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Relationship of parity and prior cesarean delivery to levonorgestrel 52 mg intrauterine system expulsion over 6 years

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Melissa L. Gilliam has no conflicts; her university department receives contraceptive research funding from Medicines360.

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David L. Eisenberg has served on a Data Safety Monitoring Board for studies sponsored by Sebela, as a trainer for Merck, and on Advisory Boards for Femasys and Medicines360. His university department receives contraceptive research funding from Medicines360.

Michael A. Thomas has no conflicts; his university department receives contraceptive research funding from Evofem, Medicines360, and Sebela.

Andrea I. Olariu is a Medicines360 employee.

Mitchell D. Creinin has served on Advisory Boards for Evofem, Mayne, Merck & Co., and TherapeuticsMD and is a consultant for Danco, Estetra, Mayne and Medicines360. His university department receives contraceptive research funding from Daré, HRA Pharma, Medicines360, Merck & Co. and Sebela.

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ABSTRACT

Objective: Assess the relationship between parity and prior route of delivery to levonorgestrel 52 mg intrauterine system (IUS) expulsion during the first 72 months of use.

Study Design: We evaluated women enrolled in the ACCESS IUS multicenter, Phase 3, open-label clinical trial of the Liletta® levonorgestrel 52 mg IUS. Investigators evaluated IUS presence at three and six months after placement and then every six months and during unscheduled visits. We included women with successful placement and at least one follow-up assessment. We evaluated expulsion rates based on obstetric history; for prior delivery method sub-analyses, we excluded 12 participants with missing delivery data. We determined predictors of expulsion using multivariable regression analyses.

Results: Of 1,714 women with IUS placement, 1,710 had at least one follow-up assessment. The total population included 986 (57.7%) nulliparous women. Sixty-five (3.8%) women experienced expulsion within 72 months, 50 (76.9%) within the first 12 months. Expulsion rates among nulliparous women (22/986 [2.2%]) or parous women with any pregnancy ending with a Cesarean delivery (6/195 [3.1%]) differed from parous women who only experienced vaginal deliveries (37/517 [7.2%]) ($p<0.001$). In multivariable regression, obesity (aOR 2.2, 95% CI 1.3-3.7), parity (aOR 2.2, 95% CI 1.2-4.1) and non-white race (aOR 1.8, 95% CI 1.1-3.2) predicted expulsion. Among parous women, obesity (aOR 2.2, 95% CI 1.2-4.2) increased the odds and having ever had a cesarean delivery (aOR 0.4, 95% CI 0.1-0.9) decreased the odds of expulsion.

Conclusion: IUS expulsion occurs in less than 4% of users over the first six years of use and occurs mostly during the first year. Expulsion is more likely among obese and parous women.

Key Words: intrauterine device, intrauterine system, expulsion, obesity, Liletta

Implications: Levonorgestrel 52 mg intrauterine system expulsion occured more commonly in parous than nulliparous women; the increase in parous women is primarily in women who had vaginal deliveries only. The association between obesity, delivery route, and IUS expulsion needs further elucidation.

1.0 INTRODUCTION

Expulsion occurs infrequently after intrauterine device (IUD) placement [1-3], but the reasons for which expulsion occurs for some users and not others remain unknown. Studies have evaluated risk factors but are limited by the type of persons included. Although many studies, especially older studies, show decreasing risk of IUD expulsion with increasing age, most did not control for other factors, like parity, race and marital status [4]. Once other factors are controlled for, this difference by age is no longer present [4]. Many of the early studies included few nulliparous women which limited the ability to control for this variable.

Contemporary studies have included significantly more nulliparous women and demonstrate that expulsion occurs more frequently in parous than nulliparous women [5,6]. Given the increased risk of expulsion in parous women, one must consider if prior delivery mode impacts this outcome. While studies of immediate post-placental IUD insertion have included type of delivery when evaluating expulsion risk [7,8], this variable has not been considered when evaluating risk with insertions remote from pregnancy.

ACCESS IUS is a U.S. based, multicenter Phase 3 open-label contraceptive clinical trial which has led to approval of a levonorgestrel 52 mg intrauterine system (IUS) for six years and is currently following women for up to 10 years of 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 nulliparous and parous women [9]. In this report, we evaluate expulsion rates by parity and other predictors of expulsion, focusing on the impact of prior delivery mode among parous women.

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). The methods of the main study have been reported previously [6,9]. A central or local Institutional Review Board for each center approved the study. All women signed written informed consents before study participation.

Briefly, investigators at 29 clinical sites 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. Follow-up visits occurred three times in the first six months and then every six months thereafter, with phone calls at the three-month interval between visits. At each visit, the investigator performed a digital or speculum examination to confirm presence of the IUS thread. The investigator performed a transvaginal ultrasound examination annually for subjects with missing threads or when clinically indicated (e.g. increased bleeding, cramping) to evaluate for possible expulsion. The protocol defined partial expulsion *a priori* as visual evidence of the lower portion of the IUS stem protruding through the cervical os, or ultrasonography findings of the IUS in the lower uterine segment in participants reporting increased bleeding and/or cramping. Investigators removed the IUS for partial expulsion. Subjects who experienced an expulsion could not receive another IUS and were discontinued from the study.

For this analysis, we included women who had at least one follow-up contact after IUS placement and evaluated outcomes through the 72-month (6-year) visit. We assessed the primary outcomes of expulsion rates among all women entering the study and based on parity and past

delivery route. We also calculated expulsion rates during the first and second 6 months of the first year of use, as well as years 2-6, with the number of women entering each time period as the denominator. For sub-analyses of prior delivery mode among parous women, we excluded participants with missing or incomplete delivery data. We used Fisher's exact and chi-square tests as appropriate. We created a multivariable logistic regression model for expulsion risk based on possible risk factors, including age, race, ethnicity, body mass index (BMI) at enrollment, parity, marital status, miscarriage history, heavy menstrual bleeding as baseline bleeding pattern prior to study entry, and hormonal contraception use in the month before enrollment. We created a second model for parous women only that also included delivery method as vaginal only versus cesarean delivery (with or without prior vaginal delivery) and time since last pregnancy; the database did not differentiate specifically time since last delivery. Additionally, we evaluated significant continuous variables in these models to assess any association of higher values with expulsion risk. We performed statistical analyses using SAS® 9.4 (Cary, NC) with a p-value of 0.05 considered statistically significant.

Clinical Trial Registration number: Clinicaltrials.gov NCT00995150

3.0 RESULTS

Of the 1714 women who had successful placement, 1710 had follow-up information. The characteristics of all evaluated subjects are presented in Table 1. We then excluded 12 parous women with missing or incomplete delivery data from the planned sub-analyses related to delivery mode and expulsion risk. Among the remaining 712 parous women, 517 (72.6%) had

only experienced vaginal deliveries, 130 (18.3%) had all prior deliveries by cesarean and 65 (9.1%) experienced both types of deliveries.

Overall, 28 (1.6%), 50 (2.9%) and 65 (3.8%) of the 1710 participants with follow-up information experienced expulsion by 6, 12, and 72 months, respectively. Complete expulsions comprised 12 (42.8%) 23 (46.0%) and 27 (41.5%), respectively, of these events with the remainder (16 [57.2%], 27 [54.0%] and 38 [58.5%], respectively) being partial expulsions. Most (50 [76.9%]) expulsions occurred in the first 12 months.

The overall expulsion rate was similar in the first six months after placement (28/1710 [1.6%]) compared to months >6 to 12 (22/1553 [1.4%]), p=0.67. The expulsion rates remained consistent in these two time periods for nulliparous women (7/986 [0.7%] vs. 10/915 [1.1%], respectively, p=0.47) and parous women (21/724 [2.9%] vs. 12/638 [1.8%], respectively, p=0.29). Expulsion rates in years two through six were 6/1400 (0.4%), 2/1148 (0.2%), 4/964 (0.4%), 1/818 (0.1%) and 2/688 (0.3%), respectively.

Table 2 shows expulsion rates by parity, delivery method, and obesity status. Parous women experience more IUS expulsion than nulliparous women, with a significant difference as early as 3 months after placement. The 17 (1.0%) expulsions by 3 months included 9 complete and 8 partial expulsions.

Expulsion rates among nulliparous women (22/986 [2.2%]) or parous women with any pregnancy ending with a Cesarean delivery (6/195 [3.1%]) differed from parous women who only experienced vaginal deliveries (37/517 [7.2%]) ($p<0.001$). Four of the 130 (3.1%) women with only prior cesarean deliveries experienced expulsion. No expulsions occurred in women with a prior cesarean delivery after 12 months of use. A single subject (25 years old, G4P1 with 3 miscarriages and one vaginal delivery, BMI 25.0 kg/m^2, 382 days since last pregnancy) who

experienced a complete expulsion during year one did not recognize the expulsion and became pregnant; no other pregnancies occurred related to expulsion during the study.

Predictors of expulsion in univariate and multivariable analyses for the total population are presented in Table 3 . Overall, obesity (aOR 2.2, 95% CI 1.3-3.7), parity (aOR 2.2, 95% CI 1.2-4.1) and non-white race (aOR 1.8, 95% CI 1.1-3.2) were significantly associated with expulsion. In a stratified analysis of expulsion type, only parity predicted complete expulsion (aOR 4.0 [95% CI 1.5-10.8]) (Online Appendix 1). However, for partial expulsion, obesity (aOR 2.5 [95% CI 1.3-4.8]) and non-white race (aOR 2.1 [95% CI 1.0-4.1]) predict expulsion. For significant continuous variables, every 1.0 kg/m^2 increase in BMI increased the odds of expulsion by about 6% (aOR 1.06, 95% CI 1.03-1.10). Every increase in parity of one delivery increased the odds of expulsion by about 30% (aOR 1.31, 95% CI 1.04-1.66), primarily because of the increase in odds of expulsion related to vaginal delivery. For every vaginal delivery, the odds of expulsion increased about 40% (aOR 1.40 [95% CI 1.11-1.75]) with no difference if persons with both previous vaginal and cesarean deliveries are included (1.42 [95% CI 1.11-1.81]).

Predictors of expulsion in univariate and multivariable analyses for parous women are presented in Table 4. Obesity (aOR 2.2, 95% CI 1.2-4.2) increases the odds and having ever had a cesarean delivery (aOR 0.4, 95% CI 0.1-0.9) and decreases the odds of expulsion. The outcomes in Table 4 did not change with evaluation using duration of use as a continuous variable (data not shown).

4.0 DISCUSSION

Expulsion of the levonorgestrel 52 mg IUS is uncommon when placed remote from pregnancy, occurring in less than 4% of users within 6 years of use. When expulsions do occur, most (77%) are during the first year of use. Expulsion rates after the first year remained very low, ranging from 0.1-0.4%. Slightly more expulsions are partial (~55%) rather than complete, and the proportion stays consistent over 6 years of use.

We found a strong association between parity (prior delivery) and expulsion, which is clinically evident as early as 3 months after IUS placement; the odds of expulsion increase with increasing parity. However, among parous women, those with a prior cesarean delivery, whether or not they also experienced vaginal delivery, have expulsion rates similar to nulliparous women; these rates are significantly lower than expulsion rates in women who only experienced vaginal delivery. It appears that the type of delivery and not just parity is the risk factor for expulsion. The expulsion rate in women who only had cesarean deliveries mirrored the rate in those with cesarean and vaginal deliveries (both 3.1%). Studies that explore the physiologic reason for this difference may help us better understand how to address similar issues, like the difference in expulsion rates with post-placental IUD placement, after which expulsion is lower when the IUD is placed at cesarean delivery compared to shortly after vaginal delivery [7,8]. The higher risk of expulsion in patients who have experienced vaginal delivery without cesarean delivery or who undergo post-placental IUD placement after vaginal delivery may not be highly modifiable.

Obesity independently increased the odds of expulsion more than two-fold in the total population and in the sub-analysis of just parous women; the odds of expulsion increase with increasing BMI. Obesity has been suggested as a risk factor for expulsion of levonorgestrel IUS but not the copper IUD [5]. The CHOICE study included 1767 obese and 3580 non-obese IUD users with high rates of IUD expulsion in both groups within 36 months of placement (11% and

7%, respectively). In multivariable analysis, obesity remained a significant predictor of expulsion over time (aHR1.27, 95% CI 1.02-1.60) for levonorgestrel IUS users and not for copper IUD users. Our expulsion rate among both obese and non-obese women was much lower than reported by the CHOICE investigators, perhaps due to a difference in population characteristics. Even with our much lower rate of expulsion, we demonstrated a relationship between obesity and expulsion. Further research should evaluate if expulsion risk with obesity is related to issues at placement.

Non-white race increased the odds of expulsion in the total population, and that link is primarily related to partial expulsion; however, this finding did not persist in parous women. This association was relatively weak (adjusted odds ratio less than 2) and may represent a Type 1 error. Most non-white participants were black (76%); however, the numbers were too small to further delineate this outcome. Further, race is a social construct; given the lack of continued association in parous women, the clinical relevance of this finding is doubtful.

This prospective study is limited by a small amount of incomplete data, with 12 (1.7%) parous women missing accurate delivery method information. This small proportion is unlikely to significantly impact the findings. Additional limitations include our inability to comment on the specific time since the last delivery (our database only had time since last pregnancy) or any specific cause of the expulsions identified or proximal factors related to expulsion, such as use of menstrual cups [10,11]. Although the study is large, the stratified analysis of predictors of complete and partial expulsion includes relatively small numbers and may not reflect true risk. A strength of the study is the regular follow-up with evaluation for presence of the IUD every six months throughout the study and pre-defined descriptions for partial and complete expulsion.

Overall, in a population of women that closely resembled the US population [7] at the time of enrollment, we found levonorgestrel 52 mg IUS expulsion to be an infrequent event over many years of follow-up. Whereas expulsion occurred in about 3% of users at one year and 4% by six years, the rate varied most significantly by obesity status, type of delivery (if any), and prior pregnancy. Nulliparous women had low expulsion rates of about 2% at one year and 3% at six years. Similarly, those with any prior cesarean deliveries had rates of about 3% at one year and no expulsions thereafter. Expulsions appear to occur most frequently in women who have experienced only vaginal deliveries (5% at one year and 7% at six years). When considering factors that could influence expulsion risk, obesity and vaginal delivery appear to have similar independent effects. The outcomes described will allow providers to more clearly explain expulsion risk to an individual patient.

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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[a]

Characteristic	Total N=1710	Nulliparous n=986	Parous n=724	P-value[b]
Age at enrollment (years)	27.3 ± 5.7	25.2 ± 4.3	30.2 ± 6.1	<0.001
<25	619 (36.2)	481 (48.8)	138 (19.1)	<0.001
25-45	1091 (63.8)	505 (51.2)	586 (80.9)	
Race				<0.001
White	1339 (78.3)	797 (80.8)	542 (74.9)	
Black or African American	224 (13.1)	85 (8.6)	139 (19.2)	
Asian	67 (3.9)	49 (5.0)	18 (2.5)	
Mixed	49 (2.9)	41 (4.2)	8 (1.1)	
Other[c]	31 (1.8)	14 (1.4)	17 (2.3)	
Ethnicity				
Hispanic or Latina	251 (14.7)	113 (11.5)	138 (19.1)	<0.001
BMI at enrollment (kg/m^2)[d]	26.9 ± 6.8	25.6 ± 5.9	28.8 ± 7.4	<0.001
Obese (≥ 30.0)	431 (25.2)	174 (17.6)	257 (35.5)	<0.001
Marital Status				<.0001
Never married	1079 (63.1)	812 (82.4)	267 (36.9)	
Married	477 (27.9)	143 (14.5)	334 (46.1)	
Divorced	122 (7.1)	28 (2.8)	94 (13.0)	
Separated/widowed	32 (1.9)	3 (0.3)	29 (4.0)	
History of Miscarriage	208 (12.2)	34 (3.4)	174 (24.0)	<0.001
Heavy menstrual bleeding at baseline	168 (9.8)	88 (8.9)	80 (11.0)	0.16

Contraceptive method at enrollment[e]				<0.001
Levonorgestrel IUS	148 (8.7)	45 (4.6)	103 (14.2)	
Copper IUD	31 (1.8)	8 (0.8)	23 (3.2)	
Hormonal Implant	9 (0.5)	6 (0.6)	3 (0.4)	
CHC	650 (38.0)	471 (47.8)	179 (24.7)	
POP	36 (2.1)	18 (1.8)	18 (2.5)	
Non-hormonal/non-IUD method	686 (40.1)	387 (39.2)	299 (41.3)	
None	150 (8.8)	51 (5.2)	99 (13.7)	

[a] Excludes 4 women with successful IUS placement and no follow-up information during the study

[b] Comparing nulliparous and parous women, Fisher exact or Chi-square testing

[c] Includes 21 American Indian or Alaska Native, 6 Native Hawaiian or Other Pacific Islander, and 4 with missing information

[d] Four persons with missing information

[e] Method used in the month before IUS placement

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

IUS: intrauterine system; BMI: body mass index; IUD: intrauterine device; CHC: combined hormonal contraception; POP: progestin-only pill

Table 2. Cumulative expulsions within 72 months after levonorgestrel 52 mg IUS placement as proportion of total population enrolled

Duration of use	**Nulliparous n=986**	**Parous n=724**	**P-value†**
3 months	4 (0.4)	13 (1.8)	<0.01
6 months	7 (0.7)	21 (2.9)	<0.001
12 months	17 (1.7)	33 (4.6)	<0.001
72 months	22 (2.2)	43 (5.9)	<0.001
	Parous* Vaginal Delivery Only n=517	**Parous* Cesarean Delivery‡ n=195**	**P-value†**
3 months	13 (2.5)	0	0.02
6 months	18 (3.5)	3 (1.5)	0.22
12 months	27 (5.2)	6 (3.1)	0.32
72 months	37 (7.2)	6 (3.1)	0.05
	Obese¥ n=430	**Non-Obese n=1275**	**P-value†**
3 months	7 (1.6)	10 (0.8)	0.16
6 months	11 (2.6)	17 (1.3)	0.12
12 months	22 (5.1)	28 (2.2)	<0.01
72 months	31 (7.2)	34 (2.7)	<0.001

* Twelve parous women had missing delivery type data and are not included in the analysis specific to delivery type

† Fisher exact test

‡ With or without prior vaginal delivery

¥ Obesity defined as body mass index ≥ 30.0 kg/m^2

Data presented as n (%)

IUS: intrauterine system

Table 3. Predictors of expulsion in women using a levonorgestrel 52 mg IUS for up to 72 months (N=1710)

Characteristic	Number of subjects	Expulsions n (%)	Odds Ratio	Adjusted Odds Ratio[a]
Age (years)				
<25	619	21 (3.4)	referent	referent
≥ 25	1091	44 (4.0)	1.2 (95% CI 0.7-2.0)	0.7 (95% CI 0.4-1.3)
Race[b]				
White	1339	42 (3.1)	referent	referent
Non-White	371	23 (6.2)	2.0 (95% CI 1.2-3.4)	1.8 (95% CI 1.1-3.2)
Ethnicity				
Non-Hispanic	1459	51 (3.5)	referent	referent
Hispanic or Latina	251	14 (5.6)	1.6 (95% CI 0.9-3.0)	1.4 (95% CI 0.8-2.7)
BMI at enrollment (kg/m^2)[c]				
<30.0	1279	34 (2.7)	referent	referent
≥ 30.0	431	31 (7.2)	2.8 (95% CI 1.7-4.7)	2.2 (95% CI 1.3-3.7)
Parity				
Nulliparous	986	22 (2.2)	referent	referent
Parous	724	43 (5.9)	2.8 (95% CI 1.6-4.7)	2.2 (95% CI 1.2-4.1)

Marital Status				
Never married	1079	33 (3.1)	referent	referent
Married/ever married	631	32 (5.1)	1.7 (95% CI 1.0-2.8)	1.4 (95% CI 0.8-2.6)
History of Miscarriage				
No	1502	54 (3.6)	referent	referent
Yes	208	11 (5.3)	1.5 (95% CI 0.8-2.9)	0.9 (95% CI 0.4-1.8)
Baseline HMB				
No	1542	54 (3.5)	referent	referent
Yes	168	11 (6.5)	1.9 (95% CI 1.0-3.8)	1.7 (95% CI 0.8-3.4)
HC use at enrollment[d]				
No	867	36 (4.2)	referent	referent
Yes	843	29 (3.4)	0.8 (95% CI 0.5-1.4)	1.1 (95% CI 0.7-1.9)

[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 IUS placement

IUS: intrauterine system; CI: confidence interval; HMB: heavy menstrual bleeding; HC: hormonal contraception (oral, implant, ring, patch, IUS)

Table 4. Predictors of expulsion in parous women using a levonorgestrel 52 mg IUS for up to 72 months (N=712[a])

Characteristic	Number of subjects	Expulsions n (%)	Odds Ratio	Adjusted Odds Ratio[b]
Age (years)				
<25	137	7 (5.1)	referent	referent
≥ 25	575	36 (6.3)	1.2 (95% CI 0.5-2.9)	1.3 (95% CI 0.5-3.2)
Race[c]				
White	534	29 (5.4)	referent	referent
Non-White	178	14 (7.9)	1.5 (95% CI 0.8-2.9)	1.8 (95% CI 0.8-3.6)
Ethnicity				
Non-Hispanic	578	31 (5.4)	referent	referent
Hispanic or Latina	134	12 (9.0)	1.7 (95% CI 0.9-3.5)	1.8 (95% CI 0.9-3.8)
BMI at enrollment (kg/m^2)[d]				
<30.0	456	20 (4.4)	referent	referent
≥ 30.0	252	23 (9.1)	2.2 (95% CI 1.2-4.1)	2.2 (95% CI 1.2-4.2)
Delivery method				
Vaginal only	517	37 (7.2)	referent	referent
Cesarean[e]	195	6 (3.1)	0.4 (95% CI 0.2-1.0)	0.3 (95% CI 0.1-0.9)

Marital Status				
Never married	262	14 (5.3)	referent	referent
Married/ever married	450	29 (6.4)	1.2 (95% CI 0.6-2.4)	1.7 (95% CI 0.8-3.5)
History of Miscarriage				
No	539	33 (6.1)	referent	referent
Yes	173	10 (5.8)	0.9 (95% CI 0.5-2.0)	0.8 (95% CI 0.4-1.7)
Baseline HMB				
No	634	35 (5.5)	referent	referent
Yes	78	8 (10.3)	2.0 (95% CI 0.9-4.4)	2.0 (95% CI 0.8-4.6)
HC use at enrollment[f]				
No	412	27 (6.6)	referent	referent
Yes	300	16 (5.3)	0.8 (95% CI 0.4-1.5)	0.9 (95% CI 0.5-1.8)
Days between last pregnancy and IUS placement[g]				
<865	356	23 (6.5)	referent	referent
≥ 865	356	20 (5.6)	0.9 (95% CI 0.5-1.6)	0.8 (95% CI 0.4-1.5)

[a] Twelve parous women had missing delivery type data and are not included in this analysis

[b] Adjusted odds ratio controlling for all factors in table

[c] Four persons with missing information

[d] Three persons with missing information

[e] With or without vaginal delivery; 130 persons had cesarean deliveries only

[f] Method used in the month before IUS placement

[g] Range 29-8954 days and not normally distributed; variable in table based on median value

IUS: intrauterine system; CI: confidence interval; HMB: heavy menstrual bleeding; HC: hormonal contraception (oral, implant, ring, patch, IUS)

Online Appendix 1. Predictors of complete expulsion in women using a levonorgestrel 52 mg IUS for up to 72 months (N=1710)

Characteristic	Number of subjects	Complete Expulsions n (%)	Odds Ratio	Adjusted Odds Ratio[a]
Age (years)				
<25	619	9 (1.5)	referent	referent
≥ 25	1091	18 (1.6)	1.1 (95% CI 0.5-2.5)	0.6 (95% CI 0.3-1.6)
Race[b]				
White	1339	19 (1.4)	referent	referent
Non-White	371	8 (2.2)	1.5 (95% CI 0.7-3.5)	1.5 (95% CI 0.6-3.6)
Ethnicity				
Non-Hispanic	1459	21 (1.4)	referent	referent
Hispanic or Latina	251	6 (2.4)	1.7 (95% CI 0.7-4.2)	1.4 (95% CI 0.6-3.7)
BMI at enrollment (kg/m^2)[c]				
<30.0	1279	15 (1.2)	referent	referent
≥ 30.0	431	12 (2.8)	2.4 (95% CI 1.1-5.2)	1.9 (95% CI 0.8-4.1)
Parity				
Nulliparous	986	7 (0.7)	referent	referent
Parous	724	20 (2.8)	4.0 (95% CI 1.7-9.4)	4.0 (95% CI 1.5-10.8)

Marital Status				
Never married	1079	13 (1.2)	referent	referent
Married/ever married	631	14 (2.2)	1.9 (95% CI 0.9-4.0)	1.3 (95% CI 0.5-3.3)
History of Miscarriage				
No	1502	24 (1.6)	referent	referent
Yes	208	3 (1.4)	0.9 (95% CI 0.3-3.0)	0.5 (95% CI 0.1-1.7)
Baseline HMB				
No	1542	13 (1.5)	referent	referent
Yes	168	14 (1.7)	1.1 (95% CI 0.5-2.4)	1.5 (95% CI 0.7-3.2)
HC use at enrollment[d]				
No	867	36 (4.2)	referent	referent
Yes	843	29 (3.4)	0.8 (95% CI 0.5-1.4)	1.1 (95% CI 0.7-1.9)

[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 IUS placement

[e] Range 29-8954 days and not normally distributed; variable in table based on median value

IUS: intrauterine system; CI: confidence interval; HMB: heavy menstrual bleeding; HC: hormonal contraception (oral, implant, ring, patch, IUS)

Online Appendix 2. Predictors of partial expulsion in women using a levonorgestrel 52 mg IUS for up to 72 months (N=1683)[a]

Characteristic	Number of subjects	Complete Expulsions n (%)	Odds Ratio	Adjusted Odds Ratio[b]
Age (years)				
<25	610	12 (2.0)	referent	referent
≥ 25	1073	26 (2.4)	1.2 (95% CI 0.6-2.5)	0.8 (95% CI 0.4-1.8)
Race[c]				
White	1320	23 (1.7)	referent	referent
Non-White	363	15 (4.1)	2.4 (95% CI 1.3-4.7)	2.1 (95% CI 1.0-4.1)
Ethnicity				
Non-Hispanic	1438	30 (2.1)	referent	referent
Hispanic or Latina	245	8 (3.3)	1.6 (95% CI 0.7-3.5)	1.4 (95% CI 0.6-3.2)
BMI at enrollment (kg/m^2)[d]				
<30.0	1260	19 (1.5)	referent	referent
≥ 30.0	419	19 (4.5)	3.1 (95% CI 1.6-5.9)	2.5 (95% CI 1.3-4.8)
Parity				
Nulliparous	979	15 (1.5)	referent	referent
Parous	704	23 (3.3)	2.2 (95% CI 1.1-4.2)	1.4 (95% CI 0.7-3.2)

Marital Status				
Never married	1066	20 (1.9)	referent	referent
Married/ever married	617	18 (2.9)	1.6 (95% CI 0.8-3.0)	1.5 (95% CI 0.7-3.1)
History of Miscarriage				
No	1478	30 (2.0)	referent	referent
Yes	205	8 (3.9)	2.0 (95% CI 0.9-4.3)	1.3 (95% CI 0.5-2.9)
Baseline HMB				
No	1518	30 (2.0)	referent	referent
Yes	165	8 (4.8)	2.5 (95% CI 1.1-5.6)	2.0 (95% CI 0.9-4.6)
HC use at enrollment[e]				
No	854	23 (2.7)	referent	referent
Yes	829	15 (1.8)	0.7 (95% CI 0.3-1.3)	0.9 (95% CI 0.5-1.8)

[a] Excludes 27 participants with complete expulsion

[b] Adjusted odds ratio controlling for all factors in table

[c] Four persons with missing information

[d] Three persons with missing information

[e] Method used in the month before IUS placement

[f] Range 29-8954 days and not normally distributed; variable in table based on median value

IUS: intrauterine system; CI: confidence interval; HMB: heavy menstrual bleeding; HC: hormonal contraception (oral, implant, ring, patch, IUS)