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Fertility after Intrauterine Device Removal: A Pilot Study

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Abstract

Background—Despite high efficacy, only 7.7% of women in the United States currently using contraception use an IUD. There is little published contemporary data about fertility rates after IUD use, especially in nulliparous women and women using the hormonal IUD.

Study Design—We recruited sexually active women 18–35 years of age enrolled in the Contraceptive CHOICE Project who had discontinued a contraceptive method and desired pregnancy.

Results—In this pilot project, we enrolled 69 former IUD users (50 copper and 19 levonorgestrel) and 42 former non-IUD users. Pregnancy rates at 12-months were similar between the two groups; 81% of IUD users became pregnant compared to 70% of non-IUD users ($p=0.18$). In the Cox model, there was no difference in the time to pregnancy in IUD users compared to non-IUD users (HR_{adj} 1.19, 95% CI 0.74–1.92). African American race was the only variable associated with reduced fertility (HR_{adj} 0.40, 95% CI 0.24–0.67).

Conclusions—We found no difference in 12-month pregnancy rates or time to pregnancy between former IUD users and users of other contraceptive methods. However, there was a clinically and statistically significant reduction in fertility in African American women.

Introduction

Intrauterine devices (IUDs) are among the most effective forms of contraception available to women in the United States today. Despite high efficacy, only 7.7% of women in the United States currently using contraception use an IUD.[1] IUD use is lower in the U.S. than in many other developed nations.[2] Health care providers and patients' concerns about

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sexually transmitted infections (STIs), pelvic inflammatory disease (PID) and risk of infertility are, in part, responsible for this low uptake.[3] In particular, reluctance to use IUDs can be attributed to complications surrounding the Dalkon Shield in the 1970s. Research over the two decades after the introduction of the Dalkon Shield supported an association between IUD use, PID, and tubal infertility. In 1985, Daling et al. published the results of a case control study that showed a 2.6-fold increased risk for tubal infertility among previous IUD users.[4] Another case-control study from the same year found a 2-fold increased risk for tubal infertility among previous users of an IUD.[5] While the significant associations between IUD use and tubal infertility were seen primarily in patients who had used the Dalkon Shield, both of these reports suggested that the IUD should be avoided nulliparous women, and considered with caution for those who desire future fertility.[4, 5] Concerns about the health risks of the Dalkon Shield led to a large reduction in all IUD use in the U.S.[6]

Many previous studies investigating the relationship between the IUD and fertility failed to control for important confounding variables such as history of infection or PID.[7–9] Many were also limited to parous women and women using copper or inert IUDs. [10–12] More recent studies have attempted to address some of these limitations, and the results are mixed regarding a link between IUD use and infertility. In 2001, Hubacher et al. conducted a case-control study of the association between the copper T380A and tubal infertility in nulliparous women. They found that the presence of serum antibodies to *Chlamydia trachomatis* was associated with an increased risk of tubal infertility; whereas there was no association between copper IUD use and infertility observed.[13] In contrast, Doll et al. conducted a prospective cohort study of 558 married nulliparous women and found that increasing duration of copper IUD use was significantly associated with lower fertility even after adjusting for age (HR_{adj} of term birth: IUD duration 48–72 months 0.69 (95% CI 0.50–0.97) and IUD duration 78+ months 0.50 (95% CI 0.34–0.73)).[14] It is important to note that neither of these studies included users of levonorgestrel-containing IUDs. A 2013 study from China found no relationship between IUD use and reduced fertility. This study was limited to parous women who were using mostly copper IUDs.[15]

The lack of consistent results about the presence or absence of an association between IUD use and fertility is confusing to healthcare providers and women. The objective of this pilot study was to compare pregnancy rates at 12 months in women who discontinued the copper T-380A or the levonorgestrel intrauterine system (LNG-IUS) to women discontinuing other contraceptive methods. We hypothesized that there would be no difference in 12-month pregnancy rates between the two groups. Our goal was to use these results to plan a larger prospective cohort study to assess the relationship between IUDs, sexually transmitted infections (STIs), and fertility.

Materials and Methods

We conducted a sub-study of the Contraceptive CHOICE Project (CHOICE). CHOICE is a prospective cohort study developed to promote the use of long-acting reversible contraceptive methods (LARC: IUD and implant) in the St. Louis region. The methodologic details of CHOICE have previously been described.[16] Eligibility for this sub-study

included age 18–35 years; sexually active with a male partner; discontinuing oral contraceptive pills (OCPs), transdermal contraceptive patch, contraceptive vaginal ring, subdermal etonogestrel implant, copper T-380A or LNG-IUS in order to attempt pregnancy; English speaking; and willing to comply with study protocol. We excluded women who used depot medroxyprogesterone acetate (DMPA) in the 5 months prior to trying to conceive from this sub-study because DMPA can be associated with a longer return to fertility.[17] We identified potentially eligible participants from the CHOICE database and screened them for eligibility by telephone. Eligible participants who agreed to participate were then verbally consented and enrolled into the study. A copy of the informed consent form was subsequently mailed to the participants. Following enrollment, a research assistant administered a survey by telephone. This survey included questions regarding date of contraceptive method discontinuation, date they started trying to conceive, prior history of infertility, partner's reproductive history, frequency and timing of intercourse, pregnancy since stopping their method of contraception, and the outcome of any pregnancies. We obtained institutional review board approval prior to participant recruitment.

Participants who were pregnant at the time of the initial survey did not require any additional follow-up. Additionally, participants who had been trying to conceive for 12 months or greater at the time of the initial contact were not re-contacted. Participants who were not yet pregnant at the time of enrollment, and had been trying to conceive for less than 12 months, were followed up with telephone surveys at 6 months and 12 months after method discontinuation to assess for pregnancy. Medical record request authorization forms were sent to all participants so that we could perform medical chart reviews to validate pregnancy outcomes.

We compared demographic, socioeconomic and other fertility-related characteristics of women in the IUD and non-IUD groups using chi-square for categorical variables and student's t-test for continuous variables. Pregnancy at 12 months was compared as a dichotomous variable with the chi-square test. Time to pregnancy was estimated using Kaplan-Meier estimator of survival function. The log-rank test was used to test for difference in time to pregnancy. Participants who were lost to follow-up were censored at the time of the last completed survey. Hazard rate ratios (HRs) and corresponding 95% confidence intervals (CI) were calculated using Cox proportional hazard models. We performed univariate and multivariable Cox proportional hazards regression to calculate the hazard ratio for factors associated with fertility. All covariates that were significantly associated with pregnancy in the univariate model (at the 0.05 level) or altered the hazard ratio by 10% or greater were included in the multivariable model. We planned to include age and parity *a priori* since these characteristics are associated with fertility.[18] We performed all statistical analyses using STATA 11 (StataCorp, College Station, TX).

Results

We identified 176 potentially eligible participants from the CHOICE database. Between June 2011 and January 2012, 132 of these women underwent telephone screening for eligibility and 111 women (69 former IUD users and 42 former non-IUD users) were enrolled. Of the 69 former IUD users, 50 (72.5%) used the levonorgestrel intrauterine

system, and 19 (27.5%) used the copper T380A IUD. Baseline demographic characteristics of IUD users and non-IUD contraceptive users are compared in Table 1. IUD users were older and were more likely to be parous, compared to non-IUD users. Otherwise, the two groups were similar in terms of race, socioeconomic status, smoking status, body mass index (BMI), and history of prior gonorrhea or chlamydia infection.

Figure 1 diagrams the study enrollment and follow-up. There were 71 women who were pregnant at the time of their initial telephone contact. Seven women were not pregnant, but had been trying for over 12 months. There were 33 women who had stopped their method of contraception within the past 12 months and who were still trying to conceive; 30 were successfully contacted for follow-up surveys. Of these, 12 were pregnant at follow-up phone interviews, and 7 were not pregnant and had been trying for 12 months or more. The additional 11 participants were eligible for a second follow-up survey at the 12-month endpoint. Ten of the 11 were contacted. Of these 2 were pregnant and 8 were not pregnant. The distribution of IUD and non-IUD users in each group at each time-point can be seen in Figure 1. There were 3 participants who were lost to follow-up at the 6-month time point and 1 participant who was lost to follow-up at the 12-month time point [total loss to follow-up = 4/132 (3%)]. There was no difference in loss to follow up between the two groups.

The 12-month pregnancy rates are shown in Table 2 and were similar between the two groups; 81% for former IUD users compared to 70% for non-IUD users achieved pregnancy within 12 months of stopping their method of contraception ($p = 0.18$). Similarly, when we stratified by age (≤ 28 or >28 years) we found no difference in pregnancy rates between the two groups. For women age 28 years or less (at the time they started trying to conceive), 81% of former IUD users were pregnant at 12 months compared to 64% of former non-IUD users ($p=0.15$). For women age 29 years or greater at the time of enrollment, the pregnancy rates were 81% for IUD users and 100% for non-IUD users ($p=0.49$). When we stratified by parity, nulliparous IUD users were more likely to become pregnant than nulliparous non-IUD users ($p=0.02$).

Figure 2 shows a Kaplan-Meier survival analysis of pregnancy rates over time for the IUD users compared to the non-IUD users. There was no statistically significant difference between the two curves (log-rank $p=0.18$). Table 3 shows the results of the univariate and multivariable Cox proportional hazards model for factors associated with successful pregnancy within 12 months of contraceptive discontinuation. Of the demographic and reproductive characteristics described in Table 1, only black race was significantly associated with pregnancy at 12 months in the univariate model; black women were less likely to become pregnant compared to white women (HR 0.40; 95% CI 0.24–0.67). After adjusting for the race, age, and nulliparity, we still did not observe any association between IUD use and pregnancy at 12 months (HR_{adj} 1.19, 95% CI 0.74–1.92) compared to non-IUD users. In the adjusted model, black race remained significantly associated with decreased fertility.

Discussion

We found no difference in pregnancy rates or time to pregnancy between former IUD users and users of other contraceptive methods including combined oral contraceptives, the contraceptive ring, the contraceptive patch and the etonogestrel implant. The findings of this study are in contrast to the previous studies that found an association between previous IUD use and infertility,[4, 5, 14] but are consistent with older studies that found no association between IUD use and reduced fertility.[new 7–13, 15] Our findings are also consistent with Hubacher et al. who found no association between IUD use and infertility once they controlled for important confounding variables, such as history of *Chlamydia trachomatis* infection.[13] It is important to note that most of these published studies included IUDs that are different from the ones currently available in the U.S.

Interestingly, we found that nulliparous IUD users were more likely to achieve pregnancy than nulliparous non-IUD users. One possible explanation for this is that users of pills, the patch or the ring were more likely to have irregular menstrual cycles and were using hormonal methods for cycle control. Given the small size of the study, it is also possible that these findings are spurious. Additional research with a larger study population is needed to verify this finding.

Our findings add to the body of scientific literature evaluating fertility after contraceptive use. There are still many women and health care providers who continue to believe that IUDs put women at risk for pelvic inflammatory disease and subsequent infertility. In a survey of women's knowledge of intrauterine contraception performed in the St. Louis area, approximately 30% of respondents agreed with the statement that IUDs increased the risk of future infertility.[19] Similarly, in a survey of U.S. office-based and Title X clinic providers, approximately 30% of respondents had misconceptions about the safety of IUDs for nulliparous women. [20] IUDs are among the most highly effective forms of contraception available; thus, it is important to dispel the negative associations between IUD use and future fertility. A study published in the New England Journal of Medicine showed the contraceptive failure rate of women who used oral contraceptive pills, the patch or the contraceptive ring to be more than 20 times higher than women who used long-acting reversible contraception such as the IUD or the contraceptive implant. Additionally, this study showed that the risk of unintended pregnancy was twice as high among women under the age of 21, making it essential for providers to consider IUDs a first-line contraceptive option in young women. [21]

We also found an association between black race and decreased fertility. This is consistent with some reports in the medical literature, which show that married, non-Hispanic, black women are more likely to experience infertility compared to white women.[22] Other studies have shown that black women are more likely to present with tubal factor infertility than white women. In a survey of women presenting to an infertility clinic in Boston, 24.0% of African American respondents had tubal factor infertility, compared with 5.3% of white participants.[23] Again, this association of African-American race and reduced fertility should be confirmed in a larger study that is able to control for important confounders such as infection and socioeconomic status. Our study did not find an association between a self-

reported history of chlamydia infection and infertility (HR 1.15, 95% CI 0.67–1.99). However, we did not perform serologic testing for chlamydial antibodies, and it is possible that inaccurate recall of a history of chlamydia led to misclassification bias.

One strength of our study is that it addresses the issue of fertility in a cohort of modern IUD users, including users of the LNG-IUS. Since the LNG-IUS is the most commonly used IUD in the US, it is important to include LNG-IUS users in studies of fertility. Our study does have limitations. Because participants were contacted sometimes a year or more after contraceptive discontinuation, it is possible that they may have not accurately recalled the date they stopped their method. Even as a pilot study, our study was underpowered. Our *a priori* sample size calculations indicated that we needed to enroll 120 IUD users and 60 non-IUD user controls (based on a 20% difference in fertility, alpha of 0.05 and power of 80%). This study was undertaken as we planned a larger, prospective study of contraception and fertility, including serologic analysis for infections; thus, our recruitment period was limited. Our small sample size resulted in decreased power to find a statistically significant difference. Given our observed rates of infertility, we would have needed a sample size of over 850 women to find a significant difference. Finally, serologic testing was not performed in this study. Thus, we were not able to control for previous STI in the relationship between IUD use and fertility. Prospective studies among a cohort of modern IUD users are needed to further assess the relationship between IUD use, prior history of STI and fertility.

We found no difference in pregnancy rates or time to pregnancy between former IUD users and users of other contraceptive methods. We also noted an association between black race and decreased fertility. Both findings should be validated in a prospective study including measures of current and past infection. Recruitment of this cohort is underway, over 340 participants are enrolled, and we will assess current and past STDs, duration and type of IUD, race, and other factors that may impact fertility. This ongoing prospective cohort study will provide additional evidence regarding the relationship of IUD use, infection, and infertility.

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Figure 1.
Participant flow diagram.

Figure 2.
Time to Pregnancy by Former Contraceptive Method

Table 1

Demographic and Reproductive Characteristics of Study Participants

	Non-IUD (n=42)		IUD (n=69)		p-value
Mean age, years (SD)	27.6	(3.9)	29.5	(3.5)	0.03
Race	n	%	n	%	
Black	16	38.1	22	31.9	0.77**
White	25	59.5	44	63.8	
Other	1	2.4	3	4.3	
Body mass index (kg/m²)					0.46**
<25	22	52.4	33	49.3	
25 to <30	6	14.3	16	23.9	
30	14	33.3	18	26.9	
Marital status					0.06**
Single	22	52.4	24	34.8	
Married/living with a partner	20	47.6	40	58.0	
Separated/divorced/widowed	0	0	5	7.2	
Education					0.46
<= High school	10	23.8	11	15.9	
Some college	18	42.9	28	40.6	
College/Graduate school	14	33.3	30	43.5	
Low SES*					0.65
Yes	17	40.5	25	36.2	
No	25	59.5	44	63.8	
Nulliparous					0.001
Yes	28	66.7	24	34.8	
No	14	33.3	45	65.2	
Nulligravid					0.03

	Non-IUD (n=42)		IUD (n=69)		p-value
Yes	18	42.9	16	23.2	
No	24	57.1	53	76.8	
Current smoker					0.41
Yes	7	16.7	16	23.2	
No	35	83.3	53	76.8	
History of chlamydia ***					0.41
Yes	7	16.7	16	23.2	
No	35	83.3	53	76.8	
History of gonorrhea ***					0.47**
Yes	4	9.5	4	5.8	
No	38	90.5	65	94.2	

SES – socioeconomic status; PID – pelvic inflammatory disease

* Low SES defined as receipt of public assistance or reported difficulty paying for transportation, housing, medical expenses or food in past 12 months

** Fisher exact test

*** Patient self-reported

Table 2

Twelve month pregnancy rates

	Non-IUD (n=42)	IUD (n=69)	p-value
Overall	70%	81%	0.18
Stratified by Age:			
Age 28 (n= 49)	64%	81%	0.15
Age 29 (n= 62)	100%	81%	0.49
Stratified by Parity:			
Nulliparous (n= 52)	61%	92%	0.02
Parous (n= 59)	89%	74%	0.38

Table 3

Univariate and multivariable Cox proportional hazards model of factors associated with pregnancy at 12-months

	Hazard Ratio	95% Confidence Interval	
Univariate			
IUD	1.36	0.87	2.14
Age (years)	1.04	0.99	1.10
Race			
White	Ref		
Black	0.45	0.27	0.76
Other	0.51	0.16	1.63
Body mass index (kg/m ²)			
<25	Ref		
25 to<30	1.56	0.89	2.72
30	0.66	0.39	1.12
Education			
<= High school	Ref		
Some college	1.01	0.52	1.96
College/Graduate school	1.50	0.78	2.89
Low SES	0.92	0.58	1.47
Nulligravid	1.16	0.72	1.87
Nulliparous	0.81	0.52	1.25
Current smoker	1.21	0.71	2.07
History of chlamydia	1.15	0.67	1.99
History of gonorrhea	0.61	0.22	1.67
Multivariable*			
IUD	1.19	0.74	1.92
Age	1.04	0.98	1.11
Race			
Black	0.40	0.24	0.67
Other	0.49	0.15	1.58
Nulliparous	0.86	0.54	1.38

* multivariable model adjusted for age, race, and parity