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Estimating six-cycle efficacy of the Dot app for pregnancy prevention☆

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ABSTRACT

Objective: To assess six-cycle perfect and typical use efficacy of Dynamic Optimal Timing (Dot), an algorithm-based fertility app that identifies the fertile window of the menstrual cycle using a woman's period start date and provides guidance on when to avoid unprotected sex to prevent pregnancy.
Study design: We are conducting a prospective efficacy study following a cohort of women using Dot for up to 13 cycles. Study enrollment and data collection are being conducted digitally within the app and include a daily coital diary, prospective pregnancy intentions and sociodemographic information. We used data from the first six cycles to calculate life-table failure rates.
Results: We enrolled 718 women age 18–39 years. Of the 629 women 18–35 years old, 15 women became pregnant during the first six cycles for a typical use failure rate of 3.5% [95% CI 1.7–5.2]. All pregnancies occurred with incorrect use, so we did not calculate a perfect use failure rate.
Conclusions: These findings are promising and suggest that the 13-cycle results will demonstrate high efficacy of Dot.
Implications: While final 13-cycle efficacy results are forthcoming, 6-cycle results suggest that Dot's guidance provides women with useful information for preventing pregnancy.
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1. Introduction

Availability and use of digital applications (smartphone apps) claiming to provide women with information about which days during their menstrual cycles they are fertile are growing rapidly. Women are already using apps for pregnancy prevention [1–4]. Evidence suggests that many of the most frequently downloaded apps do not accurately identify the fertile window, placing their users at risk of unintended pregnancy [1].

Yet, the potential of tailored, biometric data for pregnancy prevention should not be dismissed, as such apps have the potential to provide low-cost, accessible, nonhormonal methods to women who want them. These apps must be subject to the same standards as other contraceptive methods: (a) be based on reproductive biology, (b) include a defined protocol for use and (c) have been tested in appropriately designed studies to assess effectiveness under various conditions [5].

We currently are assessing the efficacy of the Dynamic Optimal Timing™ (Dot™) app using this standard. An app-based fertility awareness-based method (FABM) developed by Cycle Technologies, Inc., Dot provides direct-to-user information about fertility each menstrual cycle. Dot users download the app to their phones from the Google Play or Apple stores and set their user profile to "prevent pregnancy," "plan pregnancy" or "track cycles." Users input the first day of menses, then receive information about their daily pregnancy risk and messages alerting them to upcoming changes in their fertility status (from low to high risk and vice versa), as well as estimated start dates for pending menses. Those using Dot to prevent pregnancy receive additional messages encouraging them to either avoid sex or use a barrier method on days the app tells them are high risk.

The Dot algorithm [6] is based on Bayesian statistical analysis of approximately 7000 menstrual cycles from the WHO Ovulation Method Study [7] augmented by clinical studies of variable fecundability vis-a-vis ovulation [8,9]. Using period start dates, the algorithm calculates a user's daily pregnancy risk and identifies her personalized fertile window. Dot conservatively estimates the fertile window during the first few cycles of use and tailors the fertile window as the user enters more cycles. Through computational modeling estimating theoretical failure rates, the Dot app was calibrated to provide a failure rate of no more than 1–3 per 100 woman years of perfect use [6].

We are conducting a nonrandomized, prospective, 13-cycle efficacy study of Dot. As studies have found the probability of method failure is highest during the early cycles of use, we desired to assess initial

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outcomes with this new method, particularly because it requires user compliance [10].

2. Materials and methods

We adapted best-practice guidelines for assessing FABMs [11–13] to the context of a fertility app [14]. Georgetown University's Institutional Review Board approved the study.

A detailed description of the recruitment process is available [15]. Briefly, Dot users who lived in the continental United States, downloaded the app on their Android phone, chose to prevent pregnancy, entered their second period start date and met initial recruitment criteria were recruited from February to August 2017 via a pop-up message describing the study. Women responded to the message indicating their interest. We limited the study to women using Android phones because the study launch coincided with the launch of the Android app. Those interested responded to an in-app screening to confirm further eligibility, including being between ages 18 and 39, confirming that they have cycles between 20 and 40 days with <10 days of variation, being sexually active with a male partner (or partners), not having used hormonal contraception in the last 3 months and having had at least three menstrual periods following the most recent (if any) pregnancy [14]. Eligible women received further information about the study, completed an in-app informed consent process, enrolled in the study and completed a sociodemographic survey. While period start dates are the only input for women using the app, study participants provided additional demographic information; daily coital history, including whether they used condoms, withdrawal or emergency contraception (EC); and whether, at the beginning of each cycle, they intended to continue preventing pregnancy.

To collect these data and perform study exits, we developed Proofmode™, a multicomponent research platform that seamlessly fits over the existing app, capturing and storing data securely to the Georgetown University servers [14,15]. Proofmode collects participants' daily Dot interactions, coital behavior and use of any method or behavior to prevent pregnancy; facilitates periodic follow-up surveys; and helps retain study participants through gamification of the daily coital diary and feedback [14,15]. If a woman fails to complete a diary on a given day, Proofmode allows her to go back to any day within that cycle to enter data or make corrections. It allows participants to experience the app like any other user but provides opportunities for virtual contact with study staff when necessary [15]. Additionally, we used Amplitude™, an app analytic software that provides user behavior reports, to double-check participant self-reported data against actual interactions with the app. Amplitude also aids in limiting loss to follow-up by allowing researchers to monitor participants' interaction with the app and helping researchers determine potential ways to contact participants [15].

We used a participant's entry of a new period start date as proxy evidence that she had not conceived. If she did not enter a new period start date by the end of cycle day 40 (rendering her cycle too long for Dot), she received a pop-up notification asking her to confirm that she wanted to continue in the study and requesting that she enter her period start date. If she did not respond, she received a message asking if she might be pregnant. Regardless of her response or lack of response, we followed up via email, chat or phone. [15].

If a participant reported a possible pregnancy at any point, we contacted her and express-mailed her two pregnancy tests with instructions to confirm pregnancy via digital image and/or free return shipment [14]. We considered pregnancy to have occurred for women who returned a positive pregnancy test or confirmed pregnancy verbally or via email or chat. We exited participants who stated (prospectively) that they no longer wanted to avoid pregnancy in monthly follow-up surveys.

We classified women not continuing in the study as pregnant, not pregnant or lost to follow-up. Women discontinued the study for a variety of reasons not pertaining to pregnancy (i.e., menstrual cycles outside of Dot's recommended length or variability, changes in fertility intentions and phone-related issues). A description of study exit categories can be found in Appendix A.

With data provided by Proofmode and Amplitude, we identified and categorized pregnancies resulting from "correct use" or "incorrect use." We defined correct use as no sex or sex with a condom on days Dot identifies as fertile and incorrect use as having unprotected sex on fertile days, including the use of withdrawal, EC and/or no method specified.

We estimated Dot six-cycle efficacy using Kaplan–Meier life-table analyses to find typical-use (total of correct- and incorrect-use cycles) pregnancy rates [16] and calculated related confidence intervals. We conducted our primary efficacy analysis with women 18–35, as recommended in a recent discussion of efficacy research standards [17]. We identified cycles in which women abstained from intercourse or used a condom during the fertile window, as estimated by Dot, as correct use cycles and used these cycles to calculate perfect use. We identified cycles with one or more instances of unprotected sex, no method specified, withdrawal and/or EC use during the estimated fertile window as incorrect-use cycles.

We censored cycles used in typical-use calculations based on three criteria: (a) no sexual history data entered, (b) no sex reported and (c) participant exited the study prior to cycle completion (e.g., self-exit, lost to follow-up) [11].

As this is a virtual cohort study, we conducted sensitivity analyses recognizing the possibility of unaccounted-for pregnancies. Using the categorizations above ("pregnant," "possibly pregnant" and "very unlikely pregnant"), we calculated separate life-table estimates and confidence intervals for the "pregnant" and "possibly pregnant" scenarios. Given the definition of "very unlikely pregnant," we did not conduct a separate analysis for this scenario. For this sensitivity analysis, we classified women who discontinued after the onset of the fertile window and reported unprotected intercourse one or more times during the fertile window as "possibly pregnant." We classified women who discontinued prior to the onset of the fertile window and did not report unprotected intercourse during that fertile window as "unlikely to be pregnant."

Assessing our primary endpoint, pregnancy rate at 13 cycles, required a sample size of 255 women completing the study. This sample size provides 90% power to detect a 6% decrease in 1-year pregnancy rate of app users with one-sided type I error at 5% [14].

3. Results

We enrolled 718 participants age 18–39 into the study and report here the outcomes for the 629 women age 18–35 years. We collected data for this six-cycle analysis between February 2017 and March 2018. Table 1 provides an overview of the demographic characteristics.

Table 1
Demographic profile of Dot app efficacy study participants aged 18–35 years (N=629)

Demographic	Category answer	n (%)
Age	18–24	198 (31.5)
	25–29	230 (36.5)
	30–35	201 (32.0)
Race/ethnicity	Black/African American	118 (18.7)
	Hispanic or Latino	108 (17.2)
	White	344 (54.7)
	Other	40 (6.4)
	No response	19 (3.0)
Relationship status	Married	157 (25.0)
	Separated	6 (1.0)
	Long-term relationship (>3 months)	302 (48.0)
	New relationship (<3 months)	30 (4.8)
	Dating	89 (14.2)
	Not dating/single	26 (4.1)
	No response	19 (3.0)
Ever been pregnant	Yes	297 (47.2)
	No	313 (49.8)
	No response	19 (3.0)

Table 2
Cycles used for evaluating the six-cycle typical-use failure rate of the Dot app for pregnancy prevention

Cycle	Women enrolled at beginning of cycle	Percentage of women retained for each cycle	Censored cycles[a]	Pregnant	Self-exit, other exit & LTFU[b]	Total censored cycles	Total cycles retained for analysis
1	629	–	55	2	25	82	547
2	602	95.7%	57	2	35	94	508
3	565	93.9%	66	1	39	106	459
4	525	92.9%	48	3	41	92	433
5	481	91.6%	54	4	35	92	389
6	443	92.1%	48	3	20	72	371
Total	–	–	328	15	195	538	2707

[a] We censored cycles in which women did not report any coital diary data or sex during their cycle.
[b] Women who were lost to follow-up (LTFU), did not enter a period start date after day 40 of their menstrual cycle or did not respond to active follow-up.

Overall, 419 (66.6%) women completed six cycles of use. As shown in Table 2, completion from one cycle to the next was highest during participants' first cycle (95.7%) and lowest during the fifth cycle (91.6%), resulting in 3245 cycles for this analysis. We censored 538 cycles from the analysis for women in which less than 75% of their sexual history data was reported (n=11), in which no sexual intercourse occurred (n=317) or who self-exited or became lost to follow-up (n=210). Women most commonly exited the study because of ineligibility due to cycle length/variability or loss to follow-up; all reasons are detailed in Table 3. After censoring, we included 2707 cycles in the analyses, representing 208.2 women-years of exposure. More than 99% of women retained in each cycle completed 100% of their sexual history data during the first six cycles.

We categorized 15 confirmed pregnancies as "unplanned" (based on participants' stated intention to prevent pregnancy at the beginning of each cycle) for a 6-month typical-use failure rate of 3.5% [95% CI 1.7–5.2]. The coital behavior of these 15 women varied. During their pregnancy cycles, seven used no method during their fertile window, and one woman used only withdrawal during these days. The other seven women reported using a combination of withdrawal, condom, EC and having sex without using any method during the fertile window in the cycle in which they became pregnant. No pregnancies occurred during cycles when participants reported correct Dot use, so we did not calculate a perfect-use pregnancy rate for any age category.

We classified 17 cases of possible pregnancy (n=629) among the lost-to-follow-up cycles, i.e., cycles in which women discontinued after onset of the fertile window and had unprotected sex at least once during the fertile window. It is unlikely that all these women became pregnant during that cycle. If all these women were pregnant, they would be considered typical-use pregnancies, and the typical-use life-table failure rate would be 7.2% [95% CI 4.8–9.5].

Further, we identified 25 lost-to-follow-up cycles in which pregnancy was very unlikely but cannot be entirely discounted. In these cycles, women discontinued entering data or opening the app prior to the onset of the fertile window or actively reported that they did not have unprotected intercourse during the fertile window but did not enter a subsequent period start date or any further information. Thus, we did not calculate a scenario in which these women would be considered pregnant.

Table 3
Reasons participants exited by cycle from the Dot app efficacy study (N=629)

Reason for exit	n (%)	Number of women per cycle					
		1	2	3	4	5	6
Pregnant	15 (2.4%)	2	2	1	3	4	3
Lost to follow-up	42 (6.7%)	9	10	8	5	8	3
No longer wanted to be in the study	1 (0.2%)	0	0	1	0	0	0
No longer using the Dot app	13 (2.1%)	2	3	2	5	0	0
Technical or phone-related issue	31 (4.9%)	6	6	7	5	6	1
No longer using Dot to prevent pregnancy	39 (6.2%)	0	7	7	12	8	5
No longer eligible	69 (11.0%)	8	9	14	14	13	11
Total	210	27	37	40	44	39	23

4. Discussion

App-based FABMs for pregnancy prevention are a reality in an increasingly technology-driven world. Current findings are promising and suggest that further evaluation of Dot is warranted.

Traditional efficacy studies utilize multiple sites and include physical exams, periodic pregnancy tests and a high degree of control. The virtual nature of this study limits our ability to track some women. It also lacks the benefit of face-to-face contact (rapport, performing in-person pregnancy tests), but it facilitates an experience for participants that is more suited to the context of this method. We conducted sensitivity analyses to mitigate some of these challenges and calculated typical-use failure rates that included women designated as "possibly pregnant."

This study benefits from several unique features, including a robust coital diary, the ability to assess app usage from analytic data and dynamic client follow-up mechanisms. It also follows guidelines for contraceptive efficacy research. Yet, there are several weaknesses.

As with all contraceptive efficacy studies, it relies on self-reported coital behavior, which is impossible to confirm. To increase participant engagement, the coital diary entry process was brief (taking approximately 10 s per day) and facilitated by use of icons, a swipe mechanism and a user-set reminder.

We enrolled women in the study when they entered their second period start date after downloading Dot. This limited enrollment of participants who downloaded the app (which is free) but had no intention of actually using it. It also eliminated participants who might have become pregnant during the cycle in which they downloaded Dot. It is possible that some women who began using Dot became pregnant while using it prior to entering a second period start date.

We attempted to only include study participants potentially at risk of pregnancy through our eligibility criteria. However, we did not assess for multiple other factors that ensure normal fertility typical of US Food and Drug Administration (FDA) contraceptive approval studies such as ectopic pregnancy, pelvic infection, prior treatment for infertility or having a partner with a vasectomy. Thus, it is possible that we included some participants not actually at risk of pregnancy. Additionally, the study is unable to provide safety metrics in compliance with FDA regulation, as we did not recruit women up to age 45.

This study is an attempt to examine initial efficacy results of a fertility app for avoiding pregnancy. The full 13-cycle efficacy study will be completed by October 2018. By providing these six-cycle results, we hope to contribute to the ongoing discussion of the potential for apps to serve as a safe, effective, nonhormonal approach for women who choose them.

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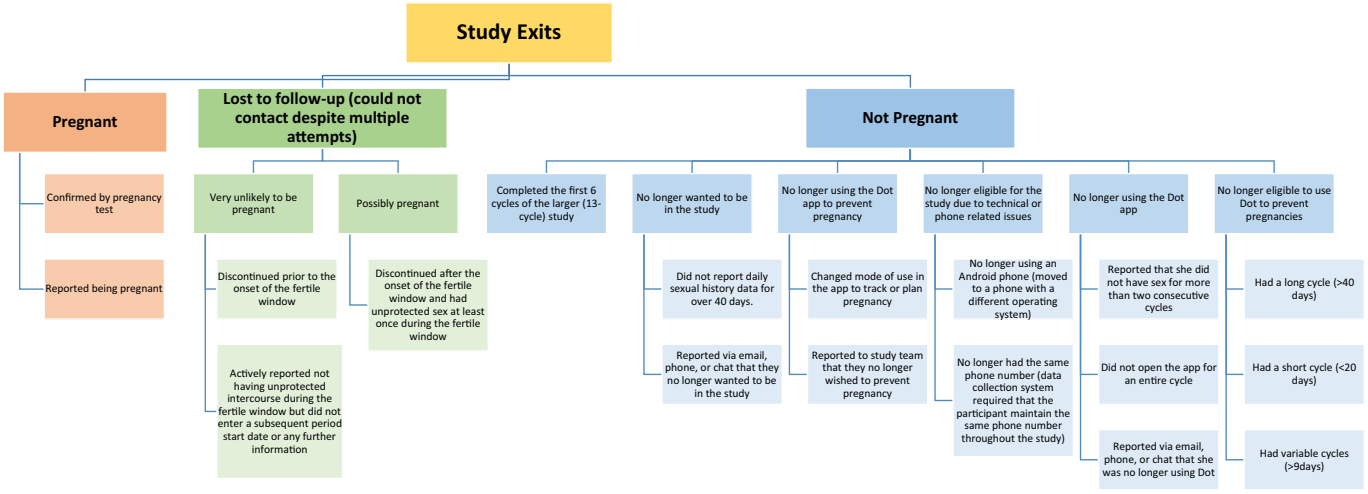
Conflict of interest

V.J., D.S., L.H. and H.F. are employed by the Institute for Reproductive Health (IRH), Georgetown University, which is recipient of a grant from the United States Agency for International Development that supports this study. The research tests an app for which a patent application has been filed by Cycle Technologies. Neither V.J., D.S., L.H., H.F. nor any other employee of Georgetown University has any financial relationship to or receive any income or royalties from Cycle Technologies, a company that is owned by a family member of the director of the institute. Cycle Technologies is solely responsible for the app that is the subject of this research. All data from this research will be made available through the Open Data Act, as required by US law. R.S., a former employee of IRH, also does not have any conflict of interest to declare.

Appendix A. Participant exit classification



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