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Conception rates in women desiring pregnancy after levonorgestrel 52 mg intrauterine system (Liletta®) discontinuation

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ABSTRACT

Objective: Evaluate reproductive function in nulligravid and gravid women after levonorgestrel 52 mg intrauterine system (IUS) discontinuation based on time to pregnancy.

Study Design: We evaluated women participating in the ACCESS IUS multicenter, Phase 3, open-label clinical trial of the Liletta levonorgestrel 52 mg IUS who discontinued the IUS within 60 months of use and desired pregnancy. Study staff contacted participants every three months after IUS discontinuation for up to 12 months to determine whether pregnancy occurred. We excluded women who opted to stop attempting to conceive before 12 months. We evaluated 12-month conception rates in participants 16-35 years at IUS placement, comparing dichotomous outcomes using Fisher's exact test. We performed a multivariable analysis to assess the association of baseline characteristics, age at discontinuation, duration of IUS use, and positive STI testing during IUS use with conception.

Results: Among 165 women who attempted to conceive, 142 (86.1%) did so within 12 months with a median time to conception of 92 days. The 12-month conception rates did not differ between nulligravid (66/76 [86.8%]) and gravid (76/89 [85.4%]) women (p=0.83) and nulliparous (78/90 [86.7%]) and parous (64/75 [85.3%]) women (p=0.83). In multivariable analysis, only obesity (OR 0.3 [95% CI 0.1-0.8]) was associated with ability to conceive.

Conclusions: After levonorgestrel 52 mg IUS discontinuation, women have rapid return of fertility in the year post-removal. Fertility rates after IUS removal do not vary based on gravidity, parity, age at discontinuation, or duration of IUS use.

Key Words: intrauterine device, intrauterine system, fertility, gravidity, Liletta

Implications: This contemporary IUS study included a large population of nulligravid and nulliparous women. IUS use over many years does not effect spontaneous fertility after IUS

discontinuation, regardless of gravidity or parity. Providers and patients should have no concern about the impact of IUS use on future fertility.

1.0 INTRODUCTION

Intrauterine contraceptive use in the United States has been steadily growing, with the most recently available data showing an increase from 2002 to 2014 from 2% to 12% of contracepting women [1,2]. Although nulliparous women were denied intrauterine device (IUD) access for decades, routine use in nulliparous women became more common. IUD utilization among nulliparous contracepting women rose from 0.5% in 2002 to 6% in 2014 [1,2].

Contemporary surveys suggest that providers still consider IUD use in women without children to be inappropriate related to concerns about infertility, pelvic infection, and insertion difficulty [3-5]. A 2014 publication reported survey results from U.S. obstetrician-gynecologists in which only 67% considered IUDs appropriate for nulliparous women and about 15% considered pelvic infection a major risk of IUD use [6].

Although clinical studies demonstrate that hormonal IUDs do not increase pelvic infection rates [7,8], the true concern about such infection is the potential for resultant infertility. Little data on fertility after discontinuation of contemporary IUDs, especially in nulligravid women, have been published. Twelve month fertility rates among 69 former IUD users (50 levonorgestrel and 19 copper) and 42 non-IUD users from the CHOICE study showed no difference in pregnancy rates among IUD (81%) and in non-IUD (70%) users (p=0.18) or time to pregnancy (adjusted HR 1.19, CI 0.74-1.92) [9]. The small size and inclusion of women who used other contraception and then attempted pregnancy at some interval after IUD discontinuation limit the generalizability of this data.

The Liletta® levonorgestrel 52 mg intrauterine system (IUS) is approved for contraception for 6 continuous years based on results from the Phase 3 ACCESS IUS study, which is currently following women for up to 10 years of IUS use. The trial included 1714

women who received an IUS, of whom more than half had never had children, enabling the potential to follow a relatively large cohort of nulligravid and gravid women for return of fertility after IUS discontinuation [8]. In this report, we detail spontaneous conception rates among women from this study who desired pregnancy after IUS discontinuation.

2.0 MATERIALS AND METHODS

This report represents a substudy of the ACCESS IUS multicenter, Phase 3, open-label clinical trial of the Liletta levonorgestrel 52 mg IUS (Medicines360, San Francisco, CA, USA and AbbVie, North Chicago, IL, USA; Liletta® is a registered trademark of Odyssea Pharma SPRL [Belgium], an AbbVie affiliate), marketed as Levosert™ in Europe. The methods of the main study have been reported previously [10,11]. A central or local Institutional Review Board for each center approved the study. Each woman signed written informed consent before study participation.

Briefly, investigators at 29 clinical sites in the United States enrolled healthy, non-pregnant, sexually active, nulliparous and parous women aged 16-45 years (inclusive) who desired a hormonal IUS for contraception beginning in December 2009. All women reported cyclic menses every 21-35 days when not using hormones with a typical cycle length variation of no more than 5 days. Clinicians performed baseline sexually transmitted infection (STI) testing for Chlamydia and gonorrhea with repeat testing during follow-up based on U.S. Centers for Disease Control and Prevention guidelines (annually for women less than 25 years old and when the participant reported having a new sexual partner) [12]. Investigators asked participants who discontinued IUS use with a desire for pregnancy to avoid attempting pregnancy in the first seven days after IUS discontinuation because such a conception would be considered “on-treatment” per United States Food and Drug Administration requirements. Study staff contacted

subjects at least every 3 months for up to 12 months or until self-reported conception had occurred. We did not require confirmation of conception via testing or other documentation. We stopped following women and did not include them in any analyses if they initiated contraception or indicated they had stopped attempting to conceive before completing 12 full months of follow-up. For women who did conceive, study staff asked them to provide a gestational age (and date of assignment) or delivery date assigned by their primary clinician to estimate time to conception after IUS discontinuation. We did not assess pregnancy outcomes.

For this analysis, we only included women 16-35 years at enrollment into the main study who used the IUS for up to 60 months and discontinued the IUS with a desire to conceive. We performed a Kaplan-Meier survival analysis of pregnancy rates over 12 months of attempting conception. We compared dichotomous outcomes using Fisher's exact test. We assessed conception rates based on duration of IUS use according to years (12-month intervals) using chi-square test for trend. We assessed baseline characteristics, duration of IUS use, and positive STI testing during IUS use in a univariate model and included all variables with a $p<0.1$ level in the multivariable model. We planned a priori to include variables related to age, gravidity, weight and duration of use regardless of univariate p-values.

3.0 RESULTS

Of the 1714 women who had successful placement, 1568 were 16-35 years old at study entry and 165 (10.5%) of these women discontinued within the first 5 years of use, desired pregnancy, and either conceived or completed 12 months of follow-up without conception after IUS discontinuation. Of note, another 53 women initially planned pregnancy but did not complete the substudy follow-up (15 lost to follow-up, 2 withdrew consent, 36 decided during

follow-up that they no longer desired pregnancy). Characteristics of the 165 women in the return to fertility assessment are presented in Table 1. We found no differences in the characteristics of women who did and did not complete study follow-up (online Appendix 1). The evaluated population had a median IUS use of 35.7 months (range 1.3-59.9 months).

Overall, 142 (86.1%) women conceived within 12 months. Life-table analysis of time to conception is presented in Figure 1. Women conceived at a median of 92 days with clinically similar medians for duration of use of one through five years (106, 95, 91, 81, and 94 days, respectively). The 12-month conception rates did not differ between nulligravid (66/76 [86.8%]) and gravid (76/89 [85.4%]) women (p=0.83) and nulliparous (78/90 [86.7%]) and parous (64/75 [85.3%]) women (p=0.83).

Table 2 shows patient factors evaluated for effect on conception rates included in the multivariable model. When considering our multivariable analysis, multiple age and weight-related variables potentially overlapped. When considering age at IUS placement and age at IUS discontinuation, we opted to use the latter since we also included IUS duration of use, which would account for the time difference between placement and discontinuation. Additionally, obesity at enrollment and discontinuation were both significantly different in univariate analysis. Because women who were obese at enrollment did not experience more weight change (increase or decrease) during IUS use than non-obese women (1.9 ± 9.4 kg vs. 1.7 ± 5.8 kg, p=0.92), we used obesity at discontinuation in the multivariable model. The model in Table 2 did not change when using obesity status at baseline instead of discontinuation (data not shown).

Table 3 reports pregnancy rates at 12 months post-discontinuation by duration of IUS use, which did not differ for the entire population (p=0.28); however, within the smaller subgroups, rates did differ in gravid women (p=0.03) and approached significance in parous

women (p=0.06). We evaluated these groups further by number of lost to follow-up or early discontinuation by year, obesity status and age to attempt to further discern this finding. We found no evidence of an impact of lost to follow-up or early discontinuation in the longer use duration groups to explain these findings (Online Appendix 1). For obesity and age, the number of women in these even smaller sub-groups was too small to identify any statistical findings (Online Appendices 2 and 3).

4.0 DISCUSSION

Our findings demonstrate that fertility returns normally in women who discontinue a levonorgestrel 52 mg IUS and desire pregnancy, with a one-year conception rate of 86%. Fertility rates after contraceptive discontinuation in the general population are approximately 83% in one year [13], with multiple factors affecting that rate including age and obesity [14,15]. Historically publications have focused on parity when discussing concerns about fertility after intrauterine contraceptive use. However, gravidity is the variable that establishes whether a woman is capable of conceiving; accordingly, we compared outcomes by both gravidity and parity, finding no difference whether a woman had previously conceived or had previously had a delivery.

Baseline characteristics in our population differed significantly between nulligravid and gravid women who initiated IUS use, with nulligravid women more commonly being white and less likely to be obese or Hispanic or have a history of STI before IUS placement. Nulligravid women attempting conception used the IUS for longer than gravid women. The most influential factor in failure to conceive in our population was obesity; duration of IUS use, gravidity, parity and other variables had no significant effect on the ability to conceive. In multivariable analysis,

obesity, a well-known cause of infertility [15], continued to be the only factor associated with failure to conceive after IUS discontinuation.

Our first month conception rate of 8.5% is lower than rates of approximately 20% (18/21) reported previously following levonorgestrel 52 mg IUS removal [16] which we believe is related to the study requirements of avoiding conception early after removal. By three months, our conception rate of 42% is similar to the approximately 40% rate estimated by Nilsson as well as the rate reported in the general community [17].

Prior studies of fertility following levonorgestrel 52 mg IUS use, although smaller, reported similar outcomes. Andersson et al [18] followed 96 mostly parous and non-obese women with a one-year conception rate of 79%, noting no significant difference in rates among women who used the IUS for less than or more than 24 months. Belhadj [19] reported preliminary data on 39 of 49 mostly parous women indicating a one-year pregnancy rate of 96%; the incomplete follow-up and small size limits the findings. More recently, Stoddard [9] reported one-year pregnancy rates of 81% in 69 IUD users, including 23% nulligravid women; however, the investigators did not differentiate copper (n=19) and hormonal IUD (n=50) outcomes.

A prior study recruited participants from 1982 to 1994 to specifically evaluate fertility in nulliparous women after copper IUD use as compared to oral contraceptive or barrier method use [20]. The study included 158 oral, 162 intrauterine and 238 barrier contraceptive users with a mean population BMI of approximately 22 kg/m^2. They reported a significant association of increasing duration of copper IUD (more than 42 months) with lower fertility among nulliparous women, even after adjusting for age. Our findings differ from this older study, which could be related to differences in fertility between long-term use of copper vs. levonorgestrel intrauterine contraceptives or other differences in our population. Importantly, our study shows no effect of

increasing duration of levonorgestrel IUS use on fertility in nulligravid or nulliparous women. The unexpected association of increased duration of use and lower fertility among gravid women, but not nulligravid women, appears spurious and likely related to the smaller group sizes as we attempted to analyze sub-populations within our cohort.

The information from this study directly addresses misconceptions about fertility after IUD use that may persist among both patients and providers. Among 1665 reproductive-age women in the St. Louis, MO area responding to a survey sent to their homes in 2008, only 8% of IUD-naive women and approximately 20% of current or past users thought IUDs did not increase the risk of infertility [21]. A survey of U.S. clinicians in 2010 suggested that approximately 30% perceived IUDs were unsafe or were unsure about the safety of IUDs for nulliparous women [22]. More recent data are not available, but we hope that guidelines from the American College of Obstetrics and Gynecology, the American Academy of Pediatrics and the Society of Family Planning have helped educate providers that nulligravid and nulliparous women are appropriate candidates for IUD use [23-25].

Our sample was limited to the number of women who discontinued the trial desiring pregnancy. Our study plan incorporated exclusion of women who changed their mind about wanting to conceive because it is possible that they did not desire pregnancy to the same extent as women who continued to attempt conception for a full 12 months. These women comprised 17% of the original study population. Because we did not collect information on sexual activity while attempting conception, we opted to not add these subjects and censor their data. We cannot address outcomes in women who conceive after levonorgestrel IUS removal as this study was not designed to follow pregnancy outcomes.

This contemporary study represents the largest Phase 3 IUS trial performed exclusively in the United States and has the largest representation of nulliparous and obese women as compared to other IUS products approved in the last few decades [26-28]. More than 60% of the initial cohort was nulliparous and 25% obese, giving this study the unique ability to provide prospective fertility outcomes with appropriate data on variables important to patients and providers. As ACCESS IUS continues, we will be able to obtain additional fertility data following IUS use for more than 5 years. Our findings that fertility rates in the year after IUS removal is normal overall and in nulligravid and nulliparous women can be helpful when providing counseling to women about levonorgestrel IUS use.

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Table 1. Demographics and contraceptive method at enrollment for women in a phase 3 study who had successful placement of a Liletta levonorgestrel 52 mg IUS and attempted conception after IUS discontinuation*

Characteristic	**Population of Women Attempting Conception**			
	Total	**Nulligravid**	**Gravid**	**P-value†**
	n=165	**n=77**	**n=88**	
Age ate enrollment (years)	26.5 ± 4.0	25.7 ± 3.0	27.2 ± 4.5	0.016
<25	58 (35.2)	30 (39.0)	28 (31.8)	0.41
25-35	107 (64.8)	47 (61.0)	60 (68.2)	
Age at IUS discontinuation (years)	29.4 ± 3.9	29.0 ± 2.8	29.7 ± 4.7	0.25
<25	22 (13.3)	6 (7.8)	16 (18.2)	0.066
25-35	143 (86.7)	71 (92.2)	72 (81.8)	
Duration of IUS use (months)	34.8 ± 15.0	39.3 ± 14.2	30.9 ± 14.7	<.001
Race				<.001
White	138 (83.6)	73 (94.8)	65 (73.9)	
Black or African American	18 (10.9)	0	18 (20.5)	
Asian	4 (2.4)	3 (3.9)	1 (1.1)	
Multiracial	2 (1.2)	0	2 (2.3)	
American Indian/Alaska Native	2 (1.2)	0	2 (2.3)	
Native Hawaiian/Other Pacific Islander	1 (0.6)	1 (1.3)	0	

Ethnicity				
Hispanic or Latina	22 (13.3)	4 (5.2)	18 (20.5)	0.005
BMI at enrollment (kg/m^2)	27.1 ± 7.3	24.5 ± 4.6	29.3 ± 8.4	<.001
Obese (≥30.0)	40 (24.2)	8 (10.4)	32 (36.4)	<.001
BMI at IUS discontinuation (kg/m^2)	27.7 ± 7.8	24.9 ± 5.2	30.1 ± 8.9	<.001
Obese (≥30.0)	43 (26.1)	8 (10.4)	35 (39.8)	<.001
Parity				
Nulliparous	90 (54.5)	77 (100)	13 (14.8)	<.001
Marital Status				0.060
Never married	95 (57.6)	50 (64.9)	45 (51.1)	
Married	62 (37.6)	26 (33.8)	36 (40.9)	
Divorced	8 (4.8)	1 (1.3)	7 (8.0)	
Pelvic infection[‡]				
STI history before IUS placement	16 (9.7)	2 (2.6)	14 (15.9)	0.004
STI during IUS use	6 (3.6)	3 (3.9)	3 (3.4)	1.00
Pelvic infection during IUS use	3 (1.8)	0	3 (3.4)	0.25

* Study enrolled women 16-45 years old; only women 16-35 years at study entry included in return to fertility analysis

† Comparing nulligravid and gravid women using Fisher's exact and t-tests as appropriate

‡ None had a history of pelvic infection prior to study enrollment
Data presented as n (%) or mean ± standard deviation
IUS: intrauterine system; BMI: body mass index; STI: sexually transmitted infection (Chlamydia or gonorrhea)

Table 2. Related characteristics and odds of conception within 12 months after levonorgestrel 52 mg IUS discontinuation

Characteristic	Conceived n=142	Did Not Conceive n=23	Odds Ratio	Adjusted Odds Ratio*
Age at IUS discontinuation (years)	29.4 ± 3.9	29.2 ± 4.2	1.0 (95% CI 0.3-3.8)	1.2 (95% CI 0.3-4.6)
<25	19 (13.4%)	3 (13.0%)		
25-35	123 (86.6%)	20 (87.0%)		
Duration of IUS use (months)	34.4 ± 15.3	37.7 ± 13.1	1.7 (95% CI 0.7-4.2)	1.8 (95% CI 0.7-4.6)
<36	74 (52.1%)	9 (39.1%)		
36-60	68 (47.9%)	20 (60.9%)		
Race			0.2 (95% CI 0.0-1.6)	0.2 (95% CI 0.0-1.1)
White	116 (81.7%)	22 (95.7%)		
Non-White†	26 (18.3%)	1 (4.3%)		
Ethnicity				
Hispanic or Latina	18 (12.7%)	4 (17.4%)	0.7 (95% CI 0.2-2.3)	0.8 (95% CI 0.2-2.7)
Obesity‡ at IUS discontinuation	33 (23.2%)	10 (43.5%)	0.4 (95% CI 0.2-1.0)	0.3 (95% CI 0.1-0.8)

Gravidity				
Nulligravid	67 (47.2%)	10 (43.5%)	1.2 (95% CI 0.5-2.8)	1.7 (95% CI 0.3-9.5)
Parity				
Nulliparous	78 (54.9%)	12 (52.2%)	1.1 (95% CI 0.5-2.7)	0.9 (95% CI 0.2-4.7)
Marital Status			1.1 (95% CI 0.4-2.6)	0.9 (95% CI 0.3-2.3)
Never married/Divorced[¥]	100 (63.4%)	13 (56.5%)		
Married	52 (36.6%)	10 (43.5%)		
STI history before IUS placement	16 (11.3%)	0	6.1 (95% CI 0.4-106)	8.7 (95% CI 0.5-156)

* Adjusted odds ratio controlling for all factors in table

[†] Includes 17 African-American, four Asian, two multiracial, two American Indian or Alaska Native, and one Native Hawaiian or Other Pacific Islander who conceived and one African-American who did not conceive

[‡] Obesity defined as body mass index ≥30.0 kg/m^2

[¥] Includes 8 divorced women (all conceived)

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

IUS: intrauterine system; STI: sexually transmitted infection (Chlamydia or gonorrhea)

Table 3. Twelve-month conception rates after levonorgestrel 52 mg IUS discontinuation based on duration of IUS use

Years of IUS use	Conception within 12 months after IUS discontinuation				
	Total	Nulligravid	Gravid	Nulliparous	Parous
	N=165	n=77	n=88	n=90	n=75
≤1	12/13 (92%)	3/3 (100%)	9/10 (90%)	4/4 (100%)	8/9 (89%)
1+ to 2	27/30 (90%)	11/12 (92%)	16/18 (89%)	11/12 (92%)	16/18 (89%)
2+ to 3	38/43 (88%)	12/15 (80%)	26/28 (93%)	17/21 (81%)	21/22 (95%)
3+ to 4	31/41 (76%)	20/23 (87%)	11/18 (61%)	21/25 (84%)	10/16 (63%)
4+ to 5	34/38 (89%)	21/24 (88%)	13/14 (93%)	25/28 (89%)	9/10 (90%)
P-value for trend across years*	0.28	0.86	0.03	0.77	0.06

* Chi-square test for trend

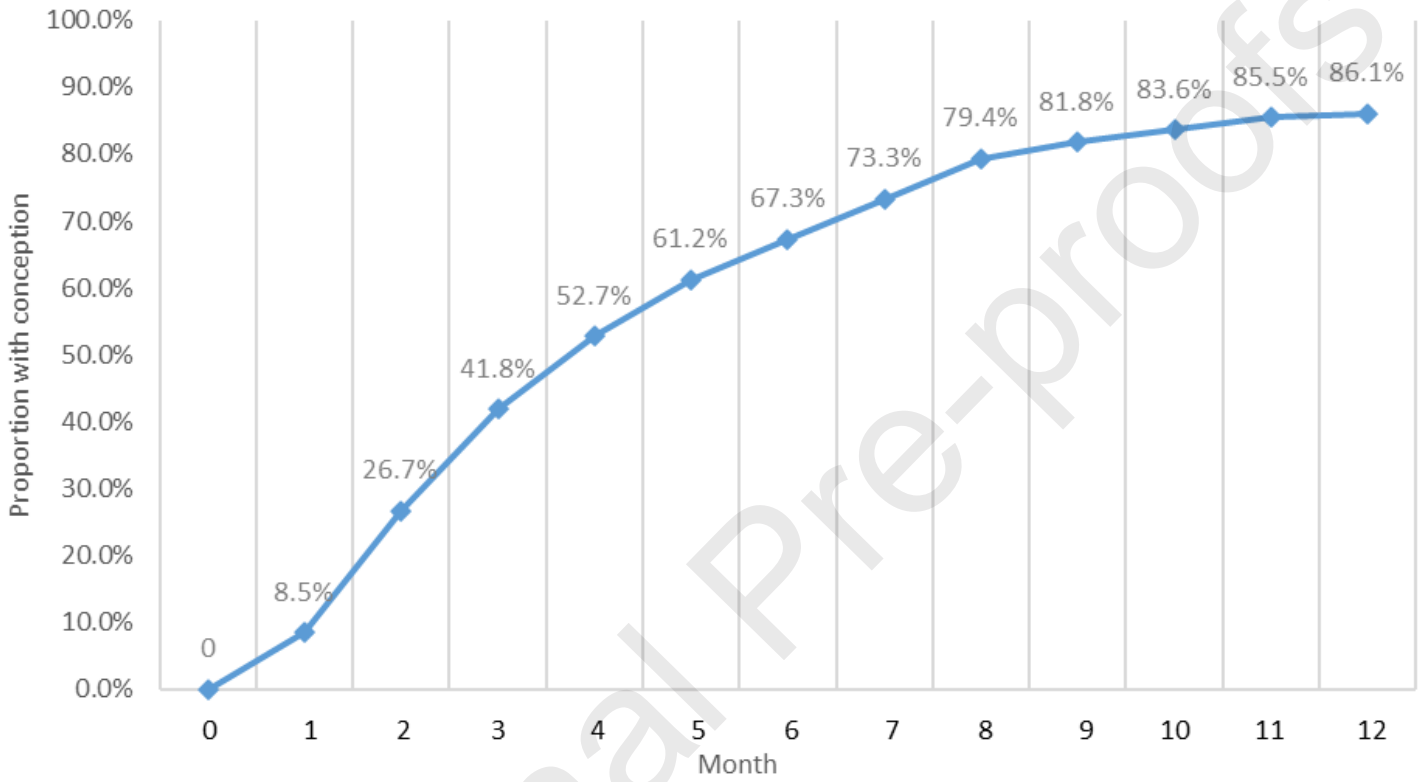
IUS: intrauterine system

Figure Legend

Figure 1.

Life-table conception rates in first 12 months after levonorgestrel 52 mg IUS discontinuation

Figure 1.



Online Appendix 1. Demographics and contraceptive method at enrollment for women in a phase 3 study who had successful placement of a Liletta levonorgestrel 52 mg IUS and planned to attempt conception after IUS discontinuation*

Characteristic	**Population of Women Planning to Attempt Conception**			
	Population followed for up to 12 months	**Lost to follow-up / Withdrew consent**	**Changed mind during follow-up†**	**P-value**
	n=165	**n=17**	**n=36**	
Years of IUS use				0.79
≤1	13 (7.9)	3 (17.6)	2 (5.6)	
1+ to 2	30 (18.2)	4 (23.5)	7 (19.4)	
2+ to 3	43 (26.1)	3 (17.6)	10 (27.8)	
3+ to 4	41 (24.8)	5 (29.4)	11 (30.6)	
4+ to 5	38 (23.0)	2 (11.8)	6 (16.7)	
Age at enrollment (years)	26.5 ± 4.0	24.1 ± 4.3	25.9 ± 4.1	0.053
<25	58 (35.2)	9 (52.9)	14 (38.9)	0.32
25-35	107 (64.8)	8 (47.1)	22 (61.1)	
Age at IUS discontinuation (years)	29.4 ± 3.9	26.4 ± 4.1	28.8 ± 4.2	0.01
<25	22 (13.3)	6 (35.3)	6 (16.7)	0.06
25-35	143 (86.7)	11 (64.7)	30 (83.3)	
Duration of IUS use (months)	34.8 ± 15.0	29.4 ± 16.4	34.9 ± 14.5	0.36

Race				0.36
White	138 (83.6)	13 (76.5)	26 (72.2)	
Black or African American	18 (10.9)	2 (11.8)	7 (19.4)	
Asian	4 (2.4)	1 (5.9)	2 (5.6)	
Multiracial	2 (1.2)	0	1 (2.8)	
American Indian/Alaska Native	2 (1.2)	1 (5.9)	0	
Native Hawaiian/Other Pacific Islander	1 (0.6)	0	0	
Ethnicity				
Hispanic or Latina	22 (13.3)	6 (35.3)	7 (19.4)	0.055
BMI at enrollment (kg/m^2)	27.1 ± 7.3	26.2 ± 5.8	27.0 ± 4.9	0.89
Obese (≥30.0)	40 (24.2)	5 (29.4)	11 (30.6)	0.66
BMI at IUS discontinuation (kg/m^2)	27.7 ± 7.8	26.8 ± 5.7	27.9 ± 6.0	0.88
Obese (≥30.0)	43 (26.1)	6 (35.3)	12 (33.3)	0.52
Parity				
Nulliparous	90 (54.5)	9 (52.9)	19 (52.8)	0.97
Marital Status				0.51
Never married	95 (57.6)	12 (70.6)	21 (58.3)	
Married	62 (37.6)	5 (29.4)	13 (36.1)	
Divorced/Separated	8 (4.8)	0	2 (5.6)	

Pelvic infection‡				
STI history before IUS placement	16 (9.7)	0	0	0.08
STI during IUS use	6 (3.6)	2 (11.8)	0	0.11
Pelvic infection during IUS use	3 (1.8)	0	0	1.00

* Study enrolled women 16-45 years old; only women 16-35 years at study entry included in return to fertility analysis

† Subjects who stopped attempting to conceive prior to completing 12 months of trying

‡ None had a history of pelvic infection prior to study enrollment

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

Statistical testing using ANOVA and t-tests as appropriate

IUS: intrauterine system; BMI: body mass index; STI: sexually transmitted infection (Chlamydia or gonorrhea)

Online Appendix 2. Twelve-month conception rates after levonorgestrel 52 mg IUS discontinuation based on duration of IUS use in gravid and parous women based on obesity status

Years of IUS use	Conception within 12 months after IUS discontinuation			
	Gravid obese n=32	Gravid non-obese n=56	Parous obese n=28	Parous non-obese n=47
≤1	2/2 (100%)	7/8 (88%)	2/2 (100%)	6/7 (86%)
1+ to 2	6/8 (75%)	10/10 (100%)	6/8 (75%)	10/10 (100%)
2+ to 3	11/12 (92%)	15/16 (94%)	10/10 (100%)	11/12 (92%)
3+ to 4	3/6 (50%)	8/12 (67%)	2/4 (50%)	8/12 (67%)
4+ to 5	4/4 (100%)	9/10 (90%)	4/4 (100%)	5/6 (83%)
P-value for trend across years*	0.18	0.15	0.11	0.25

* Chi-square test for trend

IUS: intrauterine system

Online Appendix 3. Twelve-month conception rates after levonorgestrel 52 mg IUS discontinuation based on duration of IUS use in gravid and parous women based on age

Years of IUS use	Conception within 12 months after IUS discontinuation			
	Gravid age <25 years n=28	Gravid age ≥25 years n=60	Parous age <25 years n=24	Parous age ≥25 years n=51
≤1	2/2 (100%)	7/8 (88%)	2/2 (100%)	6/7 (86%)
1+ to 2	7/7 (100%)	9/11 (82%)	7/7 (100%)	9/11 (82%)
2+ to 3	8/8 (100%)	18/20 (90%)	7/7 (100%)	14/15 (93%)
3+ to 4	4/6 (67%)	7/12 (58%)	4/5 (80%)	6/11 (55%)
4+ to 5	5/5 (100%)	8/9 (89%)	3/3 (100%)	6/7 (86%)
P-value for trend across years*	0.095	0.22	0.41	0.16

* Chi-square test for trend

IUS: intrauterine system