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Tamoxifen for the prevention of unscheduled bleeding in new users of the levonorgestrel 52-mg intrauterine system: a randomized controlled trial ☆,☆☆,★

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ABSTRACT

Objective: To determine if a course of oral tamoxifen initiated following placement of a levonorgestrel 52-mg intrauterine system (IUS) reduces bleeding/spotting days over 30 days.
Study design: In this single-center, double-blind, placebo-controlled trial, we recruited women ages 15–45 years initiating the levonorgestrel 52-mg IUS. We randomized eligible women to tamoxifen 10 mg or placebo twice daily for 7 days starting 21 days after levonorgestrel 52-mg IUS insertion. Participants tracked bleeding/spotting days via daily electronic diaries for 30 days after starting drug treatment. We assessed participant satisfaction with their bleeding pattern and the IUS using a visual analog scale (0–100 mm). A sample size of 42 provided 80% power to detect a difference of 7 bleeding/spotting days in 30 days by two-sample *t* test, accounting for an expected 20% dropout rate.
Results: From September 2016 to January 2018, 42 women enrolled. A total of 34 women provided complete bleeding/spotting data, and 30 women provided satisfaction data. Mean bleeding/spotting days over 30 days did not differ between tamoxifen (12.0±5.8 days) and placebo users (16.8±9.0 days), p=.08. We found no significant differences in mean satisfaction with bleeding profiles (51 mm tamoxifen vs. 59 mm placebo, p=.48) or with the IUS (83 mm vs. 75 mm, p=.36) between groups. Both groups reported similar rates of adverse events, with no serious adverse events reported.
Conclusion: A course of oral tamoxifen did not improve early breakthrough bleeding or satisfaction in new users of the levonorgestrel 52-mg IUS.
Implications: Although tamoxifen treatment caused a trend toward modest bleeding/spotting day reduction in new levonorgestrel 52-mg IUS users, bleeding satisfaction did not improve. Future studies of tamoxifen treatment for IUS-related bleeding issues may be best targeted toward users with ongoing bleeding irregularities or lower-dose IUS products which cause more bleeding irregularities.

1. Introduction

The levonorgestrel 52-mg intrauterine system (IUS) provides highly effective and long-acting reversible contraception with a failure rate within the first year of use of less than 1% [1]. Like other progestin-only methods, the levonorgestrel 52-mg IUS affects bleeding patterns with changes ranging from amenorrhea, infrequent and irregular bleeding, to frequent or prolonged bleeding.

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Up to a quarter of all women experience frequent or prolonged bleeding during levonorgestrel 52-mg IUS use [2–6]. New users experience the most pronounced bleeding irregularities within the first 90 days after insertion [7,8]. Levonorgestrel 52-mg IUS discontinuation rates within the first year range from 3% to 30%, with 10%–20% of women citing bleeding pattern changes as one of their primary reasons for discontinuation [2–5,7,9–11]. A large postmarketing study reported a 2.8 times higher rate of discontinuation in levonorgestrel 52-mg IUS users with excessive bleeding [5]. Thus, preventing frequent or prolonged bleeding in levonorgestrel 52-mg IUS users might further decrease discontinuation rates and improve women's experience.

Few studies have investigated medications to prevent or treat bleeding irregularities early in levonorgestrel 52-mg IUS use. Therapies tested have included selective progesterone receptor modulators, nonsteroidal anti-inflammatory drugs and estrogen patches, but none have shown a consistent, clinically significant benefit [12–15]. Ulipristal acetate taken for 3 days and repeated monthly starting 21 days after levonorgestrel 52-mg IUS insertion did show a small reduction (mean of 3 days) in bleeding/spotting days in the first 30 days after treatment, but this effect was attenuated after the second treatment [12].

We recently reported in a randomized controlled trial that tamoxifen reduced bleeding in etonogestrel implant users within 30 days after use [16], confirming previous observations in levonorgestrel implant users [17]. In both studies, tamoxifen treatment resulted in a sustained bleeding reduction lasting beyond the treatment period [16,17]. Tamoxifen could improve unscheduled bleeding through antagonism of endometrial estrogen receptor β (ERβ) cells, causing down-regulated endometrial angiogenesis [18–20].

The primary objective of this study was to evaluate whether tamoxifen reduces early bleeding issues in women initiating a levonorgestrel 52-mg IUS for contraception as compared to placebo. We hypothesized that tamoxifen would reduce total bleeding/spotting (B/S) days and increase bleeding and overall satisfaction.

2. Materials and methods

2.1. Study participants

We performed a randomized, double-blind, placebo-controlled clinical trial at Oregon Health & Science University (OHSU) in Portland, OR. The OHSU Institutional Review Board approved the study protocol, and all subjects provided written informed consent (ClinicalTrials.gov: NCT02824224).

We recruited reproductive-aged (15–45 years old) women initiating levonorgestrel 52-mg IUS for contraception at the OHSU Center for Women's Health clinics (Portland, OR, USA). The study protocol included both Mirena® (Bayer, Whippany, NJ, USA) and Liletta® (Allergan, Irvine, CA, USA and Medicines360, San Francisco, CA, USA), but all women in the study received Mirena due to formulary availability. Participants were required to have reliable cell phone or email access and be willing to receive and respond to daily text or email messages to assess bleeding. Our exclusion criteria included being postpartum within the last 6 months, current pregnancy, breast-feeding, desiring IUS use for abnormal uterine bleeding, undergoing levonorgestrel 52-mg IUS removal and replacement, undiagnosed abnormal uterine bleeding, switching to IUS from depot medroxyprogesterone, bleeding dyscrasia, anticoagulation use, active cervicitis, allergy to tamoxifen, history of venous thromboembolism, current or past breast/uterine malignancy, and use of medication contraindicated with tamoxifen (coumadin, letrozole, bromocriptine, rifampicin, aminoglutethimide, phenobarbital). Additionally, we excluded participants prior to randomization who demonstrated noncompliance with the electronic bleeding diary during a run-in time period (first 14 days after trial enrollment) or with clinical evidence of an IUS complication including suspicion of expulsion or endometritis.

2.2. Study drug

The study medication consisted of a standard capsule that contained either tamoxifen (Nolvadex®, AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA) 10-mg tablet or filler that was identical in appearance. The research pharmacy purchased tamoxifen through Cardinal Health, NDC 00378-0144-91. Placebo pills used microcrystalline cellulose purchased through Letco Medical, Lot 1710050011. The pharmacy encapsulated both products with AA DB capsules from Capsugel® (Lot 7145239) using a capsule machine. Technicians loaded active capsules with one active tablet of tamoxifen and filled the remainder of the capsule with the cellulose, while they filled placebo capsules entirely with cellulose.

2.3. Study procedures

Research staff screened women with upcoming IUS insertion appointments for study eligibility and performed previsit telephone screening of potential subjects. Study staff additionally approached eligible women identified in clinic. Providers inserted levonorgestrel 52-mg IUS according to their routine clinical practice, independent of the study. Thus, women did not have the IUS placed within any standardized window related to their menstrual cycle and could be discontinuing hormonal contraception other than injectable contraception. Women did not receive specialized counseling regarding bleeding expectation beyond the usual standard of care. Interested potential subjects could screen, sign written consent and enroll up to 3 days after their initial IUS insertion. After consenting, we obtained baseline data collection including menstrual, contraception, sexual and obstetric histories and demographic information including race/ethnicity, employment status and insurance status.

We used an automated messaging platform Mir3 (San Diego, CA, USA) to track bleeding events and study drug usage using daily text or email messages. We had subjects categorize bleeding as need for use of protection with tampon, pad or panty liner, and spotting was defined as minimal bleeding that did not require use of protection [21]. Subjects noted study drug use as a yes or no response. Participants also tracked bleeding events using a paper diary in case of inability to respond promptly to text or email messages.

We performed a bleeding diary compliance test to determine if a subject would be randomized to study drug use. Upon enrollment, participants responded to daily electronic messages during a run-in period of 14 days. We invited subjects with >90% compliance over the first 14 days (e.g., responded to text or email messages for 12 or more days) by phone to return for randomization during a second study visit occurring 14–21 days after IUS placement. We discontinued women with poor compliance prior to randomization.

At the second study visit, subjects provided baseline satisfaction data and received their study drug. They reported satisfaction with their bleeding pattern, satisfaction with the IUS and acceptability of their bleeding using a visual analog scale (VAS) from 0 to 100 mm (anchors: 0 = *not at all satisfied*, 100 mm = *very satisfied*). The OHSU research pharmacy randomized subjects through a computer-generated algorithm using a block size of six and put study capsules into sequentially numbered packaging labeled only with subject-specific information. The pharmacy maintained allocation blinding until the completion of the study. Each eligible subject received 14 capsules with instructions to use two pills daily starting 21 days after IUS insertion (day of insertion defined as day 0). We chose to initiate study drug 21 days after IUS placement to compare our results to prior studies [12], to collect baseline B/S data and to ensure participant compliance with electronic bleeding diaries prior to randomization.

Participants continued to track their B/S days for 30 days after study drug initiation. Those who failed to respond to the bleeding diary for 3 consecutive days were contacted by phone or email to inquire about technological difficulties versus disinterest in the study. Thirty days after initiating study drug, participants received

an email with a link to a final study online survey via OHSU's REDCap platform. This survey included questions assessing side effects, adverse events and bleeding and IUS satisfaction using VAS scores (0–100 mm). Participants received incentives for enrollment, randomization, daily electronic bleeding diary response and final study questionnaire completion.

2.4. Data analyses

The primary study outcome was mean number of B/S days experienced by participants in the treatment group compared to placebo group over 30 days after treatment initiation. Secondary outcomes included satisfaction with the IUS, satisfaction with the bleeding pattern, acceptability of the bleeding pattern and side effects experienced. B/S days were directly measured from the electronic diaries using paper diaries as a backup. If no data were available on either diary for a specific date, missing data were coded as no-bleeding days if bounded on both sides by no-bleeding days; otherwise, they were coded as B/S days.

We powered this study to detect a 40% reduction in B/S days over 30 days. We assumed that placebo users would have a mean of 18 days of B/S with a standard deviation of 7 days over the same interval after levonorgestrel 52-mg IUS insertion based on prior literature [12]. We calculated sample size using Power and Precision version 3.2 (Biostat, Englewood, NJ, USA), assuming a mean of 18 days of bleeding with placebo, 11 days with tamoxifen treatment, a standard deviation of 7 days, 80% power and α=0.05. This required enrollment of 17 women per group. We sought to enroll 42 women total, 21 women in each group (experimental and placebo), to account for up to a 20% dropout rate with equal participants in both groups [22].

We used two-sample t tests to compare continuous baseline characteristics between groups and χ^2 tests to compare categorical characteristics. The normality assumption for bleeding data and VAS scores was satisfied based on Shapiro–Wilk tests. We performed two-sample t tests to compare the mean B/S days and VAS scores between groups. We reported side effects and adverse events descriptively. For bleeding data, we used linear regression to adjust for baseline bleeding, body mass index (BMI) and monthly regular menses. We maintained data in a secured REDCap database and used StataSE 15 (StataCorp LP, College Station, TX, USA) for statistical analysis.

3. Results

Fig. 1 depicts the flow of subjects through the study. We enrolled 42 women, of which 37 were randomized between September 2016 and January 2018 with completion of follow-up in February 2018.

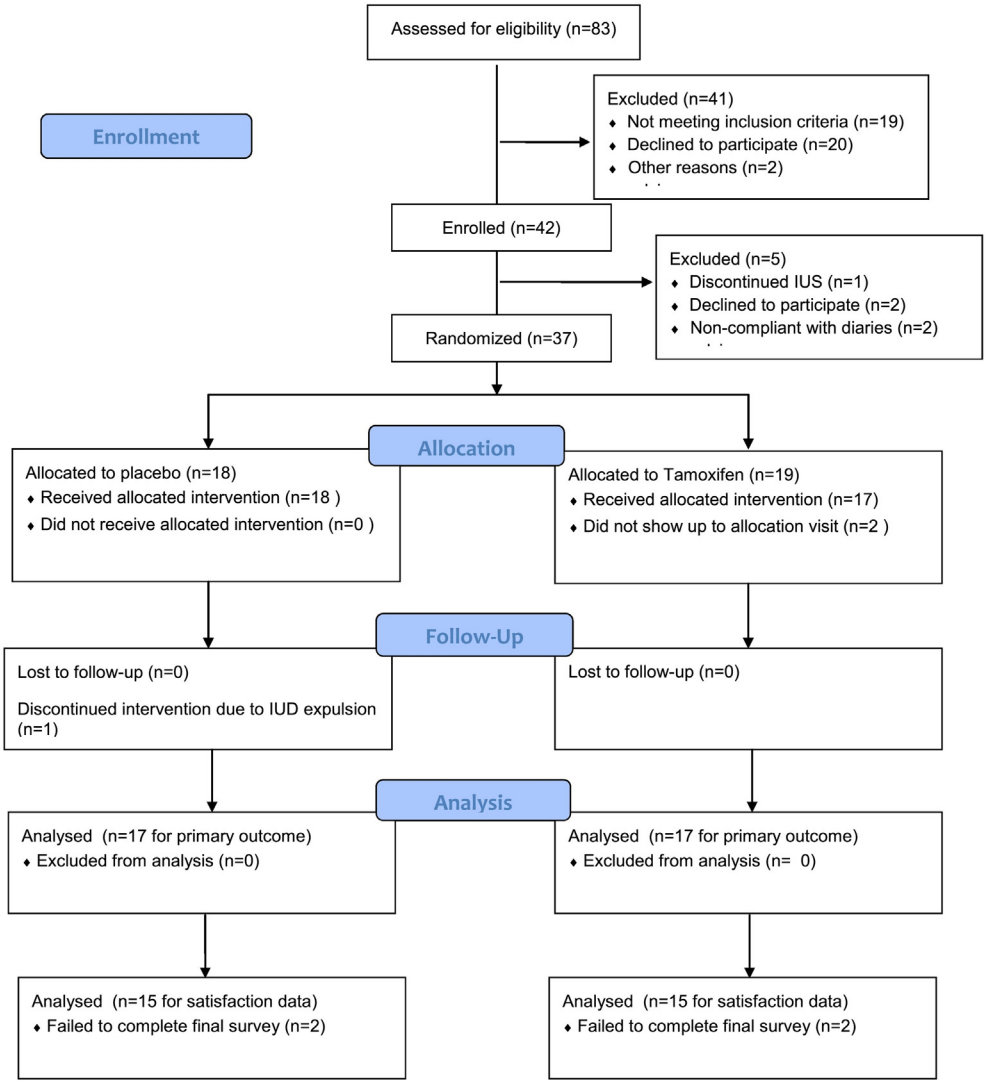

Fig. 1. CONSORT 2010 flow diagram for a randomized, placebo-controlled trial investigating a 7-day course of tamoxifen for prevention of unscheduled bleeding in new users of the levonorgestrel 52-mg IUS.

Table 1
Baseline demographic characteristics of 34 study participants by study group in a randomized, placebo-controlled trial investigating a 7-day course of tamoxifen for prevention of unscheduled bleeding in new users of the Levonorgestrel 52-mg IUS

Characteristic	Placebo (*n*=17)	Tamoxifen (*n*=17)	p value
Age (years)	28.8±6.1	30.6±7.6	.47
BMI (kg/m^2)	23.7±3.3	28.9±8.0	.02
Nulliparous	15 (88.2)	13 (76.5)	.38
Race/ethnicity			.21
White, non-Hispanic	13 (76.5)	17 (100)	
Other	4 (23.5)	0 (0)	
Marital status			.74
Single/divorced	7 (41.2)	8 (47.1)	
Partnered/married	10 (58.8)	9 (52.9)	
Employment			.21
Full time	13 (76.5)	9 (52.9)	
Part time	3 (17.7)	2 (11.8)	
Student	0 (0)	4 (23.5)	
Stay at home/unemployed	1 (5.9)	2 (11.8)	
Education			.68
High school or less	3 (17.7)	1 (5.9)	
College (any)	8 (47.1)	8 (47.1)	
Grad school (any)	6 (35.3)	8 (47.0)	
Private insurance	13 (76.5)	16 (94.1)	.15
Monthly menses	11 (64.7)	14 (82.4)	.26
Baseline bleeding/spotting (days)	13±5.4	11.8±5.0	.51
Baseline bleeding satisfaction (100-mm VAS)	58.1±22.6	57.5±23.2	.94

Baseline bleeding/spotting days, number of bleeding/spotting days out of 21 days prior to intervention.
Data are mean ± SD or *n* (%).
0–100-mm VAS (anchors: 0 = *not at all satisfied*, 100 mm = *very satisfied*).

Table 2
Side effects of study drug by group reported by 30 participants responding to electronic final study questionnaire in a randomized, placebo-controlled trial investigating a 7-day course of tamoxifen for prevention of unscheduled bleeding in new users of the levonorgestrel 52-mg IUS

	Placebo (*n*=15)	Tamoxifen (*n*=15)
Hot flashes	1 (6.7)	1 (6.7)
Mood changes	5 (33.3)	2 (13.3)
Headache	5 (33.3)	6 (40)
Nausea	3 (20)	1 (6.7)
Weight loss	0 (0)	1 (6.7)
Fluid retention	2 (13.3)	1 (6.7)
Weakness	0 (0)	0 (0)
Rash	0 (0)	0 (0)

Data are all *n* (%).

Table 3
Mean satisfaction with bleeding pattern, satisfaction with LNG 52-mg IUS and bleeding pattern acceptability by study group as reported by 30 participants responding to electronic final study questionnaire in a randomized, placebo-controlled trial investigating a 7-day course of tamoxifen for prevention of unscheduled bleeding in new users of the levonorgestrel 52-mg IUS

	Placebo (*n*=15)	Tamoxifen (*n*=15)	p value
Satisfaction with bleeding pattern	58.6±31.8	50.7±28.6	.48
Satisfaction with LNG 52-mg IUS	75.3±21.3	82.7±22.0	.36
Bleeding pattern acceptability	62.6±30.1	57.2±27.2	.61

Data are all mean ± SD derived from 0–100-mm VAS (anchors: 0 = *not at all satisfied*, 100 mm = *very satisfied*).

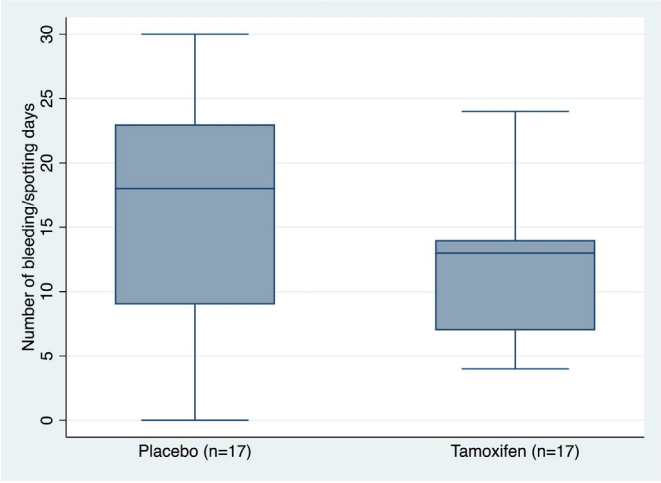

Fig. 2. Box and whisker plot of number of bleeding/spotting days over 30 days after initiation of study drug by study group for 34 participants in a randomized, placebo-controlled trial investigating a 7-day course of tamoxifen for prevention of unscheduled bleeding in new users of the levonorgestrel 52-mg IUS.

Two women were lost to follow-up prior to starting study drug, and one woman had an IUS expulsion shortly after study drug initiation. Thus, we included 34 participants in the final analysis of bleeding outcomes (*n*=17 per group). Of 1020 possible bleeding/spotting data points, we obtained 959 (94%) directly resulted from electronic bleeding diaries and 20 (2%) from paper diaries and imputed 41 (4%). Most (*n*=29, 85%) women provided electronic bleeding diaries with ≤1 missing data point. Baseline characteristics of placebo versus tamoxifen users were overall similar (Table 1), though tamoxifen users had significantly greater BMI (p=.02).

Compared to placebo users, participants who received tamoxifen had slightly decreased mean B/S days after initiating study drug (16.8±9.0 days vs. 12±5.8 days, p=.08) (Fig. 2). This equated to mean 4.8 fewer B/S days (95% confidence interval −10.1 to 0.5 days, p=.08). Adjusting for baseline B/S days, regular monthly menses prior to insertion of levonorgestrel 52-mg IUS and BMI did not affect the significance (data not shown).

Thirty women completed the side effect, satisfaction and acceptability survey (*n*=15 placebo and *n*=15 tamoxifen). One participant reported missing one study drug dose; all other women reported finishing study drug. No serious adverse events were reported. We found no significant differences in side effects reported between placebo and tamoxifen users (Table 2). The most common side effects reported included headache (five placebo; six tamoxifen), mood changes (five placebo; two tamoxifen) and nausea (three placebo; one tamoxifen). The study groups reported similar satisfaction with their bleeding patterns, satisfaction with the levonorgestrel 52-mg IUS and acceptability of bleeding patterns (Table 3). No participant in either group intentionally discontinued their IUS after randomization.

4. Discussion

Women exposed to a short course of tamoxifen starting 21 days after levonorgestrel 52-mg IUS placement had a small (mean 4.8 days), nonsignificant decrease in B/S days over the next 30 days compared to placebo. We powered our study to detect a mean 7-day decrease in bleeding with tamoxifen use. Though participants tolerated the treatment, they reported no differences in satisfaction or acceptability with bleeding patterns or with levonorgestrel 52-mg IUS as a contraceptive method. Studies of ulipristal acetate and naproxen in new users of the levonorgestrel 52-mg IUS similarly showed only minimal improvements in early unscheduled bleeding prophylaxis: mean 3-day decrease [12] or 10% decrease [14] in bleeding/spotting days with use, respectively.

Our findings differ from studies showing that tamoxifen significantly reduced unscheduled bleeding and improved satisfaction in etonogestrel and levonorgestrel implant users with bothersome

bleeding [16,17,23]. The divergent findings likely reflect a difference in the etiology of bleeding with the two methods: inactive endometrium with dilated fragile blood vessels in contraceptive implant users and unstable decidualized endometrium with down-regulation of estrogen receptors due to high local levonorgestrel levels in IUS users [24–26]. Implant users commonly report persistent problematic bleeding after many months of use. In contrast, over 75% of women experienced frequent or prolonged bleeding in the first 90 days after levonorgestrel 52-mg IUS insertion, but this typically resolves after several months [7,8].

Tamoxifen is a pure ERβ antagonist [20]. ERβ is expressed in endometrial blood vessels. We hypothesize that tamoxifen may decrease unscheduled bleeding by down-regulation of angiogenesis [18–20]. Thus, tamoxifen may be preferentially effective in treatment of unscheduled bleeding associated with medium- to long-term use of progestin-only therapy. While our study was not designed to evaluate frequent or prolonged bleeding with the levonorgestrel 52-mg IUS that some women develop in the setting of an inactive endometrium, tamoxifen may be useful in this setting. Alternatively, tamoxifen may be more advantageous for women using levonorgestrel 13.5-mg or 19.5-mg IUS who have significantly more long-term bleeding irregularities [8].

This study has several limitations. We had a greater than anticipated attrition during the lag time between enrollment and randomization and in return of final satisfaction questionnaires despite incentives for completion. Our study did have high compliance to bleeding diary completion and utilized daily electronic bleeding diaries, which have been shown to increase data completeness [27]. Our placebo group additionally had fewer mean B/S days and greater standard deviation of B//S days than anticipated, which may have resulted in the study being underpowered to detect a significant difference in the primary outcome.

For incomplete data, we used a conservative imputation method that would bias toward increased B/S days, though only 4% of B/S data required imputation. Our study also did not explicitly track NSAID use between groups, which may mitigate the effect of tamoxifen due to independent modest improvement in unscheduled bleeding [14]. Given the short prospective follow-up time, we also did not have data on number of prolonged bleeding episodes per group. We did not control for menstrual cycle phase or prior hormonal contraception use at the time of IUS placement. This may have reduced our ability to demonstrate a treatment effect.

Our study included predominantly white, non-Hispanic, nulliparous women. This limits the generalizability of the study. However, bleeding irregularities do not vary consistently between parous and nonparous women [7].

This is the first study to investigate tamoxifen for the prevention of unscheduled bleeding in new levonorgestrel 52-mg IUS users. No intervention has yet shown sustained benefit in reducing B/S days early after levonorgestrel 52-mg IUS insertion. Further research focused on mitigating the effects of short-term progestin exposure is needed.

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