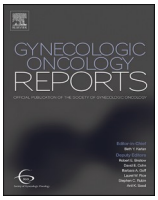
Gynecologic Oncology Reports 49 (2023) 101285

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor



Evidence for some, extrapolation for others: Levonorgestrel IUDs and health equity in Gynecologic Oncology

In this issue of *Gynecologic Oncology Reports*, Chaudhari *et al.* present a retrospective cohort study assessing whether the LILETTA® IUD (L-IUD) yielded non-inferior outcomes compared to Mirena® (M-IUD) for uterus-sparing management of endometrial intraepithelial neoplasia (EIN) or grade 1 endometrioid endometrial cancer (EEC)(Chaudhari et al., 2023). At 3, 6, and 9 months of continuous use, L-IUD had non-inferior rates of EIN regression compared to M-IUD, but no conclusions could be reached for grade 1 EEC. Fortunately, no patients who used L-IUD (n=21) had progression of disease during the study period. The authors concluded that this study provided "a limited, but evidence-based, rationale to treat EIN with the L-IUD."

Many of us think interchangeably about these two 52 mg levonorgestrel IUDs (LNG-IUDs), but we should distinguish between what has been demonstrated and what has been assumed. It is worth considering that LILETTA® IUD is an independent brand-name drug product that underwent its own trials to gain FDA approval for contraception. Both LNG-IUDs use levonorgestrel at similar (yet different) daily release rates that produce similar *contraceptive* efficacy, and these similarities provide some grounding for the assumption that L-IUD would have similar efficacy for off-label *antineoplastic* use. In the absence of testing, however, this remains an educated guess.

There is certainly a role for extrapolation in drug development, but current standards generally balance extrapolation with verification. Biosimilars must meet stringent standards for similarity in pharmacology, immunogenicity, safety, and purity before they get designated as 'interchangeable' with their studied reference drug (Lyman et al., 2018; Nahleh et al., 2022). Generic drugs must likewise go through rigorous processes to demonstrate both pharmaceutical and *in vivo* equivalence to the brand-name original (Lyman et al., 2018; Nahleh et al., 2022). These procedures are anything but casual. L-IUD, on the other hand, has appeared *de facto* in the oncology realm, as if it were a generic Mirena® but without demonstration of antineoplastic efficacy nor true equivalency to M-IUD. While it may be appropriate to use L-IUD in lower-stakes scenarios with *no* current evidence-based standard (*e.g.*, maintenance after EIN regression (ACOG, 2023), we do have a LNG-IUD with *demonstrated* efficacy against EIN and grade 1 EEC (Westin et al., 2021; Janda et al., 2021). As such, we believe we should expect a higher burden of proof than casual extrapolation for L-IUD in oncology care.

Our concerns about the limited evidence for L-IUD non-inferiority are heightened by the disproportionate use of L-IUD among individuals assigned lower socioeconomic status. Chaudhari *et al.* analyzed data from an academic center, where nearly all patients received M-IUDs, and a public safety net hospital that included most of the patients given L-IUDs. This mirrors what we have witnessed as physicians who have both worked in safety net facilities where L-IUD became the only 52 mg LNG-IUD stocked. With a justice lens, we suggest that it is especially vital in a situation like this to uphold our typical evidentiary standards. When those with economic privilege receive studied treatments but those assigned lower socioeconomic status must accept a presumptively similar – but unvetted – stand-in, health equity fully depends on whether "separate" is truly "equal."

We applaud Chaudhari *et al.* for providing initial evidence for L-IUD efficacy for EIN, since we previously had extrapolation alone. Although they do not explicitly frame their study as health equity research, in interrogating a common – even hidden – presumption unequally affecting patients in groups delineated by non-clinical factors, they have investigated a health equity question that goes "beyond documenting the existence of disparities as a novel research finding"(Doll, 2018).

Respectfully, we also need to acknowledge the limitations of this small and retrospective analysis. Chaudhari *et al.*'s paper is important work, but it is just a start rather than the final word. Critically, no conclusion can be reached regarding the non-inferiority of L-IUD in treating grade 1 EEC. This study was also not powered to demonstrate non-inferiority beyond the 9-month mark even for EIN; for individuals who receive an IUD because their comorbidities pose great surgical risk, we will need longer-duration analyses. Finally, we would benefit from more contextual information within the article, such as the reasons 77% of the potential sample became excluded, the characteristics of that excluded majority, and the reasons for attrition from one timepoint to the next (*e.g.*, treatment discontinuation to pursue pregnancy *vs.* hysterectomy).

Future opportunity exists to shift toward lower-cost products *after* appropriate evidentiary thresholds are met. The best way to gather more support for non-inferiority of L-IUD in EIN/EEC treatment is open to debate. As Chaudhari *et al.* suggest, stronger evidence could come from prospective clinical trials. As other groups provide results retrospectively for treatment that has already occurred, their work may also corroborate or disconfirm the hypothesis of L-IUD's non-inferiority. As additional pharmacologic and clinical data accrue, we would also advocate for an expert panel to review L-IUD use in the oncologic setting through a formalized, systematic process.

For now, however, presuming the efficacy of L-IUD for grade 1 EEC in particular remains a bit of a gamble for all involved – a gamble with seemingly good odds, but a gamble nonetheless. For patients, the stakes of this bet are high: preservation of fertility, cure of a curable cancer, and avoidance of surgical risk in the face of serious comorbidities. For healthcare costs, we wager about $250 savings per device (Chaudhari et al., 2023; Roth et al., 2018) against the risk that L-IUD could turn out

https://doi.org/10.1016/j.gore.2023.101285

Available online 28 September 2023

even marginally less effective. We posit that just a few additional cases of L-IUD failure leading to costly subsequent treatment could nullify the savings from utilizing less expensive devices. Finally, for providers, it is disheartening to see quite modest cost savings invoked to overrule treatment decisions that we feel are the most evidence-based at present. For now, we would advocate for payer coverage and clinical provision of well-studied cancer treatments. We also encourage transparent shared decision-making with patients who are good candidates for LNG-IUD treatment but who face barriers to M-IUD access.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Management of Endometrial Intraepithelial Neoplasia or Atypical Endometrial Hyperplasia: ACOG Clinical Consensus No. 5. Obstetrics Gynecol 142, 2023, 735–744. https://doi.org/10.1097/AOG.0000000000005297.

Chaudhari, S.R., Lai, T.S., Zakhour, M., Myung Shin, S., Baltayan, A., Tan, H., Cohen, J. G., 2023. Comparison of Mirena and Liletta levonorgestrel intrauterine devices for the treatment of endometrial intraepithelial neoplasia and grade 1 endometrioid endometrial cancer. Gynecol. Oncol. Rep. 49, 101257 https://doi.org/10.1016/j.gore.2023.101257.

Doll, K.M., 2018. Investigating Black-White disparities in gynecologic oncology: Theories, conceptual models, and applications. Gynecol. Oncol. 149, 78–83. https://doi.org/10.1016/j.ygyno.2017.10.002.

Janda, M., Robledo, K.P., Gebski, V., Armes, J.E., Alizart, M., Cummings, M., Chen, C., Leung, Y., Sykes, P., McNally, O., Oehler, M.K., Walker, G., Garrett, A., Tang, A., Land, R., Nicklin, J.L., Chetty, N., Perrin, L.C., Hoet, G., Sowden, K., Eva, L., Tristram, A., Obermair, A., 2021. Complete pathological response following levonorgestrel intrauterine device in clinically stage 1 endometrial adenocarcinoma: results of a randomized clinical trial. Gynecol. Oncol. 161, 143–151. https://doi.org/10.1016/j.ygyno.2021.01.029.

Lyman, G.H., Balaban, E., Diaz, M., Ferris, A., Tsao, A., Voest, E., Zon, R., Francisco, M., Green, S., Sherwood, S., Harvey, R.D., Schilsky, R.L., 2018. American Society of Clinical Oncology statement: biosimilars in oncology. J. Clin. Oncol. 36, 1260–1265. https://doi.org/10.1200/JCO.2017.77.4893.

Nahleh, Z., Lyman, G.H., Schilsky, R.L., Peterson, D.E., Tagawa, S.T., Chavez-MacGregor, M., Rumble, R.B., Gupta, S., 2022. Use of biosimilar medications in oncology. JCO Oncol. Pract. 18, 177–186.

Roth, L.P., Sanders, J.N., Simmons, R.G., Bullock, H., Jacobson, E., Turok, D.K., 2018. Changes in uptake and cost of long-acting reversible contraceptive devices following the introduction of a new low-cost levonorgestrel IUD in Utah's Title X clinics: a retrospective review. Contraception 98, 63–68.

Westin, S.N., Fellman, B., Sun, C.C., Broaddus, R.R., Woodall, M.L., Pal, N., Urbauer, D. L., Ramondetta, L.M., Schmeler, K.M., Soliman, P.T., Fleming, N.D., Burzawa, J.K., Nick, A.M., Milbourne, A.M., Yuan, Y., Lu, K.H., Bodurka, D.C., Coleman, R.L., Yates, M.S., 2021. Prospective phase II trial of levonorgestrel intrauterine device: nonsurgical approach for complex atypical hyperplasia and early-stage endometrial cancer. Am. J. Obstetrics Gynecol. 224 (191), e1–191.e15. https://doi.org/10.1016/j.ajog.2020.08.032.

Benjamin J. Matthews*
The Kelly Gynecologic Oncology Service, Department of Gynecology & Obstetrics, Johns Hopkins University School of Medicine, Baltimore, MD, United States

Stephen J. Fiascone
Department of Obstetrics & Gynecology, Boston Medical Center, Boston, MA, United States

* Corresponding author.
E-mail address: bmatth24@jh.edu (B.J. Matthews).