*Original Research*

# Combined Oral Contraceptive Adherence and Pregnancy Rates

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**OBJECTIVE:** To assess the relationship of adherence and pregnancy in participants using an estetrol and drospirenone combined oral contraceptive.

**METHODS:** We performed a secondary analysis for which we pooled data from two parallel, multicenter, phase 3 trials (United States and Canada, Europe and Russia) that enrolled participants 16–50 years of age to receive estetrol 15 mg and drospirenone 3 mg in a 24 hormone and four placebo pills regimen for up to 13 cycles. Participants reported pill intake, sexual intercourse, and other contraceptive use on paper diaries. We limited this efficacy analysis to at-risk cycles (one or more reported acts of intercourse and no other contraceptive use) in participants 16–35 years of age at screening. We excluded cycles with other contraceptive use unless pregnancy occurred in that cycle. We assessed primarily the relationship between number of pills not taken per cycle and pregnancies and, secondarily, when pregnancies occurred during product use with a test for trend and $\chi^2$ analyses as appropriate.

**RESULTS:** Among 2,837 participants in this analysis, 31 on-treatment pregnancies occurred during 26,455 at-risk cycles. Pregnancies occurred in 0.09%, 0.25%, 0.83%, and 1.6% of cycles in which participants reported they took all hormone pills (n=25,613 cycles) or did not take one (n=405 cycles), two (n=121 cycles), and more than two (n=314 cycles) hormone-containing pills, respectively ($P<.001$). No pregnancies occurred in 2,216 cycles when one or more pills were missed and missed-pill instructions were followed. All pregnancies related to not taking pills occurred in the first three cycles. Pregnancy rates ranged from 0% to 0.21% per cycle with no significant trend by cycle ($P=.45$).

**CONCLUSION:** Pregnancy occurs more frequently when combined oral contraceptive users report not taking all hormone-containing pills per 28-day cycle and exceeds 1% only when more than two pills are not

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taken. Pregnancies in participants who reported missed pills occurred only when missed-pill instructions were not followed. A 0.09% pregnancy risk per cycle among users of a 24 hormone and four placebo pills formulation who report taking all pills likely approximates a true method-failure rate.

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Combined oral contraceptives are among the most commonly used methods to prevent pregnancy in the United States, Canada, and Europe.[1,2] The World Health Organization and Centers for Disease Control and Prevention consider this method moderately effective,[3,4] with a real-world contraceptive failure rate of about 7% in the first year of typical use.[5]

The actual rate at which combined oral contraceptives work to prevent pregnancy has always been difficult to measure accurately. Efficacy or failure rates calculated from clinical trial populations do not necessarily reflect real-life use because people in studies are not completely generalizable to typical users. In recent years, combined oral contraceptive pregnancy rates have increased gradually because regulatory agencies have required study sponsors to be more inclusive with their study population and to conduct more frequent evaluations for pregnancy throughout a trial.[6] Still, study efficacy rates remain higher than the estimates from typical-use population-based estimates.

Clinical trial authors will calculate perfect-use or method-failure rates to create a best estimate of efficacy, evaluating only those cycles in which all pill use instructions are followed (including those for missed pills) and no medications are used that could affect combined oral contraceptive metabolism. No studies to date have assessed pregnancy risk on the basis of reported adherence alone to better understand the effects of missing pills.

We evaluated the pooled data from two parallel phase 3 trials to estimate failure rates solely on the basis of adherence in a contemporary population. Although perfect-use failure rate estimates typically remove participants who used other medications that may interact with the oral contraceptive, we chose to focus solely on adherence, understanding that other medication use or illnesses that can affect absorption may occur with typical use.

## METHODS

We performed a secondary analysis of pooled data from two parallel, multicenter phase 3 trials that evaluated the contraceptive efficacy and safety of estetrol and drospirenone for up to 13 cycles. The two trials included participants from the United States and Canada (n=1,864) and Europe and Russia (n=1,553).[7,8] The characteristics, protocols, and IRB approval information have been previously published,[7,8] as have the participant demographics from the pooled data used in this analysis.[9] Investigators conducted the trials in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

The trials enrolled healthy, heterosexually active, 16- to 50-year-old participants in monogamous relationships during 2016 through 2018. Participants agreed to use estetrol 15 mg (as monohydrate, equivalent to 14.2 mg anhydrous) and drospirenone 3 mg for up to thirteen 28-day cycles (12 months) as their only method of contraception, although condoms were permitted if needed for sexually transmitted infection prevention. Each 28-day cycle was packaged as 24 hormonal tablets and four placebo tablets.

Investigators instructed enrolled participants not currently using hormonal contraception to begin treatment on the first day of their next menses and those switching from another combined hormonal contraceptive or progestin-only pill to start treatment on the day that they would have initiated their next pill pack, patch, or ring. Participants were instructed to take one tablet daily in consecutive order for each pill pack and not to skip days between packs. Participants received written instructions for what to do if a hormone-containing pill was missed. If one pill was missed or late, participants were told to take it as soon as they remembered and take the next pill on time, which meant that two pills could be taken together on the same day. If two or more pills were missed during days 1 through 17 of the pack, participants were instructed to take only the most recent pill as soon as they remember, take the next pill on time, and use a backup method (eg, a condom) for 7 days. If two or more pills were missed during days 18 through 24 of the pack, participants were instructed to skip the missed pills and take the hormone pill for that day, continue one daily through day 24, start a new pack instead of taking the placebo pills, and use a backup method for 7 days. Participants who missed two or more pills could use emergency contraception if needed.

Investigators conducted study follow-up visits at cycles 2, 4, 7, and 10 and at the end of treatment (cycle 13 or discontinuation). Participants completed a daily paper diary to record medication intake, use of other contraceptives (hormonal or barrier methods), and sexual intercourse. During each study visit, a study coordinator reviewed the diary and collected empty study drug packets to check treatment adherence. Participants completed a urine pregnancy test before first pill intake, after any treatment cycle without withdrawal bleeding, and at the end of treatment.

For this analysis, we included all participants 16–35 years of age (at screening) who used at least one study pill and had at least one follow-up contact. We included cycles considered at risk (one or more acts of intercourse and no other contraceptive use or pregnancy occurred) and excluded cycles in which other contraceptive methods were used unless pregnancy occurred in that cycle. We considered any day without a diary entry as no pill intake. We defined an *episode of missed pills* during a cycle as consecutive days in which pills were not taken. We performed two analyses to evaluate the relationship between the number of missed pills and pregnancies in at-risk cycles. We primarily assessed this outcome on the basis of the number of pills not used in a cycle; for example, if a participant missed a pill once in a cycle and took two the next day, that would count as no missed pills for that cycle. Secondarily, we assessed this outcome according to the number of events per cycle with missed pills (both with and without appropriate correction); when a participant had multiple episodes of missed pills in one cycle, we counted the longest episode of missed pills for the analysis. We also secondarily assessed when pregnancies occurred during combined oral contraceptive use by evaluating pregnancy rates per cycle for the study population. We used a test for trend and $\chi^2$ analyses as appropriate. For 95% CI calculations, Wald asymptotic CIs were used except when the proportion equaled zero, for which Wilson (score) CIs were used. We performed all statistical analyses using SAS 9.4 for Windows.

## RESULTS

Of 3,027 participants who initiated study drug, 2,837 (93.7%) met the criteria for inclusion in this analysis and provided data for 30,831 cycles. We excluded 4,376 cycles: 2,348 for no heterosexual intercourse during the cycle, 1,924 for other contraceptive use, and 104 for other reasons. Other contraceptive use cycles included 1,871 with condoms, 14 with emergency contraception, and 14 with emergency contraception and condoms. Participants in this analysis used estetrol and drospirenone for a total of 26,455 cycles and reported 25,613 cycles (96.8%) with all pills taken, which included 2,216 cycles (8.7%) in which participants correctly followed missed pills instructions.

Thirty-one pregnancies occurred during the studies, none in cycles in which other contraception was used. Pregnancy rates based on the number of pills reported as not taken per cycle are presented in Table 1, and rates based on the number of missed pill events per cycle are presented in Table 2. Among the 22 pregnancies in participants who reported taking all pills, 21 reported daily pill use during the cycle. Only one participant who reported not taking one pill and one participant who reported not taking two pills experienced a pregnancy; both of these participants did not correctly follow missed-pill instructions. Pregnancy rates exceeded 1% only in participants who reported not using more than two pills in a cycle and occurred only in participants who did not correctly follow missed-pill instructions. All pregnancies among participants who reported missing pills and not following missed-pill instructions occurred during the first three cycles (Table 3) and only in participants in the United States and Canada trial.

Two participants had missing diary information during the month of fertilization, which did not permit any calculations for these participants related to adherence; these pregnancies occurred in the Europe and Russia trial in cycles six and eight. Only one pregnancy in this study (cycle 12, no missed pills) occurred in relation to use of a contraindicated medication (St. John's wort). Removing this cycle and pregnancy from the calculation of per cycle risk lowered the pregnancy rate in participants who reported missing no pills from 0.09% to 0.08%.

The pregnancy rates per cycle ranged from 0% to 0.21% (Fig. 1) with no difference across the 13 cycles ($P$=.45). Almost half (48.4%) of pregnancies occurred during the first four cycles of study participation, although the pregnancy rate per cycle did not differ when cycles 1–4, 5–8, and 9–13 were compared (Table 3). We evaluated the cycle day of estimated fertilization in each cycle primarily to assess whether pregnancy occurred more frequently in the early part of the cycle (shortly after the placebo pills) (Appendix 1, available online at http://links.lww.com/AOG/D107). Ten of the 31 pregnancies (32.3%, 95% CI 15.8–48.7) were estimated to have occurred fewer than 7 days into the new pill pack, and two had unknown dates.

**Table 1. Pregnancy Rate by Number of Hormone Pills Not Used per Cycle in Estetrol and Drospirenone Combined Oral Contraceptive Users**

| Hormone Pills Not Used | Cycles* | Pregnancies | Pregnancy Rate† |
|---|---|---|---|
| 0 | 25,613 | 22 | 0.09 (0.05–0.12) |
| 1 | 405 | 1 | 0.25 (0–0.73) |
| 2 | 121 | 1 | 0.83 (0–2.44) |
| More than 2 | 314 | 5 | 1.59 (0.21–2.98) |
| Missing | 2 | 2 | 100 |

Data are n or % (95% CI).
* Includes only *at-risk cycles*, defined as 28-day cycles with one or more acts of intercourse and no other contraceptive use or a cycle in which pregnancy occurred even if other contraception was used.
† Test for trend comparing zero, one, two, and more than two, $P<.001$.

## DISCUSSION

We found that the pregnancy risk per cycle was very low (0.09%) in participants who reported using all active hormone pills in a particular cycle, regardless of any new medications started or health issues. The likelihood of pregnancy occurring in a cycle remains less than 1% even among study participants who reported not using as many as two pills in a cycle. An interesting finding is that the pregnancies that occurred when participants reported not using one or more pills during a cycle were all within the first three cycles. Conversely, among participants who reported missing no pills or had no information on the number of missed pills, only 5 of the 24 pregnancies (20.8%) occurred in the first three cycles. It is important to note that cycles in which participants recorded one or more missed pills did not result in pregnancy unless the missed-pill instructions were not followed. These outcomes provide a realistic view of the potential perfect-use failure rate of oral contraceptives when simply looking at adherence per cycle and provide reassurance that patients using a 24 hormone and four placebo pill combined oral contraceptive regimen who do not take a few pills during a cycle are unlikely to conceive, especially if they follow missed-pill instructions.

Fertilization does not appear to be related to the timing of missed pills within the cycle because pregnancy did not occur more frequently earlier in the cycle (after the placebo pills). In addition, fertilization was not more common in earlier cycles compared with later cycles. This latter finding is of particular interest because contraceptive failure rates are commonly thought to decrease over the first year of use,[10] perhaps because the least compliant would get pregnant earlier such that failure rates would be lower later in the year compared with earlier in the year. We found that not to be true.

A 2016 survey with 4,500 participants found that 39% missed at least one pill in the prior month.[11] Of those who had missed at least one pill in the past year, 40% attributed it to a busy schedule and 21% to stress, among other reasons. Forgetting one to three pills per

**Table 2. Pregnancy Rate Based on Number of Hormone Pills Missed per Cycle With and Without Correct Replacement* in Estetrol and Drospirenone Combined Oral Contraceptive Users**

| Hormone Pills Missed/Cycle | Cycles† | Pregnancies | Pregnancy Rate |
|---|---|---|---|
| 0 | 23,360 | 21 | 0.09 (0.05–0.13) |
| 1 | 2,498 | 1 | 0.04 (0–0.12) |
| Correct replacement | 2,164 | 0 | 0 (0–0.18) |
| Incorrect replacement | 434 | 1‡ | 0.23 (0–0.68) |
| 2 | 191 | 2 | 1.05 (0–2.49) |
| Correct replacement | 36 | 0 | 0 (0–9.64) |
| Incorrect replacement | 155 | 2§ | 1.29 (0–3.07) |
| More than 2 | 304 | 5 | 1.64 (0.22–3.07) |
| Correct replacement | 16 | 0 | 0 (0–19.36) |
| Incorrect replacement | 288 | 5‖ | 1.74 (0.23–3.24) |
| Missing | 2 | 2 | 100 |

Data are n or % (95% CI).
* Replacement ("doubling up") based on participant instructions for what to do when pills were not taken.
† Number of cycles in which zero, one, two, and more than two pills were reported as missed; if a cycle included more than one missed pill event, the event with the higher number of missed pills was used. This includes only *at-risk cycles*, defined as 28-day cycles with one or more acts of intercourse and no other contraceptive use or a cycle in which pregnancy occurred even if other contraception was used.
‡ Occurred in cycle two.
§ Occurred in cycle one.
‖ Occurred in cycles two and three; missed three, four, four, 10, and 20 pills.

**Table 3. Pregnancy Rate During Cycle Phases in Estetrol and Drospirenone Combined Oral Contraceptive Users**

| Cycles | Participants Starting Phase | Cycles During Phase* | Pregnancies | Proportion of all Pregnancies (%) | Pregnancy Rate† |
|---|---|---|---|---|---|
| 1–4 | 3,027 | 9,091 | 15 | 48.4 | 0.17 (0.08–0.25) |
| 5–8 | 2,487 | 8,300 | 7 | 22.6 | 0.08 (0.02–0.15) |
| 9–13 | 2,180 | 9,064 | 9 | 29.0 | 0.10 (0.03–0.16) |

Data are n or % (95% CI) unless otherwise specified.
* Includes only *at-risk cycles,* defined as 28-day cycles with one or more acts of intercourse and no other contraceptive use or a cycle in which pregnancy occurred even if other contraception was used.
† Pregnancies per cycle during phase, $\chi^2$ analysis, $P$=.07.



cycle is a frequent problem among up to half of users, particularly among adolescents.[12] Formulation may affect pregnancy rates when pills are missed because hormones with long half-lives may reduce the negative consequences of missed oral contraceptive pills. Estetrol, the estrogen component of the combined oral contraceptive in this study, has a longer half-life than ethinyl estradiol and estradiol, the estrogens used in other combined oral contraceptives.[13] In addition, estetrol is not metabolized by the cytochrome P450 system and has minimal drug-drug interactions.[14] Because the estrogen component of a combined oral contraceptive affects follicular development, this longer half-life may allow more leeway compared with other estrogens. In addition, shortening the hormone-free interval has been shown to lower the risk of hypothalamic-pituitary-ovarian axis reactivation with ethinyl estradiol and drospirenone, and the 24 hormone and four placebo pill regimens have lower pregnancy rates in population-based studies than 21 hormone and seven placebo pill formulations.[15,16] Similar analyses with other combinations using different hormones will help us understand whether the findings in this report are unique to estetrol and drospirenone or similar among all combined oral contraceptives.

A strength of this study is that we evaluated clinical outcomes pregnancy using reported pill use and not predictors or characteristics of those who missed or did not miss pills. A Cochrane review that evaluated the effect of missed combined hormonal contraceptives on pregnancy rates included studies that relied on surrogate measures of pregnancy risk, such as follicular development, progesterone levels, and cervical mucus, but did not quantify the clinical end point of unintended pregnancy.[17] Although these may lend credence to potential mechanisms for pill failures, they do not quantify the clinical end point of pregnancy. A limitation of this evaluation is that we did not assess or adjust outcomes according to reported sexual acts per cycle, primarily because such an evaluation would need to attempt to assess the timing of reported acts with any missed pills and such an assessment is beyond the scope of this report. Although the use of paper diaries may be viewed as a limitation, paper diaries have been shown to have comparable data integrity compared with prospective electronic diaries for oral contraceptive adherence.[18] Still, participant characteristics may affect diary compliance and truth in reporting.

Variations in pregnancy rate can occur even with the same pill formulation regardless of whether a Pearl Index or life-table pregnancy rate is reported, as was seen between the two studies using the estetrol and drospirenone formulation.[7,8] These differences are related to the population, including demographic characteristics and whether a participant had been using a hormonal contraceptive before enrollment.[9]

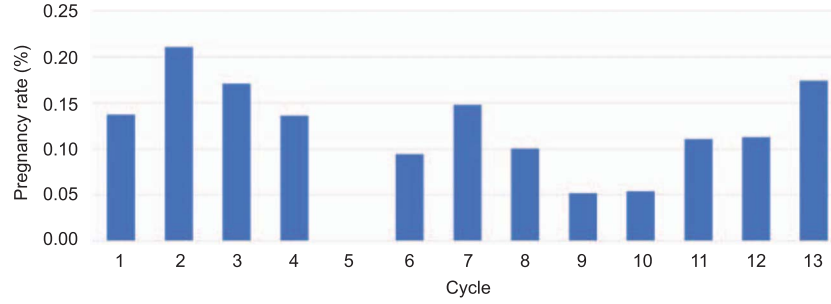


**Fig. 1.** Pregnancy rate by cycle in estetrol and drospirenone combined oral contraceptive users.
*Creinin. Oral Contraceptive Adherence and Pregnancy. Obstet Gynecol 2023.*

Finding the best way to provide clinically meaningful data of pill effectiveness is a topic of considerable debate. Unlike past clinical trial reports that describe pregnancy rates for the study population (which is then population dependent), we evaluated pregnancy risk per cycle according to adherence. Thus, if a population in another study has lower or higher adherence, the pregnancy risk per cycle based on number of pills missed or whether missed-pill instructions were followed would still be the same. A 0.09% per cycle method-failure rate extrapolates to 1.2% for 13 cycles, demonstrating reported perfect-use results in about 1% of users having a pregnancy in the first year of use. The cycle-based methodology presented in this report may give better insight into the true relationship between adherence and pregnancy risk and can be applied to both existing and future oral contraceptive studies.



## Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *No.*

What data in particular will be shared? *Not available.*

What other documents will be available? *Not available.*

When will data be available (start and end dates)? *Not applicable.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *Not applicable.*

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