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Original research article

Comparing bleeding patterns for the levonorgestrel 52 mg, 19.5 mg, and 13.5 mg intrauterine systems

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ABSTRACT

Objective: Compare bleeding patterns for levonorgestrel 52 mg, 19.5 mg, and 13.5 mg intrauterine system (IUS) products using the World Health Organization Belsey definitions.
Study design: We extracted available data on bleeding patterns from published sources. Lower dose products had published data at 1 and 3 years; the 52 mg IUS had available data for 1, 2 and 3 years for amenorrhea and 1 and 2 years for other bleeding patterns. We interpolated 2-year data for the lower dose products based on 1- and 3-year data and compared bleeding pattern rates using Fisher exact testing.
Results: The studies evaluated bleeding patterns in 1700, 1566 and 1531 women using levonorgestrel 52 mg, 19.5 mg and 13.5 mg products, respectively. Amenorrhea rates were greater by 180 days after insertion for 52 mg IUS users (11%) as compared to 19.5 mg (5%, p<.0001) and 13.5 mg (3%, p<.0001). Infrequent bleeding rates were higher for 52 mg users by the end of year 1 (31%) compared to 19.5 mg (26%, p=.01) and 13.5 mg (20%, p<.0001). Irregular bleeding rates were higher with the lower dose products by 90 days after insertion with continued lower rates at the end of year 1 for 52 mg users (6%) compared 19.5 mg (17%, p<.0001) and 13.5 mg (23%, p<.0001). Frequent and prolonged bleeding patterns were similar over the first 2 years for all products, although the rates were statistically higher for levonorgestrel 13.5 mg IUS users compared to 19.5 mg and 52 mg IUS users (p≤.03 for all time points after 90-days post-insertion).
Conclusions: Levonorgestrel 52 mg IUS users have more amenorrhea and infrequent bleeding and less irregular bleeding compared to women using lower dose levonorgestrel IUS products.
Implications Statement: All women considering levonorgestrel IUS placement should receive counseling on the differences in bleeding patterns related to the various available doses. Women who are interested in maximizing the likelihood of favorable bleeding should consider a levonorgestrel 52 mg IUS over the lower dose alternatives.

1. Introduction

Standardized reporting of bleeding with contraceptive use has been endorsed for decades [1,2]. However, research studies and pharmaceutical company clinical trial reports submitted for agency approval continue to use a variety of methods for reporting bleeding patterns [3]. The World Health Organization (WHO) recommends using the Belsey criteria when reporting hormonal contraception bleeding patterns [1] (Table 1).

We see this reporting variation in the prescribing information for the three different doses of levonorgestrel intrauterine system (IUS) products (52 mg, 19.5 mg, and 13.5 mg) in which data are provided in different ways, even among dose-equivalent products [4–7]. As such, clinically relevant differences in bleeding patterns are difficult to distill for both clinicians and patients.

A significant advantage of drug approval studies is the large size and detailed collection of bleeding data from the study population. In this report, we use published data from these contemporary studies of the available levonorgestrel IUS products to compare bleeding patterns using the WHO Belsey criteria.

2. Materials and methods

We assessed bleeding patterns using the WHO Belsey criteria (Table 1) over 90-day intervals (reference periods) [1] through 3 years for amenorrhea and two years for other bleeding descriptors for the three marketed levonorgestrel IUS dose products. We compared the patterns using published or publicly available data for the levonorgestrel 52 mg, [8] 19.5 mg [4,9] and 13.5 mg [7,10] IUS products. Although two levonorgestrel 52 mg IUS products are FDA approved in the United States, published data using the WHO Belsey criteria are available for only one (Liletta®, Medicines360, San Francisco, CA and Allergan, Irvine, CA). The available data for the

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Table 1
World Health Organization Belsey definitions of bleeding patterns with contraceptive use [1].

Bleeding/Spotting Episode	One or more consecutive days during which blood loss (bleeding or spotting) has been entered on the calendar record; each episode being bounded by bleeding/spotting-free days
Amenorrhea	No bleeding or spotting during a 90-day reference period
Prolonged bleeding	Bleeding/spotting episodes lasting more than 14 days during a 90-day reference period
Frequent bleeding	More than five bleeding/spotting episodes during a 90-day reference period
Infrequent bleeding	One or two bleeding/spotting episodes during a 90-day reference period
Irregular bleeding	Three to five bleeding/spotting episodes and less than three bleeding/spotting-free intervals of 14 days or more during a 90-day reference period

levonorgestrel 52 mg IUS includes bleeding pattern description the first and second 90-day reference periods and at 1 and 2 years as well as amenorrhea rates at 3 years. For both lower dose products, bleeding pattern descriptions are reported for the first and second 90-day reference periods and at 1 and 3 years; thus, we performed a linear interpolation of the data to derive 2-year estimates for comparisons to the levonorgestrel 52 mg IUS data. Because we estimated 2-year values for the 19.5 mg and 13.5 mg products and did not have actual numbers of subjects for the outcomes at 2 years, we did not perform statistical comparisons for this time point. We used Fisher's exact testing for comparisons of proportions with p-values≤0.05 considered significant.

3. Results

Table 2 compares amenorrhea rates between users of the levonorgestrel 52 mg, 19.5 mg and 13.5 mg IUS. Amenorrhea was uncommon in the first 90 days for all 3 IUS doses and increased over time. During the second 90-day reference period, amenorrhea rates in levonorgestrel 52 mg users (11%) were higher than the rates in levonorgestrel 19.5 mg (5%, p<.0001) and 13.5 mg IUS users (3%, p<.0001); these differences continued through 3 years at which time amenorrhea was approximately two-times and three-times higher for levonorgestrel 52 mg users compared to 19.5 mg and 13.5 mg users, respectively. Amenorrhea rates for women using the levonorgestrel 19.5 mg IUS were also significantly higher than the lower dose 13.5 mg product starting in the second 90-day reference period.

Table 3 compares infrequent, frequent, prolonged, and irregular bleeding pattern rates reported for levonorgestrel 52 mg, 19.5 mg and 13.5 mg IUS users. Infrequent bleeding was similar for all 3 products initially but then increased more quickly for women using a levonorgestrel 52 mg IUS. Frequent and prolonged bleeding were uncommon patterns for users of all three IUS doses by the end of year 1. Irregular bleeding was also similar for all three products in the first 90 days of use, at around 40% of women. Irregular bleeding rates declined for women using all three IUS doses; however, fewer 52 mg device users reported irregular bleeding at 1 year (6% compared to 17% in 19.5 mg [p<.001] and 23% in 13.5 mg [p<.001] IUS users). Supplemental color figures depicting the outcomes in Tables 1 and 2 are available in an online appendix.

Table 2
Amenorrhea rate over 3 years for women using levonorgestrel 52 mg, 19.5 mg and 13.5 mg IUS.

Levonorgestrel IUS	1st 90	2nd 90	End of	End of
Dose	Days	Days	Year 1	Year 3
52 mg [8]	n=1700	n=1621	n=1448	n=935
	7 (0.4%)	183 (11.3%)	269 (18.6%)	340 (36.4%)
19.5 mg [4,9]	n=1566	n=1511	n=1371	n=975
	3 (0.2%)	80 (5.3%)	168 (12.3%)	194 (19.9%)
13.5 mg [7,10]	n=1531	n=1475	n=1329	n=903
	5 (0.3%)	44 (3.0%)	83 (6.2%)	105 (11.6%)
p-values				
52 mg vs. 19.5 mg	.35	<.0001	<.0001	<.0001
52 mg vs. 13.5 mg	.78	<.0001	<.0001	<.0001
19.5 mg vs. 13.5 mg	.50	<.001	<.0001	<.0001

Amenorrhea defined as no bleeding or spotting during the preceding 90 days.
IUS = Intrauterine System.

4. Discussion

Bleeding pattern differences between the various doses of levonorgestrel over two years of use occur primarily in amenorrhea, infrequent bleeding and irregular bleeding rates. Women using lower dose levonorgestrel IUS products had lower rates of amenorrhea and infrequent bleeding and had higher rates of irregular bleeding as compared to women using the 52 mg IUS; rates of frequent and prolonged bleeding were similar for all three doses. None of the products reported a "regular" cyclic bleeding rate.

Women using any dose levonorgestrel IUS had very similar frequent and prolonged bleeding pattern rates over the first 2 years. For all three products, frequent bleeding rates decreased quickly to a low rate of approximately 4–8% by the end of 1 year of use. Prolonged bleeding rates were slightly higher for levonorgestrel 13.5 mg IUS users at one year than 19.5 mg or 52 mg IUS users.

A limitation of these comparisons is that the data were gathered from independent studies with different populations. The lower dose levonorgestrel IUS studies included a mix of women from 11 countries in North, Central and South America and Europe whereas the 52 mg IUS study was performed exclusively in the United States [11,12]. Women in these studies also had different rates of nulliparity and mean BMI; the levonorgestrel 52 mg IUS study included more nulliparous and obese women [12]. Although variations in characteristics of the study populations could account for some bleeding pattern differences, analyses of the levonorgestrel 52 mg IUS data shows no difference in bleeding patterns based on parity or BMI [8]. Thus, the likelihood that these differences are impacting the outcomes is low. An additional limitation is the interpolation of the 2-year data for the lower dose levonorgestrel IUS products, which is why we did not perform statistical evaluation of any differences at year 2. Whereas the overall comparison of outcomes is valid to understand general similarities and differences, a randomized study would be required for a more precise comparison.

The levonorgestrel 19.5 mg and 13.5 mg products had available diary data through 3 years [12]. We limited the comparisons of prolonged, frequent, infrequent and irregular bleeding to two years because the levonorgestrel 52 mg IUS studies only used daily diaries for the first two years after which investigators obtained bleeding information by interview [8]. The LNG 52 mg IUS data uses the interview information to provide amenorrhea rates at 3 years which allowed an amenorrhea comparison after two years.

When considering bleeding patterns with progestin-only methods, those that are related to a decrease in flow (amenorrhea, infrequent bleeding) are often considered favorable and those related to increased or unpredictable flow are often considered unfavorable (frequent, prolonged and irregular bleeding) [13]. The differences described in this analysis of published bleeding patterns for the three available doses of levonorgestrel IUS products, all using the same standard criteria, show that the 52 mg product has significantly more favorable and less unfavorable bleeding patterns across the first few years of use. Whereas a randomized trial would be the most ideal manner to compare these outcomes, our findings summarize and compare the best information available to inform clinicians and patients given that

Table 3
Infrequent, frequent, prolonged, and irregular bleeding rates over 2 years for women using levonorgestrel 52 mg, 19.5 mg and 13.5 mg IUS.

Levonorgestrel IUS	1st 90	2nd 90	End of	End of
Dose	Days	Days	Year 1	Year 2
A. Infrequent bleeding rates				
52 mg [8]	n=1700	n=1621	n=1448	n=1178
	230 (13.5%)	407 (25.1%)	443 (30.6%)	356 (30.2%)
19.5 mg [4,9]	n=1566	n=1511	n=1371	
	150 (9.6%)	307 (20.3%)	360 (26.3%)	26%*
13.5 mg [7,10]	n=1531	n=1475	n=1329	
	129 (8.4%)	282 (19.1%)	271 (20.4%)	21%*
p-values				
52 mg vs. 19.5 mg	<.001	.002	.01	
52 mg vs. 13.5 mg	<.0001	<.0001	<.0001	
19.5 mg vs. 13.5 mg	.29	.43	<.001	
B. Frequent bleeding rates				
52 mg [8]	n=1700	n=1621	n=1448	n=1178
	448 (26.4%)	152 (9.4%)	76 (5.2%)	42 (3.6%)
19.5 mg [4,9]	n=1566	n=1511	n=1371	
	391 (25.0%)	147 (9.7%)	58 (4.2%)	3%*
13.5 mg [7,10]	n=1531	n=1475	n=1329	
	468 (30.6%)	180 (12.2%)	100 (7.5%)	6%*
p-values				
52 mg vs. 19.5 mg	.38	.76	.22	
52 mg vs. 13.5 mg	.009	.01	.02	
19.5 mg vs. 13.5 mg	<.001	.03	<.001	
C. Prolonged bleeding rates				
52 mg [8]	n=1700	n=1621	n=1448	n=1178
	858 (50.5%)	157 (9.7%)	72 (5.0%)	22 (1.9%)
19.5 mg [4,9]	n=1566	n=1511	n=1371	
	887 (56.6%)	207 (13.7%)	80 (5.8%)	4%*
13.5 mg [7,10]	n=1531	n=1475	n=1329	
	903 (59.0%)	249 (16.9%)	118 (8.9%)	6%*
p-values				
52 mg vs. 19.5 mg	<.001	<.001	.32	
52 mg vs. 13.5 mg	<.0001	<.0001	<.0001	
19.5 mg vs. 13.5 mg	.19	.02	.003	
D. Irregular bleeding rates				
52 mg [8]	n=1700	n=1621	n=1448	n=1178
	648 (38.1%)	220 (13.6)%	89 (6.1%)	52 (4.4%)
19.5 mg [4,9]	n=1566	n=1511	n=1371	
	665 (42.5%)	377 (25.0%)	226 (16.5%)	14%*
13.5 mg [7,10]	n=1531	n=1475	n=1329	
	643 (42.0%)	415 (28.1%)	300 (22.6%)	20%*
p-values				
52 mg vs. 19.5 mg	.01	<.0001	<.0001	
52 mg vs. 13.5 mg	.03	<.0001	<.0001	
19.5 mg vs. 13.5 mg	.80	.051	<.0001	

See Table 1 for definitions of bleeding patterns.
IUS = Intrauterine System.
* Data only available from years 1 and 3; year 2 estimated by interpolation so number is not presented and statistical testing at end of year 2 not calculated.

such a trial has not been performed. This information can be helpful for clinicians when providing counseling to women about what patterns to expect as well as how to understand differences between the various levonorgestrel IUS products. Women who are interested in maximizing the likelihood of favorable bleeding should consider a levonorgestrel 52 mg IUS over the lower dose alternatives.

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Appendix A. Supplementary data

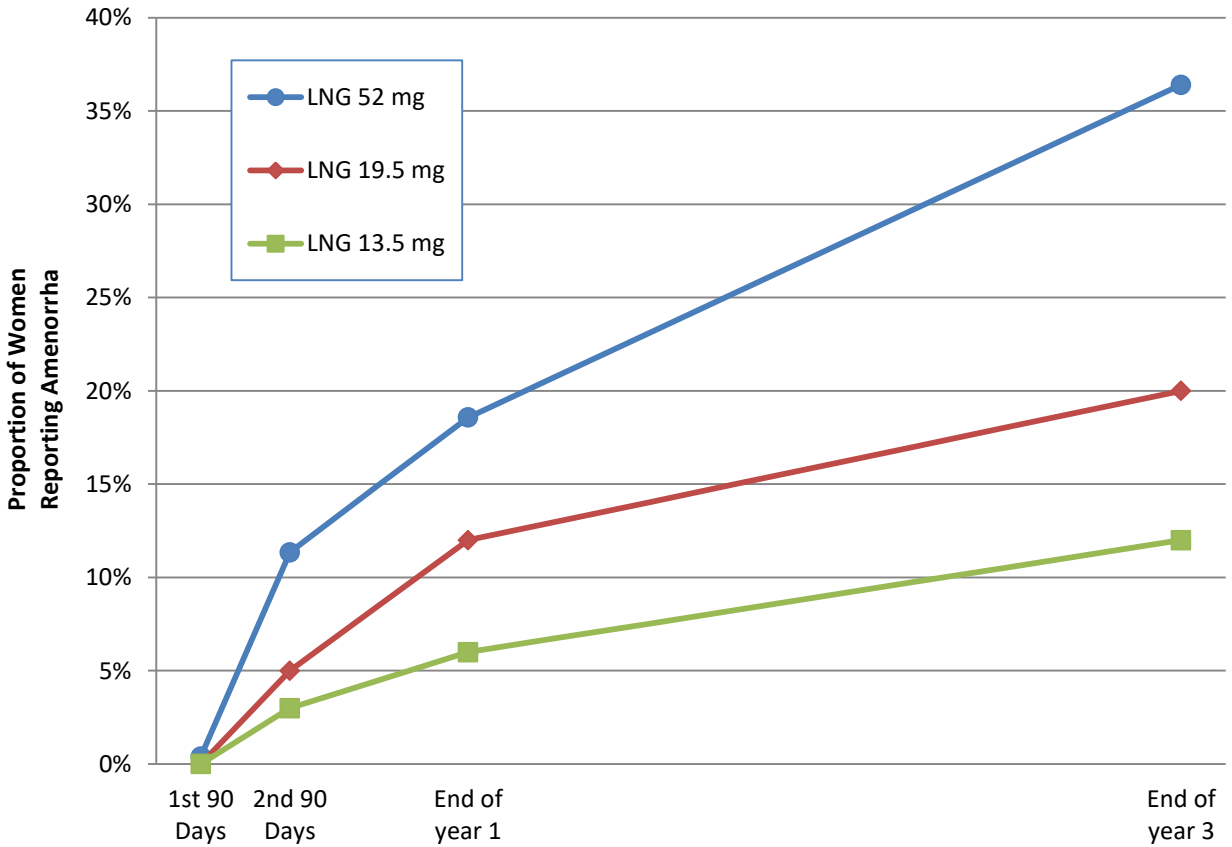
Supplementary data to this article can be found online at https://doi.org/10.1016/j.contraception.2019.03.044.

References

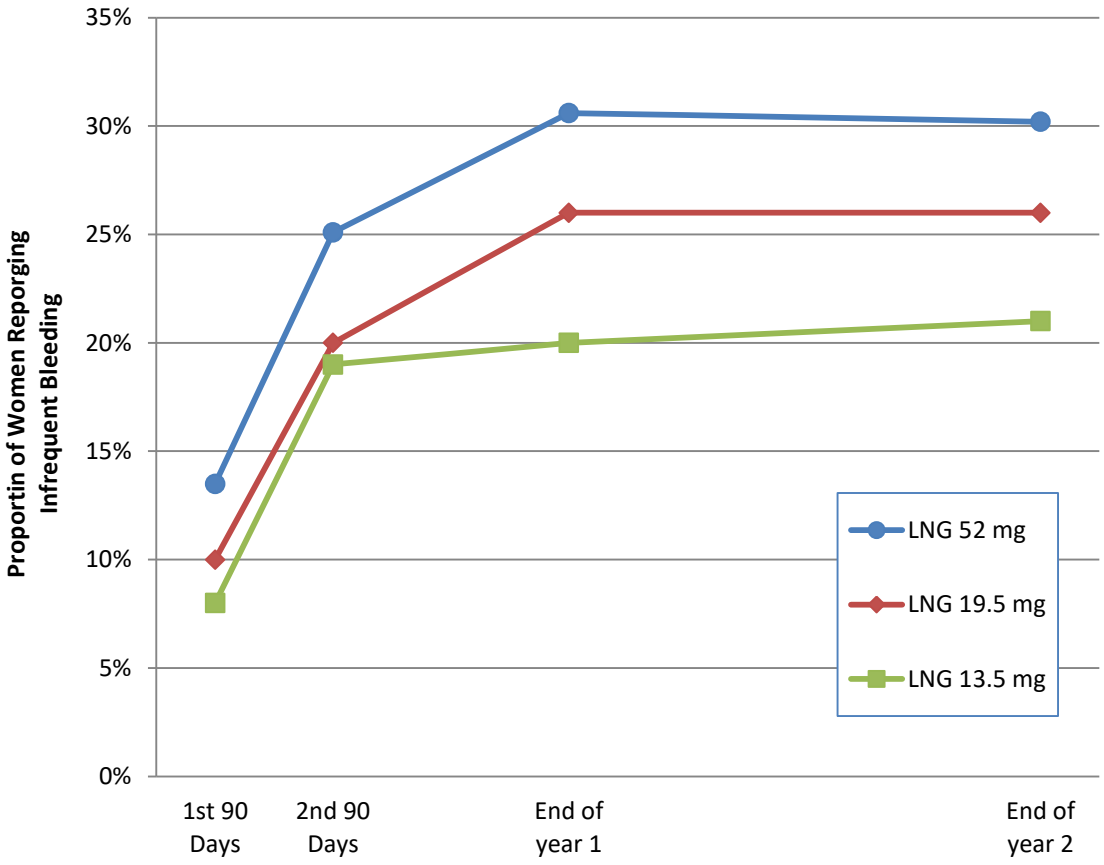
[1] Belsey EM, Machin D, d'Arcangues C. The analysis of vaginal bleeding patterns induced by fertility regulating methods. Contraception 1986;34:253–60.
[2] Mishell Jr DR, Guillebaud J, Westhoff C, Nelson AL, Kaunitz AM, Trussell J, et al. Recommendations for standardization of data collection and analysis of bleeding in combined hormone contraceptive trials. Contraception 2007;75:11–5.
[3] Mishell Jr DR, Guillebaud J, Westhoff C, Nelson AL, Kaunitz AM, Trussell J, et al. Combined hormonal contraceptive trials: variable data collection and bleeding assessment methodologies influence study outcomes and physician perception. Contraception 2007;75:4–10.
[4] Kyleena package insert: Bayer HealthCare pharmaceuticals Inc. Kyleena prescribing information; 2016.
[5] xLiletta package insert: Allergan USA Inc. and Medicines360. Liletta prescribing information; 2016.
[6] Mirena package insert: Bayer HealthCare pharmaceuticals Inc. Mirena prescribing information; 2016.
[7] Skyla package insert: Bayer HealthCare pharmaceuticals Inc. Skyla prescribing information; 2017.
[8] Schreiber CA, Teal SB, Blumenthal PD, Keder LM, Olariu A, Creinin MD. Bleeding patterns for the Liletta® levonorgestrel 52 mg intrauterine system. Eur J Contracept Reprod Health Care 2018;23:116–20.
[9] U.S. Food and Drug Administration. Kyleena FDA drug approval package, Medical Review(s). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208224Orig1s000MedR.pdf, Accessed date: 2 February 2019.

[10] U.S. Food and Drug Administration. Skyla FDA drug approval package, Medical Review(s). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203159Orig1s000MedR.pdf, Accessed date: 2 February 2019.
[11] Eisenberg DL, Schreiber CA, Turok DK, Teal SB, Westhoff CL, Creinin MD. Three year efficacy and safety of a new 52-mg levonorgestrel-releasing intrauterine system. Contraception 2015;92:10–6.
[12] Nelson A, Apter D, Hauck B, Schmelter T, Rybowski S, Rosen K, et al. Two low-dose levonorgestrel intrauterine contraceptive systems: a randomized controlled trial. Obstet Gynecol 2013;122:1205–13.
[13] Mansour D, Korver T, Marintcheva-Petrova M, Fraser I. The effects of Implanon® on menstrual bleeding patterns. Eur J Contracept Reprod Health Care 2008;13 (S1):13–28.

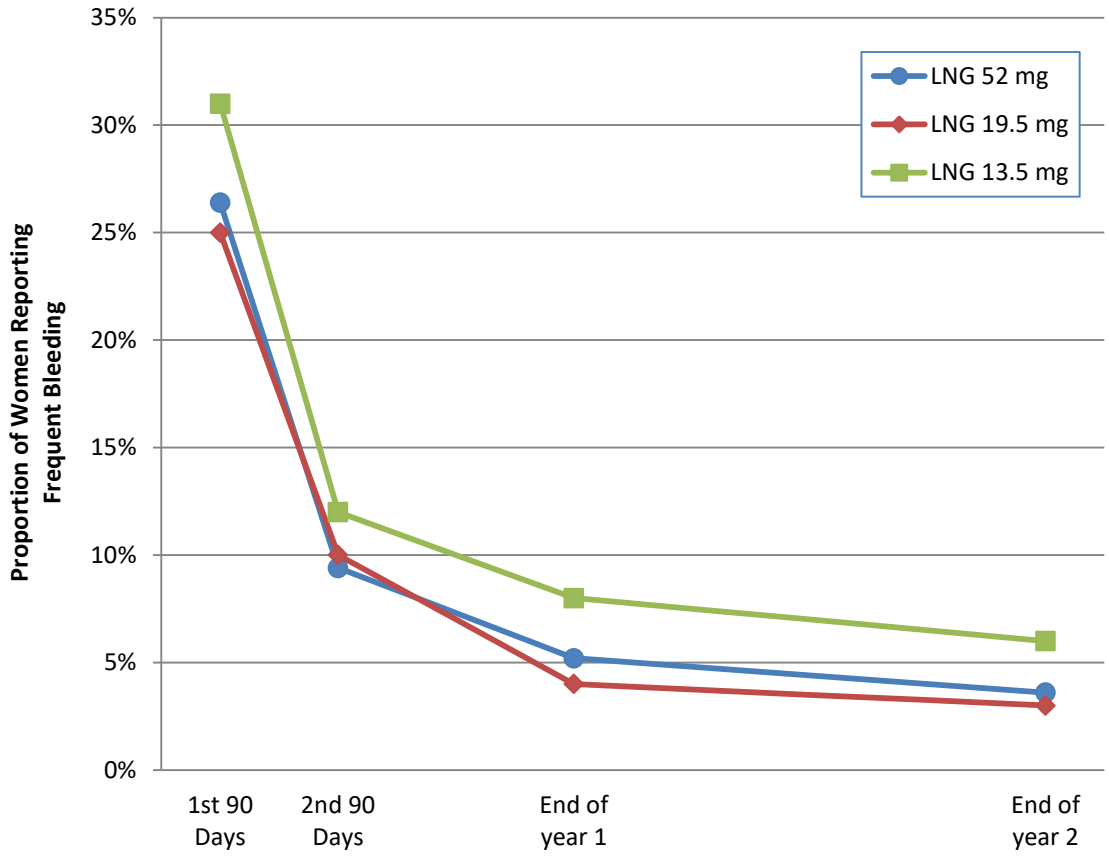
A. Amenorrhea rates over 3 years



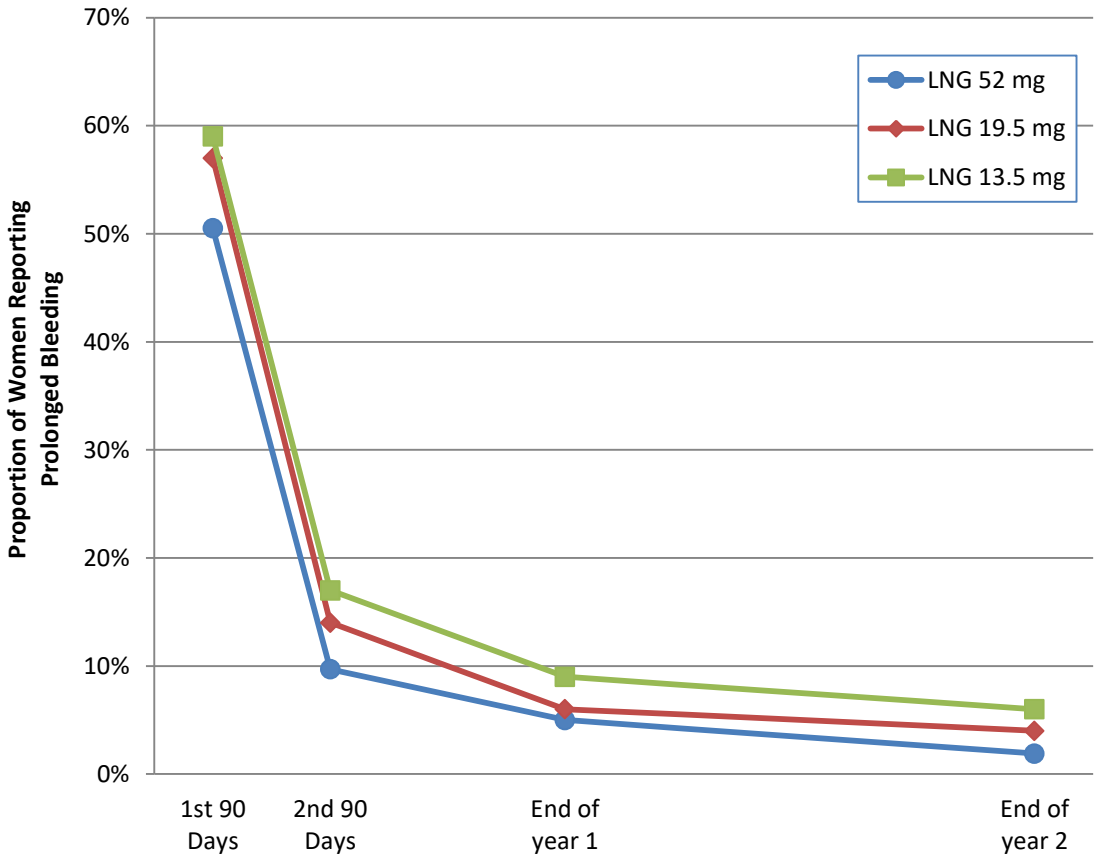
B. Infrequent bleeding rates over 2 years.



C. Frequent bleeding rates over 2 years.



D. Prolonged bleeding rates over 2 years.



E. Irregular bleeding rates over 2 years.