Original Research Article

The effect of deliberate non-adherence to a norgestrel progestin-only pill: A randomized, crossover study

Anna Glasier a,⁎, Alison Edelman b, Mitchell D. Creinin c, Vivian Brache d, Carolyn L. Westhoff e, Leo Han b, Melissa J. Chen e, Agnes Hemon f

a College of Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh, UK
b Department of Obstetrics & Gynecology, Oregon Health & Science University, Portland, OR, United States
c Department of Obstetrics and Gynecology, University of California, Davis, Sacramento, CA, United States
d PROFAMILIA, Santo Domingo, Dominican Republic
e Department of Obstetrics and Gynecology, Columbia University, New York, NY, United States
f Laboratoire HRA Pharma, Chatillon, France

ARTICLE INFO

Article history:
Received 13 July 2022
Received in revised form 10 September 2022
Accepted 12 September 2022

Keywords:
Adherence
Cervical mucus
Missed pill
Norgestrel 0.075 mg
Ovulation
Progestogen-only pill

ABSTRACT

Objectives: To estimate the effects on cervical mucus, ovarian activity and theoretical contraceptive protection of a 6-hour delay and of missing one norgestrel 0.075 mg progestogen-only pill.

Study design: In a prospective, two-site, randomized, crossover study, healthy women aged 18 to 35 with BMI <32.0 kg/m2 and regular ovulatory cycles completed a baseline 28-day cycle with correct daily pill use followed by two intervention cycles in which, around mid-cycle, one pill was taken 6 hours late or missed completely. We undertook ovarian ultrasonography, estradiol and progesterone measurement, and cervical mucus assessments every 3 to 4 days (daily around the time of the incorrect use) and based the theoretical contraceptive protection score on ovarian activity status, cervical mucus and their temporal relationship.

Results: Of 91 potential participants screened, 52 started the study and 46 provided complete data for each intervention cycle. Fourteen participants (30%) ovulated in each of the two intervention cycles, with four during the delayed pill cycle and two during the missed pill cycle having an abnormal luteal phase. Seven participants in the delayed pill cycle, and six with a missed pill had elevated cervical mucus scores temporally associated with the intervention. However only women, one in the delayed pill cycle and one in the missed pill cycle, had cervical mucus scores in the range considered favorable for fertility.

Conclusions: Delayed or missed intake of a single norgestrel 0.075 mg progestogen-only pill appears to have little effect on theoretical contraceptive efficacy.

Implications: This biomedical study suggests that taking a norgestrel 0.075mg progestogen-only pill 6 hours late or missing one pill have little effect on ovarian activity or cervical mucus and may not jeopardize contraceptive efficacy. Correlation with typical use outcomes is necessary to confirm pregnancy risk with delayed or missed norgestrel intake.

© 2022 The Author(s). Published by Elsevier Inc.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

* Conflicts of interest: AG acts as an independent, paid, medical consultant to HRA Pharma and has consulted for Medincell, France. AE receives royalties from Up to Date, Inc. Oregon Health & Science University receives research funding from OHSU Foundation, Merck, HRA Pharma, and NIH where AE is the principal investigator. MDC has received speaking honorarium from Gedeon Richter and Mayne, serves on Advisory Boards for Fuji Pharma and glassoSmithKline, and is a consultant for Eterta SRL, Libbs, Mayne, and Medicines360. The Department of Obstetrics and Gynecology, University of California, Davis, receives contraceptive research funding for MDC from Chemo Research SL, Evoform, Medicines360, Merck, and Sebela. VB reports no conflicts.CLW receives honoraria from Merck and Bayer as a DSMB member and has been an independent paid consultant to HRA Pharma. Columbia University receives research funding from Medicines360, Sebela, and Chemo Research SL. LH is an independent consultant to Biowink GmbH.MJC has received speaking honorarium from Mayne.AH is an employee of HRA Pharma.

** Funding: The study was funded by HRA-Pharma, Chatillon, France. The study was designed by the sponsor in discussion with the independent medical advisor (AG). The protocol was finalized after discussions of the feasibility and practical details with the principal investigators at the two sites (AE, MC). The authors have had unfettered access to all the data and have analyzed them independently in preparing this paper. The sponsor has had no involvement in the decision to submit the report for publication.

⁎ Corresponding author.
E-mail address: Anna.Glasier@ed.ac.uk (A. Glasier).

https://doi.org/10.1016/j.contraception.2022.09.002
0000-7824© 2022 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)
1. Introduction

Combined oral contraceptive pill users are at low risk of breakthrough ovulation following missed or late pills [1]. In contrast, low-dose progestogen-only pills (POPs) containing norethindrone, norgestrel, or levonorgestrel mainly prevent pregnancy by rendering cervical mucus hostile to sperm, an effect thought to be rapidly reversed [2]. Peak concentrations of these progestogens are reached about 2 hours after ingestion and rapid metabolism potentially results in loss of contraceptive mucus changes [3,4]. Based on scant pharmacokinetic data and according to guidelines [5], a norethindrone or norgestrel/levonorgestrel POP is considered missed if taken more than 3 hours late. While many studies have explored the effect on ovulation suppression of deliberate non-adherence with combined oral contraception [1], we know of no such data for POPs.

In preparing an application to the US Food and Drug Administration for a norgestrel 0.075 mg POP to be sold over-the-counter, we performed a pharmacodynamic study to evaluate the effect on cervical mucus characteristics and ovarian activity of deliberately delaying or missing a pill. We aimed to evaluate the effects of a 6-hour delay, and a missed pill in the middle of two consecutive 28-day cycles with otherwise correct daily use. We assessed the theoretical conception risk based on the presence of potentially fertile mucus in the fertile window of an ovulatory cycle. We have previously reported the results from a baseline cycle of correct daily use for cervical mucus characteristics [6] and ovarian activity status [7], included baseline demographics of the study population. Here we report the effects of a delayed or missed pill.

2. Materials and methods

We performed a prospective, two-center, randomized, crossover study approved by an independent research ethics committee (Advarra, Columbia, MD) and registered with clinicaltrials.gov. The detailed protocol has been published [8]. Briefly, from 07/24/18 through 04/07/2020, we recruited healthy participants aged 18 to 35 with BMI <32.0 kg/m² from Oregon Health & Science University and University of California, Davis. This was an exploratory study with no working hypothesis to confirm or reject, however we estimated a sample size based on the proportion of participants with no theoretical loss of contraceptive protection. A sample of 45 participants provides 79% power to detect a difference in protection of 14% between perfect use and imperfect use (with loss of theoretical protection and any time) if the proportion of discords between the outcomes is 17%. The power is 82% for a difference in protection of 15% between perfect use and imperfect use if the proportion of discords between the outcomes is 18%. Participants reported regular menstrual cycles (21–35 days) when not using hormonal contraception and had at least one progesterone concentration >3 ng/mL (>10 nmol/L) during the luteal phase of a screening cycle. Participants abstained from heterosexual intercourse or used a condom unless the participant (or partner) was using permanent contraception.

Study participation began in the first 5 days of the following menstrual cycle and comprised three consecutive 28-day treatment periods with up to 12 days of post-treatment follow-up and an end of study visit within 5 days of the last follow-up (Fig. 1). Participants started a baseline cycle taking the first POP in the office between 0600 and 1200 and chose a time of day within 3 hours of intake on the day of enrollment to take one pill daily throughout the remainder of the study, except for the planned delayed/missed intake. Investigators instructed participants to take the study pill no more than 1.5 hours before or after that chosen time. Participants responded to a daily text-message based e-diary to document study pill use and vaginal bleeding or spotting. Study staff reviewed the e-diary at follow-up visits.

![Fig. 1. Study procedures. Reprinted from Edelman A, Hemon A, Creinin M, Borenstein P, Scherrer B, Glasier A. Assessing the Pregnancy Protective Impact of Scheduled Non-adherence to a Novel Progestin-Only Pill: Protocol for a Prospective, Multicenter, Randomized, Crossover Study. JMIR Res Protocol. 2021;10:e29208.doi:2196/29208. Published (and can be reproduced) under the terms of Creative Commons Attribution 4.0 licence.](image)
Participants visited the clinic every 3 to 4 days for transvaginal ultrasonography (TVUS), cervical mucus evaluation, and blood sampling for progesterone, estradiol, follicle stimulating hormone, and luteinizing hormone. If an ovarian follicle >15 mm in one dimension was seen on TVUS, we undertook monitoring every other day for a maximum of 3 visits or until a postovulatory image was seen.

At the first visit in the second 28-day treatment period, staff randomized participants equally into one of two study arms using a web-based central randomization program with site-specific block sizes of four. Participants randomized to Arm A delayed pill intake by 6 hours on day 42 ± 3, followed by a missed pill on day 70 ± 3 of treatment (day 14 ± 3 of the treatment cycles), and participants in Arm B reversed the order of the interventions.

The schedule of cervical mucus sampling is shown in Appendix A. On the day of the delayed/missed pill, we sampled cervical mucus 3 hours after the delayed pill, and 6 hours after the missed pill, (corresponding to 27 and 30 hours after the last pill intake respectively). On the day after the delayed/missed pill, we sampled cervical mucus just before intake of the scheduled pill, corresponding to 17.5 hours after the last pill intake (delayed), and 47.5 hours after the last pill intake (missed).

Investigators scored cervical mucus immediately after collection using a modified Insler score of ferning, spinnbarkheit, viscosity, and cellularity based on the World Health Organization (WHO) guidelines [9]. If, on either the day of, or the day following, the delayed/missed pill, an investigator was unable to obtain mucus because it was too thick, we assigned the same score as that determined the day before the delayed/missed pill if that score was between 0 and 4; however, if the previous day score was >4, we assigned a score of four. If the mucus was too thick on all days, we assigned a score of zero. In accordance with WHO, we considered total cervical mucus scores ≥9 as favorable to fertility, scores between 5 and 8 as medium, and scores ≤4 as unfavorable to fertility. [9]

After study completion, an adjudication committee of three experts not affiliated with either study site and blinded to the randomization order reviewed the data independently. The committee then met together virtually to agree on ovarian activity status according to a modified Hoogland score [10] (Table 1) which used ovarian ultrasound findings and serum estradiol and progesterone values to classify ovarian status as quiescent; low ovarian activity; ovulation with an abnormal luteal phase; and ovulation with a normal luteal phase. The committee attributed a theoretical score for the degree of contraceptive protection according to the algorithm in Figure 2 based on the ovarian status and the highest cervical mucus score during the three visits before a postovulatory image was seen, including the visit when the postovulatory image was obtained. If a postovulatory image was not recorded, the committee used progesterone levels alone to determine ovulation and the normality of the luteal phase. If missing data prevented the committee from determining with certainty whether ovulation had occurred and whether the luteal phase was abnormal or not, the data from that cycle were judged “inevaluable.” The committee considered contraceptive protection was medium if in an ovulatory cycle the maximum cervical mucus score was five to eight, but minimal if the score was ≥9.

We used a mixed model for repeated measures to compare the effect on cervical mucus score of either delaying or missing a pill, a stratified McNemar test to compare the distribution of ovarian activity classification, and McNemar’s test to compare the effect of the delayed or missed pill on the risk of conception. We performed all analyses using SAS (ver. 9.4 or higher) and Microsoft Excel 365.

3. Results

We screened 91 women for eligibility and enrolled 52 subjects with mean age 28.3 ± 4.5 years and mean Body Mass Index (BMI) of 24.0 ± 3.7 kg/m². Demographic details of the participants are shown in Appendix B. No-one discontinued due to adverse events.

Of the 51 participants completing the baseline cycle, 46 (90%) provided data suitable for evaluation in both the intervention cycles (Fig. 3). Age, BMI, ovarian status, cervical mucus score on the day of and following the delayed/missed pill intake, maximum cervical mucus score/cycle and the estimated degree of contraceptive protection for all 51 women for the three cycles are shown in Appendix C.

Overall, excluding the deliberate infringement, 38/46 (83%) and 36/46 (78%) of participants adhered to correct pill use (defined as taking a pill every day within the 3 hour window) >95% of the time during the delayed and missed pill cycles, respectively. Three participants with evaluable cycles reported missing a scheduled pill in the delayed pill cycle and three in the missed pill cycle one of whom missed a pill on two separate occasions. No-one missed two consecutive pills and none of the episodes was in close temporal proximity to the deliberate infringement.

3.1. Ovarian status

Table 2 shows the percentage of cycles with the four types of ovarian status for delayed/missed pill cycles; Appendix C lists individual scores. In the delayed pill cycle, 14 (30%) participants had an ovulatory cycle, four with an abnormal luteal phase. Similarly, 14 (30%) participants ovulated during the missed pill cycle, two with an abnormal luteal phase. When pill intake was delayed by

<table>
<thead>
<tr>
<th>Score</th>
<th>Activity</th>
<th>Size FLS/sonographic image</th>
<th>E2 (pg/mL)</th>
<th>P4 (ng/mL)</th>
<th>Ovarian status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No activity</td>
<td>≤ 10 mm</td>
<td>Independent of E2 level</td>
<td>≤ 1.57</td>
<td>Quiescence</td>
</tr>
<tr>
<td>2</td>
<td>Potential activity</td>
<td>&gt; 10 mm and ≤ 13 mm</td>
<td>Independent of E2 level</td>
<td>≤ 1.57</td>
<td>Quiescence</td>
</tr>
<tr>
<td>3</td>
<td>Non-active FLS</td>
<td>&gt; 13 mm</td>
<td>≤ 27.24</td>
<td>≤ 1.57</td>
<td>Quiescence</td>
</tr>
<tr>
<td>4</td>
<td>Active FLS</td>
<td>&gt; 13 mm</td>
<td>≤ 27.24</td>
<td>≤ 1.57</td>
<td>Quiescence</td>
</tr>
<tr>
<td>5</td>
<td>Postovulatory, low P4 level</td>
<td>Postovulatory image</td>
<td>&gt; 27.24</td>
<td>≤ 3.14</td>
<td>Ovarian activity</td>
</tr>
<tr>
<td>6</td>
<td>Postovulatory, intermediate P4 level</td>
<td>Postovulatory image</td>
<td>&gt; 27.24</td>
<td>&gt; 3.14 and ≤ 9.42 (only once)</td>
<td>Ovulation, abnormal luteal phase</td>
</tr>
<tr>
<td>7</td>
<td>Postovulatory, high P4 level</td>
<td>Postovulatory image</td>
<td>&gt; 27.24</td>
<td>&gt; 9.42</td>
<td>Ovulation, normal luteal phase</td>
</tr>
</tbody>
</table>

* A postovulatory image was defined as follows: Image observed after abrupt disappearance of FLS OR Image observed after reduction in size of the leading follicle > 4 mm at two consecutive visits OR Hemorrhagic and cystic corpus luteum (FLS at least as large as the leading follicle before ovulation) If there was a rise in progesterone consistent with ovulation, the experts deemed the cycle to be ovulatory even if a postovulatory image was not seen.
6 hours, only two of the ten cycles with a normal luteal phase had progesterone > 9.42 ng/mL (Hoogland 7), while three of the twelve women who missed a pill and had a normal luteal phase had a progesterone greater than 9.42 ng/mL.

### 3.2. Cervical mucus scores

In each of their delayed and missed pill cycles, 27/46 (59%) participants had unfavorable cervical mucus scores (≥4) over the entire cycle, and eight of the remaining participants (17% of the total) had a single (intermediate) elevated score at a time unrelated to the day of the delayed pill (Appendix C).

In the delayed pill cycle, the increased cervical mucus scores were all intermediate (score 5–8), while in the missed pill cycle, four subjects had intermediate scores and four had scores with fertile mucus (≥9) (Appendix C). For any individual subject, a score ≥9 occurred only once in the treatment cycle, with two of the scores occurring before the subjects missed their pill, one occurring one week after the subject missed her pill and only one occurring the day after the subject missed the pill.

Ten women had a mucus score above four on either the day of or the day following the delayed/missed pill in one of the two cycles (Table 3).

Overall, cervical mucus scores did not change significantly when comparing the score on the day before either a delayed or missed pill and the score on day of the infringement, nor was there a significant change between cervical mucus score on the day following the infringement compared with the score on the day before a pill was delayed or missed (p = 0.26). Neither missing a pill nor delaying intake by 6 hours significantly changed the cervical mucus score (Mixed model for repeated measures p = 0.26) nor did the type of infringement (delayed or missed pill) have any effect on the score (p = 0.45).

---

**Table 2**

Ovarian status outcomes during the two intervention cycles

<table>
<thead>
<tr>
<th>Ovarian status</th>
<th>Delayed pill n = 46</th>
<th>Missed pill n = 46</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quiescent</td>
<td>10 (22)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Follicle only</td>
<td>22 (48)</td>
<td>25 (54)</td>
</tr>
<tr>
<td>Abnormal luteal phase</td>
<td>4 (9)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Normal luteal phase</td>
<td>10 (22)</td>
<td>12 (26)</td>
</tr>
</tbody>
</table>

Data presented as n (%).

---

**Fig. 2.** Conception protection algorithm based on ovarian activity status and cervical mucus scores.

**Fig. 3.** Disposition of subjects in the crossover trial of deliberate missing or delay of a norgestrel 0.075 mg progestin-only pill.
3.3. Assessment of contraceptive protection

Based on ovulation with favorable cervical mucus, eight women had reduced contraceptive protection at some time during the intervention cycles, one had reduced protection in both cycles (Table 4). Four of 46 participants (9%) with delayed pill intake were considered as having reduced contraceptive protection although one (Appendix C, #211) already had a cervical mucus score >4 the day before the delayed pill. All four of these participants had a medium level of contraceptive protection, one with an abnormal luteal phase. Among 46 participants who deliberately missed a pill, five (11%) were judged to have reduced contraceptive protection; all ovulated with a normal luteal phase. Three had medium contraceptive protection, one of whom (Appendix C, #103) had a cervical mucus score >4 at the time of the missed pill. Two participants had a cervical mucus score of nine or above and were considered only minimally protected, one of whom (Appendix C, #211) had an elevated cervical mucus score at the time of the missed pill. Missing a scheduled pill had no effect on theoretical contraceptive protection (Appendix C).

4. Discussion

Deliberately delaying or missing one norgestrel 0.075 mg POP appeared to have little effect on cervical mucus, ovulation or theoretical contraceptive protection. While some women had theoretically reduced contraceptive protection at some time during the study period, this finding was related to incorrect pill use in only one participant in the delayed pill cycle and two in the missed pill cycle. While we did not expect incorrect use (the delayed/missed pill intervention) to have a measurable effect on ovulation (given the time it takes to develop a dominant follicle), we were reassured by the apparent lack of effect on cervical mucus.

We compared outcomes from the two cycles of deliberate misuse of norgestrel 0.075 mg with data from the baseline cycle of correct use [6,7], and include data from this cycle in Appendix C. During correct use, 12 participants (24%) ovulated with a normal luteal phase. Similar proportions of normal ovulatory cycles occurred despite a delayed (22%) or missed pill (26%) (Appendix C). Using an exact kappa test, we found significant agreement in the paired-subject ovarian status between the correct-use period and both intervention cycles ($p < 0.001$ for each). Using an exact kappa test for cervical mucus score, we found agreement between correct-use and the missed pill cycle ($p = 0.02$) but no agreement between the correct-use and the delayed pill cycle ($p = 0.13$). While indicating statistical difference, 59% of subjects in the delayed pill cycle had only unfavorable cervical mucus scores and no subject had a score of ≥9, so perhaps not a clinically significant difference.

During correct use, 3/51 (6%) participants had contraceptive protection reduced to medium. Slightly more participants had a reduced level of protection in the intervention cycles (4/46 [9%] in the delayed pill, and 5/46 [11%] in the missed pill cycle). While this may suggest an effect on contraception protection of incorrect

---

**Table 3**
Cervical mucus scores on the day of delayed or missed pill (DMP) and the following day (DMP+1) together with the maximum score for cervical mucus, agreed ovarian status score (OS) and level of contraceptive protection (CP) in that treatment cycle for the ten women who had elevated cervical mucus score in relation to either the delayed or missed pill (or both)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Delayed pill (n = 46)</th>
<th>Missed pill (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OS</td>
<td>Cervical mucus</td>
</tr>
<tr>
<td></td>
<td>Mx</td>
<td>DMP</td>
</tr>
<tr>
<td>101</td>
<td>OSq</td>
<td>6</td>
</tr>
<tr>
<td>103</td>
<td>OSalp</td>
<td>5</td>
</tr>
<tr>
<td>106</td>
<td>OSa</td>
<td>5</td>
</tr>
<tr>
<td>113</td>
<td>OSa</td>
<td>4</td>
</tr>
<tr>
<td>125</td>
<td>OSa</td>
<td>6</td>
</tr>
<tr>
<td>126</td>
<td>OSa</td>
<td>8</td>
</tr>
<tr>
<td>202</td>
<td>OSa</td>
<td>4</td>
</tr>
<tr>
<td>211</td>
<td>OSalp</td>
<td>5</td>
</tr>
<tr>
<td>213</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>218</td>
<td>OSa</td>
<td>5</td>
</tr>
</tbody>
</table>

CP: conception protection level; Cervical Mucus Mx, maximum cervical mucus score for the treatment period; NE, not evaluable; OS: ovarian status; OSq: quiescence; OSa, active; OSalp, ovulation with abnormal luteal phase; OSnlp, ovulation with normal luteal phase; DMP: day of delayed or missed pill; DMP+1, day after delayed or missed pill; TTC, too thick to be collected.

**Table 4**
Ovarian status (OS), maximum cervical mucus score/cycle (Mx) and on the day of (DMP), and the day after (DMP+1) delayed or missed pill intake and contraceptive protection degree (CP) for the eight women deemed at risk of conception in the two intervention cycles

<table>
<thead>
<tr>
<th>Subject</th>
<th>Delayed pill (n = 46)</th>
<th>Missed pill (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OS</td>
<td>Cervical mucus</td>
</tr>
<tr>
<td></td>
<td>Mx</td>
<td>DMP</td>
</tr>
<tr>
<td>103</td>
<td>OSalp</td>
<td>5</td>
</tr>
<tr>
<td>108</td>
<td>OSalp</td>
<td>5</td>
</tr>
<tr>
<td>120</td>
<td>OSalp</td>
<td>5</td>
</tr>
<tr>
<td>129</td>
<td>OSalp</td>
<td>2</td>
</tr>
<tr>
<td>201</td>
<td>OSalp</td>
<td>6</td>
</tr>
<tr>
<td>208</td>
<td>OSalp</td>
<td>5</td>
</tr>
<tr>
<td>211</td>
<td>OSnlp</td>
<td>6</td>
</tr>
<tr>
<td>216</td>
<td>OSa</td>
<td>2</td>
</tr>
</tbody>
</table>

CP: conception protection level; Cervical Mucus Mx, maximum cervical mucus score for the treatment period; DMP: day of delayed or missed pill; DMP+1, day after delayed or missed pill; OS: ovarian status; OSq: quiescence; OSa, active; OSalp, ovulation with abnormal luteal phase; OSnlp, ovulation with normal luteal phase; TTC: too thick to be collected.
pill use, in only three subjects (one in the delayed pill, and two in the missed pill cycle) did the cervical mucus score suggest loss of contraceptive protection in relation to the episode of incorrect use.

Our study uniquely evaluates the duration of contraceptive changes beyond the 24 hour period after pill-taking. Most time-course studies focus on the rapid onset of action of an effect of cervical mucus of progestin-based therapies [11,12]. A small clinical trial from Han et al. demonstrated that even as oral norethindrone levels fall to near zero by 24 hours, mucus scores do not revert to being favorable [13]. However, that study did not examine mucus changes beyond 24 hours. Our study now provides the first measurements of mucus changes beyond 24 hours, and up to 48 hours in the case of a missed pill.

The study has important limitations. For most of the cycle we assessed cervical mucus every 3 to 4 days and may have underestimated maximum scores. However, the frequency of ultrasound and hormone evaluation increased to alternate days for three visits when we observed a follicle ≥15 mm diameter; thus, progesterone concentrations are likely to reflect the quality of the luteal phase. Only four (8%), two (4%) and three (7%) women in the correct-use cycle [6], the delayed and missed pill cycles respectively had Hoogland score of 7, suggesting that even when ovulation was appeared normal it may not have been optimal for conception [14]. The conception protection algorithm likewise may have overestimated pregnancy risk given that any cervical mucus score above four in association with ovulation, normal or inadequate, was deemed to confer reduced contraceptive protection.

We did not test delaying pill intake for different time intervals or missing more than one pill. We tested a 6-hour delay as this is well outside the recommended 3-hour window [5]. Missing a pill on two or more consecutive days would be more likely to reduce the cervical mucus effects. However, although adherence declined slightly during the study, the theoretical risk of conception was not different between the cycles. In the cycles in which women reported missing a scheduled pill, theoretical contraceptive protection remained maximal.

We limited recruitment to subjects with BMI <32 kg/m², only 13/46 (28%) had a BMI >25 kg/m². It is possible that heavier women may be more sensitive to the effects on cervical mucus of incorrect use [15].

We relied on pharmacodynamic surrogates of cervical mucus and ovulation to estimate contraceptive effects; pregnancy was not an outcome. An endometrial effect may also confer contraceptive efficacy [16], however we did not measure endometrial thickness. The chances of conception are likely lower in real life when women could take mitigating action (using condoms or abstaining from intercourse) if they made mistakes with regular pill intake. Moreover, our assessment of conception risk does not account for either fecundity or of frequency of intercourse. Only 53% (49%–57%) of US women aged 18 to 44 have sex at least once a week [17].

This study demonstrates that delayed intake of a norgestrel 0.075 mg POP or missing one pill completely appears to have little effect on theoretical contraceptive efficacy. This POP may have a greater margin for error than previously thought, and our study almost certainly overestimates the theoretical risk of pregnancy. However as this is the only study to explore the effect of deliberate non-adherence to a POP, in contrast to the wealth of evidence for the COC. We do not think one study is enough for us to recommend changing the current Selected Practice Recommendations regarding the “three-hour window” [5].

Acknowledgments

The authors would like to acknowledge Stephanie Sober of HRA Pharma for her help with editing and formatting the manuscript.

Supplementary materials


References