LEAP LNG-IUS INITIATIVE

Learning about Expanded Access and Potential of the Levonorgestrel Intrauterine System (LEAP LNG-IUS)

ANNOTATED BIBLIOGRAPHY

August, 2019

The Levonorgestrel Intrauterine System (LNG-IUS):
Resources with a Focus on Emerging Evidence from Low-income Countries

This annotated bibliography contains research, toolkits, articles, and other resources relating to the levonorgestrel intrauterine system (LNG-IUS). These resources focus particularly on use and availability of this method in low-resource settings, including insights about acceptability among clients and providers and supply-side facilitators and barriers to access. Some resources highlight potential next steps to increase method uptake at the country level.

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Global Perspectives

These resources provide global perspectives on the LNG-IUS, including benefits and challenges to introduction.

1. Hubacher D. The Levonorgestrel Intrauterine System: Reasons to Expand Access to the Public Sector of Africa. *Glob Health Sci Pract.* 2015; 3(4): 532-7. Available here.

The levonorgestrel intrauterine system has: (1) excellent effectiveness, (2) high satisfaction levels, (3) non-contraceptive benefits, and (4) potential to help reinvigorate interest in intrauterine contraception. The time is ripe for ministries and donor agencies to work together to make the product widely available across Africa. This paper outlines 6 main reasons why donor agencies should purchase the LNG IUS and why family planning programs should incorporate the method into their services.

2. Jacobstein R, Shelton JD. The levonorgestrel intrauterine system: a pragmatic view of an excellent contraceptive. *Glob Health Sci Pract*. 2015;3(4):538–543. Available here.

The levonorgestrel intrauterine system (LNG IUS) has major advantages and could be a "game-changer" in improving contraceptive choice and use. It faces important challenges, however, including: (1) high commodity cost; (2) often-strong provider resistance to IUDs and difficult programmatic requirements; (3) need for demand creation, including assessing if markedly reduced menstrual bleeding is attractive to clients; and (4) the many requirements for introducing any new contraceptive. A good next step would be a well-focused and multifaceted "learning introduction" to assess the LNG IUS's potential in several low-income countries, with rapid scale-up if results are promising.

3. Rademacher KH, Sripipatana T, Pfitzer A, Mackay A, Thurston S, Jackson A, Menotti E, Traeger H. A Global Learning Agenda for the Levonorgestrel Intrauterine System: Addressing Challenges and Opportunities to Increase Access. *Glob Health Sci Pract*. 2018;6(4):635-643. Available here.

The LNG IUS is one of the most effective forms of reversible contraception and has important noncontraceptive benefits but is currently not used at scale in any FP2020 focus country. A global working group developed a shared learning agenda to answer critical questions, harmonize approaches, avoid duplication, and facilitate introduction of the method within the context of informed choice. This paper reviews current challenges to LNG IUS access in low- and middle-income countries (LMICs), describes an introduction coordination platform that was launched in 2015 to help address these challenges and answer critical questions about the LNG IUS through a shared global learning agenda, and discusses some of the advantages and disadvantages of this type of method-specific coordination platform and provide a call to action for other organizations that are considering introducing or scaling up the LNG IUS.

Country Introduction Experiences

These resources provide country-specific insights on strategies for introducing the LNG-IUS into healthcare systems effectively. Sources include analyses of potential barriers and challenges for introduction as well as user and provider perspectives.

1. Danna, K, Jackson, A, Mann, C, Harris, D. Expanding Effective Contraceptive Options: Lessons Learned from the Introduction of the Levonorgestrel Intrauterine System (LNG-IUS) in Zambia and Madagascar. Report. 2019. Available here.

Expanding Effective Contraceptive Options (EECO) is a USAID project with funding from 2013-2022 that supports the introduction of new contraceptive options, like the SILCS diaphragm, and dual protection methods, like the women's condom. Each product in the EECO portfolio is designed to address one or more method-related reasons for non-use of contraception. Among these methods is the Levonorgestrel Intrauterine System (LNG-IUS), a contraceptive option with a side effect profile that differs from other methods and may appeal to women seeking reduced menstrual bleeding. EECO conducts pilot introductions of new contraceptive products, like the LNG-IUS, in countries that have high levels of unmet need for contraception such as Madagascar, Malawi, Niger, Nigeria, and Zambia. By the project's end, EECO will have produced step-by-step roadmaps for product introduction which can be used to scale up access to the products or expand introduction to additional countries. This program brief focuses on the lessons learned through each stage of the project's pilot introductions of the LNG-IUS in Zambia and Madagascar from 2016 to 2018.

2. Eva G, Nanda G, Rademacher KH, Mackay A, Negedu O, Taiwo A, Dal Santo L, Saleh M, Palmer L, Brett T. Experiences with the Levonorgestrel Intrauterine System among Clients, Providers and Key Opinion Leaders: A Mixed-Methods Study in Nigeria. *Glob Health Sci Pract*. 2018;6(4):680-692. Available here.

BACKGROUND: The levonorgestrel intrauterine system (LNG IUS) is one of the most effective contraceptive methods, and it has noncontraceptive health benefits, including treatment for women with heavy menstrual bleeding. In 2016, Marie Stopes International Organisation Nigeria (MSION) expanded LNG IUS provision through training and support to 9 mobile outreach teams, 105 social franchise clinics, and 20 public-sector providers in 17 states. Information about the LNG IUS was added to awareness-raising materials, and community mobilizers provided information on the LNG IUS alongside other voluntary family planning methods.
METHODS: In 2016, Marie Stopes International, MSION, and FHI 360 examined clients' and providers' experiences with the LNG IUS to assess the potential for further scale-up of the method as part of a comprehensive approach to family planning in Nigeria. A mixed-methods approach was used including analysis of routine service data, supplemental data specific to LNG IUS clients, and in-depth interviews with LNG IUS clients, providers, and key opinion leaders.
RESULTS: Just under 1,000 LNG IUS were inserted from September 2016 to December 2017 in 16 states in channels supported by MSION, representing 0.4% of all long-acting and reversible contraceptive (LARC) services provided by the participating providers during this time frame. The vast majority (82%) of LARCs provided were implants. A small pool of providers was responsible for providing almost half of the LNG IUS services. Common reasons for women choosing the LNG IUS were reduced menstrual bleeding (61%), long-acting duration (52%), effectiveness (49%), and discreetness (42%). Almost 80% of the users first heard about the method from a provider. Almost all users and providers reported positive experiences with the method, noting the noncontraceptive benefits and fewer side effects compared with other methods. All providers who were interviewed said they would continue offering the LNG IUS. Several key opinion leaders mentioned a total market approach incorporating both public and private sectors would be needed to successfully scale up the LNG IUS.
CONCLUSION: Reduced menstrual bleeding and fewer side effects compared with other methods were identified as important attributes of the LNG IUS by clients, providers, and key opinion leaders. Challenges to uptake of the LNG IUS include difficulty with introducing a new method within a busy service delivery infrastructure and limited awareness and demand-generation activities on the LNG IUS specifically. A comprehensive product introduction approach with coordinated demand- and supply-side activities may be required for this method to reach its full potential.

3. FHI 360, Society for Family Health, PSI, WomanCare Global. Market Assessment for Potential Introduction of a New Hormonal IUCD in Zambia. Report. 2016. Report available here.

The hormonal IUCD is not available in the public sector in Zambia and is only available on a very limited basis in the private sector. High quality, affordable LNG-IUS products are now being introduced in the global market. As a result, partners embarked on a national market assessment in Zambia. The market assessment included an analysis of the current reproductive health landscape in Zambia including the

current market for IUDs, interviews with Key Opinion Leaders (KOLs), healthcare providers and potential users including women currently using a short-acting family planning method, women currently using a long-acting family planning method, postpartum women and non-users of contraception; and an assessment of the regulatory landscape and documentation of partners' initial plans for introduction of a new, more affordable, quality assured hormonal IUCD product.

4. Hubacher D, Akora, V., Masaba, R., Chen, M., Veena, V. Introduction of the levonorgestrel intrauterine system in Kenya through mobile outreach: review of service statistics and provider perspectives. *Global Health: Science and Pract*. 2014. Jan 9;2(1):47-54. Available here.

BACKGROUND**:** The levonorgestrel intrauterine system (LNG IUS) was developed over 30 years ago, but the product is currently too expensive for widespread use in many developing countries. In Kenya, one organization has received donated commodities for 5 years, providing an opportunity to assess impact and potential future role of the product.
METHODS: We reviewed service statistics on insertions of the LNG IUS, copper intrauterine device (IUD), and subdermal implant from 15 mobile outreach teams during the 2011 calendar year. To determine the impact of the LNG IUS introduction, we analyzed changes in uptake and distribution of the copper IUD and subdermal implant by comparing periods of time when the LNG IUS was available with periods when it was not available. In addition, we interviewed 27 clinicians to assess their views of the product and of its future role.
RESULTS: When the LNG IUS was not available, intrauterine contraception accounted for 39% of long-acting method provision. The addition of the LNG IUS created a slight rise in intrauterine contraception uptake (to 44%) at the expense of the subdermal implant, but the change was only marginally significant ($P = .08$) and was largely attributable to the copper IUD. All interviewed providers felt that the LNG IUS would increase uptake of long-acting methods, and 70% felt that the noncontraceptive benefits of the product are important to clients.
CONCLUSIONS: The LNG IUS was well-received among providers and family planning clients in this population in Kenya. Although important changes in service statistics were not apparent from this analysis (perhaps due to the small quantity of LNG IUS that was available), provider enthusiasm for the product was high. This finding, above all, suggests that a larger-scale introduction effort would have strong support from providers and thus increase the chances of success. Adding another proven and highly acceptable long-acting contraceptive technology to the method mix could have important reproductive health impact.

5. Hubacher D, Masaba R, Manduku CK, Chen M, Veena V. The levonorgestrel intrauterine system: cohort study to assess satisfaction in a postpartum population in Kenya. *Contraception*. 2015 Apr;91(4):295-300. Available here.

BACKGROUND**:** The levonorgestrel intrauterine system (LNG IUS) may become the next long-acting contraceptive to be introduced in public sector programs of resource-poor countries. Whereas service

provision for subdermal implants and intrauterine devices is growing, little is known about how the LNG IUS might fit in.
STUDY DESIGN**:** We conducted a cohort study of 313 women in Kenya who were 6–12 weeks postpartum when they started using these methods: subdermal implant (205), LNG IUS (93), and copper intrauterine device (15). Participants returned for visits at 6 and 12 months to share information on bleeding patterns, side effects, satisfaction, and continued use of the products. We used Kaplan–Meier techniques to estimate method continuation rates and chi-square tests of association to identify differences in experiences with the methods.
RESULTS**:** The 12-month continuation rate for the LNG IUS was 89.1 (95% confidence interval [CI] = 86.9–94.9) and statistically equivalent to that of the subdermal implant (91.8: 95% CI = 80.6–94.0). Nearly 87% of LNG IUS users were very satisfied with the method at 6 months compared to 75% of implant users; this gap closed somewhat at 12 months as satisfaction levels of implant users rose. At 12 months 78% of LNG IUS users felt that their bleeding pattern was highly acceptable compared with about 66% of implant users.
CONCLUSIONS: This study found that the LNG IUS compared favorably to the subdermal implant in terms of satisfaction levels and continued use. The LNG IUS will provide another long-acting option for postpartum women.
IMPLICATIONS: The LNG IUS may soon be purchased by international donor agencies for use in public sector programs in sub-Saharan Africa and other resource-poor countries. The results of this study suggest that the product will be successful in future introduction activities.

6. Hubacher, D., Masaba, R., Manduku, C., Veena, V. Uptake of the levonorgestrel intrauterine system among recent postpartum women in Kenya: factors associated with decision-making. *Contraception,* 2013: 88(1):97-102. Available here.

BACKGROUND: The levonorgestrel intrauterine system (LNG IUS) may become more available in the public sector of resource-poor countries, but it is unclear what product features might be attractive to users and what factors will influence uptake.
STUDY DESIGN: We recruited 671 women in Kenya who were seeking contraception at 6–12 weeks postpartum and gave them an opportunity to try the LNG IUS. We asked why they did or did not choose it, relative to the alternative options. χ^2 tests of association were done to examine participant characteristics and decision-making associated with choice.
RESULTS: Participants chose the following methods: LNG IUS (16%), injectable (36%), subdermal implant (30%), progestin-only pills (15%) and copper intrauterine device (IUD) (3%). Reasons for not choosing the LNG IUS included fear of pain/injury/discomfort (34%), modesty issues regarding insertion (33%) and fear of hormonal/health side effects (31%). Nearly a third of LNG IUS acceptors said they would have chosen a short-acting method if the LNG IUS were not available, and only 21% would have chosen the copper IUD.
CONCLUSION: The LNG IUS could be an ideal method for increasing uptake of long-acting methods among recent postpartum women. Product attributes and comparisons to other contraceptive options are important factors in decision-making. Even among women comfortable with intrauterine contraception, great distinctions and preferences are apparent. Addressing specific misconceptions and fears with better information can help women make the best personal choices.

7. LNG-IUS Dashboard: Perspectives of LNG-IUS Users Across Introduction Programs: available here

This dashboard compiles data collected from multiple organizations from interviews of LNG-IUS adopters so that results can be compared.

8. Nanda G, Rademacher KH, Solomon M, Mercer S, Wawire J, Ngahu R. Experiences with the Levonorgestrel Intrauterine System (LNG-IUS) in Kenya: Qualitative Interviews with Mirena Users and their Partners. *Eur J Contracept Reprod Health Care*. 2018; 10:1-6. Available here.

OBJECTIVES: The levonorgestrel-releasing intrauterine system (LNG-IUS) is an underused contraceptive method in sub-Saharan Africa. A recent market assessment in Kenya found that if a more affordable version of the method were available it may increase demand and uptake of the method. We therefore aimed to examine attitudes and perceptions around the LNG-IUS and experiences of method use, including exploring attributes such as bleeding changes, contraceptive-related amenorrhoea and perceived non-contraceptive benefits.
METHODS: Qualitative interviews were conducted among 29 women who were current or recent users of the LNG-IUS, and among a subset (*n* = 9) of their husbands/partners.
Results: Our findings indicate that women's main reason for choosing the LNG-IUS for contraception was their perception that the method had fewer side effects compared with other contraceptive methods. Women had favourable attitudes towards using the LNG-IUS. Husbands were also very positive about their partner's use of the method.
CONCLUSION: Understanding the motivations and experiences of early adopters of the LNG-IUS can help inform the development of demand creation and communication strategies to influence uptake and continuation of the LNG-IUS both in Kenya and perhaps more broadly. Communication efforts that emphasise the positive attributes of the LNG-IUS could help promote wider use of the method, especially if new, more affordable product(s) become available.

9. Nyarko P, Adohinzin C, Tapsoba P, Esantsi S, Townsend J, Kanlisi N, et al. Acceptability and promotion strategies for LNG-IUS in Ghana: a public health assessment. Accra, Ghana: Population Council, Regional Office for Sub-Saharan Africa; 2009. Available here.

The main objectives of the study were to evaluate client knowledge and acceptability of Levonorgestrel intrauterine contraceptives, provider training and competence, product affordability and accessibility. The study also explored promotion and sustainability strategies that would enhance the integration of the product into the family planning method mix. The results indicate that the product is universally accepted by women who had had the product inserted. More than 90 percent of LNG-IUS clients expressed satisfaction with the colour, shape, size and overall packaging of the product. The overall mean satisfaction score was very high, with four out of five women expressing satisfaction with the product. Providers and non-LNG-IUS users also had similar views. Both users and providers were quite

knowledgeable about the product. In addition, providers had the skills to insert and remove the product, although a few were unsure of their competence. Non-users, on the other hand, mostly did not know about the existence of the product and those who had heard about the product were not adequately informed about it. Almost a third (28%) of LNG-IUS acceptors were new acceptors of contraception. The rest had mostly switched from the injectable, IUD, pill and natural family planning method.

10. Rademacher KH, Solomon M, Brett T, Bratt JH, Pascual C, Njunguru J, Steiner MS. Expanding access to a new, more affordable levonorgestrel intrauterine system in Kenya: A comparison of service delivery costs and perspectives from Key Opinion Leaders. *Glob Health Sci Pract*. 2016;4 Suppl 2:S83-S93. Available here.

BACKGROUND: The levonorgestrel intrauterine system (LNG IUS) is one of the most effective forms of contraception and offers important non-contraceptive health benefits. However, it is not widely available in developing countries, largely due to the high price of existing products. Medicines360 plans to introduce its new, more affordable LNG IUS in Kenya. The public sector transfer price will vary by volume between US$12 to US$16 per unit; for an order of 100,000 units, the public-sector transfer price will be approximately US$15 per unit.
METHODS: We calculated the direct service delivery cost per couple-years of protection (CYP) of various family planning methods. The model includes the costs of contraceptive commodities, consumable supplies, instruments per client visit, and direct labor for counseling, insertion, removal, and resupply, if required. The model does not include costs of demand creation or training. We conducted interviews with key opinion leaders in Kenya to identify considerations for scale-up of a new LNG IUS, including strategies to overcome barriers that have contributed to low uptake of the copper intrauterine device.
RESULTS: The direct service delivery cost of Medicines360's LNG IUS per CYP compares favorably with other contraceptive methods commonly procured for public-sector distribution in Kenya. The cost is slightly lower than that of the 3-month contraceptive injectable, which is currently the most popular method in Kenya. Almost all key opinion leaders agreed that introducing a more affordable LNG IUS could increase demand and uptake of the method. They thought that women seeking the product's non-contraceptive health benefits would be a key market segment, and most agreed that the reduced menstrual bleeding associated with the method would likely be viewed as an advantage. The key opinion leaders indicated that myths and misconceptions among providers and clients about IUDs must be addressed, and that demand creation and provider training should be prioritized.
CONCLUSION: Introducing a new, more affordable LNG IUS product could help expand choice for women in Kenya and increase use of long-acting reversible contraception. Further evaluation is needed to identify the full costs required for introduction—including the cost of demand creation—as well as research among potential and actual LNG IUS users, their partners, and health care providers to help inform scale-up of the method.

Menstrual Bleeding Changes

These resources provide data about the incidence and impact of bleeding changes among users of the LNG-IUS, a noncontraceptive side-effect of the method that may positively or negatively influence uptake and acceptability.

1. **Beckert, V., C. Ahlers, et al. "Bleeding patterns with the 19.5 mg LNG-IUS, with special focus on the first year of use: implications for counselling."** ***Eur J Cont Rep Health Care.*** **(2019). 24(4): 251-259.**

Objective: The aim of the study was to provide an additional, detailed description of early bleeding patterns with the 19.5 mg levonorgestrel-releasing intrauterine system (LNG-IUS). Methods: We conducted a pooled analysis of the bleeding diaries of participants in a previously reported phase II randomised controlled study (n = 741) and a phase III study (n = 2904), with 2-year extension phase (n = 707), of the 19.5 mg LNG-IUS. Main outcome measures were the median number of bleeding and/or spotting days per 30-day reference period for 12 months and the influence of the previous contraceptive method and levonorgestrel dose on bleeding patterns. Results: The pooled analysis comprised 1697 women. There was a progressive decline in the number of bleeding and/or spotting days from month 1: the proportion of women with </=4 bleeding and/or spotting days per month increased from 6.2% in month 1 to 15.8% in month 2, 26.0% in month 3, 39.3% in month 6 and 54.1% in month 12. The median number of bleeding and/or spotting days in month 1 was lowest in women who had previously been using an LNG-IUS. Conclusion: Analysis of bleeding diaries using 30-day reference periods provides detailed insight into bleeding changes in the first months following placement of the 19.5 mg LNG-IUS. This insight may prove useful when counselling women about contraceptive choice and method continuation.

2. Darney PD, Stuart GS, Thomas MA, Cwiak C, Olariu A, Creinin MD.
Amenorrhea rates and predictors during 1 year of levonorgestrel 52 mg intrauterine system use.
Contraception**. 2018;97(3):210-214. Available here.**

OBJECTIVE: The objective was to evaluate amenorrhea patterns and predictors of amenorrhea during the first year after levonorgestrel 52 mg intrauterine system (IUS) placement.
STUDY DESIGN: This cohort analysis includes 1714 nulliparous and parous women who received a Liletta® levonorgestrel 52 mg IUS in a multicenter trial to evaluate efficacy and safety for up to 8 years. Participants maintained a daily diary with bleeding information. We assessed bleeding patterns in 90-day intervals; amenorrhea was defined as no bleeding or spotting in the preceding 90 days. We employed multivariable regression to identify predictors of amenorrhea at 12 months. The predictor analysis only included women not using a levonorgestrel IUS in the month prior to study enrollment.
RESULTS: In the month before enrollment, 148 and 1566 women, respectively, had used and not used a levonorgestrel IUS. Prior users averaged 50±19 months of use before IUS placement; 38.4% of these women reported amenorrhea at 12 months. Amenorrhea rates for non-prior-users at 3, 6, 9 and 12 months were 0.2%, 9.1%, 17.2% and 16.9%, respectively. During the first 12 months, 29 (1.7%) women discontinued for bleeding irregularities; no women discontinued for amenorrhea. The only significant predictor of amenorrhea at 12 months was self-reported baseline duration of menstrual flow of fewer

than 7 days vs. 7 or more days (18.2% vs. 5.2%, adjusted odds ratio 3.70 [1.69, 8.07]). We found no relationships between 12-month amenorrhea rates and age, parity, race, body mass index, baseline flow intensity or hormonal contraception use immediately prior to IUS placement.
CONCLUSIONS: Amenorrhea rates during the first year of levonorgestrel 52 mg IUS use are similar at 9 and 12 months. Amenorrhea at 12 months is most common among women with shorter baseline duration of menstrual flow.

3. Polis CB, Hussain R, Berry A. There might be blood: a scoping review on women's responses to contraceptive-induced menstrual bleeding changes. *Reprod Health*. 2018;15(1):114. Available here.

INTRODUCTION: Concern about side effects and health issues are common reasons for contraceptive non-use or discontinuation. Contraceptive-induced menstrual bleeding changes (CIMBCs) are linked to these concerns. Research on women's responses to CIMBCs has not been mapped or summarized in a systematic scoping review.
METHODS: We conducted a systematic scoping review of data on women's responses to CIMBCs in peer-reviewed, English-language publications in the last 15 years. Investigator dyads abstracted information from relevant studies on pre-specified and emergent themes using a standardized form. We held an expert consultation to obtain critical input. We provide recommendations for researchers, contraceptive counselors, and product developers.
RESULTS: We identified 100 relevant studies. All world regions were represented (except Antarctica), including Africa (11%), the Americas (32%), Asia (7%), Europe (20%), and Oceania (6%). We summarize findings pertinent to five thematic areas: women's responses to contraceptive-induced non-standard bleeding patterns; CIMBCs influence on non-use, dissatisfaction or discontinuation; conceptual linkages between CIMBCs and health; women's responses to menstrual suppression; and other emergent themes. Women's preferences for non-monthly bleeding patterns ranged widely, though amenorrhea appears most acceptable in the Americas and Europe. Multiple studies reported CIMBCs as top reasons for contraceptive dissatisfaction and discontinuation; others suggested disruption of regular bleeding patterns was associated with non-use. CIMBCs in some contexts were perceived as linked with a wide range of health concerns; e.g., some women perceived amenorrhea to cause a buildup of "dirty" or "blocked" blood, in turn perceived as causing blood clots, fibroids, emotional disturbances, weight gain, infertility, or death. Multiple studies addressed how CIMBCs (or menstruation) impacted daily activities, including participation in domestic, work, school, sports, or religious life; sexual or emotional relationships; and other domains.
CONCLUSIONS: Substantial variability exists around how women respond to CIMBCs; these responses are shaped by individual and social influences. Despite variation in responses across contexts and sub-populations, CIMBCs can impact multiple aspects of women's lives. Women 's responses to CIMBCs should be recognized as a key issue in contraceptive research, counseling, and product development, but may be underappreciated, despite likely – and potentially substantial – impacts on contraceptive discontinuation and unmet need for modern contraception.

4. Rademacher KH, Sergison S, Glish L, Maldonado LY, Mackenzie A, Nanda G, Yacobson I. Menstrual Bleeding Changes are NORMAL: Proposed Counseling Tool to Address Common Reasons for Non-Use and Discontinuation of Contraception. *Glob Health Sci Pract*. 2018;6(3)603-610. Available here.

A new family planning counseling tool uses the simple mnemonic device "NORMAL" to help family planning counselors and providers communicate to their clients key messages about menstrual bleeding changes associated with use of hormonal contraception and the copper IUD. The authors noted that development of a counseling tool could help health care providers better communicate with clients about potential bleeding changes associated with contraceptive use. The work described here was undertaken to address this gap.

5. Sergison, JE, Maldonado, LY, Gao, X, Hubacher, D. Levonorgestrel Intrauterine System associated amenorrhea: a systematic review and meta-analysis. Amer Journal of Obstet and Gynecol. 2018. Available here.

OBJECTIVE DATA: Amenorrhea is a polarizing noncontraceptive effect of the levonorgestrel intrauterine system. Composite amenorrhea prevalence estimates that summarize all clinical data for the first-year after insertion currently are not available. The purpose of this study was to investigate the validity of existing prevalence estimates by the systematic calculation of amenorrhea measures for a general population of levonorgestrel intrauterine system users and to provide 90-day interval point estimates for the first year of use.
STUDY: We identified clinical trials, randomized controlled trials, and randomized comparative trials that were published in English between January 1970 and September 2017 through electronic searches of 12 biomedical and scientific literature databases that included MEDLINE and ClinicalTrials.gov.
STUDY APPRAISAL AND SYNTHESIS METHODS: We considered studies that clearly defined amenorrhea per World Health Organization standards (the complete cessation of bleeding for at least 90 days), collected data from written daily bleeding diaries (the gold standard data collection technique on menstrual bleeding changes), and evaluated levonorgestrel intrauterine system devices that released 20 μg of levonorgestrel per day. We assessed study quality using guidelines established by the US Preventive Services Task Force and Cochrane handbook for systematic reviews of interventions. Two reviewers independently conducted all review stages; disagreements were resolved by a third reviewer. Where possible, data were pooled with the use of a random-effects model.
RESULTS: Of 2938 potentially relevant studies, we included 9 in our meta-analysis. We calculated amenorrhea prevalence, which was weighted for inter- and intrastudy variance, for 4 90-day intervals and months 0–12. Our results demonstrated few levonorgestrel intrauterine system users (0.2%; 95% confidence interval, 0.0–0.4) experienced amenorrhea during the first 90 days after insertion; however, prevalence increased to 8.1% (95% confidence interval, 6.6–9.7) on days 91–180. Finally, 18.2% (95% confidence interval, 14.9–21.5) of users experienced amenorrhea for at least 1 90-day interval during the first year. Although interstudy heterogeneity limited reliability of days 181–271 and 272–365 measures, prevalence increased from 13.6% (95% confidence interval, 9.3–18.0) to 20.3% (95% confidence interval, 13.5–27.0), respectively.
CONCLUSION: Approximately 20% of levonorgestrel intrauterine system users experience amenorrhea during at least 1 90-day interval by the first year after insertion. This composite estimate is consistent with the product labeling and demonstrates that most users do not experience amenorrhea during the first year. These results provide accurate summary measures to facilitate counselling and informed method selection.

6. Schreiber CA, Teal SB, Blumenthal PD, Keder LM, Olariu AI, Creinin MD. Bleeding patterns for the Liletta® levonorgestrel 52 mg intrauterine system. *The European Journal of Contraception & Reproductive Health Care*, 2018;23(2):116-120. Available here.

PURPOSE: Evaluate bleeding patterns for the Liletta® levonorgestrel 52 mg intrauterine system (IUS) using the World Health Organization Belsey definitions.
MATERIAL AND METHODS: This prospective multicenter trial evaluates the efficacy and safety of Liletta® (Clinicaltrials.gov NCT00995150). We evaluated bleeding patterns for 1700 nulliparous and multiparous women using a daily diary completed by participants for the first 2 years and by questionnaire every 3 months thereafter. We assessed amenorrhea rates over 3 years and the proportion of subjects with infrequent, frequent, prolonged and irregular bleeding per 90-day reference period over 2 years for the entire study population as well as comparing nulliparous and parous women and obese and non-obese women.
RESULTS: Amenorrhea rates at 1 and 3 years in levonorgestrel 52 mg IUS users were 19 and 37%, respectively. The infrequent bleeding rate increased from 14% in the first 90 days to 30% at the end of Year 1, and was maintained at the same rate through Year 2. Frequent, prolonged and irregular bleeding declined to low levels by the end of the first year. Discontinuation for bleeding-related complaints occurred in 35 (2.1%, 95% CI 1.3–2.7%) women during the first 36 months; only one subject discontinued for amenorrhea (in Year 2). Outcomes did not vary for nulliparous versus parous or obese versus non-obese women.
CONCLUSIONS**:** Among Liletta users, amenorrhea and infrequent bleeding become more prevalent over time and amenorrhea rates continue to increase after the first year of use. Bleeding patterns do not differ significantly by parity or by obesity-status. Discontinuation for bleeding concerns is uncommon with this product.

General Resources

These resources contain general information about the LNG-IUS

1. WHO Essential Medicines List addition of the LNG-IUS: available here.

This page contains information and peer review reports about the LNG-IUS, as well as the method's application for addition to the WHO Essential Medicines List, which was approved in 2015.

2. K4Health IUD Toolkit with LNG-IUS resources: available here.

This toolkit is for health policy makers, program managers, and service providers who are interested in adding new IUD services to their family planning programs or in improving existing IUD services. The Toolkit also contains information related to the importance of ensuring access and availability to long-acting and permanent methods—IUDs, implants, female sterilization, and vasectomy.

Manufacturers

Websites of Manufacturers with LNG-IUS product(s) approved by Stringent Regulatory Authority (SRA)

1. ICA Foundation: http://www.ica-foundation.org/
2. Medicine360: http://www.medicines360.org
3. Bayer Healthcare: www.mirena-us.com/