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GYNECOLOGY

Hormone-related side effects in new users of a levonorgestrel 52-mg intrauterine device

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BACKGROUND: Although the levonorgestrel 52 mg intrauterine device is locally active and has low systemic hormone exposure, hormonal intrauterine device users sometimes report hormone-related side effects.
OBJECTIVE: Evaluate hormone-related adverse event rates among all participants and compare these among those who used combined hormonal or no hormonal contraception in the month before enrollment.
STUDY DESIGN: A total of 1714 women aged 16 to 45 years old received a levonorgestrel 52 mg intrauterine device in a multicenter phase 3 trial to evaluate contraceptive efficacy and safety for up to 10 years. This analysis evaluated a subset of participants who used combined hormonal or no hormonal contraception in the month prior to device placement. We assessed all nonexpulsion, nonbleeding-related events with ≥1% incidence at 180 days with a plan to include weight increase regardless of incidence; we excluded events considered nonhormonal. We computed 180-day side effect frequency rates based on the number of days a side effect was reported during the study period. We created a multivariable model for side effect incidence at 180 days based on age, race, ethnicity, body mass index at enrollment, parity, and contraception use in the month before enrollment. For those side effects with a P value <.2 on univariate comparison between combined hormonal and no hormonal contraception users, we secondarily evaluated 360-day event rates.
RESULTS: Overall, 644 participants used combined hormonal contraception (primarily oral [n=499, 77.5%]) and 855 used no hormonal method before intrauterine device placement. Individual side effect rates over the first 180 days did not differ between prior combined hormonal and no hormonal contraception users except for acne (84 [13.0%] vs 73 [8.5%], respectively), P=.006, odds ratio 1.61 (95% confidence interval 1.15–2.24). However, this association was weaker after adjustment for age, race, ethnicity, obesity status, and parity (adjusted odds ratio 1.40, 95% confidence interval 0.99–1.98) At 360 days, prior combined hormonal contraception users were more likely to report acne (101 [15.7%] vs 91 [10.6%], respectively, P=.005) and orgasm/libido problems (20 [3.1%] vs 12 [1.4%], respectively, P=.03). Over the first 180 days, all side effects other than acne were reported in less than 3% of days; acne was reported an average of 13 days (7.4%) per prior combined hormonal contraception user and 9 days (5.0%) per prior nonhormonal contraception user (P<.0001). Discontinuation for evaluated side effects occurred in 83 (5.5%) participants with no difference between those who used combined hormonal (36 [5.6%]) or no hormonal contraception (47 [5.5%], P=1.0) before study entry.
CONCLUSION: Using combined hormonal contraception prior to levonorgestrel 52 mg intrauterine device placement is weakly associated with reporting hormonally related side effects like acne. Only a small percentage of levonorgestrel 52 mg intrauterine device users experienced potentially hormone-related side effects during the initial 6 months of use that resulted in discontinuation.

Key words: contraception, intrauterine device, levonorgestrel, Liletta, side effects

Introduction

Contraceptive clinical trials evaluating efficacy require enrollment of heterosexually active participants; such couples may be commonly using a contraceptive method prior to starting the study. Thus, some side effects reported in the early months of a trial could be related to cessation of the prior method. When these studies are performed for regulatory approval, adverse event reporting, as required by regulatory agencies, includes new events or worsening of existing conditions that occur after study product initiation.

Intrauterine devices (IUDs) have the benefit of being locally active and highly effective. Although hormonal IUDs have very low systemic hormone exposure,[1] participants in some IUD clinical trials reported hormone-related side effects.[2–5] We hypothesized that some side effects may be related to recent cessation of estrogen-containing combined hormonal contraception (CHC) and not necessarily related to initiating a progestin-only IUD. To evaluate this hypothesis, we reviewed available data from A Comprehensive Contraceptive Efficacy and Safety Study of an IUS (ACCESS IUS), the phase 3 study trial performed for regulatory approval of Liletta (Medicines360, San Francisco, CA and Abbvie, North Chicago, IL; Liletta is a registered trademark of Odyssea Pharma SPRL [Belgium], an Abbvie affiliate).[4–6]

Materials and methods

This report represents a secondary analysis of data from the ACCESS IUS multicenter trial; the methods of the main study have been reported previously.[4,5] A central or local Institutional Review Board for each center approved the study. All participants signed written informed consents before study participation.

Briefly, investigators at 29 clinical sites in the United States invited healthy, nonpregnant, sexually active (at least 4 times monthly), nulliparous

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AJOG at a Glance

Why was this study conducted?

To evaluate whether side effects reported shortly after levonorgestrel 52-mg intrauterine device (IUD) placement are related to other factors, especially the contraceptive method the person was using prior to placement.

Key findings

Some side effects, specifically acne and orgasm/libido problems, are reported more frequently in persons who stop combined hormonal contraceptives to start a levonorgestrel 52-mg IUD compared to prior users of nonhormonal contraception. Study participants recently using combined hormonal contraception more frequently reported acne after starting a levonorgestrel 52-mg IUD as compared to participants who had been using nonhormonal contraception; obesity and nulliparity were associated with reporting acne during the first year after IUD placement.

What does this add to what is known?

No information is available for providers or patients about early side effects reported in new users of a levonorgestrel 52-mg IUD. These findings are novel and will help providers and patients understand which effects might be more related to stopping a combined hormonal contraceptive.

and parous women aged 16 to 45 years (inclusive) with regular menstrual cycles (21−35 days when not using hormones and with a variation of typical cycle length of no more than 5 days), and who desired a hormonal IUD for contraception to participate. After IUD placement (enrollment), participants received a daily paper diary to record spotting, bleeding, cramping, and additional contraceptive use. During the first year, participants had in-person follow-up visits at 1, 3, 6, and 12 months and a phone call at 9 months. During each interaction, study staff asked in an open-ended manner about new health concerns and considered any new health issue or worsening of an existing condition as an adverse event.

Investigators at each study site assessed the severity of adverse events (safety outcomes) and their relationship to IUD use, placement, or removal. We organized adverse events into standardized terms using the Medical Dictionary for Regulatory Activities (MedDRA) in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

For this analysis, our primary aim was to evaluate nonbleeding-related adverse events that could represent a hormone-related side effect from the IUD during the first 180 days of IUD use. We included participants with successful IUD placement and at least one 28-day cycle of follow-up and excluded those who used a progestin-only IUD, pill, or implant in the month before enrollment. Participants who had recently used injectable contraception were not eligible for enrollment. We included all events reported, even if the investigator assessed the event as not related to the IUD. We assessed the primary outcomes of hormone-related adverse event rates among all participants in the analysis and compared these rates among those who used CHC or no hormonal contraception (NHC) in the month before enrollment. For the evaluation, we initially included all nonexpulsion, nonbleeding-related events with ≥1% incidence at 180 days in prior CHC or NHC users with a plan to include weight increase regardless of incidence. We condensed similar MedDRA terms as shown in Appendix 1. We excluded upper respiratory or gastrointestinal illnesses, vulvovaginal infections or pruritus, cervical dysplasia, contusion, insomnia, back pain, dizziness, and presyncope as nonhormonally related. For those side effects with a P value <.2 on univariate comparison between CHC and NHC users at 180 days, we secondarily evaluated 360-day event rates. We also evaluated side effect frequency rates based on the number of days of a side effect reported during the 180-day study period.

We used Fisher exact and chi-square testing for comparisons of proportions. We created a multivariable model to evaluate correlates of reporting a side effect with a significant difference at 180 or 360 days in incidence between prior CHC and NHC users based on age, race, ethnicity, body mass index at enrollment, parity, and CHC use in the month before enrollment. We performed statistical analyses using SAS 9.4 (SAS Institute, Inc, Cary, NC) with a P value of .05 considered statistically significant.

Results

Of the 1714 with successful IUD insertion, 1499 (87.5%) met the criteria for this analysis. Demographic characteristics differed significantly between prior CHC and NHC users and appear in Table 1. Among the 644 prior CHC users, the contraceptive method used in the month before enrollment was a pill (n=499 [77.5%]), ring (n=136 [21.1%]), or patch (n=9 [1.4%]). The 855 prior NHC participants reported using a nonhormonal/non-IUD method (n=676 [79.1%]), a copper IUD (n=30 [3.5%]), or no method (n=149 [17.4%]). Overall, 1487 (99.2%), 1440 (96.1%), 1369 (91.3%), and 1237 (82.5%) participants in this analysis continued IUD use at 1, 3, 6 (180 days), and 12 (360 days) months, respectively.

Side effect rates over the first 180 days of IUD use are presented in Table 2 for all participants in the analysis by prior CHC and NHC use. Acne was the only side effect that differed between new IUD users who had used CHCs (84 [13.0%]) vs NHCs (73 [8.5%]), P=.006 before IUD use. Of note, orgasm/libido problems among prior CHC and NHC users were infrequent but almost

TABLE 1
Demographics of participants in a phase 3 study of a levonorgestrel 52-mg IUD based on contraceptive use in the month prior to enrollment[a]

Characteristic	Total N=1499	CHC n=644	NHC n=855	*P* value[b]
Age at enrollment (y)	27.0±5.6	26.7±5.1	27.2±5.9	.06
<25	576 (38.4)	268 (41.6)	308 (36.0)	.03
25–45	923 (61.6)	376 (58.4)	547 (64.0)	
Race				
White	1170 (78.1)	545 (84.6)	625 (73.1)	<.001
Black or African American	199 (13.3)	45 (7.0)	154 (18.0)	
Asian	62 (4.1)	26 (4.0)	36 (4.2)	
Multiracial	40 (2.7)	17 (2.6)	23 (2.7)	
Other[c]	28 (1.9)	11 (1.7)	17 (2.0)	
Ethnicity				
Hispanic or Latina	221 (14.7)	56 (8.7)	155 (18.1)	<.001
BMI at enrollment (kg/m^2)[d]	26.9±6.7	26.1±6.3	27.5±6.9	<.001
Obese (≥30.0)	372 (24.8)	130 (20.2)	242 (28.3)	<.001
Parity				
Nulliparous	907 (60.5)	466 (72.4)	441 (51.6)	<.001

Data presented as n (%) or mean±standard deviation.

BMI, body mass index; *CHC*, combined hormonal contraceptive; *IUD*, intrauterine device; *NHC*, no hormonal contraceptive.

[a] Excludes 23 women with successful IUD placement and no follow-up information during the study period, 147 with levonorgestrel IUD use in the month prior to enrollment, and 45 with other progestin-only hormonal contraception use in the month prior to enrollment; [b] Comparing CHC and NHC users, Fisher exact or chi-square testing; [c] Includes 19 American Indian or Alaska Native, 5 Native Hawaiian or Other Pacific Islander, and 4 with missing information; [d] Two persons with missing information.

reached statistical significance at 180 days (13 [2.0%] vs 7 [0.8%], respectively, *P*=.07). We evaluated 6 side effects with a *P* value <.2 at 180 days for the 360-day analysis (Appendix 2); from 180 to 360 days, the rates for these 6 side effects increased slightly for acne (10.5% to 12.8%), alopecia (1.3% to 1.7%), breast pain/tenderness (4.5% to 5.3%), mood changes (4.5% to 5.2%), weight increase/poor weight loss (2.6% to 3.6%), and orgasm/libido problems (1.3% to 2.1%). At 360 days, more prior CHC than NHC users reported acne (101 [15.7%] vs 91 [10.6%], *P*=.005) and orgasm/libido problems (20 [3.1%] vs 12 [1.4%], *P*=.03).

When averaged across the study population over the first 180 days of IUD use, the event frequency rate (number of days of each side effect) of all side effects other than acne were reported in less than 3% of days (Appendix 3). Acne, however, was reported an average of 13 days (7.4%) per prior CHC user and 9 days (5.0%) per prior NHC user (*P*<.0001). Table 3 includes the number of days that a participant who reported the event experienced that side effect. Of note, days per affected participant were 100 days or more for a few categories, including acne among 73 prior NHC users (100 days), alopecia among 12 prior CHC users (103 days), anxiety/panic issues among 9 prior CHC users (101 days), orgasm/libido issues among 12 prior CHC users (106 days) and 7 prior NHC users (111 days), and weight increase/poor weight loss among 27 prior NHC users (110 days).

Despite these high number of adverse event days reported by a few users over the first 180 days, discontinuation for any of these side effects occurred in only 83 (5.5%) participants (Table 4), with no difference between those who used CHCs or NHCs prior to study entry ((36 [5.6%]) vs (47 [5.5%]), *P*=1.0). In the first 180 days, the only side effects with a discontinuation rate of 1% or more were mood changes (1.1%) and acne (1.0%). Most of the individual adverse event category numbers are small and no statistical differences are evident.

In multivariable modeling to evaluate factors associated with reporting acne or orgasm/libido issues during the first 6 months of IUD use (Table 5), the unadjusted odds for reporting acne based on method used (CHC or NHC) prior to IUD insertion (odds ratio 1.61, 95% confidence interval [CI] 1.15–2.24) are no longer significant (adjusted odds ratio 1.40, 95% CI 0.99–1.98). Notably,

TABLE 2
Nonexpulsion side effects[a] over the first 180 days of levonorgestrel 52-mg IUD use

Side effect	Total N=1499	CHC users[b] n=644	NHC users[b] n=855	*P* value[c]
Abdominal discomfort/pain	43 (2.9)	18 (2.8)	25 (2.9)	>.99
Acne	157 (10.5)	84 (13.0)	73 (8.5)	.006
Alopecia	20 (1.3)	12 (1.9)	8 (0.9)	.17
Anxiety/panic issues	26 (1.7)	9 (1.4)	17 (2.0)	.43
Breast pain/tenderness	67 (4.5)	34 (5.3)	32 (3.7)	.16
Depression	30 (2.0)	12 (1.9)	18 (2.1)	.85
Dyspareunia	64 (4.3)	31 (4.8)	33 (3.9)	.53
Fatigue	15 (1.0)	6 (0.9)	9 (1.0)	>.99
Headache (nonmigraine)	86 (5.7)	34 (5.3)	52 (6.1)	.58
Migraine headache	22 (1.5)	9 (1.4)	13 (1.5)	>.99
Mood changes	67 (4.5)	22 (3.4)	44 (5.2)	.13
Nausea[d]	43 (2.9)	16 (2.5)	27 (3.1)	.53
Orgasm/libido problems	19 (1.3)	12 (1.9)	7 (0.8)	.10
Ovarian cyst	22 (1.5)	11 (1.7)	11 (1.3)	.52
Pelvic pain/discomfort	61 (4.1)	23 (3.6)	38 (4.4)	.43
Vaginal odor/discharge	55 (3.7)	20 (3.1)	35 (4.1)	.33
Weight increase/poor weight loss	39 (2.6)	12 (1.9)	27 (3.2)	.14

Data presented as n (%).

CHC, combined hormonal contraceptive; *IUD*, intrauterine device; *NHC*, no hormonal contraceptive.

[a] New events or worsening of preexisting conditions with an incidence ≥1%; [b] Method used in the mo before IUD placement; [c] Comparing CHC and NHC users, Fisher exact test; [d] Vomiting (1.3% overall) not included because we could not separate participants who had nausea and vomiting from those with just vomiting.

both obese and nulliparous participants had significantly higher adjusted odds (70% and 60%, respectively) of reporting acne compared to their counterparts. No factors were associated with orgasm/libido issues, though the number of cases was small.

Comment

Principal findings

New levonorgestrel 52-mg IUD users were more likely to report acne in the first 180 days of use if they had used a CHC immediately prior to IUD initiation as compared to those who had not used hormones. However, this association was weaker after adjustment for age, race, ethnicity, obesity status, and parity. In extension through the first year of use, prior CHC users were more likely to report acne or orgasm/libido issues than participants who had not used any hormones in the month prior to IUD insertion. In the adjusted analysis, prior CHC use did not predict acne or orgasm/libido issues. The prior CHC and NHC groups were demographically very dissimilar, which demonstrates the inherent differences in the characteristics of people who use CHCs as compared to nonhormonal methods. Interestingly, nonobese and parous participants had approximately 40% lower odds of reporting acne with levonorgestrel 52-mg IUD use.

Event rates for any side effect do not reflect the significance of that effect since an event that occurs for 1 day counts the same as an event that occurs for 3 months. Overall, the number of days of experiencing a hormone-related side effect were relatively small for the total population of levonorgestrel 52-mg IUD users. Over the first 180 days of IUD use, all side effects other than acne were reported in less than 3% of days (5 days per participant). When limiting the calculation to those who reported the side effect, the number of days the event was experienced was notably high for acne (73 prior NHC users) and alopecia (12 prior CHC users). We can postulate that most of these events were relatively mild in nature as few discontinued IUD use as a result.

Similarly, discontinuation rates also may provide significant insight into how bothersome the side effect is for a participant. Overall, few (5.5%) participants discontinued for a potentially hormone-related side effect in the first 180 days with the most common still only having rates of about 1% (mood changes and acne). The side effects reported with more frequency, although by few participants, did not correlate with the most common side effects resulting in discontinuation, implying that the events were relatively mild in nature or there were other unmeasurable factors.

Results in the context of what is known

Patients use CHCs for acne treatment and several placebo-controlled trials have demonstrated therapeutic benefit of combined oral contraceptives (COCs) for acne.[7,8] A retrospective analysis of a commercial claims database published in 2020 included more than 330,000 patients, of which 279,144 used a COC, 35,597 used a levonorgestrel IUD, 7203 used a copper IUD, and the remainder used progestin-only pills, implants, or injectables.[9] The authors reported similar increases in risk of a clinical encounter for acne among those who switched from a COC to a levonorgestrel IUD (aHR 1.93, 95% CI 1.69−2.22) and copper IUD (aHR 1.70, 95% CI 1.23−2.35). These risks were higher than the risk of incident acne or treatment escalation from topical to oral acne treatment during the first year of use with either IUD as compared to COC

TABLE 3
Frequency (percent of total days) and days of nonexpulsion side effects[a] reported over the first 180 days of levonorgestrel 52-mg IUD use

	CHC users[b] IUD exposure (d)=112,373			NHC users[b] IUD exposure (d)=148,085		
Side effect	Days with side effect [n (%)]	# with event n=644	Days per affected person	Days with side effect [n (%)]	# with event n=855	Days per affected person
Abdominal discomfort/pain	1017 (0.91)	18	56.5	1514 (1.02)	25	60.6
Acne	8336 (7.42)	84	99.2	7326 (4.95)	73	100.4
Alopecia	1235 (1.10)	12	102.9	548 (0.37)	8	68.5
Anxiety/panic issues	908 (0.81)	9	100.9	1191 (0.80)	17	70.1
Breast pain/tenderness	2304 (2.05)	34	67.8	1741 (1.18)	32	54.4
Depression	948 (0.84)	12	79.0	1455 (0.98)	18	80.8
Dyspareunia	1834 (1.63)	31	59.2	2460 (1.66)	33	74.6
Fatigue	276 (0.25)	6	46.0	682 (0.46)	9	75.8
Headache (nonmigraine)	2294 (2.04)	34	67.5	2581 (1.74)	52	49.6
Migraine headache	491 (0.44)	9	54.6	652 (0.44)	13	50.2
Mood changes	1351 (1.20)	22	61.4	3811 (2.57)	44	86.6
Nausea[c]	601 (0.54)	16	37.6	873 (0.59)	27	32.3
Orgasm/libido problems	1273 (1.13)	12	106.1	774 (0.52)	7	110.6
Ovarian cyst	717 (0.64)	11	65.2	551 (0.37)	11	50.1
Pelvic pain/discomfort	1011 (0.90)	23	44.0	2173 (1.47)	38	57.2
Vaginal odor/discharge	741 (0.66)	20	37.1	2154 (1.45)	35	61.6
Weight increase/poor weight loss	1049 (0.93)	12	87.4	2977 (2.01)	27	110.3

CHC, combined hormonal contraceptive; *IUD*, intrauterine device; *NHC*, no hormonal contraceptive.

[a] New events or worsening of preexisting conditions with an incidence ≥1%; [b] Method used in the mo before IUD placement; [c] Vomiting (1.3% overall) not included because we could not separate participants who had nausea and vomiting from those with just vomiting.

TABLE 4
Discontinuation rates for nonexpulsion side effects[a] over the first 180 days of levonorgestrel 52-mg IUD use

Side effect	Total N=1499	CHC users[a] n=644	NHC users[b] n=855	*P* value[c]
Abdominal discomfort/pain	2 (0.1)	0	2 (0.2)	.51
Acne	15 (1.0)	8 (1.2)	7 (0.8)	.44
Alopecia	2 (0.1)	2 (0.3)	0	.18
Anxiety/panic issues	2 (0.1)	0	2 (0.2)	.51
Breast pain/tenderness	0	0	0	
Depression	2 (0.1)	0	2 (0.2)	.51
Dyspareunia	3 (0.2)	2 (0.3)	1 (0.1)	.58
Fatigue	1 (0.1)	0	1 (0.1)	>.99
Headache (nonmigraine)	5 (0.3)	4 (0.6)	1 (0.1)	.17
Migraine headache	0	0	0	
Mood changes	17 (1.1)	7 (1.1)	10 (1.2)	>.99
Nausea[d]	2 (0.1)	0	2 (0.2)	.51
Orgasm/libido problems	4 (0.3)	2 (0.3)	2 (0.2)	>.99
Ovarian cyst	3 (0.2)	3 (0.5)	0	.08
Pelvic pain/discomfort	13 (0.9)	6 (0.9)	7 (0.8)	>.99
Vaginal odor/discharge	2 (0.1)	0	2 (0.2)	.51
Weight increase/poor weight loss	10 (0.7)	2 (0.3)	8 (0.9)	.20

Data presented as n (%).

CHC, combined hormonal contraceptive; *IUD*, intrauterine device; *NHC*, no hormonal contraceptive.

[a] Includes side effects with a reported incidence ≥1%; [b] Method used in the month before IUD placement; [c] Comparing CHC and NHC users, Fisher exact test; [d] Vomiting not included because we could not separate participants who had nausea and vomiting from those with just vomiting.

users. The authors concluded that these observations demonstrate that some of the observed association between non-COC use and acne may be related to COC discontinuation and its associated benefits when starting the new method. Our findings from this prospective study support those of the large retrospective analysis.

Though infrequent, some people report a decrease in sexual desire with levonorgestrel IUD use.[10,11] The small numbers and cross-sectional design of those evaluations limit their ability to evaluate appropriately for confounders such as prior CHC use. Although we found a higher incidence of orgasm/libido issues in prior CHC users by 1 year after levonorgestrel 52-mg IUD placement, the overall rate remained very low.

Clinical implications

The hormonal side effect data in this analysis provide clear information for clinicians to counsel patients on realistic expectations after hormonal IUD placement. Importantly, the discontinuation rate for these events is relatively low, which implies the severity of these issues is minor for most IUD users. Clinicians should advise patients discontinuing CHCs who have past issues with acne or orgasm/libido issues that discontinuing the CHC may result in recurrence of these side effects.

Research implications

This study provides prospective data on hormonal side effects in the first year of levonorgestrel 52-mg IUD use. Because phase 3 studies like this one have no control group, we do not have a comparator population to know if these hormonal side effect rates exceed what might occur in a similar population not using any hormonal contraception.

Strengths and limitations

A strength of this study is the prospective collection of adverse events in a diverse study population. We did not include vulvovaginal infections or pruritis as hormonal side effects as levonorgestrel IUDs are not known to cause alterations of the vaginal microbiome.[12,13] However, recognizing that some IUD users do feel they have more vaginal complaints, we did include vaginal odor/discharge in the assessments. We chose to not include bleeding events as bleeding changes reflect an outcome, often desired, with levonorgestrel 52-mg IUD use. Of note, 3 published reports from this study have extensively detailed bleeding changes during the first year of IUD use.[14–16]

A weakness of this study is that we did not assess whether participants who had previously been using CHCs were partly doing so for secondary reasons, like acne treatment. As a secondary analysis, the prior CHC and NHC groups were demographically very dissimilar, which demonstrates the inherent differences in the characteristics of people who use CHCs as compared to no hormonal methods. These differences, as demonstrated in the multivariable analysis, result in the pre-IUD contraceptive method no longer being a significant predictor of acne or sexual complaints with levonorgestrel IUD use.

Conclusions

During the initial 6 months of use, only a small percentage of levonorgestrel 52-mg IUD users will experience potentially hormone-related side effects that will result in IUD discontinuation. Furthermore, using CHCs prior to placement is not associated with who will report acne. Clinicians can use this information to provide relevant

TABLE 5
Factors associated with acne and orgasm/libido side effects over 180 d of levonorgestrel 52-mg IUD use (N = 1499)

Characteristic	Number of subjects	Acne			Orgasm/libido issues		
		n (%)	Odds ratio	Adjusted odds ratio[a]	n (%)	Odds ratio	Adjusted odds ratio[a]
Age (y)							
<25	576	54 (9.4)	Referent	Referent	8 (1.4)	Referent	Referent
≥25	923	103 (11.2)	1.21 (95% CI 0.86–1.72)	1.44 (95% CI 1.00–2.07)	16 (1.7)	1.25 (95% CI 0.53–2.95)	1.35 (95% CI 0.56–3.30)
Race[b]							
White	1170	132 (11.3)	Referent	Referent	18 (1.5)	Referent	Referent
Non-White	329	25 (7.6)	0.65 (95% CI 0.41–1.01)	0.77 (95% CI 0.49–1.22)	6 (1.8)	1.19 (95% CI 0.47–3.02)	1.32 (95% CI 0.51–3.41)
Ethnicity							
Non-Hispanic	1288	138 (10.7)	Referent	Referent	19 (1.5)	Referent	Referent
Hispanic or Latina	211	19 (9.0)	0.82 (95% CI 0.50–1.36)	0.98 (95% CI 0.58–1.64)	5 (2.4)	1.62 (95% CI 0.60–4.39)	1.92 (95% CI 0.69–5.33)
BMI at enrollment (kg/m^2)[c]							
<30.0	1125	133 (11.8)	1.94 (95% CI 1.24–3.05)	1.69 (95% CI 1.07–2.69)	17 (1.5)	0.80 (95% CI 0.33–1.94)	0.77 (95% CI 0.31–1.94)
≥30.0	372	24 (6.5)	Referent	Referent	7 (1.9)	Referent	Referent
Parity							
Nulliparous	907	112 (12.3)	1.71 (95% CI 1.19–2.46)	1.58 (95% CI 1.07–2.33)	15 (1.7)	1.09 (95% CI 0.47–2.51)	1.13 (95% CI 0.46–2.80)
Parous	592	45 (7.6)	Referent	Referent	9 (1.5)	Referent	Referent
Contraception use at Enrollment[d]							
CHC	644	84 (13.0)	1.61 (95% CI 1.15–2.24)	1.40 (95% CI 0.99–1.98)	14 (2.2)	1.88 (95% CI 0.83–4.26)	2.13 (95% CI 0.90–5.03)
NHC	855	73 (8.5)	Referent	Referent	10 (1.2)	Referent	Referent

BMI, body mass index; *CHC*, combined hormonal contraception; *CI*, confidence interval; *IUD*, intrauterine device; *NHC*, no hormonal contraception.

[a] Adjusted odds ratio controlling for all factors in table; [b] Four persons with missing information; [c] Three persons with missing information; [d] Method used in the month before IUD placement.

counseling to patients considering a levonorgestrel IUD. ■

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Appendix 1. Medical Dictionary for Regulatory Activities terms used for determination of reported side effects

Abdominal discomfort or pain

- Abdominal discomfort
- Abdominal pain
- Abdominal pain lower
- Abdominal pain upper

Acne
- Acne
- Acne cystic

Alopecia

Anxiety or panic issues

Breast pain or tenderness
- Breast discomfort
- Breast pain
- Breast tenderness
- Nipple pain

Depression
- Depression
- Depressed mood
- Major depression

Dyspareunia

Fatigue

Headache

Migraine
- Migraine
- Migraine with aura

Mood changes
- Affect lability
- Mood altered
- Mood swings

Nausea

Orgasm or libido problems
- Anorgasmia
- Libido decreased
- Loss of libido
- Orgasm abnormal

Ovarian cyst
- Ovarian cyst
- Ovarian cyst ruptured

Pelvic pain or discomfort
- Pelvic discomfort
- Pelvic pain
- Uterine spasm
- Uterine hypertonus

Vaginal discharge or odor
- Vaginal discharge
- Vaginal odor

Weight increase or loss poor
- Abnormal weight gain
- Weight increased
- Weight loss poor

APPENDIX 2
Select nonexpulsion side effects[a] over the first 360 days of levonorgestrel 52-mg IUD use

Side effect	Total N=1499	CHC users[a] n=644	NHC users[b] n=855	*P* value[c]
Acne	192 (12.8)	101 (15.7)	91 (10.6)	.005
Alopecia	25 (1.7)	14 (2.2)	11 (1.3)	.22
Breast pain/tenderness	79 (5.3)	38 (5.9)	41 (4.8)	.35
Mood changes	78 (5.2)	26 (4.0)	52 (6.1)	.08
Orgasm/libido problems	33 (2.1)	20 (3.1)	12 (1.4)	.03
Weight increase/poor weight loss	54 (3.6)	19 (3.0)	35 (4.1)	.26

Data presented as n (%).

CHC, combined hormonal contraceptive; *IUD*, intrauterine device; *NHC*, no hormonal contraceptive.

[a] New events or worsening of preexisting conditions, only includes events with CHC vs NHC incidence comparison with *P* value <.2 at 6 months (180 days); [b] Method used in the month before IUD placement; [c] Comparing CHC and NHC users, Fisher exact test.

APPENDIX 3
Frequency (percent of total days) of nonexpulsion side effects[a] for all participants over the first 180 days of levonorgestrel 52-mg IUD use

Side effect	CHC users[b] n=644 IUD exposure (d)=112,373	NHC users[b] n=855 IUD exposure (d)=148,085	*P* value[c]
Abdominal discomfort/pain	1017 (0.91)	1514 (1.02)	.003
Acne	8336 (7.42)	7326 (4.95)	<.0001
Alopecia	1235 (1.10)	548 (0.37)	<.0001
Anxiety/panic issues	908 (0.81)	1191 (0.80)	.92
Breast pain/tenderness	2304 (2.05)	1741 (1.18)	<.0001
Depression	948 (0.84)	1455 (0.98)	.0002
Dyspareunia	1834 (1.63)	2460 (1.66)	.56
Fatigue	276 (0.25)	682 (0.46)	<.0001
Headache (nonmigraine)	2294 (2.04)	2581 (1.74)	<.0001
Migraine headache	491 (0.44)	652 (0.44)	.90
Mood changes	1351 (1.20)	3811 (2.57)	<.0001
Nausea[d]	601 (0.54)	873 (0.59)	.07
Orgasm/libido problems	1273 (1.13)	774 (0.52)	<.0001
Ovarian cyst	717 (0.64)	551 (0.37)	.52
Pelvic pain/discomfort	1011 (0.90)	2173 (1.47)	<.0001
Vaginal odor/discharge	741 (0.66)	2154 (1.45)	<.0001
Weight increase/poor weight loss	1049 (0.93)	2977 (2.01)	.14

Data presented as n (%).

CHC, combined hormonal contraceptive; *IUD*, intrauterine device; *NHC*, no hormonal contraceptive.

[a] New events or worsening of preexisting conditions with an incidence ≥1%; [b] Method used in the month before IUD placement; [c] Comparing CHC and NHC users, chi-square test; [d] Vomiting (1.3% overall) not included because we could not separate participants who had nausea and vomiting from those with just vomiting.