

PROGESTERONE VAGINAL RING

BENEFICIAL ROLE IN BIRTH SPACING

The Progesterone Vaginal Ring (PVR) is a vaginal ring which contains progesterone and can enhance the effect of breastfeeding on birth spacing.

CONTRACEPTIVE EFFECT OF EXCLUSIVE BREASTFEEDING

Postpartum family planning has received renewed focus with the issuance of new guidelines from the World Health Organization; some estimates of unmet need for contraception among women during the postpartum period are more than 60% in developing countries^{1,2}.

In this context, the lactational amenorrhea method (LAM) is recognized as an effective means of postponing the return to fertility in breastfeeding mothers as indicated by the onset of menstrual bleeding³⁻⁹. LAM is defined as a method that can effectively protect a woman from pregnancy if she meets all of the following three criteria: 1) Her period has not returned since her baby was born; 2) She is breastfeeding exclusively (fully) day and night, i.e. breast milk is the only source of water or nutrients during the first six months as long as the infant's growth is adequate; 3) Her baby is less than six months old. As soon as the woman no longer meets one of these criteria, pregnancy rates increase and she needs to begin using another contraceptive method.

Based on recent DHS surveys, however, a low proportion of women report compliance with the three criteria for the use of LAM in DHS surveys (usually less than 5% of breastfeeding women)¹⁰, although results from a large multicenter study on efficacy of LAM conducted in the early 1990s, suggest that deviation from specific use of each of the three criteria does not cause a significant upsurge in pregnancy rates¹¹. It has been shown that the PVR as a new method of contraception during lactation, can provide additional protection to breastfeeding women who want to space their pregnancies for more than one year, but may not comply with the strict criteria of LAM.



Lactational amenorrhea and its associated infertility have been shown to contribute to birth spacing, although variable effectiveness has been reported among different communities. In a population of highly motivated Chilean women (n=236) who breastfed up to 8 times per day, the risk of experiencing the first bleeding was reduced while fully breastfeeding with a high number of nursing episodes per day and night, but 25% and 50% of the women had started to cycle by the end of the fifth and eighth postpartum month respectively³.

After the first postpartum menses, the risk of pregnancy for breastfeeding women increases substantially^{3,12}. The cumulative probability of pregnancy changes from 0.9% in amenorrheic women to 36% in cycling women at 6 months

postpartum; and at 12 months, the pregnancy rate increases further from 17% (in amenorrheic women) to 55% (in cycling women)¹².

Diaz et al⁴ demonstrated that the onset of bleeding before the sixth postpartum month, in fully breastfeeding women, predicts a higher risk of pregnancy. The investigators calculated the probability of experiencing the first bleeding and the probability of pregnancy in 236 women who were fully breastfeeding and not using contraception and enrolled during the first month postpartum^{4,11}. The cumulative probability of bleeding and of pregnancy was 52% and 9.4% at day 180 postpartum, respectively. The risk of pregnancy was less than 2% in the subset of amenorrheic women⁴. These results confirmed that lactational amenorrhea provides effective contraceptive protection during the first six months postpartum. They also suggested that the first postpartum bleeding marks a discernible increase in the risk of pregnancy^{4,12}.

After the sixth month postpartum, when breastfeeding will probably cease to be “full” or nearly full, it is increasingly likely that ovulation will precede the first vaginal bleed. Therefore, the protection against pregnancy that is afforded by breastfeeding decreases over time to levels lower than those of other family planning methods⁵.

Based on these data, participants in a Bellagio consensus conference⁵ concluded that the maximum birth spacing effect of breastfeeding is achieved when a mother “fully” or nearly fully breastfeeds **and** remains amenorrheic. When these two conditions are fulfilled, breastfeeding provides more than 98% protection from pregnancy in the first six months⁵.

CONTRACEPTIVE METHODS IN BREASTFEEDING WOMEN

As a result of the growing urbanization and changing social norms about the role of women in developing countries, the duration of exclusive breastfeeding and its impact as a contraceptive strategy has been reduced. This situation has given rise to the need for a contraceptive method that could extend the infertile period following delivery, especially in countries where access to other contraceptives is limited and where longer duration of breastfeeding is a social norm and a major benefit to infant health.

According to WHO Medical Eligibility Criteria (MEC), several methods are suitable for women who are breastfeeding and can be recommended¹³. Progestin-only pills (POP) have a longer half-life than progesterone, but need to be taken daily at approximately the same time. Long-acting methods such as the progestin implant or an intrauterine device (IUD) require access to trained health care providers for insertion and removal. The PVR was

developed as a new user-controlled method that delivers a natural hormone for 3 consecutive months, hence not requiring daily attention by the user. Progesterone is metabolized quickly after ingestion in breast milk, limiting the steroid exposure to the infant.



MECHANISM OF ACTION OF THE PVR

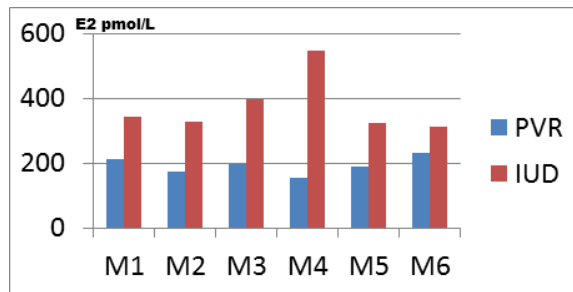
The contraceptive mechanism of action of natural progesterone is similar to that of progestin-only pills, i.e. it suppresses ovulation, and reinforces the prolactin response to suckling⁹.

Diaz et al⁹ explored the mechanism of action of progesterone rings in lactating women by comparing ovarian function and prolactin levels between women who chose either a PVR or a Copper IUD at day 60 postpartum. Data were provided based on monthly follow up during one year of use. Frequency of breastfeeding and pregnancy rates in women who were relying only on lactational infertility were collected **separately** for comparative purposes^{9,12}.

The women (defined as fully or exclusively breast-feeding) were instructed not to give their babies any liquid or solid food or water during the first 6 months postpartum and to use the breast as the only source of fluids and nutrients, with the exception of vitamin drops. Milk supplements were indicated only when inadequate infant growth was diagnosed. Non-dairy meals were introduced after the sixth postpartum month.

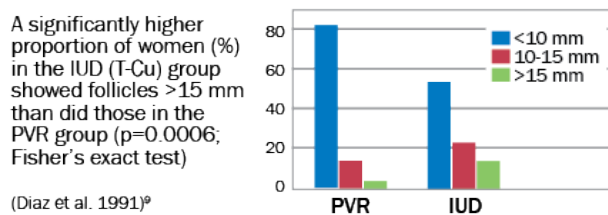
The endocrine profile during the first 8 months postpartum was assessed in a sub-group of breastfeeding women including 36 PVR-treated women and 28 IUD-users. Pre- and post-suckling prolactin (PRL) levels were measured at fortnightly intervals and E2 determinations and ovarian ultrasound were performed twice a week. Post-suckling PRL levels were significantly higher among PVR users (n=20) compared with IUD users (n=12); p=0.009. In PVR users, progesterone plasma levels ranged from 10 to 20 nmol/L, at lower levels than in a normal luteal phase. Similarly, E2 levels were lower, and follicular growth was arrested at earlier stages in the PVR vs. the IUD groups (*Figures 1 & 2*).

FIGURE 1 ESTRADIOL SERUM LEVELS BY MONTH OF EXPOSURE



Mean of the Highest E2 Level in Lactating Women Treated with a Progesterone Vaginal Ring (PVR) or a Copper-T Device (IUD) $p < 0.05$ except in month 6 (M6). (Adapted from Diaz et al⁹)

FIGURE 2 FOLLICLE DIAMETER AMONG USERS OF PVR OR IUD (3–8 MOS. POSTPARTUM)



A significantly higher proportion of women (%) in the IUD (T-Cu) group showed follicles >15 mm than did those in the PVR group ($p=0.0006$; Fisher's exact test)

(Diaz et al. 1991)⁹

The authors concluded that progesterone increases the sensitivity of the breast-hypothalamic-pituitary system to suckling, as shown by the higher PRL levels in women using the PVR, and reinforces the mechanism of lactational infertility⁹. They also concluded that progesterone may affect the GnRH-releasing process independently of suckling⁹. These results, therefore, support the efficacy of the PVR in suppressing ovulation for a longer duration as compared with “untreated” women who demonstrate resumption of follicle growth and possible ovulation even when fully breastfeeding.

CONTRACEPTIVE EFFICACY OF THE PVR

In the study by Diaz et al⁹, pregnancy rates at the end of the year were 0.6% in PVR users and 0.7% in IUD users. In another study that included the population of 236 breastfeeding only women, the pregnancy rates at one year were 39%¹² (Table 1).

TABLE 1 CONTRACEPTIVE EFFICACY OF THE PVR IN NURSING WOMEN

	PVR Users	T-CU Users	Untreated Women ^c
Women	246 ^a	442	226
Pregnancies/WM ^b	1/2016	2/3461	50/1552
Pearl Index	0.6	0.7	38.7

Adapted from Diaz et al⁹.

^aPVR 5 mg (n = 76), 10 mg (n = 109), or 15 mg (n = 61). ^bWM= woman-month; PVR and T-Cu were administered at day 60 ± 5 postpartum and the women were followed until month 14 postpartum. Untreated women were followed until month 12 postpartum. ^cThe untreated group has been collected in another study¹² and used in this table as historical comparison.

All women in the PVR and IUD groups were amenorrheic at admission. By the end of month 8 postpartum, 78% of PVR users and 29% of T-Cu users remained so. The PVR group experienced a significantly lower risk of bleeding ($p < 0.0001$) than did the IUD group.

Massai et al¹⁴ also studied the contraceptive efficacy and safety of the PVR compared to the Copper T 380A IUD (T-Cu) in breastfeeding women enrolled at three Chilean clinics. A total of 285 volunteers chose to use the PVR and 262 women used the T-Cu. Ring replacement was scheduled every 3 months. Volunteers continued in the study until weaning or completing the continuous use of four PVRs over one year. **No pregnancies occurred in 2,320 and 2,183 woman-months of exposure with the PVR and the T-Cu, respectively.**

The mean duration of lactational amenorrhea was 361 ± 9 days in the PVR group and 198 ± 8 days in the T-Cu group ($p < 0.0001$). The proportion of amenorrheic women at the 6th month postpartum was 87.4% among PVR users and 41.5% among T-Cu users ($p = 0.0001$). These percentages were three- and six fold higher in the PVR than in the T-Cu groups at months 9 and 12, respectively¹⁴. The mean number of breastfeeding episodes was similar in both groups, decreasing from a mean of 10.1 episodes/day at month 3 to a mean of 5 episodes/day at month 14 postpartum. Infant weights were similar in both groups¹⁴.

In the Population Council's large comparative multicentric trial that compared 802 women using the PVR and 734 women who received a copper-T 380A IUD, the 1-year pregnancy rate with the ring was at 1.5 per 100 (431 women-years) and 0.5 per 100 in the copper-T 380A cohort (533 women-years). The percentage of women who were amenorrheic at 6 months postpartum was 67.4% in the PVR group and 43.7% among IUD users ($p=0.0001$); and at month 12, the rate of amenorrhea remained higher in the PVR group at 46.2% vs 16.1% in the IUD group ($p=0.0001$). There was no difference between groups in the mean number of breastfeeding episodes per day (d) which was around 9 meals/day at initiation and 6meals/d at 12 months¹⁵. In addition, the weight of the infants did not differ between PVR or IUD users except at 12 months and attributed to more supplements given in the IUD group¹⁵.

Preliminary results from a recent study of PVR vs. IUD use conducted in India (2012-2015) provides similar results with respect to rates of lactational amenorrhea and average daily breastfeeding episodes over time. Pregnancy rates were identical (1 pregnancy in each group) as were infant growth patterns (ICMR & Population Council Internal Data – Protocol 418).

SUMMARY

Results of clinical trials completed to date support the following conclusions regarding the role of breast-feeding and use of the PVR to promote child spacing:

- Breastfeeding protects against pregnancy if a woman is fully breastfeeding and remains in amenorrhea; in this case her pregnancy risk will be about 0.9% at 6 months postpartum¹².
- When a first bleeding occurs before the 6th month, the risk of pregnancy increases to 9% and higher^{5,12}.
- The risk of experiencing the first bleeding is reduced while fully breastfeeding with a high number of nursing episodes per day and night, but nevertheless 25% and 50% of the women start to cycle by the end of the fifth and eighth postpartum month, respectively³.
- Using a Progesterone Vaginal Ring (PVR) prolongs amenorrhea in a higher proportion of women compared to women who are breastfeeding only. At 6 months, 87.4% of PVR users are amenorrheic versus 41.5% in IUD users¹⁴.
- Users of a PVR show a higher suppression of ovarian follicles as compared with women using an IUD, with a majority of follicles at a diameter <10mm (82%), while IUD users show only 54% of follicles at <10mm. Follicles of >15mm were seen in 4% of PVR users and 23% of IUD users⁹.
- In fully breastfeeding women, pregnancy rates at the end of one year are observed at < 1% in PVR users (treated) and at 39% in breastfeeding women not using any other contraception^{9,12}. This low failure rate of the PVR appears to have been replicated in a recent study in India.

Based on the review of the literature herein discussed, as well as preliminary findings from the recent study in India, it may be concluded that the PVR is effective in preventing an early return of follicle growth and ovulation, and preventing the return of cycling and fertility that may occur even in women who are fully breastfeeding^{9,12}. A recent review of unmet need among postpartum women also suggests that in contexts where breastfeeding is common, counseling women about LAM and urging contraceptive adoption within six months of birth has programmatic rationale¹⁶.

These conclusions support the position of offering the PVR to women who plan to breastfeed in the context of postpartum contraceptive counseling. In this regard, WHO has 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 method¹³.



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