11% vs. 20%, for PVR and Cu-IUD groups, respectively. Infant weight: No significant differences in absolute or average infant weight gain. Discontinuation: PVR =23, Cu-IUD=10. Loss to follow-up: PVR=5, Cu-IUD=11	Strengths: Loss to follow-up: PVR=4%, Cu-IUD=9% Weaknesses: Limited information on additional placebo group	II-2, fair

B/S=bleeding/spotting.
HPV=human papilloma virus.
NS=not significant.

LNG implant [19], POPs [19], or LAM [19] in studies conducted in Egypt, China, and Chile. According to a large multicountry study, patterns of infant weight were similar among women using a PVR or the Cu-IUD through 12 months of observation; however, at 12 months follow-up, infants whose mothers used a Cu-IUD weighed more [mean weight: 9528 g (Cu-IUD) vs. 9307 g (PVR)], and the difference was statistically significant (p=.02) [18]. Finally, an observational study of Egyptian women reported no significant differences in "infant health" between PVR and Cu-IUD users during a 12-month period; however, the investigator failed to describe the health outcomes that were collected to define infant health.

3.4. Discontinuation/continuation

Discontinuation of self-selected methods prior to the completion of the included studies was common and variable. In general, more studies reported higher rates of discontinuation among women who elected to use the PVR compared with women who chose the Cu-IUD [16–18,20,21]. Reasons for discontinuation varied across the studies. Significantly higher proportions of PVR users described difficulties using the method compared with women using other methods. Difficulties cited included vaginal problems, bleeding irregularities, or other personal reasons. No serious adverse events occurred or contributed to the discontinuation rates observed in all studies.

3.5. Bone health

One study included in this review examined several measures of bone health among a small sample (N=129) of Chilean breastfeeding women. The women self-selected to use the PVR, the LNG implant, or the Cu-IUD. This observational study assessed differences between markers of bone metabolism (calcium, phosphorus, magnesium, alkaline phosphatases, and hydroxyproline/creatinine) and bone density (total body, lumbar spine, right femoral neck, and right trochanter). The participants underwent evaluation of the above described parameters during the 12-month study period and after weaning (6 months for PVR users and 12 months for Cu-IUD and LNG implant users). At 1 month postpartum, breastfeeding participants exhibited lower bone density levels at the lumbar spine compared with an external nonbreastfeeding comparison cohort (these women were not enrolled in the study). However, no differences in bone density measures were observed after weaning between breastfeeding women who used the PVR, Cu-IUD, or LNG implant, as well as the nonbreastfeeding comparison cohort. With the exception of lower levels of alkaline phosphatases at 6 months follow-up among PVR users compared with Cu-IUD users, no other significant differences in markers of bone metabolism were noted during the study [22].

4. Discussion

The seven studies included in this review were assessed to be of poor (three studies [17,19,20]) to fair (four studies [16,18,21,22]) methodological quality. Four of the seven studies were conducted in public sector settings in Latin America. Results from these studies consistently showed that use of the PVR did not affect breastfeeding performance or infant weight gain, and that the PVR was as effective at preventing pregnancy during 12 months postpartum or postmethod initiation (depending upon the study design) as both the highly effective Cu-IUD and LNG implant. The studies suggested limited evidence that overall infant health was not affected by PVR use; however, this outcome measure was poorly defined.

Expanding the use of modern contraceptive methods among women who breastfeed is a vitally important individual and public health issue. To ensure that these advantages are maximized, a variety of safe and effective contraceptive methods are necessary so that breastfeeding women are able to choose a method that meets their own personal preferences, values and circumstances.

Despite the reassuring findings derived from this review, it is important to recognize several limitations to this small body of evidence that may limit the generalizability of the results. None of the included studies were randomized controlled trials comparing the PVR to nonhormonal contraceptive methods or to other progestogen-mediated methods; participants in all of the studies selected their contraceptive method. While all of the studies relied upon self-reported/subjective accounts of breastfeeding and bleeding episodes, these outcome measures remain appropriate in the context of the desired assessments. Although no significant adverse effects were noted in any studies with regard to infant weight gain, few measures of other aspects of infant health were collected and there was limited information on the specific measures that were collected. Moreover, the timing of PVR initiation postpartum within the studies varied from 29 to 270 days; it is not known whether breastfeeding performance or infant health measures would vary depending upon earlier initiation of PVR use. Two studies experienced high rates of loss to follow-up [20,22]. The study examining the effect of the PVR, LNG implant, and Cu-IUD on maternal bone turnover and density had a small sample size [22].

Additionally, there was a notable difference in continuation rates between contraception methods in several studies [17,18,20,21]; in particular, two studies reported higher rates of PVR discontinuation compared with other methods [19,20]. The reasons cited by the participants in these studies included complaints such as unscheduled vaginal bleeding, increased vaginal discharge, and ring expulsion. In addition, participants were instructed to discontinue the PVR with weaning, which may also partially explain higher discontinuation rates among these women, particularly when compared with the Cu-IUD and LNG implant both of which

are long-acting reversible devices. Potential users of the PVR should thus be counseled appropriately with regard to proper use and expectations for irregular bleeding patterns and other minor side effects. Acceptors of the PVR should also be counseled about transitioning to another effective method of contraception during the weaning process as the effectiveness of the PVR in nonbreastfeeding women is not known.

In March 2014, a WHO GDG reviewed the body of evidence presented in this systematic review, as well as a Grading Recommendations, Assessment, Development and Evaluation profile that summarized the strength of the evidence to assess eligibility for inclusion of the PVR among postpartum breastfeeding women in the *WHO MEC for Contraceptive Use, 5th Edition*. During the deliberations, the Group noted that additional studies are needed to examine whether PVR use can be safely initiated prior to 4 weeks postpartum and whether the contraceptive effectiveness of the PVR is dependent upon the mother fully breastfeeding. After consideration of the evidence provided by this systematic review and discussion among the Group, WHO issued the following recommendation for use of the PVR:

> Women who breastfeed and are four or more weeks postpartum can use the PVR without restrictions (MEC category 1). The Guideline Development Group advised that women who use the PVR must be actively breastfeeding (e.g. at least four breastfeeding episodes per day) to maintain the efficacy of the method.

5. Conclusion

Summary of evidence: direct, level II-2, poor to fair.

In general, evidence from seven prospective observational studies consistently showed that use of the PVR among women who breastfeed compares favorably to other highly effective methods of contraception and does not compromise a woman's breastfeeding performance nor adversely affect infant weight gain during the first year postpartum.

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