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Bleeding Complications Associated With Intrauterine Contraception in Women Receiving Anticoagulation Therapy

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Abstract

Objective: To determine whether anticoagulation therapy is associated with an increased risk of complications after initiation of intrauterine contraception (IUC).

Patients and Methods: We retrospectively reviewed records of women receiving anticoagulation therapy at the time of IUC placement from 2000 to 2017 and records of controls (no anticoagulation), matched by race, age, and body mass index. The primary outcome was the cumulative incidence of bleeding (more than spotting [World Health Organization bleeding grades 2 to 4]), IUC expulsion, and IUC removal. Secondary outcomes included treatment for bleeding and bleeding patterns stratified by medication and IUC type. Outcomes were assessed at 24 hours, 30 days, and 6 months after IUC placement.

Results: We matched 208 women taking anticoagulants with 421 controls. The most common anticoagulant agents were aspirin (60.1%) and warfarin (36.1%). Most women received the levonorgestrel IUC. No complications occurred within 24 hours. Patients receiving anticoagulants had higher rates of the primary composite outcome at 30 days (odds ratio, 1.77 [95% CI, 1.04 to 3.04]; P=.04) and at 6 months (odds ratio, 2.05 [95% CI, 1.29 to 3.26]; P=.002). Primary complications did not differ by IUC type among control patients, but among women receiving anticoagulants, nonhormonal IUC was associated with an increased rate of complications (P=.04).

Conclusion: Anticoagulation therapy was associated with higher rates of bleeding at 30 days and 6 months, and nonhormonal IUC plus anticoagulation therapy was associated with higher rates of primary complications. Our findings support current periprocedural anticoagulation guidelines, which state that anticoagulation and antiplatelet therapy can be continued at the time of IUC insertion.

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Patients needing anticoagulation therapy may be treated with antithrombotic agents (eg, warfarin, direct oral anticoagulants, low-molecular-weight heparin) and antiplatelet agents (eg, aspirin, clopidogrel). For women taking anticoagulants who want contraception, hormonal intrauterine contraception (IUC) has a favorable complication profile, with decreased risks of clots and bleeding compared with other options, such as hysterectomy.[1,2] Hormonal IUC is a first-line therapy for many patients because it has several benefits. The 52-mg levonorgestrel IUC provides 7 years of contraception, does not require daily attention to prevent unintended pregnancy, is readily reversible, reduces bleeding by 71% to 91% (for women not receiving anticoagulation therapy), and acts on the endometrium with little systemic effect.[1] The nonhormonal (copper) intrauterine device (IUD) provides contraception for up to 10 years, but bleeding may be unchanged or even heavier, which can be problematic for women receiving therapeutic anticoagulation.[3]

Women who are considering IUC in the setting of anticoagulation therapy have an increased risk of immediate (periprocedural) and delayed bleeding. Bleeding may lead to additional treatment, spontaneous device

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expulsion, and the patient's dissatisfaction and request for IUC removal.[4] Although current guidelines suggest that an IUC may be inserted without interrupting anticoagulation treatment, little direct evidence supports this practice.[5,6] For women who are not receiving anticoagulation therapy, the rate of bleeding complications that prompt removal of hormonal or nonhormonal IUCs is 0.3%; however, complication rates are unknown for women receiving anticoagulation therapy.[7] Limited studies have focused on the longer-term effects of IUC and anticoagulation therapy or on the varying effects of different types of IUC.[8] More data are needed to further inform clinicians and women about bleeding risk in this setting. In this study, we compared rates of postprocedural bleeding and other complications for up to 6 months after IUC placement in women who were or were not receiving anticoagulation therapy.

PATIENTS AND METHODS

This retrospective, matched-cohort study was approved by the Mayo Clinic Institutional Review Board. Informed consent was waived for patients authorizing use of their health records for research. The reporting of this study is in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology statement.[9]

Study Setting, Population, and Design

We identified adult women, aged 18 to 55 years, who underwent hormonal or nonhormonal IUD insertion at Mayo Clinic (Rochester, Minnesota) from January 1, 2000, through December 31, 2017. Patients were identified by searching electronic health records for *Current Procedural Terminology* code 58300 or *International Classification of Diseases, Ninth Revision* procedure code 69.7. We identified women receiving anticoagulation therapy (categorized as the *anticoagulation group*) at the time of IUC insertion by cross-referencing their medication list for antithrombotic medications (apixaban, betrixaban, dabigatran, dalteparin, edoxaban, enoxaparin, fondaparinux, unfractionated heparin, rivaroxaban, or warfarin) and antiplatelet medications (aspirin, clopidogrel, prasugrel, ticagrelor, or ticlopidine). We next identified a matched group of women undergoing IUC insertion who were not taking any antithrombotic or antiplatelet medications (categorized as the *control group*). We originally identified 2 matched controls for each case, but after clinical review, some controls did not fit the parameters of the study and were subsequently excluded. Patients and controls were all community patients with IUC insertion, to avoid bias in demographic factors that could affect risk of bleeding complications. Patients and controls were matched by race, age (with 90% of controls being ±1 year of the patient's age), and body mass index (BMI). No power calculation was performed because all eligible records were included.

We retrospectively reviewed patient records to determine the rates of bleeding and nonbleeding complications that occurred within 24 hours, 30 days, and 6 months after IUC insertion. We also recorded the patient's race, age, BMI, pregnancy history (number of pregnancies, number of live births), menstrual and gynecologic history (history of heavy menstrual bleeding, endometriosis, or adenomyosis), underlying bleeding disorder (thrombocytopenia, abnormal coagulation studies, or history of excessive postoperative bleeding), type of IUC (hormonal IUC [52-mg levonorgestrel], nonhormonal IUD [copper]), anticoagulant medication, indication for anticoagulation treatment (atrial fibrillation, venous thromboembolism [VTE], mechanical heart valve, or other), and use of other contraceptives (estrogen-containing or progestin-only therapies). Women without a medication list at the time of IUC insertion and those who were unavailable for follow-up at 30 days and 6 months were excluded. Women receiving low-dose hormonal IUC were also excluded because they were less likely to have amenorrhea or hypomenorrhea.

Outcomes

Our primary outcome was a composite of postprocedural bleeding complications (defined as World Health Organization [WHO] bleeding grades 2 to 4 [grade 2, more than spotting; grade 3, requiring transfusion; grade 4, severe hemodynamic instability or fatal][10]), IUC expulsion, and request for IUC removal. We did not include WHO grade 1 bleeding (spotting) in the primary outcome because spotting can be common with IUC.

Secondary outcomes were treatment for bleeding (unanticipated complete blood count or transfusion), bleeding outcomes stratified by anticoagulation medication type (antiplatelet vs antithrombotic agents), and bleeding outcomes stratified by IUC type. The primary and secondary outcomes were assessed at 24 hours, 30 days, and 6 months after IUC placement.

Statistical Analyses

Descriptive characteristics are summarized with frequency and percentage for categorical variables and mean and standard deviation for continuous variables. Complication rates between groups were compared by using the χ^2 test. Logistic regression models were used to compare adverse events within 30 days or 6 months of IUC insertion. Independent variables of interest, including age, race, and BMI, were included in the full model. Stepwise deletion and clinical judgment were used to determine the final models. The final models adjusted for race. A subgroup analysis was performed with the anticoagulation group to compare the complication rates associated with different medications. A separate subgroup analysis of the full cohort assessed the effects of hormonal vs nonhormonal IUD. *P* values of .05 or less were considered statistically significant. All data were analyzed with SAS statistical software (version 9.4, SAS Institute Inc).

RESULTS

Included in the analysis were 629 women who met the study criteria (208 were receiving anticoagulants; 421 were control patients). Demographic data are summarized in Table 1. The mean age was 36.6 years, 593 (94.3%) of women identified as White, and the mean BMI was 31.4 kg/m^2. Hormonal IUC was more commonly used than nonhormonal IUC (n=574 [92.1%]; *P*<.001). In the anticoagulation group, 131 women (63.0%) were receiving antiplatelet agents, 88 (42.3%) were receiving antithrombotic agents, and 11 (5.3%) were receiving both types concurrently. Aspirin, an antiplatelet agent, was the most common medication used (n=125 [60.1%]), followed by warfarin, an antithrombotic agent (n=75 [36.1%]).

Primary outcomes are summarized in Table 2. Neither group had any complications within 24 hours after IUC insertion. After adjustment for race, the multiple logistic regression model showed higher rates of the primary composite outcome at 30 days (odds ratio, 1.78 [95% CI, 1.04 to 3.06]; *P*=.04) and at 6 months (odds ratio, 2.04 [95% CI, 1.28 to 3.25]; *P*=.003) for the anticoagulation group.

We did not observe any difference between the anticoagulation and control groups for individual secondary outcomes (Table 3). Treatment for bleeding (unanticipated complete blood count or transfusion) was reported for 5 women (2.4%) receiving anticoagulation therapy and for 8 control patients (1.9%; *P*=.67).

In the subgroup analysis, we compared the 30-day complication rates stratified by the type of IUC (Table 4). In the anticoagulation group, the nonhormonal IUD was associated with an increased rate of bleeding complications compared with hormonal IUC (25.9% vs 11.4%; *P*=.04). In the control group, no difference between IUC types was observed. In another subgroup analysis, we assessed bleeding complication rates among women receiving anticoagulation therapy, stratified by whether they were receiving antithrombotic or antiplatelet agents (Table 5). The type of anticoagulation agent did not significantly affect complication rates at 30 days (*P*=.30) or at 6 months (*P*=.97).

DISCUSSION

This study reports preliminary findings regarding the risk of immediate or delayed complications after IUC placement for women receiving anticoagulation therapy. Women in the anticoagulation group did not have an increased risk of complications within 24 hours of IUC placement, consistent with current guidelines about continuing periprocedural anticoagulation therapy when starting IUC.[5,6]

We observed an increased risk of bleeding (grades 2 to 4) and other complications within 30 days and 6 months among women receiving anticoagulation therapy compared with control patients. Our findings support providing counseling to patients about the risk of bleeding complications after initiation

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TABLE 1. Characteristics of Patients[a,b]

Characteristic	Anticoagulation group (n=208)	Control group (n=421)	Total (N=629)	*P* value
Demographic features				
Age, years	37.4 (9.4)	36.2 (8.7)	36.6 (9.0)	.10[c]
Body mass index, kg/m^2				.01[c]
Mean (SD)	34.0 (12.3)	30.3 (8.6)	31.4 (10.0)	
Missing data	82	115	197	
White race	196 (94.2)	397 (94.3)	593 (94.3)	.97[d]
Pregnancy history				
No. of pregnancies				.01[c]
Mean (SD)	2.2 (1.7)	2.6 (1.8)	2.4 (1.8)	
Missing data	3	2	5	
No. of live births				.001[c]
Mean (SD)	1.7 (1.3)	2.0 (1.3)	1.9 (1.3)	
Missing data	9	3	12	
Pregnancy-related bleeding				<.001[d]
Yes	5 (2.6)	15 (3.6)	20 (3.3)	
Unknown	61 (31.3)	59 (14.0)	120 (19.5)	
Missing data	13	1	14	
Postpartum hemorrhage	1 (0.6)	18 (4.6)	19 (3.5)	.02[e]
Missing data	51	31	82	
Menstrual, gynecologic, and medical history				
Menorrhagia	96 (46.8)	163 (38.7)	259 (41.4)	.05[d]
Missing data	3	0	3	
Endometriosis or adenomyosis	20 (9.7)	17 (4.0)	37 (5.9)	.005[d]
Missing data	1	0	1	
Bleeding disorder	33 (16.1)	32 (7.6)	65 (10.4)	.001[d]
Missing data	3	0	3	
Atrial fibrillation	6 (2.9)	0 (0)	6 (1.0)	.001[e]
Venous thromboembolism	89 (42.8)	27 (6.4)	116 (18.4)	<.001[e]
Mechanical heart valve	7 (3.4)	0 (0)	7 (1.1)	<.001[e]
Type of contraceptive				<.001[d]
Nonhormonal IUD	28 (13.7)	21 (5.0)	49 (7.9)	
Hormonal (levonorgestrel) IUC	177 (86.3)	397 (95.0)	574 (92.1)	
Missing data	3	3	6	
Medication exposure				
Any antiplatelet medication	131 (63.0)	NA	131 (20.8)	NA
Any antithrombotic medication	88 (42.3)	NA	88 (14.0)	NA
Warfarin	75 (36.1)	NA	75 (11.9)	
Apixaban	1 (0.5)	NA	1 (0.2)	
Rivaroxaban	3 (1.4)	NA	3 (0.5)	
Enoxaparin	14 (6.7)	NA	14 (2.2)	
Dalteparin	2 (1.0)	NA	2 (0.3)	

[a]IUC, intrauterine contraception/contraceptive; IUD, intrauterine device; NA, not applicable.
[b]Values are reported as number (percentage) unless otherwise indicated.
[c]Kruskal-Wallis test.
[d]χ^2 test.
[e]Fisher exact test.

of IUC if they are also taking anticoagulants. However, providers should also reassure patients that the most common complication is spotting (WHO bleeding grade 1) rather than severe bleeding, and this pattern is consistent with our observations. In comparing outcomes

TABLE 2. Primary Outcome

Outcome[a,b]	No. of patients	Anticoagulation group, No. (%)	Control group, No. (%)	Odds ratio (95% CI)	*P* value
30-day complications	627	206 (32.9)	421 (67.1)		
Simple logistic regression model				1.77 (1.04-3.04)	.04
Multiple logistic regression model[c]				1.78 (1.04-3.06)	.04
6-month complications	603	194 (32.2)	409 (67.8)		
Simple logistic regression model				2.05 (1.29-3.26)	.002
Multiple logistic regression model[c]				2.04 (1.28-3.25)	.003

[a]Complications were defined as bleeding that was more severe than spotting.
[b]No patients had complications within 24 hours of intrauterine device insertion. (Data for 24-hour outcomes were missing for 19 patients in the anticoagulation group and for 2 patients in the control group.)
[c]The multiple logistic regression model adjusted for race. Stepwise deletion was used to create the final model from the adjusted variables of age, body mass index, antiplatelet medication, anticoagulation medication, and race.

associated with hormonal and nonhormonal IUC, nonhormonal IUC unsurprisingly was associated with higher bleeding rates only among women taking anticoagulants (P=.04), further informing IUC choice and highlighting the risks and benefits of contraceptive type.

Reversible alternatives to IUC include combined hormonal contraception (CHC), depot medroxyprogesterone acetate, progestin-only contraception, and barrier methods, all of which have their own risks and benefits. Combined hormonal contraception reduces bleeding, suppresses ovulation, and decreases the risk of ovarian cysts.[4] The higher risk of VTE with CHC may be mitigated by concomitant anticoagulation therapy.[4] The International Society on Thrombosis and Haemostasis has deemed CHC acceptable in select high-risk women (eg, women with increased risk of VTE), as long as anticoagulation therapy is continued.[4] The WHO medical eligibility criteria for CHC differ from those of the International Society

TABLE 3. Individual Components of Primary Outcomes

Outcome	Anticoagulation group, No. (%) (n=208)	Control group, No. (%) (n=421)	Total, No. (%) (N=629)	*P* value[a]
Complications within 30 days				.05
Bleeding				
Spotting	36 (17.5)	52 (12.4)	88 (14.0)	
More than spotting	16 (7.8)	18 (4.3)	34 (5.4)	
Expulsion	6 (2.9)	6 (1.4)	12 (1.9)	
Removal	5 (2.4)	9 (2.1)	14 (2.2)	
Missing data	2	0	2	
Complications within 6 months				.02
Bleeding				
Spotting	24 (12.4)	45 (11.0)	69 (11.4)	
More than spotting	14 (7.2)	19 (4.6)	33 (5.5)	
Expulsion	7 (3.6)	10 (2.4)	17 (2.8)	
Removal	19 (9.8)	17 (4.2)	36 (6.0)	
Missing data	14	12	26	
Additional complications (within 6 months)[b]				.67
Yes	5 (2.4)	8 (1.9)	13 (2.1)	
Missing data	1	0	1	

[a]χ^2 test.
[b]Defined as having an unanticipated blood test (eg, complete blood count), office visit, or transfusion.

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TABLE 4. 30-Day Complications, Stratified by Type of Contraception[a]

Treatment group	Patients with 30-day complications, No. (%)		P value[b]
	Nonhormonal IUD	Hormonal IUC	
Anticoagulation group[c]	7/27 (25.9)	20/176 (11.4)	.04
Control group	1/21 (4.8)	32/397 (8.1)	.59

[a]IUC, intrauterine contraception/contraceptive; IUD, intrauterine device.
[b]χ^2 test.
[c]Value for the 30-day outcome was missing for 1 patient in the nonhormonal IUD group.

on Thrombosis and Haemostasis; it has contraindicated use of CHC in high-risk women because of increased risk of VTE and insufficient data on risk overall (ie, risk for all women, regardless of whether anticoagulation is established).[4] A higher-dose progestin, depot medroxyprogesterone acetate, can provide adequate contraception and often reduces menstrual bleeding, but it has been associated with an increased risk of VTE.[1] Other forms of progestin-only contraception include a low-dose pill and an etonogestrel implant, neither of which has been found to increase risk of VTE.[1] However, the etonogestrel implant and progestin-only pills have less favorable bleeding profiles compared with that of hormonal IUC.[1,11] Compliance can be more difficult with progestin-only pills because timing must be exact for optimum efficacy.[1] Barrier methods do not reduce bleeding, and their efficacy is lower and user dependent.[5]

We acknowledge several limitations to our study. We had fewer than expected patients receiving anticoagulation therapy who underwent IUC placement and therefore had to combine the antiplatelet and antithrombotic groups into 1 group in the analysis to have enough power to detect a difference in our primary outcome (comparing the anticoagulation group with the control group). In the study cohort, 11 women took both an antithrombotic and antiplatelet agent, which may have increased their risk of bleeding compared with women taking a single agent.[12,13] Although we did not observe higher rates of complications in the antithrombotic subgroup compared with the antiplatelet subgroup, additional research in this area is warranted because patient numbers in each group were small and limited our power to detect a difference. Aspirin was the most commonly used antiplatelet agent, and warfarin was the most common antithrombotic agent, which limits the generalizability of our conclusions for women treated with other agents. We did not have many patients taking direct oral anticoagulants, and our results may not apply to this population. We did not have data regarding international normalized ratios at the time of IUC placement for patients taking warfarin. Women receiving anticoagulation therapy more commonly chose a nonhormonal IUD (13.7% vs 5.0%); nonhormonal IUDs are associated with a higher risk of bleeding, which may have influenced the overall increase in bleeding rates observed in the

TABLE 5. 30-Day and 6-Month Outcomes, Stratified by Type of Anticoagulation Agent

Outcome[a]	Receiving anticoagulation therapy, No. (%)		P value[b]
	With an antithrombotic agent	With an antiplatelet agent only (no antithrombotic agent)	
Bleeding complications within 30 days	14/88 (15.9)	13/118 (11.0)	.30
Bleeding complications within 6 months	17/82 (20.7)	23/112 (20.5)	.97

[a]Outcomes were defined as any bleeding that was more severe than spotting.
[b]χ^2 test.

anticoagulation group. We also noted that the anticoagulation group had a higher rate of bleeding disorders, endometriosis, and adenomyosis, which could have influenced bleeding rates. Finally, we were missing some data for BMI, obstetric and gynecologic history, indication for anticoagulation therapy, and other comorbidities (eg, kidney and liver disease), which may be associated with an increased risk of bleeding. All these factors could skew the groups toward having a higher rate of bleeding. The magnitude of this potential bias is difficult to ascertain, but the higher rates of bleeding disorders in the anticoagulation group may suggest that they were more prone to bleeding at baseline.

CONCLUSION

Anticoagulation therapy was not associated with an increased risk of bleeding complications immediately after the procedure (<24 hours after IUC placement). Intrauterine contraception is generally well tolerated in women receiving anticoagulation therapy, although rates of bleeding complications at 30 days and 6 months were significantly higher compared with those of control patients. Subgroup analysis of IUC type found a lower bleeding complication rate for hormonal IUC than for nonhormonal IUC in the anticoagulation group. However, nonhormonal IUC could be considered for women with contraindications to hormonal contraception, such as a history of hormone-dependent malignant disease.

Our findings support current periprocedural anticoagulation guidelines stating that anticoagulation and antiplatelet therapy can be continued at the time of IUC insertion. Our findings also help inform clinician counseling of women receiving anticoagulation therapies who request contraception, in that IUC bleeding may be higher; however, IUC still can be reasonably considered in these patients, with appropriate counseling. More research is needed to evaluate bleeding risk of IUC with newer antithrombotic agents (eg, direct oral anticoagulants) and with low-dose hormonal IUC.

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Abbreviations and Acronyms: **BMI,** body mass index; **CHC,** combined hormonal contraception; **IUC,** intrauterine contraception/contraceptive; **IUD,** intrauterine device; **VTE,** venous thromboembolism; **WHO,** World Health Organization

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REFERENCES

1. Rivara A, James AH. Managing heavy menstrual bleeding in women at risk of thrombosis. *Clin Obstet Gynecol*. 2018;61(2):250-259.
2. Pisoni CN, Cuadrado MJ, Khamashta MA, Hunt BJ. Treatment of menorrhagia associated with oral anticoagulation: efficacy and safety of the levonorgestrel releasing intrauterine device (Mirena coil). *Lupus*. 2006;15(12):877-880.
3. Bonnington A, Autry AM. Abnormal vaginal bleeding in women desiring contraception who are taking anticoagulation therapy. *Obstet Gynecol*. 2018;131(4):632-634.
4. Godin R, Roy G, Douketis J. An opinion on the benefits of concomitant oral contraceptive therapy in premenopausal women treated with oral anticoagulants. *Thromb Res*. 2018;165:14-17.
5. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. medical eligibility criteria for contraceptive use, 2016. *MMWR Recomm Rep*. 2016;65(3):1-103.
6. American College of Obstetricians, Gynecologists' Committee on Adolescent Health Care. Gynecologic considerations for adolescents and young women with cardiac conditions: ACOG Committee Opinion, Number 813. *Obstet Gynecol*. 2020;136(5):e90-e99.
7. Celen S, Moroy P, Sucak A, Aktulay A, Danisman N. Clinical outcomes of early postplacental insertion of intrauterine contraceptive devices. *Contraception*. 2004;69(4):279-282.
8. Roos-Hesselink JW, Cornette J, Sliwa K, Pieper PG, Veldtman GR, Johnson MR. Contraception and cardiovascular disease. *Eur Heart J*. 2015;36(27):1728-1734, 1734a-1734b.
9. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61(4):344-349.

10. Stanworth SJ, Estcourt LJ, Powter G, et al. A no-prophylaxis platelet-transfusion strategy for hematologic cancers. *N Engl J Med.* 2013;368(19):1771-1780.
11. Organon & Co. Highlights of prescribing information: Nexplanon (etonogestrel implant). 2021. https://www.merck.com/product/usa/pi_circulars/n/nexplanon/nexplanon_pi.pdf. Accessed August 11, 2021.
12. Schaefer JK, Li Y, Gu X, et al. Association of adding aspirin to warfarin therapy without an apparent indication with bleeding and other adverse events. *JAMA Intern Med.* 2019;179(4):533-541.
13. Schaefer JK, Errickson J, Li Y, et al. Adverse events associated with the addition of aspirin to direct oral anticoagulant therapy without a clear indication. *JAMA Intern Med.* 2021;181(6):817-824.