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Effect of Levonorgestrel Implant on Lactation and Infant Growth: A Review

(*Review : Pengaruh Implan Levonorgestrel pada Laktasi dan Pertumbuhan Bayi*)

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ABSTRACT

Background: Family Planning is a way to regulate the number of children born and the spacing of pregnancies through information, education, and the use of contraceptives. Postpartum contraception is important to obtain an optimal interpregnancy interval. Postpartum contraception should be initiated early; one of which is Long-Acting Reversible Contraception (LARC). Levonorgestrel can be used to prevent pregnancy because it interferes with ovulation, implantation, and fertilization. Objectives: This study aimed to assess the efficacy and effects of using levonorgestrel implants on breastfeeding and infant growth. **Methods:** Primary data were in the form of research papers obtained from PubMed®, and Google Scholar® published from the period 2010-2018. The keywords for the searches included: "levonorgestrel", "levonorgestrel (LNG)-releasing implant", "levonorgestrel on lactogenesis", "levonorgestrel on infant growth", and "levonorgestrel on breastfeeding", which were used alone or in combination. **Results:** The 20 selected articles were reviewed based on five identified phrases. Levonorgestrel subdermal implants were shown to be a good choice for women who wanted effective contraception. When used by breastfeeding mothers, levonorgestrel subdermal implants affected neither infant growth (0-1 year of age) nor lactation duration. **Conclusions:** Levonorgestrel subdermal implants can be effective long-term contraception. These implants are safe for breastfeeding mothers and do not affect infant growth.

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INTRODUCTION

Family planning is a way to regulate the number of children born and the spacing of pregnancies through information, education, and the use of contraceptives. There have been various contraceptive methods in the last few years, yet 50% of all pregnancies in the world are not planned; those can be found dominantly in developing countries (Kols, 2008). There are various factors of these unplanned pregnancies, i.e., difficulties obtaining contraceptives; contraceptive users not receiving sufficient contraceptive-related guidance; the selected contraceptive method failing to prevent pregnancy; difficulty being independent in terms of the selection of a contraceptive method; and it is difficulty accessing health services. WHO recommends spacing births at least 2 years before the next (World Health Organisation, 2005). Meanwhile, the American College of Obstetricians and Gynecologists (ACOG) has suggested birth spacing in the range between 18 months to 5 years (Stuebe, Borders and Bingham, 2016).

Postpartum contraception is important to obtain an optimal interpregnancy interval. Postpartum contraception should be initiated early; one of which is Long-Acting Reversible Contraception (LARC), to provide protection for women with short birth spacing. Further, ACOG even recommends immediate postpartum LARC to lower the rate of unplanned pregnancy, particularly in women who have a high risk of a short birth spacing. However, initiating contraception at a 6-week postpartum visit may not be feasible for most patients. Almost 40% of postpartum women do not have this visit (ACOG) and almost half of them have resumed sexual intimacy by that time (Leeman and Rogers, 2012; Stark et al., 2022).

LARC, including the levonorgestrel (LNG)-releasing implant, is a highly effective contraceptive which lasts no less than 3 years. In fact, levonorgestrel is a biologically active and synthetic progesterone associated with 19-nortestosterone. It can be used alone or in combination with estrogen which is a female contraceptive. Levonorgestrel, which is the levorotatory form of Norgestrel, is a synthetic progestin. It contains androgenic and pregestational activities. Levonorgestrel can bind to the progesterone receptor in the target cell nucleus, which then stimulates the resulting hormone-receptor complex, initiates transcription, and increases the synthesis of certain proteins. These cause luteinizing hormone (LH) activity to be suppressed, ovulation to be inhibited, as well as cervical mucus and endometrium to be altered (Stoddard et al., 2013).

Levonorgestrel can be used to prevent pregnancy because it interferes with ovulation, implantation, and fertilization. The effectiveness of the levonorgestrel tablet reaches 89% if used according to the instructions within 72 hours after intercourse. In addition, the effectiveness of the intrauterine and implantable devices that release levonorgestrel to prevent pregnancy is even higher than 99%. Levonorgestrel which serves as a component of hormonal therapy helps prevent endometrial carcinoma

which is related to unopposed estrogen administration. However, there has been controversy regarding postpartum hormonal contraception which is related to exogenous progestin that affects lactogenesis or reduces breast supply. In fact, there have been no successful previous studies, showing that hormonal contraception has adverse effects on breastfeeding (Perheentupa et al., 2003; Shaamash et al., 2005; Singhal et al., 2014).

We conducted a literature review to determine the appropriate time for the insertion of levonorgestrel (LNG)-releasing implant and the impact of LNG implant insertion on lactogenesis, breastfeeding continuation, and infant growth.

MATERIAL AND METHODS

Materials

We identified the results of a literature search (English articles) to determine the right time for the insertion of levonorgestrel (LNG)-releasing implant and the impact on lactogenesis, breastfeeding continuation, and infant growth. Relevant articles were searched on Pubmed®, and Google scholar® using various search terms which were used alone or in combination, including "levonorgestrel", "levonorgestrel (LNG)-releasing implant", "levonorgestrel on lactogenesis", "levonorgestrel on infant growth" and "levonorgestrel on breastfeeding". We hand-searched the reference lists of the original articles and systematic reviews to seek other relevant articles.

The considered inclusion criteria were as follow: published in English language and full-text articles and publication date match the years lying between 2000 to 2022. Exclusion criteria include articles in the form of case reports, narrative reviews, systematic reviews, or meta-analyses. The literature search conducted in both Pubmed®, and Google scholar® databases yielded a total of 32 articles that merited further examination. Out of these, 18 articles were excluded from consideration due to their nature as case reports, in vivo studies, and incomplete articles. Fourteen studies met the criteria for inclusion in this review and were selected for analysis.

RESULTS AND DISCUSSION

Overview of Implant and Pharmacology Profile of Levonogestrel (LNG)

A variety of subdermal contraceptive implants have been created, utilizing four distinct progestogens and two types of non-biodegradable polymers. Some of these implants have already been registered, while numerous other systems are currently being developed (Croxatto, 2002). The implants are placed beneath the skin, using a trocar and local anesthesia, often on the inner side of the non-dominant arm. The daily rate at which steroids are released gradually decreases during the lifespan of the implant, which ranges from 6 months to over 5 years (Meirik et al., 2003).

Levonorgestrel (LNG) is a synthetic progestogen of the second generation. It is the active ingredient in the racemic mixture of norgestrel. It attaches to progesterone and androgen receptors, leading to a postponement of the release of gonadotropin-releasing hormone from the hypothalamus. This action inhibits the surge of luteinizing hormone that takes place during the pre-ovulation stage. In essence, it can hinder or impede the release of an egg from the ovaries, thereby preventing fertilization and ovulation by inhibiting follicular rupture. Maximum effectiveness can also be attained when it is consumed during the pre-ovulation phase. Levonorgestrel also stimulates the thickening of cervical mucus, which hinders the movement and passage of sperm. Recent studies have found no evidence indicating that levonorgestrel has a significant impact on the endometrium, thereby preventing pregnancy (Kahlenborn, Peck and Severs, 2015; Basaraba et al., 2016).

Clinical Efficacy of Levonogestrel (LNG)

Pregnancy rates can be used as an indicator of the efficacy of Levonorgestrel (LNG) implant after implant has been inserted. Bahamondes (2015) conducted a study which showed that the pregnancy rates in two groups, namely LNG and Etenogestrel (ENG) implant users, were not significantly different during a 3-year follow-up. Based on the follow up, the cumulative pregnancy rate of both the ENG and LNG implant groups was 0.4 per 100 W-Y (95% CI 0.1-1.4), while that of the combination of both groups was 0.4 per 100 W-Y (95% CI 0.2-1.0) {RR 5.7 (95% CI 4.4-7.3)]. That of the TCu380A IUD group, on the other hand, was much higher than the rate of the combination between the ENG and LNG groups, namely 2.8 per 100 W-Y (95% CI 1.3-6.0) (Bahamondes et al., 2015). This result means that the used of implants, including ENG and LNG, was more efficient compared to the use of IUD, as evident from the statistically lower pregnancy rate during the 3-year follow-up (Bahamonde, 2015). In addition, another study conducted by Ali et al., (2016) also showed statistically similar efficacy between the use of LNG and ENG implants for 5 years (Ali et al., 2016). Additionally, a study done by Che et al (2019) revealed that LNG implants exhibit a high level of efficacy as a contraceptive technique among Chinese women in this particular group for a duration of 5 years (Che et al., 2019).

For family planning, it is important to clinically observe the effectiveness of LNG implant in 5 years. The data collection was done using a standardized case report form by the clinic staffs. The pregnancy rate in the 5-year study was 3.3 ± 1.2 per 100 women; there were 7 pregnancies found. Five of which were caused by a method failure; one was caused by a drug interaction because the pregnant woman took anticonvulsant drugs; one was a luteal phase in a woman with irregular periods with LNG implant insertion on the 7th day of the period. Based on the 5-year study on LNG implant, it can be concluded that the implant was effective in preventing pregnancy among Senegal women (Ba et al., 1999). A post-marketing cohort study of LNG implant was conducted for 5 years. LNG implant users and those with female sterilization had a lower pregnancy rate than both IUD users. The pearl rates for copper IUDs,

LNG implant, and female sterilization per 100 women-years were 0.88, 0.27, and 0.17, respectively. In fact, the study showed that LNG implant users had a lower pearl index than IUD users (Farley and Sivin, 2001).

Stainer et al., (2019) conducted a study aimed at observing the efficacy of implants containing the hormone levonorgestrel required to meet the World Health Organization (WHO) prequalification. This randomized controlled trial involved 650 participants who had one of two types of insertion of the levonogestrel implant product. This study shows that both implant products have good effectiveness for up to three to five years of use. The current development of levonorgestrel implant products is also economically beneficial. This suggests that it is possible for women who live in many low-income countries to get better access to contraceptive implants with a high level of effectiveness (Steiner et al., 2019). In addition, research carried out by the Australian Contraceptive ChOice Project (ACCORd) revealed that hormonal long-acting reversible contraceptive (LARC) techniques have superior rates of continuation and satisfaction when compared to the oral contraceptive pill (OCP). Given the superior contraceptive effectiveness of hormonal LARC methods, it is recommended to prioritize offering these methods as the initial choice for women (Black et al., 2021; Weisberg et al., 2013).

Lactation and Infant Growth

Previous studies have shown neither a negative effect on breast milk quality nor an increase in milk supply after using levonorgestrel implants as contraception starting 5 days or later after birth (Massai et al., 2001; Díaz, 2002; Steiner et al., 2019; Stanton and Blumenthal, 2019). For instance, a study conducted in Brazil made a comparison of the breastfeeding rate and infant growth among women who received COC (Combined Oral Contraceptives) which contains 30 µg ethinyl-estradiol (EE)/150 µg levonorgestrel (LNG) or subdermal etonogestrel (ENG)-releasing implant or levonorgestrel-releasing intrauterine system (LNG-IUS) and those who was given a copper intrauterine device (IUD) during 42-63 days after birth. Infant growth was evaluated based on some indicators, namely height, length of tibia, and body weight on 42 days after delivery. Whereas, milk intake was measured with deuterium equilibrium time from infant's saliva sample on days 52 and 63 postpartum. According to that study, the infant growth had no significant difference among all groups who used contraceptives which was measured based on the body height, weight, and length of tibia on the left. Contraceptive steroids, either progestin-only pills or combined estrogen-progestin pills, have been shown to affect neither milk intake nor infant growth in fully breastfed infants. Similarly, the administration of a low-EE COC at 42 to 63 days postpartum did not affect the milk intake of fully breastfed infants (Bahamondes et al., 2013). Additional studies have discovered that the results of breastfeeding were comparable in women who had

the implant shortly after childbirth compared to those who received it at the usual postpartum time (Gurtcheff et al., 2011).

Bryant et al. conducted a research which revealed that 15% (127 out of 852) of women experienced new or increased milk supply issues after initiating hormonal contraception. Women who used hormonal contraception had a greater incidence of reported milk supply issues compared to those who did not (44% vs. 40%; p=.05). The adjusted hazard ratios (HRs) examining the relationship between contraceptive usage and the duration until milk supply difficulties arise were not statistically significant (HR 1.18, 95% confidence range 0.94-1.47 for any form of hormonal contraception) (Bryant et al., 2019).

Further, Schiappacasse at al., investigated the health and growth (0-6 years of age) of infants whose breastfeeding mothers used LNG Copper T 380 (T-Cu) when she was still breastfeeding. This study revealed that the two groups had a similar proportion of infants fully breastfed until they were 11 months old. However, at 12 months old, the control group had a much higher number of fully breastfed infants than the LNG group. Regardless of those findings, none of the differences were significant in terms of both time of weaning and proportion of the breastfed infants at different ages between the control and treated group could be observed. The mean duration (±SE) of full breastfeeding in the LNG and the control group were 7.8 ± 0.3 and 8.7 ± 0.4 months, respectively, while the total duration of breastfeeding in the LNG and the control group were 16.5 ± 0.8 and 17.7 ± 0.8 months, respectively (Schiappacasse et al., 2002).

In addition, this research also found infants' normal growth (0-1 year of age). In both sexes and groups, the 50th percentile of weight in these infants was similar to that of the WHO reference. A significant difference in the mean weight of infants in both the T-Cu and Norplant groups were not observed in three times data collection, i.e., at patient's admission, at 6 months (7743.1 ± 770.9 g and 7870.9 ± 866.1 g), and at 12 months of infants aged (9659.6 ± 883.9 g and 9799.4 ± 1020.9 g). However, there were differences at 6 months and 12 months (127.8 g and 139.8 g, respectively) but not statistically significant. This study aligns with the research done by Phillips et al, which discovered that the majority of data does not support the existence of bad breastfeeding outcomes or unfavorable health outcomes in newborns, such as stunted growth, health issues, or impaired development (Phillips et al., 2016).

Averbach et al. and Turok et al. studied the timing of stage II lactogenesis, infant parameters, and breastfeeding rates were examined. The study by Averbach et al (2017) randomly selected their patients for the administration of either immediate (within 5 days after birth) or delayed (6-8 weeks after birth) two-rod levonorgestrel (LNG) implants. In a study by Turok et al.'s, patients were randomly selected

for the administration of immediate (within 30 min of placenta delivery) or delayed (4-12 weeks after birth) LNG intrauterine device (IUD). Although the insertion time have differences for the immediate insertion period, The mean time to lactogenesis in both studies was similar, namely 65 vs. 63 h, P=0.84 under Averbach's investigation (Averbach et al., 2017) and 65.4 ± 25.7 vs. 63.6 ± 21.6 h, P=0.22 in Turok et al.'s (Turok et al., 2017). Moreover Turok et al.' study showed no significant difference in delayed lactation (6 vs 9%, P=0.84), but two women in the immediate group faced lactogenesis failure.

Additionally, Averbach et al. study found similar exclusive breastfeeding rates between the immediate and delayed groups at 3 months postpartum (74 vs 71%, P=0.74) and 6 months postpartum (48 vs 52%, P=0.58). A total of 96% of the respondents reported some degree of breastfeeding at 6 months. Contrastly this finding, Turok et al. reported that, at 8 weeks after birth, the breastfeeding rates of the immediate group were non inferior [79%, 95% confidence interval (CI) 70-86%] were non inferior (P=0.28) to the delayed one (84%, 95% CI: 76-91%) based on the results of a per-protocol analysis. However, the results of the post-hoc analysis revealed that the exclusive breastfeeding rates in the two groups at 6 months after birth were similar (33 vs 40%, P=0.27).

Regarding infant growth, Averbach et al. also analyzed through infant parameters. A total of 60/96 infants (62.5%) belonging to the delayed group came at the 6-month postpartum exam. However, significant differences were not observed in terms of weight (4632 ± 1020 vs. 4407 ±957.3 g, P=0.26), head circumference (9.3 ± 2.6 vs. 9.5 ± 2.7 cm, P=0.70), or length (14.7 ± 5.3 vs. 15.2 ± 5.1 cm, P=0.63). In addition, the weight of premature infants in both the delayed and immediate groups increased (4563 vs. 6033 g, P=0.006) (Averbach et al., 2017).

CONCLUSION

Levonorgestrel subdermal implants can be an effective long-term contraception. These implants are safe for breastfeeding mothers and do not affect infant growth.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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