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Insights into the COVID-19 vaccine's effects on menstrual cycle irregularities; results of an RCT that examined the use of drospirenone 4 mg in a 24/4 regimen as an AUB treatment; a systematic review on placing a levonorgestrel-releasing intrauterine system after endometrial ablation; and a cost-effectiveness analysis of 2 treatments for HMB

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In this Update, we focus on therapies for abnormal uterine bleeding (AUB) that include a new formulation of a progesterone-only pill (POP), drospirenone 4 mg in a 24/4 regimen (24 days of drospirenone/4 days of inert tablets), which recently showed benefit over the use of desogestrel in a European randomized clinical trial (RCT). Two other commonly used treatments for AUB—the levonorgestrel-releasing intrauterine

system (LNG IUS) and endometrial ablation—were studied in terms of cost-effectiveness as well as whether they should be used in combination for added efficacy. In addition, although at times either COVID-19 disease or the COVID-19 vaccine has been blamed for societal and medical problems, one study showed that it is unlikely that significant changes in the menstrual cycle are a result of the COVID-19 vaccine.

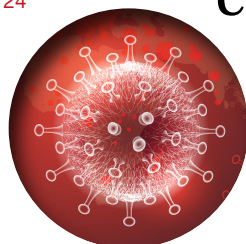
COVID-19 vaccination had minimal effects on menstrual cycle length

Edelman A, Boniface ER, Benhar W, et al. Association between menstrual cycle length and coronavirus disease 2019 (COVID-19) vaccination: a US cohort. *Obstet Gynecol.* 2022;139:481-489.

Does receiving the COVID-19 vaccination result in abnormal menstrual cycles? Patients often ask this question, and it has been a topic of social media

discussion (including NPR) and concerns about the possibility of vaccine hesitancy,^{1,2} as the menstrual cycle is often considered a sign of health and fertility.

To better understand this possible association, Edelman and colleagues conducted a study that prospectively tracked menstrual cycle data using the digital app Natural Cycles in US residents aged 18 to 45 years for



3 consecutive cycles in both a vaccinated and an unvaccinated cohort.³ Almost 4,000 individuals were studied; 2,403 were vaccinated and 1,556 were unvaccinated. The study vaccine types included the BioNTech (Pfizer), Moderna, Johnson & Johnson/Janssen, and unspecified vaccines.

The primary outcome was the within-individual change in cycle length in days, comparing a 3-cycle postvaccine average to a 3-cycle prevaccination average in the 2 groups. (For the unvaccinated group, cycles 1, 2, and 3 were considered the equivalent of prevaccination cycles; cycle 4 was designated as the artificial first vaccine dose-cycle and cycle 5 as the artificial second-dose cycle.)

Increase in cycle length clinically negligible

The investigators found that the vaccinated cohort had less than a 1-day unadjusted increase in the length of their menstrual cycle, which was essentially a 0.71-day increase (98.75% confidence interval [CI], 0.47–0.94). Although this is considered statistically significant, it is likely clinically insignificant in that the overlaid histograms comparing the distribution of change showed a cycle length distribution in vaccinated individuals that is essentially equivalent to that in unvaccinated individuals. After adjusting for confounders, the difference in cycle length was reduced to a 0.64 day (98.75% CI, 0.27–1.01).

An interesting finding was that a subset of individuals who received both vaccine doses in a single cycle had, on average, an adjusted 2-day increase in their menstrual cycle compared with unvaccinated individuals. To explain this slightly longer cycle length, the authors postulated that mRNA vaccines create an immune response, or stressor, which could temporarily affect the hypothalamic-pituitary-ovarian axis if timed correctly. It is certainly possible for an individual to receive 2 doses in a single cycle, which could have both been administered in the early follicular phase. Such cycle length variability can be caused by events, including stressors, that affect the recruitment and maturation of the dominant follicle.

Counseling takeaway

This study provides reassurance to most individuals who receive a COVID-19 vaccine that it likely will not affect their menstrual cycle in a clinically significant manner.

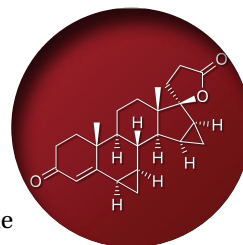
WHAT THIS EVIDENCE MEANS FOR PRACTICE

This robust study by Edelman and colleagues on COVID-19 vaccination effects on menstrual cycle length had more than 99% power to detect an unadjusted 1-day difference in cycle length. However, given that most of the study participants were White and had access to the Natural Cycles app, the results may not be generalizable to all individuals who receive the vaccine.

Drospirenone improved bleeding profiles, lowered discontinuation rates compared with desogestrel

Regidor PA, Colli E, Palacios S. Overall and bleeding-related discontinuation rates of a new oral contraceptive containing 4 mg drospirenone only in a 24/4 regimen and comparison to 0.075 mg desogestrel. Gynecol Endocrinol. 2021;37:1121-1127.

A new POP, marketed under the name Slynd, recently came to market. It contains the progestin drospirenone (DRSP) 4 mg in a 24/4 regimen. This formulation has the advantage of being



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Adherence to a contraceptive method is influenced by patient satisfaction, and this is particularly important in patients who cannot take COCs. It also should be noted that the discontinuation rate for DRSP as a POP used in this 24/4 regimen was similar to discontinuation rates for COCs containing 20 µg and 30 µg of ethinyl estradiol. Cost, however, may be an issue with DRSP, depending on a patient's insurance coverage.

an antiandrogenic progestin, with a long enough half-life to allow for managing a missed pill in the same fashion as combined oral contraceptives (COCs).

Investigators in Europe conducted a double-blind, randomized trial to assess discontinuation rates due to adverse events (mainly bleeding disorders) in participants taking DRSP 4 mg in a 24/4 regimen compared with those taking the POP desogestrel (DSG) 0.075 mg, which is commonly used in Europe.⁴ Regidor and colleagues compared 858 women

with 6,691 DRSP treatment cycles with 332 women with 2,487 DSG treatment cycles.

Top reasons for stopping a POP

The discontinuation rate for abnormal bleeding was 3.7% in the DRSP group versus 7.3% in the DSG group (55.7% lower). The most common reasons for stopping either POP formulation were vaginal bleeding and acne. Both of these adverse events were less common in the DRSP group. Pill discontinuation due to vaginal bleeding was 2.6% in the DRSP group versus 5.4% in the DSG group, while discontinuation due to acne occurred in 1% in the DRSP group versus 2.7% in the DSG group.

New oral contraception option

This study shows improved acceptability and bleeding profiles in women using this new DRSP contraception pill regimen.



Placing an LNG IUS after endometrial ablation for heavy menstrual bleeding reduced risk of hysterectomy

Oderkerk TJ, van de Kar MMA, van der Zanden CHM, et al. *The combined use of endometrial ablation or resection and levonorgestrel-releasing intrauterine system in women with heavy menstrual bleeding: a systematic review. Acta Obstet Gynecol Scand. 2021;100:1779-1787.*

Over the years, a smattering of articles have suggested that a reduction in uterine bleeding was associated with placement of an LNG IUS at the conclusion of endometrial ablation. We now have a systematic review of this surgical modification.

Oderkerk and colleagues sifted through 747 articles to find 7 publications that could

provide meaningful data on the impact of combined use of endometrial ablation and LNG IUS insertion for women with heavy menstrual bleeding.⁵ These included 4 retrospective cohort studies with control groups, 2 retrospective studies without control groups, and 1 case series. The primary outcome was the hysterectomy rate after therapy.

Promising results for combined therapy

Although no statistically significant intergroup differences were seen in the

combined treatment group versus the endometrial ablation alone group for the first 6 months of treatment, significant differences existed at the 12- and 24-month mark. Hysterectomy rates after combined treatment varied from 0% to 11% versus 9.4% to 24% after endometrial ablation alone. Complication rates for combined treatment did not appear higher than those for endometrial ablation alone.

The authors postulated that the failure of endometrial ablation is generally caused by either remaining or regenerating endometrial tissue and that the addition of an LNG IUS allows for suppression of endometrial tissue. Also encouraging was that, in general, the removal of the LNG IUS was relatively simple. A single difficult removal was described due to uterine synechiae, but hysteroscopic resection was not necessary. The authors acknowledged that the data from

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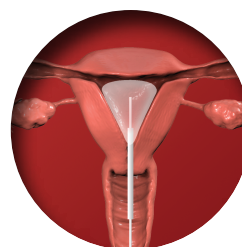
The data provided by Oderkerk and colleagues' systematic review are promising and, although not studied in the reviewed publications, the potential may exist to reduce the risk of endometrial hyperplasia and endometrial cancer by adding an LNG IUS.

these 7 retrospective studies are limited and that high-quality research from prospective studies is needed.

Bottom line

The data available from this systematic review suggest that placement of an LNG IUS at the completion of an endometrial ablation may result in lower hysterectomy rates, without apparent risk, and without significantly difficult LNG IUS removal when needed.

LNG IUS is less expensive, and less effective, than endometrial ablation for heavy menstrual bleeding, cost analysis shows



van den Brink MJ, Beelen P, Herman MC, et al. The levonorgestrel intrauterine system versus endometrial ablation for heavy menstrual bleeding: a cost-effectiveness analysis. BJOG. 2021;128:2003-2011.

To assess the cost-effectiveness of the LNG IUS versus endometrial ablation in the treatment of heavy menstrual bleeding, van den Brink and colleagues conducted a multicenter randomized, noninferiority trial.⁶

Part of the rationale for this study was to better understand the cost differences between the LNG IUS and second-generation endometrial ablation. Some data have suggested that the LNG IUS is cost-effective when compared with first-generation endometrial

ablation; however, definitive evidence about its cost compared with second-generation endometrial ablation is lacking, as these procedures should be less expensive than first-generation endometrial ablation since they frequently are performed in the office rather than in an operating room.

Cost-effectiveness and noninferiority assessed

A total of 270 women were randomly assigned to 1 of 2 treatment strategies. Eventually, 132 women were treated first with the 52-mg LNG IUS, and 138 were treated first with endometrial ablation by

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It is interesting that there are minimal differences between satisfaction rates and PBAC scores less than 75, yet the mean PBAC scores were significantly more favorable for endometrial ablation. This study's results support the use of a sequential therapy of a less invasive therapy, such as the LNG IUS, prior to performing endometrial ablation.

radiofrequency ablation. Menstrual blood loss after 24 months was the primary outcome.

At 24 months, the mean pictorial blood loss assessment chart (PBAC) scores were 64.8 in the LNG IUS group compared with 14.2 in the endometrial ablation group. Given that the noninferiority margin was defined as 25 points, noninferiority could not be demonstrated.

However, when looking at PBAC scores less than 75 points, the LNG IUS group met this secondary end point in 87% of women versus 94% in the endometrial ablation group. When satisfaction was assessed, 74% of women in the LNG IUS group were satisfied compared with 84% in the endometrial ablation group.

Overall, the total costs per patient were €2,285 in the LNG IUS strategy and €3,465 in the endometrial ablation strategy (costs convert to \$2,285 and \$3,465 as of this writing).

Key takeaway

Treatment of heavy menstrual bleeding starting with the LNG IUS is cheaper, but it is slightly less effective than endometrial ablation. ●

References

- Blumfiel G. Why reports of menstrual changes after COVID vaccine are tough to study. *NPR*. August 9, 2021. Accessed August 30, 2022. <https://www.npr.org/sections/health-shots/2021/08/09/1024190379/covid-vaccine-period-menstrual-cycle-research>
- Lee KMN, Junkins EJ, Fatima UA, et al. Characterizing menstrual bleeding changes occurring after SARS-CoV-2 vaccinations. *MedRxiv*. February 11, 2022. doi:10.1101/2021.10.11.21264863
- Edelman A, Boniface ER, Benhar W, et al. Association between menstrual cycle length and coronavirus disease 2019 (COVID-19) vaccination: a US cohort. *Obstet Gynecol*. 2022;139:481-489.
- Regidor PA, Colli E, Palacios S. Overall and bleeding-related discontinuation rates of a new oral contraceptive containing 4 mg drospirenone only in a 24/4 regimen and comparison to 0.075 mg desogestrel. *Gynecol Endocrinol*. 2021;37:1121-1127.
- Oderkerk TJ, van de Kar MMA, van der Zanden CHM, et al. The combined use of endometrial ablation or resection and levonorgestrel-releasing intrauterine system in women with heavy menstrual bleeding: a systematic review. *Acta Obstet Gynecol Scand*. 2021;100:1779-1787.
- van den Brink MJ, Beelen P, Herman MC, et al. The levonorgestrel intrauterine system versus endometrial ablation for heavy menstrual bleeding: a cost-effectiveness analysis. *BJOG*. 2021;128:2003-2011.