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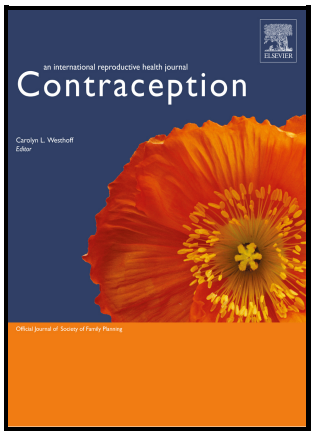

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Menstrual Cup Use and Intrauterine Device Expulsion in a Copper Intrauterine Device Randomized Trial

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Conflicts of Interest:

JB: Dr. Brown has received contraceptive research funding from the Uniformed Services University.

MDC: Dr. Creinin has received speaking honorarium from Gedeon Richter, Mayne, and OLIC, served on an Advisory Board for Gedeon Richter, Mayne, and Organon, has stock options with Femasys, and consulted for Estetra SRL, Mayne, and Medicines360. The Department of Obstetrics and Gynecology, University of California, Davis, has received contraceptive research funding for Dr. Creinin from Chemo Research SL, Evofem, Medicines360, Merck, Sebela, and NIH/NICHD.

HW: Dr. Wu has no conflicts of interest.

DH: Dr. Hubacher has received contraceptive research funding from NIH/NICHD, the Bill & Melinda Gates Foundation, USAID, and speaking honorarium from 3Daughters, Inc.

CAS: Dr. Schreiber reported receiving contracts from Athenium Pharmaceuticals and the National Institutes of Health and grants from Independence Blue Cross outside the submitted

work; in addition, Dr. Schreiber had a patent (19-8815) issued for medical management of nonviable pregnancy and a patent (18-8692) with royalties paid. No other disclosures were reported.

BK: Dr. Kaneshiro has received research support from Contramed Pharmaceuticals (Sebela Pharmaceuticals) and Evofem Biosciences; consultant for UpToDate and a trainer for Nexplanon (Merck).

KN: FHI 360 has received contraceptive research funding for Dr. Nanda from NIH/NICHD, USAID, and the Gates Foundation.

DB: NICHD has a Cooperative Research and Development Agreement (CRADA) with industry partner Daré in which Dr. Blithe serves as the Principal Investigator.

ABSTRACT

Objective: To evaluate menstrual cup use and intrauterine device (IUD) expulsion.

Study Design: We performed a secondary analysis of a 3-year contraceptive efficacy trial comparing two copper 380 mm^2 IUDs. Investigators randomized participants approximately 1:4 to the TCu380A or NTCu380-Mini IUD. Approximately 12-months after enrollment began, we advised participants against menstrual cup use due to observed IUD expulsions in cup users. We evaluated IUD expulsion (including spontaneous partial and complete expulsion and accidental self-removal) at 12- and 36-months. We used multivariable logistic regression to evaluate IUD expulsion by age, baseline menstrual volume, body mass index, IUD type, menstrual cup use, parity, and uterine length.

Results: This analysis included 1046 participants (203 TCu380A and 843 NTCu380-Mini), with 879(84.0%) nulliparas. Through 12- and 36-months, expulsion occurred in 74(7.1%, 95%CI 5.5-

8.6%) and 133(12.7%, 95%CI 10.7-14.7%) participants, respectively. Overall, 250(23.9%) reported menstrual cup use. More menstrual cup users than non-users experienced expulsion through 12-months (32/203[15.8%] vs. 42/843[5.0%]) and 36-months (58/250[23.2%] vs. 75/796[9.4%]). Through 36 months, NTCu380-Mini menstrual cup users had higher expulsion odds, while TCu380A cup users did not. Menstrual cup users more frequently experienced accidental self-removal than non-users in participants using the TCu380A (3/53[5.7%] vs. 0/150[0.0%]) and the NTCu380-Mini (20/197[10.2%] vs. 7/646[1.1%]). In multivariable regression, we found increased odds of expulsion through 36-months in participants using menstrual cups with the NTCu380-Mini (aOR 3.13, 95%CI 1.16-8.46) and <25 years (aOR 1.59, 95%CI 1.07-2.34).

Conclusions: We found higher odds of IUD expulsion with menstrual cup and concurrent NTCu380-Mini IUD use over 36 months of use, but not with concurrent TCu380A IUD use. Menstrual cup users experienced higher likelihood of accidental self-removal regardless of IUD type.

Implications Statement: Menstrual cup and NTCu380-Mini use may increase IUD expulsion risk and may increase accidental self-removal risk with TCu380A and NTCu380-Mini use. Clinicians should advise patients of these risks and consider warning patients using an IUD shaped like the NTCu380-Mini (Nova-T frames) of expulsion risk with menstrual cup use.

Keywords:

menstrual cup; copper IUD; expulsion; nulliparas; randomized trial

1.0 Introduction

Intrauterine devices (IUDs) are the most commonly used long-acting reversible contraceptive in the United States (U.S.), used by approximately 13% of contraceptors [1]. Expulsion rates during the first year vary between 2-10% in different studies with varying study populations [2]. A large retrospective cohort study found one- and five-year cumulative copper 380 mm^2 IUD expulsion rates of 2.3% and 4.8%, respectively [3]. One- and three-year cumulative expulsion rate estimates from prospective studies are generally higher: 5-6% and 9-11%, respectively [4-5]. Whereas older studies did not include nulliparas, newer studies including nulliparas show that nulliparity, age < 25 years, obesity, parity of four or more, baseline heavy menstrual bleeding, and prior vaginal delivery are risk factors for expulsion [4,6-11].

A small case series reported 7 IUD (6 hormonal, 1 copper) expulsions in patients using menstrual cups [12]. Menstrual cups are bell-shaped, reusable menstrual fluid collection devices that create a seal against the vaginal walls. Menstrual discs, another reusable menstrual fluid collection device, are flat and circular and sit in the vaginal vault below the cervix, typically not creating a seal. Use of menstrual cups and discs has become increasingly popular in recent years, particularly given the potentially lower environmental impact compared to disposable products [13].

Copper IUDs commonly increase menstrual bleeding, especially in the first several cycles, [14,15], thus may increase the need for menstrual product use. A 2018 survey of IUD users reported 11% concurrent menstrual cup use, with expulsion rates three-fold higher in cup users than non-cup users [16]. To date, no prospective evaluation of concurrent IUD and menstrual cup

use has been reported. We report on IUD expulsion rates by menstrual product use during 36 month follow-up as a secondary analysis from a randomized trial of two copper 380 mm^2 IUDs.

2.0 Materials and Methods

We enrolled eligible participants at sixteen U.S. clinical sites into a single (participant)-masked, randomized trial to primarily evaluate contraceptive efficacy of two copper IUDs in predominantly nulliparas over 36 months of use. The study products included two copper 380 mm^2 IUDs, the TCu380A IUD (Paragard®, Cooper Surgical, Trumbull, CT), available in the U.S., and an investigational IUD, the NTCu380-Mini (Mona Lisa® Mini, Mona Lisa N.V., Belgium), not available in the U.S. but currently marketed in 19 countries. The TCu380A is a polyethylene Tatum-T frame with 32 mm arms and 36 mm stem. The NTCu380-Mini is a smaller polyethylene Nova-T frame, with 24 mm arms and 30 mm stem.

We included sexually active participants aged 16-40 years with regular menses when not using hormonal contraception, an intact uterus and at least one ovary, willing to use the study IUD as the only method of contraception, and willing to be randomized to one of the study IUDs. We excluded persons with known infertility, with copper allergy or sensitivity, within 30 days from pregnancy, at high-risk for sexually transmitted or pelvic infection (per investigator determination), with anticipated need for regular condom use, or with medical contraindications to copper IUDs based on U.S. Centers for Disease Control and Prevention criteria [17]. Investigators randomized participants using a central SAS-based computer-generated randomization scheme 1:4 to receive the TCu380A or the NTCu380-Mini, stratified by parity and study site, with a goal of enrolling 80% nulliparas. We chose this scheme to optimize evaluating efficacy and safety of the investigational IUD, NTCu380-Mini, within an achievable

sample size, given that the TCu380A has an established efficacy and safety profile. We planned to enroll 1000 participants with approximately 200 receiving the TCu380A and 800 receiving the NTCu380-Mini with 90% of the population 16-35 years old. Because of a higher than expected first-year discontinuation rate, we increased the sample size to 1100 participants 18 months after the study began.

Enrolled participants underwent IUD placement according to the manufacturer's instructions including trimming IUD strings approximately 3 cm. All investigators underwent training on proper placement technique for the investigational IUD (NTCu380-Mini). Follow up visits occurred at 1.5, 3, 6, 12, and 24 months. To ensure that we included pregnancies diagnosed within seven days of IUD discontinuation as on-treatment (as required by the U.S. Food and Drug Administration), the study exit visit was planned at 37 months to allow for full evaluation of outcomes with use through 36 completed months (1095 days). IUD presence was verified at each visit by digital, speculum, or sonographic examination. Additional visits occurred via phone at 9, 18, and 30 months. Approximately nine months after initiating enrollment, investigators observed a possible association between menstrual cup use and IUD expulsion. In response, at 12 months after beginning enrollment, we advised new and already enrolled participants to stop using menstrual cups and to break the vaginal seal prior to cup removal if a cup was used. We also modified the protocol to collect information prospectively on menstrual hygiene product use (i.e., tampons, pads, menstrual cups, menstrual discs, other). We categorized menstrual discs as menstrual cups for analysis and performed expulsion analyses with and without inclusion of menstrual disc-only users. For participants who experienced IUD expulsion prior to the modification, investigators contacted participants to inquire whether the reported expulsion had

occurred in association with menstrual hygiene product removal, which we categorized as accidental self-removal. We grouped spontaneous expulsions (complete and partial) and accidental self-removals together as we cannot differentiate a spontaneous expulsion unrelated to menstrual hygiene use and one that may have been started by menstrual hygiene product removal and was later evident as a partial or complete expulsion. Partial expulsion was defined as visualization or palpation of any portion of the IUD (other than strings) at the cervical os, or ultrasound identification of any part of the IUD in the cervical canal.

Our analysis population included all participants with successful IUD placement, at least one follow-up visit, and available menstrual product use data. We defined menstrual cup use as the primary exposure variable and examined its relationship to IUD expulsion. We performed stratified analyses to examine other factors as possible confounders or effect modifiers in the menstrual cup/IUD expulsion relationship [18]. We considered the following factors and strata: age (<25 or ≥ 25 years), BMI (<30 or ≥30 kg/m^2), IUD type (TCu380A or NTCu380-Mini), parity (nulliparous or parous), self-reported description of baseline menstrual volume (light/moderate or heavy), self-reported race (White, Black, Asian, or other), and uterine sounding length (<8 cm or ≥ 8 cm) prior to IUD placement. We chose two stratas for factors other than race due to small subgroup sizes, e.g., TCu380A menstrual cup users experiencing an expulsion, for which additional stratas would create inordinate uncertainty in the model. We used the results of the stratified analyses to create interaction terms to assess effect modification. We first calculated crude odds ratios for menstrual cup use and other possible risk factors for IUD expulsion. To assess the independent effects of menstrual cup use and other factors on IUD expulsion, we constructed a logistic regression model that first considered all main effects and

interaction terms in the model [19]. We then removed non-significant interaction terms that provided no value to the model and next removed non-significant factors that were not confounders or not deemed clinically important. We retained all terms that independently had statistically significant influence on the odds of IUD expulsion. We examined potential multicollinearity among independent variables and the possible negative effects on validity of parameter estimates; neither slope coefficients nor standard errors had high, unstable values. As a sensitivity analysis, we repeated the logistic regression model excluding participants with accidental self-removal. We used SAS version 9.4 (SAS Institute, Cary, North Carolina) for all analyses.

3.0 Results

Study enrollment began June 2017 and completed February 2019, with 1105 participants enrolled and 1088 (98.5%) with successful IUD placement. Of these, 41 participants had no post-enrollment menstrual product use data because they exited the study before this information was collected, and one participant had her IUD inadvertently removed during a study exam, leaving 1046 for this analysis (Figure 1). Less than half (42.7%) of follow-up visits in the first 12 months occurred before advising against menstrual cup use and requiring tracking of menstrual product use, resulting in 809 (19.3%) of the total follow-up visits without documented menstrual hygiene product use. Most participants who enrolled before the advisory (94%) had subsequent follow up visits with collection of menstrual hygiene product use. Thirty-six month discontinuation probability did not differ for NTCu380-Mini users who used or did not use menstrual cups (95/197 [48.2%] and 316/646 [48.9%], respectively, p=0.87). The 36-month discontinuation probability also did not differ for TCu380A users, 58.5% (31/53 [58.5%] and 82/150 [54.7%],

respectively, p=0.75). Investigators confirmed IUD presence at 4188 study visits using visual inspection (speculum exam), digital palpation, sonography, and abdominal X-ray at 76.9%, 45.3%, 2.9% and 0.05% of study visits, respectively. Investigators used more than one method at 18.5% of visits.

Characteristics of the study participants by menstrual cup use are presented in Table 1. Two-hundred and fifty (23.9%) participants reported any menstrual cup or disc use at least once during follow up; 30 reported menstrual disc use only without menstrual cup use. Menstrual cup use did not differ by IUD type; however, menstrual cup users had different characteristics than non-users, most notably they were less often of Hispanic or Latina ethnicity, were less likely to have BMI > 30 kg/m^2, and were more often nulliparous (Table 1). Most (n=727 [69.5%]) participants primarily used tampons and 69 (6.6%) primarily used pads, although many (n=799 [76.4%]) reported using a combination of products. At the time of the protocol advisory, 537 participants had been enrolled, of whom 136 (25.3%) reported menstrual cup use. After the advisory, 27 (19.9%) of these participants continued menstrual cup use. Among the 509 participants enrolled after the advisory, 114 (22.4%) reported menstrual cup use for sanitary protection during the study.

Overall, 74 (7.1%, 95% CI 5.5-8.6) and 133 (12.7%, 95% CI 10.7-14.7) participants experienced IUD expulsion through 12- and 36-months, respectively. Among TCu380A menstrual cup users, 8/53 (15.1%, 95% CI 5.5-24.7) experienced expulsion over 36-months, while 50/197 (25.4%, 95% CI 19.3-31.5) NTCu380-Mini menstrual cup users experienced expulsion over this time (*P*=0.12). Among participants not using menstrual cups, 20/150 (13.3%, 95% CI 7.9-18.8)

TCu380A users and 55/646 (8.5%, 6.4-10.7) NTCu380-Mini users experienced expulsion over 36-months (*P*=0.07).

IUD expulsion occurred more frequently in menstrual cup users compared to non-users at both 12- (cOR 3.57, 95% CI 2.19–5.82) and 36-months (cOR 2.90, 95% CI 1.99–4.24). One participant who reported only menstrual disc use experienced expulsion. For participants using menstrual cups prior to the advisory, 36/136 (26.5%) experienced expulsion. Of those continuing menstrual cup use after the advisory, 3/27 (11.1%) experienced expulsion. Table 2 demonstrates IUD expulsion rates through 12- and 36-months based on whether or not participants reported menstrual cup use. NTCu380-Mini menstrual cup users had higher expulsion odds over 36-months (cOR 3.65, 95% CI 2.39-5.58), while TCu380A menstrual cup users did not (cOR 1.16, 95% CI 0.48-2.81). We found similar results when we repeated the analysis with menstrual disc only users excluded (Supplemental Table 1).

Categories of IUD expulsion (spontaneous complete, spontaneous partial, and accidental self-removal) at 36-months by IUD type and menstrual cup use are presented in Table 3. Accidental self-removals accounted for 30/133 (22.5%) of all IUD expulsions over 36-months. Menstrual cup users more frequently experienced accidental self-removal than non-users in participants using the TCu380A (3/53[5.7%] vs. 0/150[0.0%], cOR 20.86, 95% CI 1.06-410.85) and the NTCu380-Mini (20/197[10.2%] vs. 7/646[1.1%], cOR 10.31, 95% CI 4.29-24.79).

In univariate analysis through 36 months of use, parity and BMI were the only two factors associated with menstrual cup use, and categorical age (<25 years) was the only factor associated

with IUD expulsion (Supplemental Table 2). Notably, IUD type alone did not impact overall expulsion rate, with expulsion occurring in 28/203 (13.8%) of TCu380A and 105/843 (12.5%) NTCu380-Mini users (*P*=0.61) (Table 2). Adjusted modeling (Table 4) demonstrated that age <25 years remained independently associated with expulsion (aOR, 1.59, 95% CI 1.07–2.34). Because we found higher expulsion odds in NTCu380-Mini cup users and not TCu380A cup users on stratified analysis, we performed an assessment of interaction between menstrual cup and NTCu380-Mini use, which showed the interaction was significant (aOR, 3.13, 95% CI 1.16-8.46). These relationships persisted when removing accidental self-removals from the analyses (Supplemental Table 3).

4.0 Discussion

Without considering IUD type or other factors, IUD expulsion rates were 3-fold higher in menstrual cup users compared to non-users through 36-months of IUD use. However, when IUD type and other variables were considered, the increased expulsion risk was observed in NTCu380-Mini menstrual cup users and not TCu380A users. Accidental self-removal was highly associated with menstrual cup use and significant regardless of IUD type. It is possible that other expulsions were related to cup removal but did not fully occur at the time of removal or created a partial expulsion that was diagnosed later. One participant who reported only menstrual disc use experienced an expulsion. However, the number of menstrual disc users was relatively small (n=30) for any accurate comparison to other menstrual product use, and some users did not specify whether they used a menstrual cup or disc. Our finding of higher expulsion rates in younger participants (<25 years) is consistent with the findings of the CHOICE trial, which included hormonal and copper IUD users, but not with contemporary trials evaluating only

hormonal IUDs [4,8-9]. Importantly, nulliparity was not an independent risk factor for expulsion in our study. The higher expulsion rates seen in this study compared to historically reported rates are potentially related to high menstrual cup use in our study population and associated expulsion risk. The 12-month expulsion rate we observed in non-menstrual cup users (5.0%) is consistent with the rate reported in the TCu380A label (5.7%) [5].

The difference in expulsion risk with cup use by IUD type is interesting as we cannot discern if this difference is related to the different sizes of the IUDs or the different shapes. The arms of the TCu380A are rigidly perpendicular to the stem (Tatum-T frame) and not designed to flex upward as easily as the NTCu380-Mini, which uses a Nova-T frame (similar to currently available hormonal IUDs). The prior case series of IUD expulsions with menstrual cup use and survey showing elevated IUD expulsion risk in menstrual cup users consisted primarily users of hormonal IUDs with a similar frame (Nova-T) to the NTCu380-Mini [12,16]. As we did not see a higher expulsion risk in TCu380A users, which has a Tatum-T frame, this finding suggests that frame shape may be a factor. More studies are needed to understand if cup users are at a higher risk of IUD expulsion with any Nova-T frame IUD, smaller IUDs regardless of frame type, or just smaller Nova-T IUDs.

Because menstrual cups create a vacuum seal in the vagina, the removal process could pull the IUD strings. Although we advised subjects to break the vacuum seal in the vagina before menstrual cup removal, we do not know if a specific technique of menstrual cup removal alters this expulsion risk. In our study of only copper IUD users, menstrual cup use was higher than the 11% reported in a 2018 survey which included 81.7% hormonal IUD and 22.6% copper IUD use

[16]. Despite our warning about a potential increase in expulsion, many participants continued to use menstrual cups. We surmise that menstrual cup use was highly prioritized in this participant population. We did see a lower expulsion rate in participants enrolled before the advisory who continued to use menstrual cups. This cohort may have been more careful about their menstrual cup removal technique or had another commonality that made them less at risk for expulsion.

This study has several strengths, including prospective evaluation of menstrual cup use and IUD expulsion, participants had regular follow-up in which IUD position was verified, and participants were drawn from diverse geographic areas in the United States. However, as a secondary analysis, this study has many limitations. First, we did not collect menstrual hygiene use at baseline or for follow-up visits early in the study (19.3% of all follow up visits). Second, we do not know the time between menstrual cup use and expulsion events (outside of accidental self-removal); still, any menstrual cup use could start the process of withdrawing the IUD from the uterine cavity but not be evident as an expulsion until later. Third, we did not collect timing and frequency of each menstrual product use so we cannot evaluate the relevance of these factors to the outcomes. Fourth, we do not know whether string length impacted expulsion risk as string length was not measured as part of the study although the protocol dictated strings to be cut to approximately 3 cm. Lastly, the number of menstrual disc-only users was too small for definitive recommendations on concurrent menstrual disc and IUD use.

The study design presented some additional limitations to this analysis. Given the small number of parous participants, we did not have had sufficient power to determine a difference in expulsion risk based on parity. The 1:4 randomization scheme was designed to provide robust

efficacy and safety data for the investigational NTCu380-Mini, as the TCu380A profile is well understood. However, a limitation of this design is that effects seen in the NTCu380-Mini population may dominate results in the overall population. We saw this in the higher expulsion odds in menstrual cup users in the total population and the NTCu380-Mini cohort, but lack of higher expulsion odds when looking at menstrual cup users in the TCu380A group alone. As this study only evaluated copper IUDs, it is unknown whether menstrual cup use with hormonal IUDs (having Nova-T frames) increases the risk of IUD expulsion.

Our results provide reassurance that TCu380A users do not appear to have increased IUD expulsion risk with concurrent menstrual cup use as compared to other sanitary products, and NTCu380-Mini use has a higher expulsion risk only when paired with menstrual cup use. However, both IUD types were associated with an increased accidental self-removal risk with concurrent menstrual cup use. In parts of the world in which the NTCu380-Mini IUD is available, healthcare providers should advise patients about the increased risk of IUD expulsion with concurrent menstrual cup use. Accidental self-removal risk with concurrent menstrual cup use should be discussed with NTCu380-Mini and TCu380A users. Clinicians may wish to provide a more global warning for IUD users with a frame similar to the NTCu380-Mini IUD (Nova-T) until more data are available.

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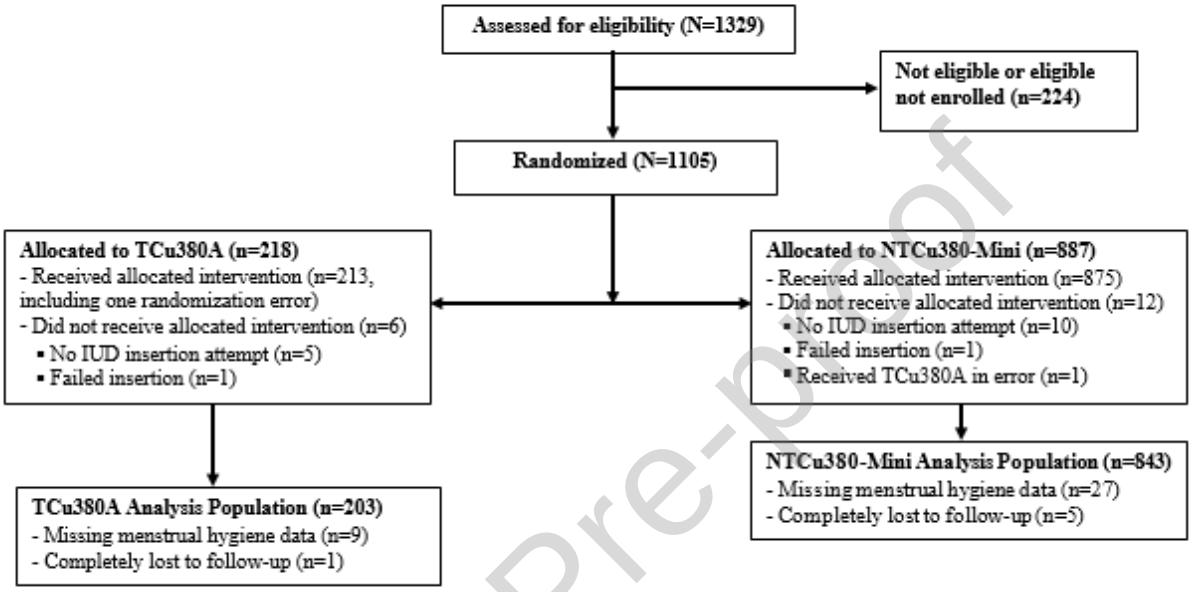
Figure 1. Flowchart of analysis populations for participants in a multi-center randomized trial comparing TCu380A and NTCu380-Mini Intrauterine Devices, United States 2019



IUD: intrauterine device

Table 1. Baseline characteristics of participants in a multicenter randomized trial comparing TCu380A and NTCu380A-Mini Intrauterine Devices by menstrual cup use, United States 2019

	Menstrual cup used n=250	**No Menstrual cup used** n=796	*P*-value*
IUD type by randomization			0.41
TCu380A	53 (21.2)	150 (18.8)	
NTCu380A-Mini	197 (78.8)	646 (81.2)	
Age (years)	26.5 + 4.92	26.2 + 5.25	0.42
<25	97 (38.8)	340 (42.7)	0.27
Ethnicity			0.04
Hispanic or Latina	23 (9.2)	116 (14.6)	
Not Hispanic or Latina	227 (90.8)	676 (84.9)	
Not Reported	0	4 (0.5)	

	Menstrual cup used n=250	No Menstrual cup used n=796	*P*-value*
IUD type by randomization			0.41
TCu380A	53 (21.2)	150 (18.8)	
NTCu380A-Mini	197 (78.8)	646 (81.2)	
Race			0.87
White	180 (72.0)	566 (71.1)	
Asian	26 (10.4)	68 (8.5)	
Black	20 (8.0)	74 (9.3)	
Multiple	17 (6.8)	52 (6.5)	
American Indian or Alaska Native	1 (0.4)	11 (1.4)	
Native Hawaiian or Pacific Islander	1 (0.4)	3 (0.4)	
Other†	4 (1.6)	5 (0.6)	
BMI (kg/m^2)	25.4 + 5.6	26.9 + 7.0	0.002
> 30	38 (15.2)	199 (25.1)	0.009
Nulliparous	193 (77.2)	542 (68.1)	0.006
Uterine length at sounding (cm)			0.26
< 8	157 (62.8)	528 (66.7)	
> 8	93 (37.2)	264 (33.3)	
Baseline menstrual bleeding			0.53
Light/moderate	161 (64.7)	532 (66.8)	
Heavy	88 (35.3)	264 (33.2)	
Cycle length (days)	28.6 + 1.9	28.5 + 2.0	0.34

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

BMI: body mass index

*Chi-square test or Fisher's exact test for categorical data, t-test for numeric data

† Includes Bi-racial (1), Hispanic (2), Indigenous (3), Latina (4), Mexican-American (1), Middle Eastern (1), Multiracial (1), Portuguese (1), Puerto Rican (2), Salvadorean (1), unknown (4)

Table 2. IUD expulsions through 12- and 36-months by menstrual cup use and type of IUD in a multicenter randomized trial comparing two copper 380 mm^2 IUDs, United States 2019

IUD Type	Menstrual Cup Used	No Menstrual Cup Used	OR (95% CI)*

	N	Expulsion n (%, 95% CI)	N	Expulsion n (%, 95% CI)	
12-months					
Total	203	32 (15.8, 10.8-20.8)	843	42 (5.0, 3.5-6.5)	3.57 (2.19-5.82)
TCu380A	48	4 (8.3, 5.1-16.2)	153	12 (7.8, 3.6-12.1.9)	1.07 (0.33-3.48)
NTCu380-Mini	155	28 (18.1, 12.0-24.1)	690	30 (4.3, 2.8-5.9)	4.85 (2.80-8.40)
36-months[†]					
Total	250	58 (23.2, 18.0-28.4)	796	75 (9.4, 7.4-11.5)	2.90 (1.99-4.24)
TCu380A	53	8 (15.1, 5.5-24.7)	150	20 (13.3, 7.9-18.8)	1.16 (0.48-2.81)
NTCu380-Mini	197	50 (25.4, 19.3-31.5)	646	55 (8.5, 6.4-10.7)	3.65 (2.39-5.58)

IUD: intrauterine device

* comparing Menstrual Cup Used and No Menstrual Cup Used outcomes

[†] the number of menstrual cup users is higher at 36 than 12 months because some participants started using menstrual cups after 12 months of study participation.

Table 3. Categories of IUD expulsion by menstrual cup use and IUD type in a multicenter randomized trial comparing two copper 380 mm^2 IUDs over 36-months of IUD use, United States 2019

Population	**Menstrual Cup Used**		**No Menstrual Cup Used**		***P*-value***
	N	Spontaneous Complete Expulsion n (%, 95% CI)	n	Spontaneous Complete Expulsion n (%, 95% CI)	
Total	250	17 (6.8, 3.7-9.9)	796	23 (2.9, 1.7-4.1)	0.008
TCu380A	53	0	150	5 (3.3, 0.5-6.2)	0.3
NTCu380-Mini	197	17 (8.6, 4.7-12.6)	646	18 (2.8, 1.5-4.1)	<0.001

	N	Spontaneous Partial Expulsion	N	Spontaneous Partial Expulsion	
Total	250	18 (7.2, 4.0-10.4)	796	45 (5.0, 3.5-6.4)	0.4
TCu380A	53	5 (9.4, 1.6-17.3)	150	15 (10.0, 5.2-14.8)	1.0
NTCu380-Mini	197	13 (6.6, 3.1-10.1)	646	30 (4.6, 3.0-6.3)	0.3

	N	Accidental Self-Removal	N	Accidental Self-Removal	
Total	250	23 (9.2, 5.6-12.8)	796	7 (0.9, 0.2-1.5)	<0.0001
TCu380A	53	3 (5.7, 0-11.9)	150	0	0.02
NTCu380-Mini	197	20 (10.2, 5.9-14.4)	646	7 (1.1, 0.3-1.9)	<0.0001

IUD: intrauterine device

* Fisher exact test

Table 4. Multivariable risk factors for IUD expulsion through 36-months of IUD use in a multicenter randomized trial comparing two copper 380 mm^2 IUDs, United States 2019

Factor	**Crude Odds Ratio (95% CI)**	**Adjusted Odds Ratio* (95% CI)**
Menstrual cup use		
No	Referent	Referent
Yes	2.90 (1.99-4.24)	1.21 (0.50 – 2.96)
IUD type		
TCu380A	Referent	Referent
NTCu380-Mini	0.89 (0.57 -1.39)	0.60 (0.35 – 1.04)
Parity		
Parous	Referent	Referent
Nulliparous	1.57 (0.89 – 2.76)	1.19 (0.65 – 2.18)
Age (years)		
<25	1.54 (1.07-2.22)	1.59 (1.07 - 2.34)
≥25	Referent	Referent
Heavy menstrual bleeding (baseline)		
Light/moderate	Referent	Referent
Heavy	1.13 (0.77-1.65)	1.11 (0.75 – 1.64)
BMI (kg/m^2)		
<30.0	1.01 (0.65-1.56)	0.79 (0.50 - 1.25)
≥30.0	Referent	Referent
Uterine length at sounding (cm)		

<8	Referent	Referent
≥8	0.94 (0.64-1.39)	0.94 (0.62 – 1.41)
IUD with menstrual cup use[†]		
NTCu380-Mini and menstrual cup	N/A	3.13 (1.16 – 8.46)
TCu380A IUD or no menstrual cup		Referent

BMI: body mass index; N/A: not applicable; IUD: intrauterine device

* Adjusted odds ratio includes all above factors in model

[†] Interaction term