



Published in final edited form as:

Contraception. 2026 July ; 159: 110898. doi:10.1016/j.contraception.2025.110898.

Hormonal Contraception after Use of Ulipristal Acetate as Emergency Contraception: A Systematic Review

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Abstract

Objectives: To systematically review literature on whether hormonal contraception following ulipristal acetate (UPA) for emergency contraception decreases the effectiveness of either drug.

Study design: We searched multiple databases through December 2022 for studies assessing the interaction between UPA and hormonal contraception. The primary outcome was contraceptive effectiveness, measured by pregnancy rates or proxy measures (e.g., ovarian activity). We extracted and summarized findings from identified studies, assessed risk of bias for each study, and determined certainty of evidence for all outcomes.

Results: Four studies met inclusion criteria; all had low risk of bias. Two studies assessed whether UPA use affected the ability of oral contraceptives (OCs) to inhibit ovulation; no differences were observed in ovarian activity when starting OCs one day after UPA compared with starting OCs one day after placebo. Two studies assessed whether OC use affected the ability of UPA to delay ovulation; both studies observed higher proportions of ovulation when UPA was followed by OC use versus delayed or no OC use. One study assessed ovulation risk when UPA was taken after missed OCs, followed by immediate versus delayed OC resumption; no ovulations occurred within the first five days after UPA administration in either group, but there was greater risk of ovulation beyond five days with delayed versus immediate OC resumption.

Conclusions: While there is no evidence that UPA affects the ability of hormonal contraception to inhibit ovulation, hormonal contraception use immediately or soon after UPA may decrease UPA's ability to delay ovulation. The certainty of evidence ranged from moderate to very low.

Implications: If a patient desires hormonal contraception after UPA, an interaction with UPA can be avoided by delaying initiation or resumption of hormonal contraception. The risk of pregnancy due to decreased effectiveness of UPA with immediate hormonal contraception should

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be balanced against the risk of subsequent pregnancy due to delay or non-start of hormonal contraception.

Keywords

Contraception; Emergency contraception; Systematic review; Ulipristal acetate

1. Introduction

Emergency contraceptive pill (ECP) use has increased in recent years in the United States, from 11% of sexually experienced women ages 15–44 years having ever used ECPs in 2008 to 25% of women ages 15–49 years in 2017–2019 [1, 2]. Of the two ECP formulations currently available in the United States, ulipristal acetate (UPA) has been shown to be more effective than levonorgestrel (LNG) with similar risks of side effects and adverse events [3]. UPA is taken as a single dose (30 μ g) within five days of unprotected intercourse [4]. UPA is only available in the United States via prescription, presenting an opportunity for patient counseling on the use of regular contraception, if desired, as well as the risks and benefits of starting or resuming contraception after the use of UPA as emergency contraception.

UPA works to prevent pregnancy primarily by delaying ovulation [5]. Therefore, UPA use will not prevent pregnancy later in the same cycle, so starting or resuming hormonal contraception can be considered if ongoing pregnancy prevention is desired by the patient. UPA is a selective progesterone receptor modulator and there is concern about the potential for an interaction between UPA and the progestin component of hormonal contraceptive methods, all of which contain a progestin, either alone or in combination with estrogen [6, 7]. Due to the anti-progestin properties of UPA, starting or resuming hormonal contraception soon after taking UPA for emergency contraception may impair the ability of UPA to delay ovulation after unprotected intercourse or decrease the contraceptive effectiveness of the newly started or resumed hormonal contraception to inhibit ovulation and prevent pregnancy from subsequent acts of intercourse in the same cycle. Because of this concern, clinical guidelines recommend a delay of five days between UPA use and starting or resuming hormonal contraception [4, 8, 9]. Abstaining from sex or using back-up barrier contraception for seven days after starting or resuming hormonal contraception is needed for pregnancy prevention until the regular method takes effect [4].

The US Centers for Disease Control and Prevention (CDC) publishes the *US Selected Practice Recommendations for Contraceptive Use* (US SPR), which provides evidence-based guidance for health care providers on the provision of contraceptive methods and the management of side effects and other issues related to contraceptive use [4]. The US SPR includes recommendations on use of regular contraception after emergency contraceptive pills, including UPA [4]. Previous systematic reviews described the theoretical concern about interactions between UPA and hormonal contraception [6, 10]. A 2013 review found no direct evidence on potential drug-drug interactions, [6] and a subsequent 2017 review included two studies and concluded that starting hormonal contraception immediately after UPA does not decrease the effectiveness of the hormonal contraception but can decrease the ability of UPA to delay ovulation [10]. The objective of this review, as part of the process

to update the US SPR, was to provide an updated summary of the evidence on whether the timing of initiation or resumption of hormonal contraception after use of UPA alters the effectiveness of UPA or hormonal contraception.

2. Materials and Methods

We conducted this systematic review according to an *a priori* protocol, which has been registered in the international prospective register of systematic reviews (PROSPERO) under the registration number: CRD42022350930 [11] and reported according to Preferred Reporting Items for Systematic Reviews and Meta-analyses [12].

2.1 Eligibility criteria

We included studies that examined the timing of starting or resuming hormonal contraception after UPA use. The study population of interest was women of reproductive age (e.g., 15–49 years, but the specific age range varied based on the criteria used in individual studies). The exposure of interest was initiation or resumption (e.g., after missing pills) of hormonal contraception immediately or soon after UPA use. Hormonal contraception methods included: combined oral contraceptives (COCs), combined injectable contraceptives, contraceptive patch, contraceptive ring, progestin-only pills (POPs), progestin-only injectables, progestin-only implants, and LNG-releasing intrauterine devices (IUDs). The comparator was delayed initiation or resumption of hormonal contraception or no use of hormonal contraception after UPA use. The primary outcomes were 1) effectiveness of UPA and 2) effectiveness of regular hormonal contraception in preventing pregnancy, as measured by pregnancy rates and proxy measures for risk of pregnancy, such as ovulation, follicular rupture, ovarian activity, and hormone levels (e.g., progesterone, estradiol, and luteinizing hormone). Secondary outcomes included adverse events, side effects such as vaginal bleeding, and patient satisfaction. Eligible study designs included randomized clinical trials (RCTs), non-randomized trials, cohort studies (comparative and non-comparative), and case-control studies. We excluded cross-sectional studies, case reports, commentaries, and reviews.

2.2 Search strategy

We worked with a Centers for Disease Control and Prevention (CDC) research librarian to review the research question and develop a comprehensive search strategy to identify articles relevant to the review question. The search was conducted in MEDLINE, EMBASE, Cochrane, [ClinicalTrials.gov](https://clinicaltrials.gov), and CINAHL databases from database inception to December 15, 2022 (Online Appendix A). We also reviewed references in systematic reviews to optimize our search. Articles in all languages were considered for inclusion.

2.3 Study selection and data extraction

Two authors independently screened each title and abstract identified in the search to identify full-text articles for review using Covidence software [13]. Two authors then independently reviewed full-text articles to identify articles that met inclusion criteria. Any conflicts identified in the screening process were resolved through discussion among authors. We scanned reference lists of included articles and relevant review

articles to identify any additional studies. We used a standardized evidence table to record study information, including authors, publication year, study location, years of data collection, study design and objective, study population, intervention, outcomes, measurement/definition of ovulation, results, and study strengths and limitations into the evidence table. The lead author extracted data from each study and a co-author performed quality control checks of the extracted data. Discrepancies were resolved through discussion among authors.

2.4 Risk of bias assessment

We used the Cochrane approach to assess risk of bias for RCTs and evaluated the following domains: randomization processes, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results [14]. We used a modified version of the Cochrane approach to assess risk of bias in non-randomized studies, including assessment of selection bias, information bias (exposure and outcome), and confounding [15]. Two authors independently assessed the risk of bias of each included study and any conflicts were resolved through discussion among authors.

2.5 Data synthesis

We summarized descriptive statistics, unadjusted and adjusted point estimates, results of significance tests, and interval estimates. We did not conduct meta-analyses because of the limited number of studies and the heterogeneity of exposures, outcomes, and study populations across the included studies.

2.6 Certainty of evidence

We used the GRADE approach to assess the certainty of evidence [16–18]. Certainty of evidence was rated as high, moderate, low, or very low depending on criteria including risk of bias, indirectness, imprecision, and inconsistency. Initially, RCTs are considered to have high certainty and non-randomized trials and observational studies have low certainty; these ratings are adjusted according to the previously mentioned criteria. We evaluated certainty of evidence for the primary outcome of effectiveness (measured via pregnancy rates and proxy measures for risk of pregnancy, such as ovulation) and secondary outcomes of adverse events and side effects such as vaginal bleeding for the studies that reported these outcomes. Patient satisfaction was not reported by included studies and therefore not assessed as an outcome.

3. Results

The search identified 3026 articles, 3004 of which were screened out for irrelevance and 8 as duplicates (Figure 1). Fourteen full text articles were reviewed, 10 of which were excluded (four ineligible study design, three abstracts without full text, two duplicates, one wrong outcome). Four articles were included (Table 1) [7, 19–21]. Three studies examined initiation of hormonal contraception during the study menstrual cycle [7, 19, 20]; of these, two studies assessed whether UPA modified the effectiveness of hormonal contraception [7, 19], and two studies assessed whether hormonal contraception modified the effectiveness of UPA [7, 20]. The fourth study assessed current COC users who were asked to miss pills

and then resume regular pill use after UPA use [21]. Three studies were RCTs [7, 19, 21], and one was a non-randomized trial [20]. Three studies examined COCs containing 30 µg ethinyl estradiol (EE) and 150 µg LNG [19–21], and one study used a POP containing 75 µg desogestrel (DSG) [7]. All four studies measured ovarian activity as a proxy measure for contraceptive effectiveness through ultrasound assessment of follicular rupture and serum progesterone levels; two studies also reported side effects and adverse events [19, 20]. One study reported on cervical mucus changes, hormonal and clinical characteristics of the menstrual cycle under treatment, and pharmacokinetic parameters for UPA and DSG [7]. None of the studies assessed patient satisfaction.

3.1 Risk of bias

The risk of bias among the four included studies was low (Table 2). The three RCTs had low risk of bias because they had adequate randomization processes, no deviations from intended outcomes or missing outcome data, used appropriate measurements, and reported all pre-specified outcomes [7, 19, 21]. One RCT did not blind outcome assessors but assessment of the outcomes (hormone levels and follicle size) was not likely to be affected [21]. The non-randomized trial also had low risk of bias because participants served as their own controls which minimized selection bias, exposures and outcomes were measured appropriately, and participants served as their own controls to minimize confounding [20].

3.2 Summary of results: initiation of hormonal contraception after UPA

Three of the four studies examined initiation of hormonal contraception after UPA administration in the study cycle. Of these, two studies assessed the effect of UPA on the ability of hormonal contraception to suppress ovulation [7, 19]. An RCT enrolled 76 healthy women, ages 18–35 years, with body mass index (BMI) < 30 kg/m², and who had regular, normal menstrual cycles or were current COC users before the study cycle [19]. During the study cycle, each participant was followed until a lead follicle of > 13 mm in mean diameter was observed and then randomized to receive either UPA or placebo. All participants started 21 days of COCs (EE 30 µg and LNG 150 µg) on the day following UPA or placebo administration. Ovarian activity was measured using a Hoogland score [22], which includes follicle growth measured through transvaginal ultrasound and serum concentrations of estradiol and progesterone, with Hoogland scores of 1–3 indicating ovarian quiescence, a score of 4 indicating active follicle like structure, a score of 5 indicating luteinized unruptured follicle, and a score of 6 indicating ovulation. Results indicated no significant differences overall in ovarian activity between the UPA and placebo groups after 21 days of COC use (p=0.95). No significant differences in the proportions in each group who ovulated (33% in the UPA group and 32% in the placebo group) nor in the proportions who reached ovarian quiescence (62% in both groups) were observed, suggesting that UPA did not have an effect on the ability of the COC to inhibit ovulation. When separately assessing ovulatory activity among those who were initiating COCs as part of the study and those who had been current users of COCs (i.e., had used COCs in the cycle previous to the study cycle), no significant differences were observed, although the proportion reaching quiescence was higher among those previously using COCs (66%) than those initiating COCs (52%). Five women in the UPA group and eight in the placebo group experienced unscheduled vaginal bleeding during COC use; duration was similar in both groups. No

serious adverse events were reported. Another RCT examined the pharmacokinetic and pharmacodynamic interactions between UPA and a POP (DSG 75 μg) [7]. This study enrolled 49 healthy women ages 18–35 years with BMI < 30 kg/m², who had not been using hormonal contraception for at least one complete menstrual cycle. Participants were randomized to two of three treatment sequences separated by a washout cycle: 1) UPA followed the next day by POP (DSG) for 20 days, 2) UPA followed the next day by placebo for 20 days, and 3) placebo followed the next day by POP (DSG) for 20 days. Treatment or placebo was initiated in each treatment sequence when a lead follicle was ≥ 14 to < 16 mm diameter on transvaginal ultrasound. The occurrence of ovulation within the first five days following UPA administration (to approximate ovulation around the time of unprotected intercourse) and within 21 days of UPA administration (to assess ovulation that could lead to pregnancy later in the cycle) was measured via ultrasound assessment of follicular rupture and serum progesterone levels. Cervical mucus permeability was also measured, as well as pharmacokinetic parameters for UPA and DSG. No significant differences were found between the UPA+POP (DSG) and placebo+ POP (DSG) sequences within 21 days of UPA use in the occurrence of ovulation (52% for UPA+POP (DSG) and 38% for placebo+POP (DSG); $p=0.6753$) or median days to ovulation (day 4 for UPA+POP (DSG) and day 3 for placebo+POP (DSG); $p=0.5485$), suggesting that UPA use did not affect the ability of POP (DSG) to inhibit ovulation later in the cycle. Cervical mucus scores were similar in all three groups ($p=0.421$), and there were no differences in the pharmacokinetic parameters for UPA or POP (DSG) between groups. This study did not report on adverse events or side effects.

Two studies assessed the effect of initiating hormonal contraception on the ability of UPA to delay ovulation [7, 20]. The RCT examining the pharmacokinetic and pharmacodynamic interactions between UPA and a POP (DSG 75 μg) also assessed the effect of initiating POP (DSG) versus placebo after taking UPA [7]. Ovulation within five days after treatment initiation occurred more frequently in the UPA+POP (DSG) sequences (45%) compared with the UPA+placebo sequences (3%; $p=0.0054$), suggesting that immediate POP (DSG) use after UPA affected the ability of UPA to delay ovulation. Additionally, the median time to ovulation was four days for the UPA+POP (DSG) sequences and eight days for the UPA+placebo sequences ($p<0.0001$). The second study was a non-randomized trial that examined the effect of COCs (EE 30 μg and LNG 150 μg) on the ability of UPA to delay ovulation [20]. This study included 36 healthy women, ages 18–35 years, with BMI < 28 kg/m², and regular menstrual cycles and followed them for three menstrual cycles. During cycle 1, participants received UPA when a dominant follicle size of 15 mm was observed, followed by a washout period for cycle 2. During cycle 3, participants again received UPA at the time of a 15 mm dominant follicle and two days later initiated COCs for five days. Participants were followed for seven days after UPA dosing in cycles 1 and 3 for follicle rupture. The primary outcome was the difference in the proportion of participants with a delay in follicle rupture of five days between cycle 1 and cycle 3. Follicle rupture was assessed via transvaginal ultrasound; if the date of follicle rupture was unclear, serum luteinizing hormone and progesterone levels were used to determine date of rupture. More participants demonstrated follicle rupture within five days during the UPA+COC cycle (27%) than during the UPA-only cycle (3%; $p=0.008$), suggesting that immediate COC use

after UPA affected the ability of UPA to delay ovulation. No serious adverse events were reported.

3.3 Summary of results: resumption of hormonal contraception after UPA

An RCT examined the effect of resuming COCs (after missing three consecutive pills during the study cycle) either immediately or five days after UPA administration on ovarian activity at different time points in the cycle [21]. This study examined the effect of immediate versus delayed COC resumption on the ability of UPA to delay ovulation, in the setting of missed pills. Participants included 49 healthy women, ages 18–30 years, with BMI < 30 kg/m² who took COCs (EE 30 µg and LNG 150 µg) during a baseline cycle, followed by a 7-day hormone-free interval. Participants then took COCs on days 1–4 of the study cycle, deliberately missed pills on days 5–7, and then took UPA (30 mg) on day 8. Half of the participants resumed COCs immediately (on the same day as UPA) and half delayed resumption by five days. The primary outcome was the proportion of participants with ovulation associated with a theoretical risk of pregnancy (based on a modified Hoogland score with a postovulatory ultrasound image and progesterone concentrations >30 nmol/l on one occasion or between 10 and 30 nmol/l on two consecutive occasions) and time to ovulation through day 26 of the cycle. None of the participants in either group ovulated with theoretical risk of pregnancy during the first five days after taking UPA, suggesting that immediate resumption of COC use after UPA did not increase the risk of ovulation within five days of UPA administration compared with delayed COC use. Beyond the fifth day, four participants in the delayed start group experienced ovulation with theoretical risk of pregnancy (days 15–17) compared with no participants in the immediate start group (p=0.042), suggesting that delayed resumption of COCs after UPA use increased the risk of ovulation beyond five days after UPA administration. There was also higher risk of ovarian activity without theoretical risk of pregnancy through 22 days in the delayed restart compared with the immediate restart group (OR 7.78 [95% CI: 1.38; 43.95], p=0.02). This study did not report on adverse events or side effects.

3.4 Certainty of evidence

The certainty of the evidence for the primary outcome of effectiveness (measured via ovulation) from the RCTs was assessed as moderate (Table 2) [23]. The RCTs were generally well designed with no serious concerns for risk of bias, inconsistency, or imprecision, but had serious concerns for indirectness due to the use of ovulation as a proxy measure of risk of pregnancy. The outcomes of adverse events and vaginal bleeding had moderate certainty of evidence because of serious concerns for imprecision; the studies had relatively small sample sizes and were not powered to detect differences in these outcomes. The non-randomized trial was also well designed with no serious concerns for risk of bias, imprecision, or inconsistency, but had very low certainty of evidence for effectiveness because of the use of ovulation as a proxy measure of risk of pregnancy and very low certainty for adverse events because of serious concerns for imprecision.

4. Discussion

Given the anti-progestin properties of UPA, there is theoretical concern about an interaction between UPA and progestin-containing hormonal contraception methods that could decrease the effectiveness of either drug, affecting the ability of UPA to delay ovulation after unprotected intercourse or affecting the ability of hormonal contraception to inhibit ovulation and prevent pregnancy from subsequent acts of intercourse in the same cycle. This systematic review identified four studies that provide evidence about this potential interaction. The findings suggest that UPA does not affect the ability of OCs to inhibit ovulation, but that the use of OCs immediately or soon after UPA decreases UPA's ability to delay ovulation. These findings are consistent with a drug-drug interaction between UPA and OCs that may lead to decreased effectiveness of UPA when the two drugs are taken in close proximity of each other. Evidence is limited to specific populations and contraception formulations. In the context of UPA use after missed pills, the risk of ovulation likely depends on the number and timing of missed pills as well as any effect of a drug-drug interaction between UPA and OCs.

Two studies assessed the impact of UPA on the ability of subsequent use of hormonal contraception to inhibit ovulation [7, 19]. Both studies found no differences in ovarian activity with use of a hormonal contraception method (COC or DSG) started one day after UPA administration compared with starting COCs one day after placebo, suggesting no effect of UPA on the effectiveness of subsequent hormonal contraception use. Two studies assessed the effect of hormonal contraception on the ability of UPA to delay ovulation [7, 20]. Both studies observed a higher risk of ovulation within five days of UPA administration when COCs or DSG were started immediately after UPA compared with delayed or no use of a hormonal method, suggesting an interaction between the two drugs that could lead to decreased effectiveness of UPA. Finally, one study focused on the use of UPA in the context of missed COCs [21]. When UPA was used by COC users who had missed three pills, no participants ovulated within five days of UPA administration, regardless of whether they resumed COC use immediately or delayed resumption for five days. Because participants were continuing COC users and had taken four pills in the study cycle before missing pills, they may have been at low risk for ovulation [24]. However, beyond five days from UPA administration, those who delayed resuming COCs were more likely to ovulate later in the cycle, potentially putting them at risk for pregnancy, compared with those who had resumed COCs at the time of UPA use. These findings are consistent with data suggesting missing one to four pills at times not adjacent to the hormone-free interval is associated with low risk of ovulation; however, eight days of missed pills (e.g., like those in the delayed group in this study) may be more likely to increase risk of ovulation [24]. Overall, the studies found few side effects and no serious adverse events, although not all studies reported on these outcomes.

This body of evidence has several limitations. Ovulation was used as a proxy measure for effectiveness of contraception; none of the studies measured pregnancy directly as an outcome. In addition, each study had different definitions and methods for identifying ovulation, including Hoogland scores [19, 21], interpretation of transvaginal ultrasound images [7, 19–21], and pharmacological parameters [7, 19–21]; the use of different

measures can complicate interpretation of results across studies. A major limitation of this body of evidence is limited generalizability as they were conducted among specific populations. The studies included a small number (range 36–76) of healthy women, ages 18 to 35 years (18–30 years [21]), with BMI < 30 kg/m² (<28 kg/m² [10]) and normal menstrual cycles. Although the sample sizes were generally sufficient for internal validity based on power calculations [7, 19, 20], they were small for extrapolating and applying results to larger and more diverse populations. Three of the included studies examined COCs containing EE 30 µg and LNG 150 µg [19–21], and the fourth examined DSG-only pills [7], excluding all the other hormonal contraception methods. It is unclear whether results from these specific formulations can be extrapolated to other hormonal contraception, especially to other POPs that may not suppress ovulation to the same extent as DSG [7]. Finally, there is only one study that examined outcomes with resumption of hormonal contraception after missed pills; it is unclear whether the results from this study can be extrapolated to patients who miss different amounts of pills or at different times in the cycle [21].

The four studies included in this review provide data about the theoretical concern for an interaction between UPA and hormonal contraception. Since UPA is an emergency contraceptive, offering hormonal contraception is important if ongoing prevention of pregnancy is desired. Patient-centered counseling can include an explanation of the possible risk of interaction and recommendation to delay hormonal contraception to prevent pregnancy, and the importance of using hormonal contraception to prevent pregnancy later in the cycle and in subsequent cycles, along with the recommendation to use a back-up method for seven days after starting the hormonal contraception [4].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors would like to thank Joanna Taliano, MA, MLS, for helping to build the literature search strategy and running the searches.

Funding source:

This project was supported in part by an appointment to the Research Participation Program at the Centers for Disease Control and Prevention administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and the Centers for Disease Control and Prevention.

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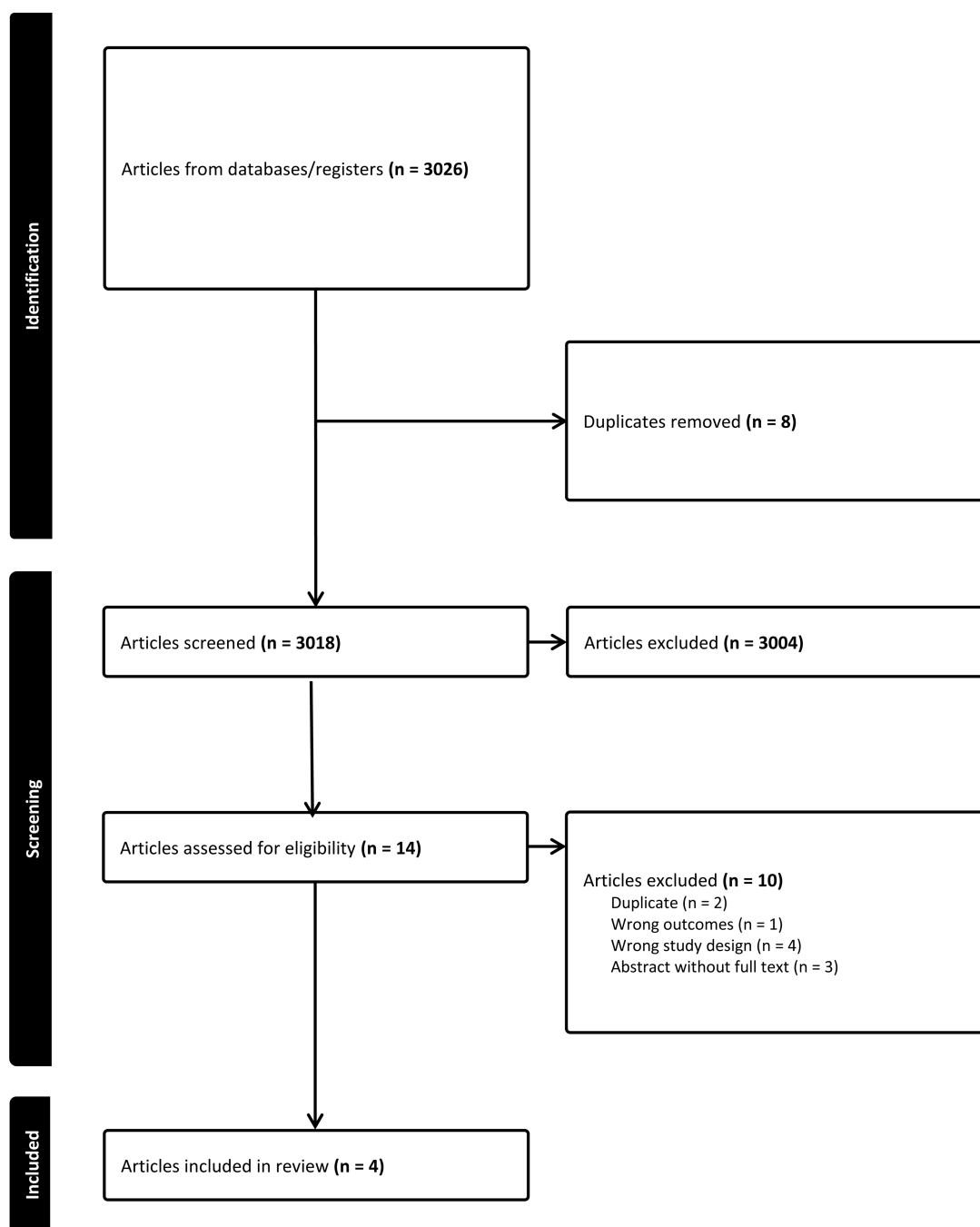


Figure 1.
PRISMA flow chart for articles providing evidence on hormonal contraception after use of
ulipristal acetate for emergency contraception

Table 1.
Summary of evidence on use of hormonal contraception after ulipristal acetate

Authors, Publication Year, Location, and Years of Data Collection	Study Design and Objective	Population	Intervention	Outcomes	Measurement/ Definition of Ovulation	Results
Cameron et al. 2015 [19] Scotland, Sweden, Netherlands	RCT Assess the effect of UPA on the effectiveness of COC to suppress ovulation	n=76 healthy women ages 18–35 with BMI < 30 kg/m ² and regular, normal menstrual cycles or current users of a COC	30 mg UPA (n=39) or placebo (n=37), followed the next day by COCs (30 µg EE / 150 µg LNG) for 21 days	Ovarian activity, including ovulation and quiescence, during 21 days of COC use Vaginal bleeding Adverse events	Ovarian activity as measured by Hoogland score Ovulation: Hoogland 6 (follicular diameter > 13 mm and ruptured, estradiol > 100 pmol/l, and progesterone > 5 nmol/l) Quiescence: Hoogland 1–3	No significant differences overall in ovarian activity between UPA group and placebo group (p=0.95) 13/39 (33%) women in UPA group and 12/37 (32%) women in placebo group ovulated (not significant, p-value not reported) 47 women (62%) in both groups reached quiescence (OR 0.97 [95% CI: 0.39–2.46])
					Active follicle like structure: Hoogland 4 Luteinized unruptured follicle: Hoogland 5	No significant differences in proportions of those ovulating or reaching quiescence between participants who had used COCs in the cycle previous to the study cycle and those who had not (OR 0.97 [95% CI: 0.39–2.46]) 5 women in UPA group and 8 in placebo group experienced unscheduled vaginal bleeding during COC use; duration was similar in both groups (UPA group: median of 1 day, range of 1–6 days; placebo group: median of 3 days, range of 1–9 days) No serious adverse events reported
Brache et al. 2015 [7] Dominican Republic, Netherlands	RCT Assess the effect of UPA on the effectiveness of DSG to suppress ovulation	n=49 healthy women ages 18–35 with BMI < 30 kg/m ² and who had not been using hormonal contraception for at least one complete menstrual cycle	Participants were randomized to 2 of 3 treatment sequences, with washout cycle in between. Treatment sequence 1 (n=17): single dose of 30 mg UPA followed the next day by 75 µg per day DSG for 20 days Treatment sequence 2 (n=16): single dose of 30 mg UPA followed the next day by 20 days of placebo	Occurrence of ovulation either within 5 days or within 21 days after treatment initiation Number of days between treatment initiation and effective inhibition by cervical mucus Hormonal and clinical characteristics of the menstrual cycle under	Ovulation was identified through follicular rupture by TVUS and serum progesterone levels ≥ 10 nmol/l on two consecutive visits	61 (61.6%) adverse events observed after UPA and 38 (38.4%) after placebo Ovulation ≤ day 5: 45% in UPA+DSG group vs 3% in UPA +placebo group ovulated (p=0.0054) Median day to ovulation was Day 4 for UPA+DSG vs Day 8 for UPA +placebo (p<0.0001) Ovulation ≤ day 21: 52% in UPA+DSG group vs 38% in placebo+DSG group ovulated (p=0.6753) Median day to ovulation was Day 4 for

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			Treatment sequence 3 (n=16): one tablet of placebo UPA followed the next day by 75 µg per day DSG for 20 days	treatment PK parameters of UPA and DSG		UPA+DSG vs Day 3 for DSG+placebo (p=0.5485) No differences in cervical mucus scores across the three groups (p=0.421) No differences in Cmax or AUC for UPA in the UPA + DSG cycle compared with UPA alone
Edelman et al. 2018 [20] United States 2015–2017	Non-randomized trial Assess the effect of a COC on the ability of UPA to delay ovulation	n= 36 healthy women, ages 18–35 with BMI < 28 kg/m ² , and regular menstrual cycles	Cycle 1: 30 mg UPA only Cycle 2: washout Cycle 3: 30 mg UPA followed 2 days later by COCs (30 µg EE / 150 µg LNG)	Proportion of women with delayed follicle rupture of 5 days, comparing Cycle 1 with Cycle 3 Adverse events	Follicular rupture was assessed by TVUS and defined as complete disappearance or >50% reduction of the mean size of the leading follicle; If date of follicular rupture could not be determined by TVUS, serum LH and P concentrations were used to adjudicate	Follicle rupture within 5 days: 3% in Cycle 1 27% in Cycle 3 (p=0.008) No serious adverse events reported One participant reported rash with UPA dosing in Cycle 1
Banh et al. 2020 [21] Germany 2017–2018	RCT Assess the effect of delaying restarting COC versus immediately restarting COC after missing three pills and taking UPA	n=49 healthy women ages 18–30 years with BMI < 30 kg/m ² and already using a COC (30 µg EE/ 150 µg LNG)	All participants took COCs on days 1–4 of the study cycle, deliberately missed pills on days 5–7, and took 30 mg UPA on morning of day 8. Arm 1 (n=27; 26 completed and analyzed): restarted COCs on evening of day 8 (immediate restart) Arm 2 (n=27; 23 completed and analyzed): restarted COCs 5 days after UPA on evening of cycle day 13 (delayed start)	Proportion ovulating with theoretical risk of pregnancy (based on ovarian activity) in the 5 days following UPA Occurrence and patterns of ovarian activity (other than ovulation) during baseline and UPA-exposure cycles Adverse events	Ovulation (based on Hoogland score) was considered to be associated with a theoretical risk of pregnancy if there was a postovulatory image on TVUS and progesterone concentrations were >30 nmol/l on one occasion or between 10 and 30 nmol/l on two consecutive occasions through 26 days of COC use	First 5 days after UPA: no ovulations with theoretical risk of pregnancy More than 5 days after UPA: Cycle 1 (immediate restart): 0 ovulations with theoretical risk of pregnancy Cycle 2 (delayed restart): 4 women ovulated all with normal luteal phase progesterone levels (days 15–17) p= 0.042 (compared to none in immediate restart group) Significantly greater risk of ovarian activity without theoretical risk of pregnancy among delayed than immediate restart (OR 7.78 [95% CI: 1.38; 43.95], p=0.02) Information on adverse events was not reported

AUC, area under the curve; BMI, body mass index; CI, confidence interval; Cmax, maximum concentration; COC, combined oral contraceptive; DSG, desogestrel; EE, ethinyl estradiol; LH, luteinizing hormone; LNG, levonorgestrel; OR, odds ratio; P, progesterone; PK, pharmacokinetic; RCT, randomized control trial; TVUS, transvaginal ultrasound; UPA, ulipristal acetate

Table 2.
Risk of bias in studies included in a systematic review on hormonal contraception after ulipristal acetate use for emergency contraception

Table 2a. Randomized clinical trials						
	Randomization process	Deviation from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall risk of bias
Banh 2020 [21]	+	+	+	+	+	+
Brache 2015 [7]	+	+	+	+	+	+
Cameron 2015 [19]	+	+	+	+	+	+

Table 2b. Non-randomized studies

Non-randomized studies					
	Selection bias	Information bias: Exposure	Information bias: Outcome	Confounding	Overall risk of bias
Edelman 2018 [20]	+	+	+	+	+

Key: + Low risk of bias ? Moderate risk of bias - High risk of bias