Evaluation of adherence to a daily progestin-only pill in a simulated over-the-counter setting

Contraception

Evaluation of Adherence to a Daily Progestin-only Pill in a Simulated Over-the-Counter Setting

--Manuscript Draft--

Manuscript Number:	CONTRACEPTION-D-23-00395R2
Article Type:	Original Research Article
Keywords:	adherence; drug facts label; norgestrel; oral contraceptive; over-the-counter; progestin-only pill
Corresponding Author:	Irene Laurora, Pharm.D. HRA Pharma, A Perrigo Company UNITED STATES
First Author:	Irene Laurora, Pharm.D.
Order of Authors:	Irene Laurora, Pharm.D.
	Brandon Henrie
	Hélène Guillard, PharmD
	Russell Bradford, MD, MSPH
	Stephanie Sober, MD, MPH
	Anna Glasier, MD
Abstract:	Objective: The Adherence with Continuous Dose Oral Contraceptive: Evaluation of Self-Selection and Use (ACCESS) study assessed whether consumers can adhere to the regimen for a progestin-only pill (norgestrel 0.075 mg) in an over-the-counter (OTC) setting. Study Design: An actual use study in a simulated OTC environment assessed adherence to directions to take norgestrel 0.075 mg every day at the same time in 883 participants for up to 24 weeks. Results: Eighty-five percent (747/883) of participants reported ≥85% adherence to taking norgestrel 0.075 mg every day and reported taking their dose within three hours of their scheduled dosing time on 96% of days. When accounting for use of a condom for 48 hours if a pill was missed, participants reported correctly following the label's directed use for 97% of doses overall, with 95% of participants following label directions for ≥85% of doses. The main limitations were related to finding a balance between intensely collecting data to ensure accurate assessment of adherence and leaving users to behave as they would in a real OTC situation without healthcare practitioner intervention. We observed that some participants reported taking more doses than they could have based on the supply of medication given to them. To fully examine the situation, and the impact on the conclusions, additional post hoc sensitivity analyses were performed, and showed remarkably consistent results. Conclusions: Consumers were highly adherent to taking norgestrel 0.075 mg when using only the information provided by the proposed OTC label.

February 5, 2024

Carolyn Westhoff, MD, MSc
Editor
Contraception

Dear Dr. Westhoff,

On behalf of my coauthors, please find the enclosed revised manuscript entitled "Evaluation of Adherence to a Daily Progestin-only Pill in a Simulated Over-the-Counter Setting" and the detailed Response to Reviewers, which we are re/submitting for consideration for publication as an Original Research Article in *Contraception*. Ref. No.: CONTRACEPTION-D-23-00395.

We are happy that you have accepted the manuscript pending some final changes. These changes have been completed and we thank you for these final edits and all comments that have made this manuscript better.

We would be grateful if you would both publish and post this manuscript on-line together with ms 23-00396, entitled "Evaluation of Consumer Self-Selection of a Proposed Over-the-Counter Progestin-Only Daily Oral Contraceptive, in the same issue/at the same time.

Thank you for considering the manuscripts,

Stephanie Sober, MD, MPH and Irene Laurora, PharmD on behalf of the authors

Response to the editor “Evaluation of Adherence to a Daily Progestin-only Pill in a Simulated Over-the-Counter Setting”; Ref. No.: CONTRACEPTION-D-23-00395.

L57 - ....this study sought to determine...

Added “sought”

L57 This study sought to determine if consumers can adhere to a regimen of a daily oral contraceptive following the directions on a proposed over-the counter (OTC) label aims to make a more effective contraceptive method more widely available in the US.

L93 - word missing

Added “at”

We enrolled participants at 25 retail pharmacies (participants of all ages), 10 women’s health/adolescent clinics (participants aged <18 years), and one remote site (PEGUS Research Inc., Salt Lake City, UT; participants aged <18 years after the onset of the COVID-19 pandemic).L192 - six, six

L234 - This analysis identified...

Added “analysis”

L234 This analysis identified no systematic problems with the study, including the e-diary. One potential causal factor that could not be ruled out was the participant incentive.

L237 - improbable-dose reporting

Corrected

L237 However, for participants who engaged in improbable-dose reporting to a large extent, it seems likely that reporting of excess doses was deliberate.

L256 - correct the citation (? remove [3,8])

Removed [3,8]

L259 = actually this is a six-hour window.

Corrected

L259 We measured strict adherence to take the pill every day at the same time within a brief six-hour window.

L264 - Guillard et al [10]....

Added citation number next to author name

Appendix table 1 - spell our hormonal contraception (not HBC).

Completed

Evaluation of Adherence to a Daily Progestin-only Pill in a Simulated Over-the-Counter Setting

ClinicalTrials.gov Identifier: NCT04112095

Irene Laurora, PharmD[a]; Brandon Henrie[b]; Hélène Guillard, PharmD[a]; Russell Bradford, MD, MSPH[b]; Stephanie Sober, MD, MPH[a]; Anna Glasier, MD[c]

[a]HRA Pharma, A Perrigo Company

[b]PEGUS Research Inc

[c]Department of Obstetrics and Gynaecology, University of Edinburgh, Queen's Medical Research Institute

Corresponding Author

Irene Laurora, PharmD

HRA Pharma, A Perrigo Company, 200 Avenue de Paris, 92320 Châtillon, France

Email address: irene.laurora@perrigo.com

Word Counts

Abstract: 243/250 words

Main text:2560/2500 words

Abstract

Objective: The Adherence with Continuous Dose Oral Contraceptive: Evaluation of Self-Selection and Use (ACCESS) study assessed whether consumers can adhere to the regimen for a progestin-only pill (norgestrel 0.075 mg) in an over-the-counter (OTC) setting.

Study Design: An actual use study in a simulated OTC environment assessed adherence to directions to take norgestrel 0.075 mg every day at the same time in 883 participants for up to 24 weeks.

Results: Eighty-five percent (747/883) of participants reported ≥85% adherence to taking norgestrel 0.075 mg every day and reported taking their dose within three hours of their scheduled dosing time on 96% of days.

When accounting for use of a condom for 48 hours if a pill was missed, participants reported correctly following the label's directed use for 97% of doses overall, with 95% of participants following label directions for ≥85% of doses.

The main limitations were related to finding a balance between intensely collecting data to ensure accurate assessment of adherence and leaving users to behave as they would in a real OTC situation without healthcare practitioner intervention. We observed that some participants reported taking more doses than they could have based on the supply of medication given to them. To fully examine the situation, and the impact on the conclusions, additional post hoc sensitivity analyses were performed, and showed remarkably consistent results.

Conclusions: Consumers were highly adherent to taking norgestrel 0.075 mg when using only the information provided by the proposed OTC label.

Keywords (6/6 keywords): adherence; drug facts label; norgestrel; oral contraceptive; over-the-counter; progestin-only pill;

Implications (44/50 words)

Adherence to a daily oral contraceptive pill was high when obtained OTC. This suggests that effectiveness of an OTC pill is likely to be like that of a prescribed pill and easier access to this effective contraceptive should allow more opportunity to prevent pregnancy.

Abbreviations

ACCESS, Adherence with Continuous Dose Oral Contraceptive: Evaluation of Self-Selection and Use

e-diary/ies, electronic diary/ies

OC, oral contraceptive

OTC, over the counter

POP, progestin-only pill

1. Introduction

Correct and consistent use of effective contraception prevents pregnancy [1]. This study sought to determine if consumers can adhere to a regimen of a daily oral contraceptive following the directions on a proposed over-the counter (OTC) label aims to make a more effective contraceptive method more widely available in the US.

Oral contraceptives (OCs) must be taken every day, and norgestrel is to be taken at the same time every day [2]. If a pill is taken > three hours late (ie, >27 hours after the previous pill intake), it is considered missed, and users should abstain from vaginal intercourse or use a condom for 48 hours while resuming correct pill taking. If a POP is purchased OTC, users would depend on the information on the label to guide their usage.

Studies with a range of methodologies suggest that most users are not fully adherent when using OCs and that there is significant variability in adherence behaviors between users and between cycles within the same user [1, 3-9]. Two studies on adherence among combined OC users using daily electronic diaries (e-diary/ies) show that approximately 82% of women typically take 85% or more of their active pills per cycle [3, 8], and we used this information to establish a basis to evaluate adherence in this study.

We undertook a study, Adherence with Continuous Dose Oral Contraceptive: Evaluation of Self-Selection and Use (ACCESS), to evaluate the adequacy of a proposed OTC label to guide purchasers to use the pill safely and correctly in a simulated OTC setting.

Our primary objective was to learn how well users adhere to the instruction to take one pill at the same time every day in an OTC setting. We also sought to understand the behavior of three subgroups: participants with low health literacy, and adolescent participants aged 12 to 14 years and 15 to 17 years.

2. Materials and Methods

The Sterling Institutional Review Board approved the study (ClinicalTrials.gov Identifier: NCT04112095).

A brief description of the methodology has been published [10], as has a more detailed account of the ability of potential users to determine if the drug was appropriate for them to use [11]. In a single-arm, nonrandomized, open-label, multicenter, 24-week prospective study across the US, we screened individuals who responded to an advertisement offering the opportunity to buy an OC pill OTC . Participants had to be able to read, speak, and understand the label; and be aged ≥11 years. We enrolled participants at 25 retail pharmacies (participants of all ages), 10 women's health/adolescent clinics (participants aged <18 years), and one remote site (PEGUS Research Inc., Salt Lake City, UT; participants aged <18 years after the onset of the COVID-19 pandemic).

A standardized health literacy assessment, Rapid Estimate of Adult Literacy in Medicine or Rapid Estimate of Adolescent Literacy in Medicine, was administered (low health literacy was defined as a score of ≤60 or a ≤8th grade reading level). We obtained informed consent and conducted a urine pregnancy test. Participants aged <18 years provided either informed consent or assent with parental consent. Those electing to purchase the POP entered the "use" phase of the study. Participants decided how many packs (28 norgestrel 0.075 mg tablets per pack) to purchase (pharmacy sites) or acquire free of charge (clinic sites and remote site) and could request additional supply, up to eight packs total.

The study was designed to mimic an OTC setting and minimize study personnel interactions with participants to avoid guiding or cueing behaviors. Participants recorded each day, in an e-diary, whether, on the day before, they had taken any pill, at what time, whether they had sexual intercourse (not asked of participants aged <18 years), and whether they used any back-up contraception. If no pill was taken, participants recorded explicitly that no pill was taken, and indicate the reason(s) from a list of options. We sent text reminders to complete the e-diary every four days. Participants could

enter data up to 10 days in arrears. We compensated them up to $458 for their participation, including completion of the e-diary. The incentive was constructed to encourage e-diary completion but not to influence pill-taking behaviors. Trained nurse interviewers working from a central research site telephoned participants at weeks two, four, eight, 12, 16, 20, and 24 to collect information on adverse events, and use of concomitant medications. They also clarified use on days when no e-diary entry had been made since the last phone interview. If the interviewer determined that the participant had discontinued norgestrel 0.075 mg, or if the participant completed 24 weeks of use, we conducted an end-of-study interview and asked participants to do a urinary pregnancy test and return any unused study medication and/or packaging.

2.1 Measures

We analyzed the following as primary endpoints: (1) the proportion of days when a pill was reported taken (overall daily adherence) and (2) the proportion of participants who reported taking a pill on ≥85% of their days (referred to as "adherent participants"). Days with no e-diary entry were considered missing. If a pill was missed by participants aged ≥18 years, an evaluation was conducted to determine whether mitigating action was taken (barrier method use or abstention from sexual intercourse for 48 hours after missing a pill) and analyzed the following as secondary endpoints: (1) the proportion of days and (2) of adherent participants when "correct" pill taking included label-directed mitigating behaviors. Adherence to the three-hour window was evaluated as a primary endpoint, which was defined as reported dosing within ± three hours of the time of day of the immediately preceding pill, and (as a secondary endpoint) pill intake within 27 (24 + 3) hours of the dose on the previous day, with consideration for mitigating behavior in the case of late doses. Simple proportions with 95% confidence intervals (exact method) were calculated for all measures.

We recorded the number of pregnancies based on an end-of-study pregnancy tests or any participant report.

After the study was completed, analyses revealed that some participants had run out of pills but continued to report doses taken in their e-diary. We defined participants reporting one or more doses than the total number of tablets they had received/returned, as "improbable dosers." Two post hoc sensitivity analyses were conducted, thereby analyzing the adherence endpoints using three datasets:

- The total sample (Dataset A, prespecified analysis)
- A sample excluding all improbable dosers (Dataset B, post hoc analysis)
- A sample that censored e-diary data for all participants beyond a "revised stop date" based on a conservative definition (date at which the supply of norgestrel 0.075 mg would have been exhausted based on recorded use, date when they reported stopping to the nurse interviewers, or the last day of use reported in the e-diary, whichever was earliest; Dataset C, post hoc analysis)

3. Results

Nine hundred fifty-five (955) participants purchased or obtained norgestrel 0.075 mg, and 883 reported in their e-diary using it at least once, including 200 adolescents aged <18 years and 120 people with low health literacy. Two hundred sixty-one (261) participants were improbable dosers. Demographic details of the total population are shown in Appendix Table 1, with those of the non improbable dosers and the improbable dosers shown separately. The population comprised a diverse group of participants, with over-representation of participants aged <18 years.

Dataset A comprised 883 participants who started the study and reported on 90,128 days of POP use. Dataset B (the sample excluding all improbable dosers) comprised 622 participants reporting on 61,001 days of norgestrel 0.075 mg POP use. Dataset C (the sample that censored participants' e-diary data after the "revised stop date") comprised 883 participants that reported on 72,610 days of POP use.

3.1 Taking a Pill Every Day

3.1.1 Overall daily adherence

In Dataset A, participants reported taking norgestrel 0.075 mg on 92.5% of the total number of days of possible pill taking (Table 1). Adolescents aged <18 years and participants with low health literacy performed similarly. The proportion of "correct" use days increased to 97% when mitigating behavior (abstaining from sex or using a barrier method) was considered (no days mitigated in adolescents aged <18 years; Table 1). Results in Datasets B and C were consistent (Table 1).

3.1.2 Individual participant daily adherence

In Dataset A, a total of 84.6% of participants reported taking norgestrel 0.075 mg on ≥85% of the days they participated in the study (Table 2). The results in adolescents aged <18 years and participants with low health literacy were consistent. The proportion of participants adherent ≥85% of the time rose to 95% when mitigating behavior was included (Table 2). Results in Datasets B and C were again consistent with Dataset A (Table 2).

3.2 Taking a Pill at the Same Time

In Dataset A, participants reported taking their dose ± three hours of the time of day of the previous dose 96% of the time (Table 3). Adolescents and participants with low health literacy performed similarly. Norgestrel 0.075 mg was reported as taken within 27 hours of the dose taken on the previous day, or appropriate mitigating behavior was taken on 99% of evaluable days (Table 3). Results in Datasets B and C were consistent (Table 3).

3.3 Reasons for Missing Pills and Discontinuation

In Dataset A, participants reported missing a pill on only 7% of days. Almost 60% of the 6,780 missed doses arose because participants ran out of supplies (Figure 1). Sixty-eight percent of incidences of missed pills reported were a single missed day. Figure 2 displays participant continuation over the course of the study in all datasets. Approximately 50% of participants continued for six months in Datasets A and B, while 30% reported continuing until six months in Dataset C. The most common reason for discontinuing the product was also due to running out of supplies.

3.4 Pregnancies

Fourteen pregnancies were reported during the study among the 955 participants who purchased norgestrel 0.075 mg. Six participants conceived while using norgestrel 0.075 mg. Three participants conceived before starting norgestrel 0.075 mg, and five conceived after stopping.

4. Discussion

Overall, participants reported consistently following the label directions, including taking appropriate mitigating action when a pill was missed.

The user population in ACCESS comprised a diverse group that reflected the diversity of the population of US women at risk for unintended pregnancy in terms of age, race, ethnicity, education level, income level, and prior experience with hormonal contraception. The population of adolescents was intentionally over-represented in ACCESS to ensure an adequate estimate of adherence in this important population.

We intended to mimic the OTC experience, and most participants were enrolled in a pharmacy where they purchased the drug with their own funds. However, there are elements of the OTC experience that cannot be replicated in a study. For example, product availability remained limited, as it could only be obtained from a research site (only 36 sites, including one remote site, across the entire US). This may have contributed to missed pills and discontinuation of the product (Figures 1 and 2). OTC access will allow norgestrel 0.075 mg users to purchase pill packs whenever they need them.

When planning and executing the study, we had to balance intensive data collection while ensuring a naturalistic study. We designed the tools used to collect the data with the intent to avoid cueing participants to take the product or to bias other behaviors of interest.

Self-report is the most common method for assessing medication adherence in research and clinical care [12]. However, self-report tends to overestimate adherence [12]. In two OC studies which

compared self-report of medication intake with the medication supply (per pharmacy claims), 8%-21% of participants reported taking more medication than was available to them based on pharmacy records [13, 14]. The rate of contraceptive pill adherence is likely over-estimated in OC adherence studies most of which rely solely on self-report only [7].

In this study, reliant on self-report and "actual use" design methods, we observed that some participants engaged in "improbable dosing". Once this behavior was identified, we undertook a comprehensive evaluation to understand it and its implications, which included an independent root-cause analysis conducted by a third-party (Clinical Pathways, LLC; https://www.clinicalpathwaysresearch.com) with expertise in root-cause analyses in clinical studies.

This analysis identified no systematic problems with the study, including the e-diary. One potential causal factor that could not be ruled out was the participant incentive. Participants who reported only a few excess doses may have made inadvertent data entry mistakes. However, for participants who engaged in improbable-dose reporting to a large extent, it seems likely that reporting of excess doses was deliberate. We conducted two post hoc analyses to assess the impact of over-reporting on study conclusions (Datasets B and C). Importantly, the subset of participants who did not over-report (Dataset B) included a robust sample, greater than the preplanned sample size considered adequate to assess the study objectives, providing data on 622 participants, with >60,000 days of norgestrel 0.075 mg use. The poststudy review identified no evidence that the data from these participants were unreliable. Finally, the post hoc sensitivity analyses (Datasets B and C) did not meaningfully change the estimates of consumer adherence and related behaviors, nor the interpretation of the results.

The comparison of participants with over-reporting to those without over-reporting shows that there are demographic differences between these groups (Appendix Table 1). There was an over-representation in the improbable dosers with regard to race, annual household income, and health literacy.

It is well established that adherence to all types of daily medications, especially preventive medications [15], including OCs [3, 7, 8], is less than perfect despite the involvement of a learned intermediary. Published data on adherence to combined OCs from studies with a range of methodologies suggest that most people are not fully adherent to daily dosing and that there is significant variability in adherence behaviors between people and between cycles within the same person [1, 3-9, 16]. The ACCESS study showed adherence behaviors consistent with those observed in the prescription setting.

We measured strict adherence to take the pill every day at the same time within a brief six-hour window. Participants were very adherent to this dosing direction. However, recent pharmacodynamic data are reassuring [17] and suggest that a wider window likely exists for maintaining efficacy if a pill is delayed or missed than previously thought.

Guillard et al [10] used data on the contraceptive methods used by participants at the time they enrolled in the ACCESS study to model the potential impact of OTC availability on the rate of unintended pregnancy. The model showed clinically meaningful reductions in unintended pregnancies with the use of OTC norgestrel 0.075 mg versus current contraception methods, even with the most conservative assumptions.

The benefits for individuals and for public health in terms of preventing unintended pregnancy and its consequences are potentially large [10]. In the US, 40 million people are at risk of unintended pregnancy, and 15 million of them currently use a less effective method or no method at all. Each year, 2.7 million pregnancies are unintended, most of which could have been prevented by effective contraception. Pregnancy itself is not without risk. Every year, >1,200 people in the Untied States die from pregnancy-related causes [18]; contraception could prevent the deaths from unintended pregnancies.

The study supports that norgestrel 0.075 mg can be used effectively in the OTC setting to help reduce unintended pregnancies.

Acknowledgments

The authors would like to thank the team at PEGUS Research, especially Eva DeJong, for their work to oversee and monitor the study and to review the clinical study report and this manuscript. The authors would also like to thank Eric Brass, MD, PhD for his support in review of the data from this study and this manuscript, Ibis Reproductive Health for their partnership in support and funding of research to make norgestrel available over-the counter, and Advocates for Youth for their support in recruiting young adolescent participants.

Editorial support was provided by Leslie Moody, PhD, CMPP and Daneal Doub, PharmD, BCMAS, of Lumanity Communications Inc., and was funded by HRA Pharma.

Funding

This work was supported by HRA Pharma and Ibis Reproductive Health.

Declarations of interest

IL is an employee of HRA Pharma/Perrigo. BH is a paid consultant for HRA Pharma/Perrigo. HG is an employee of HRA Pharma/Perrigo. RB is a paid consultant for HRA Pharma/Perrigo. SS is a paid medical consultant for HRA Pharma/Perrigo. AG is a paid medical consultant for HRA Pharma/Perrigo.

References (13/35 references)

[1] Aubeny E, Buhler M, Colau JC, Vicaut E, Zadikian M, Childs M. The Coraliance study: non-compliant behavior. Results after a 6-month follow-up of patients on oral contraceptives. Eur J Contracept Reprod Health Care. 2004;9:267-77. https://doi.org/10.1080/13625180400017776.

[2] McCann MF, Potter LS. Progestin-only oral contraception: a comprehensive review. Contraception. 1994;50:S1-195. https://doi.org/10.1016/0010-7824(94)90113-9.

[3] Potter L, Oakley D, de Leon-Wong E, Canamar R. Measuring compliance among oral contraceptive users. Fam Plann Perspect. 1996;28:154-8.

[4] Woods JL, Shew ML, Tu W, Ofner S, Ott MA, Fortenberry JD. Patterns of oral contraceptive pill-taking and condom use among adolescent contraceptive pill users. J Adolesc Health. 2006;39:381-7. https://doi.org/10.1016/j.jadohealth.2005.12.014.

[5] Huber LR, Broel EC, Mitchelides AN, Dmochowski J, Dulin M, Scholes D. Comparison of prospective daily diaries and retrospective recall to measure oral contraceptive adherence. Contraception. 2013;88:492-7. https://doi.org/10.1016/j.contraception.2013.02.007.

[6] Hughey AB, Neustadt AB, Mistretta SQ, Tilmon SJ, Gilliam ML. Daily context matters: predictors of missed oral contraceptive pills among college and graduate students. Am J Obstet Gynecol. 2010;203:323 e1-7. https://doi.org/10.1016/j.ajog.2010.05.039.

[7] Hou MY, Hurwitz S, Kavanagh E, Fortin J, Goldberg AB. Using daily text-message reminders to improve adherence with oral contraceptives: a randomized controlled trial. Obstet Gynecol. 2010;116:633-40. https://doi.org/10.1097/AOG.0b013e3181eb6b0f.

[8] Fox MC, Creinin MD, Murthy AS, Harwood B, Reid LM. Feasibility study of the use of a daily electronic mail reminder to improve oral contraceptive compliance. Contraception. 2003;68:365-71. https://doi.org/10.1016/j.contraception.2003.08.013.

[9] Oakley D, Sereika S, Bogue EL. Oral contraceptive pill use after an initial visit to a family planning clinic. Fam Plann Perspect. 1991;23:150-4.

[10] Guillard H, Laurora I, Sober S, Karapet A, Brass EP, Glasier A. Modeling the potential benefit of an over-the-counter progestin-only pill in preventing unintended pregnancies in the U.S. Contraception. 2023;117:7-12. https://doi.org/10.1016/j.contraception.2022.10.006.

[11] Sober S, et al Evaluation of Consumer Self-Selection of a Proposed Over-the-Counter Progestin-Only Daily Oral Contraceptive. Contraception. 2024;submitted.

[12] Stirratt MJ, Dunbar-Jacob J, Crane HM, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. Transl Behav Med. 2015;5:470-82. https://doi.org/10.1007/s13142-015-0315-2.

[13] Nelson HN, Borrero S, Lehman E, Velott DL, Chuang CH. Measuring oral contraceptive adherence using self-report versus pharmacy claims data. Contraception. 2017;96:453-9. https://doi.org/10.1016/j.contraception.2017.08.013.

[14] Triebwasser JE, Higgins S, Secura GM, Zhao Q, Peipert JF. Pharmacy claims data versus patient self-report to measure contraceptive method continuation. Contraception. 2015;92:26-30. https://doi.org/10.1016/j.contraception.2015.03.016.

[15] Durand H, Hayes P, Morrissey EC, et al. Medication adherence among patients with apparent treatment-resistant hypertension: systematic review and meta-analysis. J Hypertens. 2017;35:2346-57. https://doi.org/10.1097/HJH.0000000000001502.

[16] Wiegratz I, Elliesen J, Paoletti AM, Walzer A, Kirsch B. Adherence with ethinylestradiol 20 µg/drospirenone 3 mg in a flexible extended regimen supported by the use of a digital tablet dispenser with or without acoustic alarm: an open-label, randomized, multicenter study. Int J Womens Health. 2015;7:19-29. https://doi.org/10.2147/IJWH.S71906.

[17] Glasier A, Edelman A, Creinin MD, et al. The effect of deliberate non-adherence to a norgestrel progestin-only pill: A randomized, crossover study. Contraception. 2023;117:1-6. https://doi.org/10.1016/j.contraception.2022.09.002.

[18] Hoyert DL. Maternal mortality rates in the United States, 2021, https://stacks.cdc.gov/view/cdc/124678; 2023 [accessed September 8, 2023].

Figure

Figure 1. ACCESS Study: Reasons for Missing Pills in ACCESS Study (N = 6,780 Missed Pills)
United States 2022

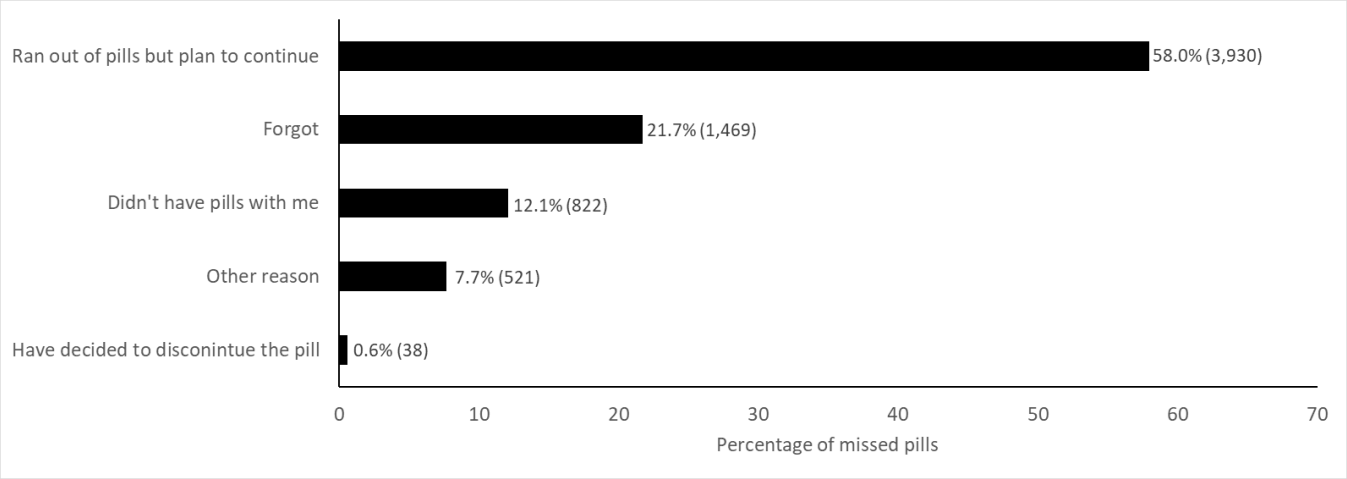
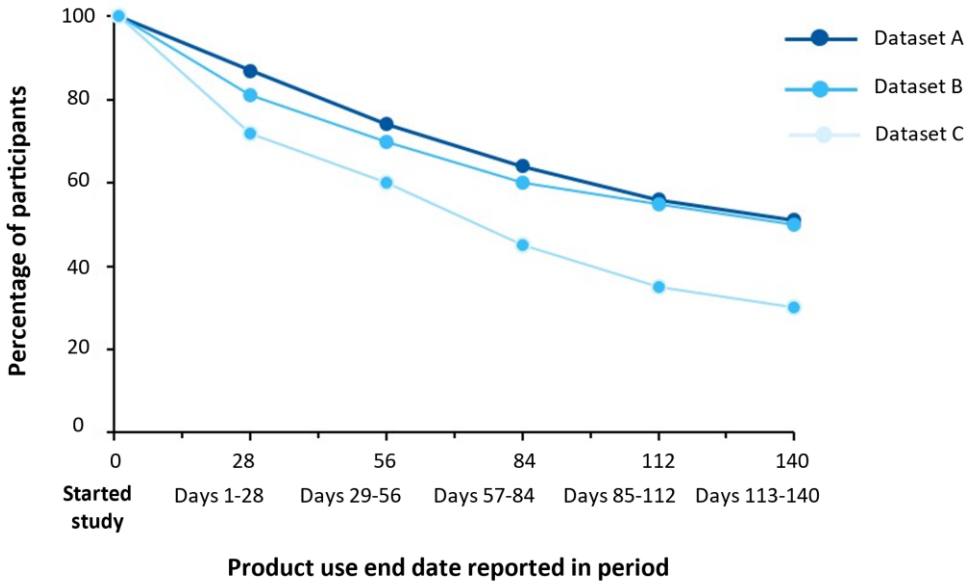


Figure 2. ACCESS Study: POP Continuation Rate in ACCESS Study United States 2022



POP, progestin-only pill; ACCESS, Adherence with Continuous Dose Oral Contraceptive: Evaluation of Self-Selection and Use.

Table 1. ACCESS Study: Adherence to Taking an Oral Contractive Pill Every Day (Overall Daily Adherence), United States 2022

	Days n/N	% (95% CI)
Dataset A (prespecified analysis)		
Primary endpoint (taking pill every day)	83,348/90,128	92.5% (92.3, 92.6)
Low health literacy	11,637/12,571	92.6% (92.1, 93.0)
Age 12-14 years	5,266/5,737	91.8% (91.0, 92.5)
Age 15-17 years	13,629/14,834	91.9% (91.4, 92.3)
Secondary endpoint (taking pill every day considering mitigating behaviors)*	87,537/90,128	97.1% (97.0, 97.2)
Low health literacy	12,075/12,571	96.1% (95.7, 96.4)
Dataset B (excluding participants who overreported dosing)		
Primary endpoint	55,967/61,101	91.6% (91.5, 92.0)
Secondary endpoint*	59,043/61,101	96.6% (96.6, 96.9)
Dataset C (participants' days censored after revised stop date)		
Primary endpoint	69,061/72,610	95.1% (95.0, 95.3)
Secondary endpoint*	71,208/72,610	98.1% (98.0, 98.2)

n = number of days participants reported taking norgestrel 0.075 mg; N = total number of days.
Assessed in the user population (883 participants) over a course of up to 6 months.
*Did not ask participants <18 years of age about sexual behaviors; therefore, the secondary endpoint only include nonmitigated behaviors for this age group.

Table 2. ACCESS Study: Adherence to Taking an Oral Contraceptive Pill Every Day Over the Course of Study Participation (Participant-level Adherence) United States 2022

	Participants n/N	% (95% CI)
Dataset A (prespecified analysis)		
Primary endpoint (≥ 85% adherent to daily dosing)	747/883	84.6% (82.0, 86.9)
Low health literacy	98/120	81.7% (73.6, 88.1)
Age 12-14 years	40/49	81.6% (68.0, 91.2)
Age 15-17 years	125/151	82.8% (75.8, 88.4)
Secondary endpoint (≥85% adherent to daily dosing considering mitigating behaviors)*	837/883	94.8% (93.1, 96.2)
Low health literacy	109/120	90.8% (84.2, 95.3)
Dataset B (excluding participants who overreported dosing)		
Primary endpoint	519/622	83.4% (80.3, 86.3)
Secondary endpoint*	588/622	94.5% (92.4, 96.2)
Dataset C (participants' days censored after revised stop date)		
Primary endpoint	793/883	89.8% (87.6, 91.7)
Secondary endpoint*	855/883	96.8% (95.4, 97.9)

n = number of participants ≥85% adherent; N = number of participants in user population.

*Did not ask participants <18 years of age about sexual behaviors; therefore, secondary endpoint only includes nonmitigated behaviors for this age group.

Table 3. ACCESS Study: Adherence to Taking an Oral Contraceptive Pill at the Same Time of Day United States 2022

	Days n/N	% (95% CI)
Dataset A (prespecified analysis)		
Primary endpoint (pill used ± 3 hours since time of last dose)	78,946/82,465	95.7% (95.6, 95.9)
Low health literacy	10,927/11,517	94.9% (94.9, 95.3)
Age 12-14 years	5,020/5,217	96.2% (95.7, 96.7)
Age 15-17 years	12,853/13,478	95.4% (95.0, 95.7)
Secondary endpoint (pill used within 27 hours of dose on prior day or mitigating action taken)*	79,316/80,107	99.0% (98.9, 99.1)
Low health literacy	11,070/11,231	98.6% (98.3, 98.8)
Dataset B (excluding participants who overreported dosing)		
Primary endpoint	52,692/55,345	95.2% (95.0, 95.4)
Secondary endpoint*	52,987/53,580	98.9% (98.8, 99.0)
Dataset C (participants' days censored after revised stop date)		
Primary endpoint	65,020/68,178	95.4% (95.2, 95.5)
Secondary endpoint*	65,551/66,278	98.9% (98.8, 99.0)

n = number days norgestrel 0.075 mg was reported as taken at the correct time; N = number of days evaluable for timing of dose.

*Did not ask participants <18 years of age about sexual behaviors; therefore, secondary endpoint only includes nonmitigated behaviors for this age group.

Appendix Table 1. ACCESS Study: Demographic Data and Baseline Characteristics by ACCESS Analysis Population United States 2022

	Total user population (Dataset A) (N = 883)	Non–improbable dosers (Dataset B) (n = 622)	Improbable dosers (Dataset C) (n = 261)
Sex			
Female	883 (100%)	622 (100.0%)	261 (100.0%)
Race[a]			
American Indian or Alaska Native	24 (2.7%)	19 (3.1%)	5 (1.9%)
Asian	50 (5.7%)	39 (6.3%)	11 (4.2%)
Black or African American	267 (30.2%)	153 (24.6%)	114 (43.7%)
Native Hawaiian or other Pacific Islander	12 (1.4%)	9 (1.4%)	3 (1.1%)
White	527 (59.7%)	413 (66.4%)	114 (43.7%)
Other	57 (6.5%)	34 (5.5%)	23 (8.8%)
Refused	8 (0.9%)	5 (0.8%)	3 (1.1%)
Ethnicity			
Hispanic or Latino/Latina	161 (18.2%)	108 (17.4%)	53 (20.3%)
Not Hispanic or Latino/Latina	722 (81.8%)	514 (82.6%)	208 (79.7%)
Age group, years			
Age 12-14	49 (5.5%)	34 (5.5%)	15 (5.7%)
Age 15-17	151 (17.1%)	110 (17.7%)	41 (15.7%)
Age 18-19	76 (8.6%)	53 (8.5%)	23 (8.8%)
Age 20-24	195 (22.1%)	143 (23.0%)	52 (19.9%)
Age 25-34	259 (29.3%)	178 (28.6%)	81 (31.0%)
Age 35+	153 (17.3%)	104 (16.7%)	49 (18.8%)
Age 35-45	139 (15.7%)	95 (15.3%)	44 (16.9%)
Age 46-55	12 (1.4%)	7 (1.1%)	5 (1.9%)
Age 56+	2 (0.2%)	2 (0.3%)	0 (0.0%)
Age distribution			
Mean, years	25.5	25.3	25.9
SD	8.59	8.56	8.66
Median	24.0	24.0	24.0
Range	12, 61	12, 61	12, 51
BMI category[b]			
Underweight	16 (1.8%)	N/A	N/A
Normal weight	331 (37.5%)	N/A	N/A
Overweight	202 (22.9%)	N/A	N/A
Obese	318 (36.0%)	N/A	N/A
Missing/refused	16 (1.8%)	N/A	N/A
Health literacy			
Normal	763 (86.4%)	555 (89.2%)	208 (79.7%)
Low	120 (13.6%)	67 (10.8%)	53 (20.3%)

History of Hormonal Birth Control use			
Yes	633 (71.7 %)	449 (72.2%)	184 (70.5%)
History of oral contraceptive use	543 (61.5%)	394 (63.3%)	149 (57.1%)
No	250 (28.3%)	173 (27.8%)	77 (29.5%)
Education level (age 18+ years)			
8th grade or less	2 (0.2%)	1 (0.2%)	1 (0.4%)
Some high school	21 (2.4%)	8 (1.3%)	13 (5.0%)
High school graduate or GED	158 (17.9%)	101 (16.2%)	57 (21.8%)
Some college or technical school	315 (35.7%)	224 (36.0%)	91 (34.9%)
College graduate	156 (17.7%)	121 (19.5%)	35 (13.4%)
Postgraduate degree	31 (3.5%)	23 (3.7%)	8 (3.1%)
Education level (11-17 years)			
7th grade or less	18 (2.0%)	13 (2.1%)	5 (1.9%)
8th grade	27 (3.1%)	20 (3.2%)	7 (2.7%)
9th grade	27 (3.1%)	21 (3.4%)	6 (2.3%)
10th grade	46 (5.2%)	32 (5.1%)	14 (5.4%)
11th grade	60 (6.8%)	39 (6.3%)	21 (8.0%)
12th grade	9 (1.0%)	7 (1.1%)	2 (0.8%)
High school graduate, GED, or certificate	11 (1.2%)	10 (1.6%)	1 (0.4%)
Some college or technical school	2 (0.2%)	2 (0.3%)	0 (0.0%)
College graduate	0 (0.0%)	0 (0.0%)	0 (0.0%)
Estimated annual household income			
<$25,000	282 (31.9%)	181 (29.1%)	101 (38.7%)
$25,001-$50,000	297 (33.6%)	209 (33.6%)	88 (33.7%)
$50,001-$75,000	124 (14.0%)	91 (14.6%)	33 (12.6%)
$75,001-$100,000	53 (6.0%)	41 (6.6%)	12 (4.6%)
$100,001-$150,000	51 (5.8%)	42 (6.8%)	9 (3.4%)
>$150,000	19 (2.2%)	18 (2.9%)	1 (0.4%)
Don't know	56 (6.3%)	39 (6.3%)	17 (6.5%)
Refused	1 (0.1%)	1 (0.2%)	0 (0.0%)

ACCESS, Adherence with Continuous Dose Oral Contraceptive: Evaluation of Self-Selection and Use; SD, standard deviation; BMI, body mass index; N/A, not available; HBC, hormonal birth control; GED, general education development.

[a]Answers are not mutually exclusive.

[b]BMI (in kilograms/meter^2) category: adults, age 20+ years: underweight BMI <18.5, normal BMI 18.5 to 24.9, overweight BMI 25 to 29.9, obese BMI ≥30; age 11 to 19 years: underweight BMI <5th percentile for age and gender, healthy weight 5th to 85th percentile for age and gender, overweight 86th to <95th percentile for age and gender, obese ≥95th percentile for age and gender.