RISK OF PREGNANCY IN BREASTFEEDING MOTHERS: ROLE OF THE PROGESTERONE VAGINAL RING ON BIRTH SPACING

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ABSTRACT

The progesterone vaginal ring (PVR) Progering® has been shown to be effective as a contraceptive in breastfeeding women who need safe and effective methods of spacing pregnancies. Previous clinical trials, of 1-year duration, demonstrated its efficacy to be similar to that of the intra-uterine device (IUD) during lactation. The duration of lactational amenorrhoea is significantly prolonged in PVR users in comparison with IUD users with fewer median numbers of bleeding/spotting episodes and days. This delivery system designed for 3-month use needs to be renewed every 3 months as long as breastfeeding continues, for up to 1 year. The frequency of breastfeeding, breast milk volume, and infant growth were not different in PVR or IUD users, and the safety of this new method has been well documented. This article reviews the literature and describes the mechanism of action of the PVR during lactation to bring additional protection over exclusive breastfeeding only, during the first year postpartum. Further evaluation of the PVR acceptability in different populations where breastfeeding is popular and highly recommended for the infant's benefit is warranted.

Keywords: Progesterone, lactational amenorrhoea, vaginal ring, contraception.

INTRODUCTION

The progesterone vaginal ring (PVR) Progering® 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 (WHO). Some estimates suggest that the unmet need for contraception among women during the postpartum period is >60% in developing countries.[1,2]

In this context, the lactational amenorrhoea method (LAM) is recognised as an effective means of postponing the return to fertility in breastfeeding mothers as indicated by the onset of menstrual bleeding.[3-9] 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 6 months as long as the infant's growth is adequate; and 3) her baby is <6 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 demographic and health surveys however, a low proportion of women report compliance with the three criteria for the use of LAM (usually <5% of breastfeeding women).[10] The results from a large multicentre 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 rates.[11] 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 >1 year but may not comply with the strict criteria of LAM.

Lactational amenorrhoea 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 Chilean women highly-motivated for prolonged breastfeeding (N=236), who breastfed up to 8 times per day, the risk of experiencing the first bleeding was reduced. Of the fully breastfeeding women, with a high number of nursing episodes across day and night, 25% and 50% had started their menstrual cycle by the end of 5 and 8 months postpartum, respectively.[3] 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 amenorrhoeic women to 36% in cycling women at 6 months postpartum, and at 12 months the pregnancy rate increases further from 17% (in amenorrhoeic women) to 55% (in cycling women).[12]

Díaz et al.[4] demonstrated that the onset of bleeding before 6 months postpartum 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, not using contraception, and enrolled during Month 1 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 <2% in the subset of amenorrhoeic women.[4] These results confirmed that the LAM provides effective contraceptive protection during the first 6 months postpartum. They also suggested that the first postpartum bleeding marks a discernible increase in the risk of pregnancy.[4,12]

After Month 6 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 methods.[5]

Based on these data, participants in a Bellagio Consensus Conference[5] concluded that the maximum birth spacing effect of breastfeeding is achieved when a mother 'fully' or 'nearly fully' breastfeeds and remains amenorrhoeic. When these two conditions are fulfilled, breastfeeding provides >98% protection from pregnancy in the first 6 months.[5]

CONTRACEPTIVE METHODS IN BREASTFEEDING WOMEN

As a result of growing urbanisation 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 a longer duration of breastfeeding is a social norm and a major benefit to infant health.

According to WHO Medical Eligibility Criteria (MEC), several suitable methods for women who are breastfeeding can be recommended.[13] Progestin-only pills have a longer half-life than progesterone but need to be taken daily at approximately the same time. Long-acting reversible contraceptives (LARCs) such as the progestin implant or an intrauterine device (IUD) require access to trained healthcare 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. As opposed to oral contraceptives taken daily or LARCs, vaginal rings designed for 3-month use are often called mid-acting delivery systems. Since progesterone in breast milk is metabolised quickly after ingestion, the steroid exposure to the infant is limited.

MECHANISM OF ACTION OF THE PROGESTERONE VAGINAL RING

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 suckling.[9] Díaz et al.[9] 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.

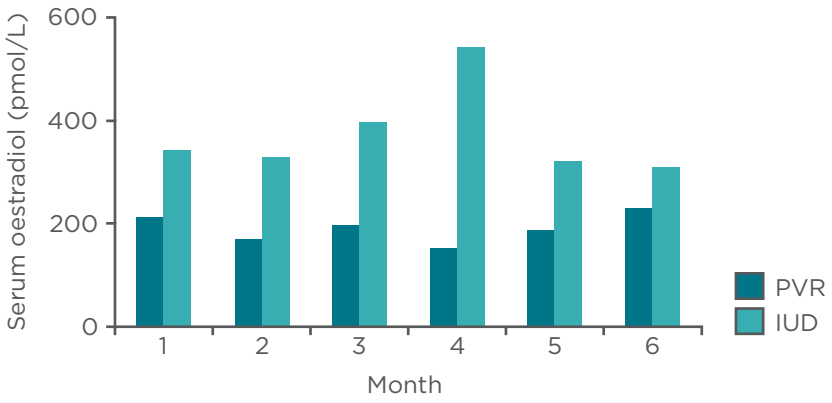

Figure 1: Mean oestradiol serum levels by month of PVR or IUD use.
Mean of the highest oestradiol level in lactating women treated with a PVR or a copper-T IUD $p<0.05$ except in Month 6.
PVR: progesterone vaginal ring; IUD: intrauterine device.
Adapted from Díaz et al.[9]

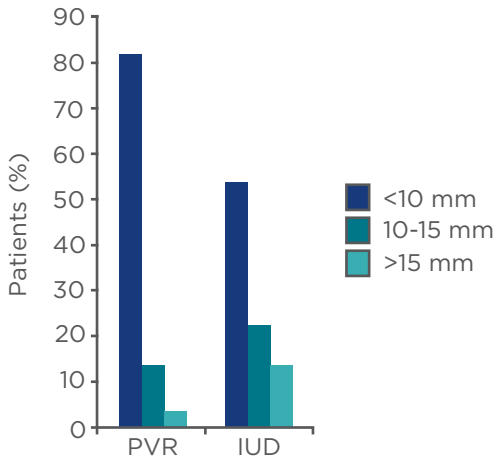

Figure 2: Follicle diameter in users of PVR or IUD from 3–8 months postpartum.
A significantly higher proportion of women (%) in the copper-T IUD group showed follicles >15 mm than those in the PVR group ($p=0.0006$; Fisher's exact test).
PVR: progesterone vaginal ring;
IUD: intrauterine device.
Adapted from Díaz et al.[9]

Data were provided based on monthly follow-ups during 1 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 breastfeeding) were instructed not to give their babies any liquid or solid food or water, and to use the breast as the only source of fluids and nutrients during the first 6 months postpartum except for the administration of vitamin drops. Milk supplements were indicated only when inadequate infant growth was diagnosed. Non-dairy meals were introduced after Month 6 postpartum.

The endocrine profile was assessed during the first 8 months postpartum in a subgroup of breastfeeding women including 36 PVR-treated women and 28 IUD-users. Pre and post-suckling prolactin (PRL) levels were measured every 2 weeks; oestradiol determinations and ovarian ultrasound were performed 2-times 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 10–20 nmol/L, at lower levels than in a normal luteal phase. Similarly, oestradiol levels were lower and follicular growth was arrested at earlier stages in the PVR versus the IUD groups (Figures 1 and 2).

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 infertility.[9] They also concluded that progesterone may affect the gonadotrophin-releasing hormone discharging process independently of suckling.[9] 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 whilst fully breastfeeding.

Table 1: Contraceptive efficacy of progesterone vaginal rings 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

[a]PVR 5 mg (n=76), 10 mg (n=109), or 15 mg (n=61).
[b]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.
[c]The untreated group has been collected in another study[12] and used in this table in a paper by Díaz et al.[9] as a historical comparison.
WM: woman-month; T-Cu: copper-T;
PVR: progesterone vaginal ring.

CONTRACEPTIVE EFFICACY OF THE PROGESTERONE VAGINAL RING

In the study by Díaz et al.,[9] 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 a population of 236 breastfeeding-only women, the pregnancy rates at 1 year were 39% (Table 1).[12] In the Díaz et al.[9] study, all women in the PVR and IUD groups were amenorrhoeic at admission. By the end of postpartum Month 8, 78% of PVR users and 29% of copper-T (T-Cu) 380A IUD users remained amenorrhoeic. The PVR group experienced a significantly lower risk of bleeding (p<0.0001) than the IUD group.

Massai et al.[14] also studied the contraceptive efficacy and safety of the PVR compared with the T-Cu IUD 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 1 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 amenorrhoea was 361±9 days in the PVR group and 198±8 days in the T-Cu group (p<0.0001). The proportion of amenorrhoeic women at 6 months postpartum was 87.4% among PVR users and 41.5% among T-Cu users (p=0.0001). These percentages were 3 and 6-fold higher in the PVR than in the T-Cu groups at Months 9 and 12, respectively.[14] The mean number of breastfeeding episodes was similar in both groups, decreasing from a mean of 10.1 episodes per day at Month 3 to a mean of 5 episodes per day at Month 14 postpartum. Infant weights were similar in both groups.[14]

In the Population Council's large comparative multicentre trial comparing 802 women using the PVR and 734 women who received a T-Cu 380A IUD, the 1-year pregnancy rate with the ring was 1.5 per 100 (431 woman-years) and 0.5 per 100 in the T-Cu 380A cohort (533 woman-years). The percentage of women who were amenorrhoeic 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 amenorrhoea remained higher in the PVR group at 46.2% versus 16.1% in the IUD group (p=0.0001). There was no difference between groups in the mean number of breastfeeding episodes per day which was around nine meals per day at initiation and six meals per day at 12 months.[15] In addition, the weight of the infants did not differ between PVR or IUD users except at 12 months; this was attributed to more supplements given in the IUD group.[15] One weakness of this study is the large inter-study centre differences. Also, neither of the above studies are randomised controlled studies.[14,15] However, in contraceptive clinical trials most of the studies are open in design and the guidelines from stringent regulatory authorities indicate that non-comparative studies are accepted.[16]

Results of clinical trials completed to date support the following conclusions regarding the role of breastfeeding and use of the PVR to promote child spacing: breastfeeding protects against pregnancy if a woman is fully breastfeeding and remains amenorrhoeic; in this case her pregnancy risk will be about 0.9% at 6 months postpartum.[12] When a first bleeding occurs before 6 months postpartum 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.[3] Using a PVR prolongs amenorrhoea in a higher proportion of women compared with women who are breastfeeding only. At 6 months, 87.4% of PVR users are amenorrhoeic versus 41.5% in IUD users.[14]

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 <10 mm (82%), while IUD users show only 54% of follicles at <10 mm. Follicles of >15 mm were seen in 4% of PVR users and 23% of IUD users.[9] In fully breastfeeding women, pregnancy rates at the end of 1 year are observed at <1% in PVR users (treated) and at 39% in breastfeeding women not using any other contraception.[9,12]

SAFETY OF THE PROGESTERONE VAGINAL RING

Breastfeeding and Infant Growth

It should be noted that in all clinical studies involving a PVR, no deleterious effects on the frequency of breastfeeding, breast milk volume, or infant growth have been observed.[14,15] The transfer of progesterone to the infants via breast milk of mothers using progestogen-only subdermal implants was evaluated by measuring urinary pregnanediol-3-glucuronide, a progesterone metabolite.[17] At 3–4 months postpartum in nine infants and at 9–12 months postpartum in seven infants, the metabolite levels were 6.3 and 15.7 ng/L, respectively, values that did not differ significantly from those in infants whose mothers were using a T-Cu 380A IUD.[17] Based on the pregnanediol-3-glucuronide levels, it was estimated that infants ingesting 800 mL of breast milk daily were receiving approximately 5 µg of progesterone from breast milk which is almost negligible when compared to the European Medicines Agency (EMA) recommended maximum intake of exogenous progesterone that should not exceed 150 µg/day.[18]

Since the progesterone levels in milk are highly correlated with the plasma progesterone levels,[18] a child taking 600 mL of breast milk from a mother wearing a PVR will ingest (~7 ng/mL×600 mL) around 4.2 µg of progesterone per day, which represents less than the maximum recommended intake of 150 µg/day.[18] Moreover, progesterone has a short half-life when given orally (3–90 minutes) and is extensively degraded after ingestion, its bioavailability being <10%.[19] Therefore, it is unlikely that this low amount of progesterone excreted in the milk can affect the infant. This has been confirmed by controlled clinical trials where infant growth was monitored for 1 year and no difference in growth and development was noted between infants of mothers using either PVR or IUD.[15]

Adverse Events Reported in Previous Studies

The most frequent adverse events among ring users that were reported in the Chilean trial[14] included vaginal complaints (e.g. vaginal discharge, non-specific vaginitis, fungal or yeast infections, trichomonal infection, and urinary discomfort), with the rate being 3.5 per 100 women-months; significantly higher as compared with a rate of 1.9 per 100 women-months reported in the IUD group. Low abdominal pain and dysmenorrhoea were more frequent in the T-Cu IUD group. In the multicentre trial,[15] while medical complaints centred on vaginal conditions were higher among PVR users (25.8% in PVR group versus 16.8% in IUD group), objective findings at clinical examinations indicated that PVR users were diagnosed with fewer genital and pelvic conditions such as cervical and adnexal disorders compared with IUD users.[14,15]

No serious adverse events have been reported in either of the studies. The reasons for discontinuation cited by the participants in these studies included complaints such as unscheduled vaginal bleeding, increased vaginal discharge, and ring expulsion. This latter finding highlights the need for proper counselling for correct insertion of the ring. In another study, no differences were found between groups in any measurement of bone density; bone density in the lumbar spine decreased in comparison to that seen in non-breastfeeding women in the first month after delivery; no differences were found among groups after weaning.[20]

RECENT AND FUTURE RESEARCH

A large 20-centre study comparing the PVR versus an IUD has recently been completed in India.[21] Its preliminary findings are comparable to those of the studies in Chile and the low failure rate of the PVR appears to have been replicated, with a higher continuation rate in some centres.[21] More recent studies have assessed the acceptability of the PVR in breastfeeding women in Sub-Saharan Africa and one of the reasons cited for accepting the ring was the autonomy it gives to the user.[22,23]

Future research will include post-marketing safety surveillance once the product is approved in other countries and introductory research within health systems will be conducted. In addition, research on the effect of product delivery by non-physicians in developing country health systems, client

preferences, and the determinants of choice of product may bring additional information useful to tailoring the method to women's needs.

Assessing the comparative cost of the PVR to other contraceptive products in developing country markets is of high relevance; an IUD offers protection from pregnancy for many years, meaning that the average annual direct cost of an IUD is $0.58, whereas hormonal contraceptives range from $7.51-7.90.[24] The PVR brings a shorter-term user-controlled option for birth spacing, with additional benefit in breastfeeding support as compared with LARCs, and no additional cost for trained health providers.

CONCLUSION

Based on the review of the literature discussed, 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. Data from the clinical studies confirm the efficacy, acceptability, and safety of the PVR for contraceptive use by lactating women. The PVR has been shown to be safe also for breastfed infants with no difference in growth rate as compared with infants breastfed by mothers using an IUD. The fact that it is user-controlled and contains a natural hormone contributes to its acceptability by women, especially for those unable to gain access to provider-dependent methods for various reasons. Use of the ring would help to empower more women allowing them to take control of their fertility while they continue breastfeeding. The increase in the duration of lactational amenorrhoea is also of interest for women with low haemoglobin values as it decreases blood loss; this may represent an additional health benefit of the method.

A systematic review conducted by the WHO[25] concluded that the PVR is a safe and highly effective method of contraception for use among breastfeeding women and it should be offered to women who plan to breastfeed in the context of postpartum contraceptive counselling. In addition, in the WHO MEC the PVR has been assigned a Category 1 with the recommendation 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.[13]

A recent review of unmet need among postpartum women also suggests that in contexts where breastfeeding is common, counselling women about LAM and recommending contraceptive adoption possibly from Week 4 postpartum has programmatic rationale.[26,27]

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REFERENCES

1. World Health Organization. Programming Strategies for Postpartum Family Planning. Available at: http://apps.who.int/iris/bitstream/10665/93680/1/9789241506496_eng.pdf. Last accessed: 20 April 2016.

2. Ross JA, Winfrey WL. Contraceptive use, intention to use and unmet need during the extended postpartum period. Int Fam Plan Perspect. 2001;27(11):20-7.

3. Díaz S et al. Breastfeeding pattern and the duration of lactational amenorrhea in urban Chilean women. Contraception. 1988; 38(1):37-51.

4. Díaz S et al. Lactational amenorrhea and the recovery of ovulation and fertility in fully nursing Chilean women. Contraception. 1988;38(1):53-67.

5. Kennedy KI et al. Consensus statement on the use of breastfeeding as a family planning method. Contraception. 1989; 39(5):477-96.

6. Kennedy KI, Visness CM. Contraceptive efficacy of lactational amenorrhoea. Lancet. 1992;339(8787):227-30.

7. Kennedy KI, "Efficacy and effectiveness of LAM," Davis MK et al. (eds.), Integrating Population Outcomes, Biological Mechanisms and Research Methods in the Study of Human Milk and Lactation (2002), New York: Springer Science+Business Media, pp.202-16.

8. Valdés V et al. The efficacy of the lactational amenorrhea method (LAM) among working women. Contraception. 2000;62(5):217-9.

9. Díaz S et al. Mechanism of action of progesterone as contraceptive for lactating women. Ann N Y Acad Sci. 1991; 626:11-21.

10. Fabic MS, Choi Y. Assessing the quality of data regarding use of the lactational amenorrhea method. Stud Fam Plann. 2013;44(2):205-21.

11. Labbok MH et al. Multicenter study of the Lactational Amenorrhea Method (LAM): I. Efficacy, duration and implications for clinical application). Contraception. 1997;55(6):327-36.

12. Díaz S et al. Contraceptive efficacy of lactational amenorrhea in urban Chilean women. Contraception. 1991;43(4): 335-52.

13. World Health Organization. Medical

Eligibility Criteria for Contraceptive Use. Fifth edition, 2015. Available at: http://apps.who.int/iris/bitstream/10665/172915/1/WHO_RHR_15.07_eng.pdf. Last accessed: 20 April 2016.

14. Massai R et al. Preregistration study on the safety and contraceptive efficacy of a progesterone-releasing vaginal ring in Chilean nursing women. Contraception. 1999;60(1):9-14.

15. Sivin I et al. Contraceptives for lactating women: A comparative trial of a progesterone-releasing vaginal ring and the copper T 380A IUD. Contraception. 1997;55(4):225-32.

16. European Medicines Agency. Guideline on Clinical Investigation of Steroid Contraceptives in Women. EMEA/CPMP/EWP/519/98 Rev 1. 2005. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003349.pdf. Last accessed: 28 July 2016.

17. Croxatto HB, Diaz S, "Subdermal progesterone implants for fertility regulation in nursing women," Zatuchni GI et al. (eds.), Long-Acting Contraceptive Delivery Systems (1984), Philadelphia: Harper and Row, pp.441-9.

18. EMEA Committee for Veterinary Medicinal Products. Progesterone: Summary Report. Report No. EMEA/MRL/146/96 FINAL. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Maximum_Residue_Limits_-_Report/2011/07/WC500108427.pdf. Last accessed: 20 April 2016.

19. Stanczyk FZ. Pharmacokinetics and potency of progestins used for hormone replacement therapy and contraception. Rev Endocr Metab Disord 2002;3(3):211-24.

20. Díaz S et al. Norplant® implants and progesterone vaginal rings do not affect maternal bone turnover and density during lactation and after weaning. Hum Reprod 1999;14(10):2499-505.

21. Evaluation of a progesterone vaginal ring as a new contraceptive option in India. (Population Council and ICMR Protocol 418) [Data on file].

22. RamaRao S et al. Enhancing contraceptive choice for postpartum women in sub-Saharan Africa with the progesterone vaginal ring: A review of the evidence. Open Access J Contracep. 2015;6:117-23.

23. RamaRao S et al. Progesterone vaginal ring: introducing a contraceptive to meet the needs of breastfeeding women. Contraception: 2013;88(5):591-8.

24. Singh S et al. Adding It Up: The Costs and Benefits of Investing in Sexual and Reproductive Health 2014, New York: Guttmacher Institute. 2014. Available at: https://www.guttmacher.org/sites/default/files/report_pdf/addingitup2014.pdf Last accessed: 27 July 2016.

25. Carr SL et al. Safety of the progesterone-releasing vaginal ring (PVR) among lactating women: A systematic review. Contraception. 2015. [Epub ahead of print].

26. Cleland J et al. A fresh look at the level of unmet need for family planning in the postpartum period, its causes and program implications. Int Perspect Sex Reprod Health. 2015;41(3):155-62.

27. Van der Wijden C, Manion C. Lactational amenorrhoea method for family planning. Cochrane Database of Systematic Reviews. 2015;10:CD001329.