HHS Public Access

Author manuscript

Contraception. Author manuscript; available in PMC 2019 May 13.

Published in final edited form as:

Contraception. 2016 December ; 94(6): 605–611. doi:10.1016/j.contraception.2016.05.002.

Safety and effectiveness data for emergency contraceptive pills among women with obesity: a systematic review☆,☆☆

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Abstract

Objective: This study aims to determine whether emergency contraceptive pills (ECPs) are less safe and effective for women with obesity compared with those without obesity.

Study design: We searched PubMed for articles through November 2015 regarding the safety and effectiveness of ECPs [ulipristal acetate (UPA), levonorgestrel (LNG) and combined estrogen and progestin] among obese users. We assessed study quality using the United States Preventive Services Task Force evidence grading system.

Results: We identified four pooled secondary analyses (quality: poor to fair), two of which examined UPA and three examined LNG formulations. Three analyses pooled overlapping data from a total of three primary studies and demonstrated significant associations between obesity and risk of pregnancy after ECP use. One analysis reported a 4-fold increased risk of pregnancy among women with obesity (BMI≥30 kg/m^2) compared with women within normal/underweight categories (BMI<25 kg/m^2) after use of LNG ECPs [odds ratio (OR)4.4; 95% confidence interval (CI) 2.0–9.4]. Further analysis of the same LNG data found that, at an approximate weight of 80 kg, the rate of pregnancy rose above 6%, which is the estimated pregnancy probability without contraception; at weights less than 75 kg, the rate of pregnancy was less than 2%. Two analyses examining UPA suggested an approximate 2-fold increased risk of pregnancy among women with obesity compared with either normal/underweight women or nonobese (BMI<30 kg/m^2) women (OR 2.6; 95% CI 0.9–7.0 and OR 2.1; 95% CI 1.0–4.3, respectively), but CIs were wide. Finally, the fourth secondary analysis pooled data from three separate randomized controlled trials on LNG ECPs and found no increase in pregnancy risk with increasing weight or BMI and found no consistent association between pregnancy and both factors when adjusted for other covariates.

Conclusion: While data are limited and poor to fair quality, findings suggest that women with obesity experience an increased risk of pregnancy after use of LNG ECP compared with those normal/underweight. Women with obesity may also experience an increased risk of pregnancy compared with women without obesity after use of UPA ECP, though differences did not reach statistical significance. Providers should counsel all women at risk for unintended pregnancy, including those with obesity, about the effectiveness of the full range of emergency contraception

☆Financial Disclosures: None.

☆☆Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

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options in order for them to understand their options, to receive advanced supplies of emergency contraception as needed and to understand how to access an emergency copper intrauterine device if desired.

Keywords

Obesity; Weight; BMI; Emergency contraception

1. Introduction

While data demonstrate pharmacokinetic differences between women with obesity and those without using certain contraceptive methods [1], limited clinical data do not show a strong association between contraceptive failure and obesity [2–4]. There have been recent debates over new evidence that emergency contraceptive pill (ECP) failure may be associated with obesity. For women who do not consistently use a reliable form of contraception or who experience a contraceptive malfunction, emergency contraception may provide contraception after unprotected intercourse in the form of levonorgestrel (LNG) and combined oral contraceptive pills, ulipristal acetate (UPA) pills or copper-bearing intrauterine devices (Cu-IUDs). Compared with women without obesity, whether those with obesity are at differential risk for unintended pregnancy is unclear; however, they are more likely to use no contraceptive method or the least effective methods, which may make this patient population in greater need of emergency contraception [5–7].

The World Health Organization (WHO) Medical Eligibility Criteria for Contraceptive Use, 2009 (MEC) and the US Medical Eligibility Criteria for Contraceptive Use, 2010 provide recommendations for the safe use of the following contraceptives among women with obesity: combined hormonal contraceptives, combined injectable contraceptives, progestin-only pills, DMPA, NET-EN, LNG and ETG implants, as well as the Cu-IUD and LNG-IUD [8,9]. The MEC also provides recommendations for LNG and combined oral contraceptive pill (Yuzpe method) formulations as ECPs among women with several medical conditions or personal characteristics. The MEC previously has not included recommendations for UPA and has not included recommendations for ECP use among women with obesity. New evidence has been published suggesting that the effectiveness of ECPs may be different among women who have obesity compared with women who are not obese.

To our knowledge, no previous systematic review has been conducted for the safety and effectiveness of ECPs among women with obesity. Our current systematic review question asks, “Among women who use ECPs (by formulation), are women with obesity at increased risk for pregnancy or adverse events compared with women without obesity using the same formulation?”

2. Materials and methods

We conducted this systematic review according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [10]. In order to answer our question, we searched PubMed from database inception to November 2015, using the following search strategy: (obesity or weight or BMI) AND (“emergency contraception” OR “morning after

pill" OR "emergency hormonal contraception" OR "Plan B" OR "post coital contraception" OR "Yuzpe" OR "levonorgestrel" OR "ulipristal acetate").

We included primary research articles in all languages that identified the outcomes of pregnancy, ovulation or steroid hormone levels or serious adverse medical events among women with obesity using either LNG or UPA ECPs or combined oral contraceptives for the purpose of emergency contraception. We also searched review articles for any pertinent references.

The two coauthors then independently graded the articles included in this review according to the United States Preventive Services Task Force evidence grading system[11]. We assessed quality factors including exposure assessment (methods for height and weight assessment), outcome assessment (pregnancy), adequate randomization and blinding, assessment of potential confounders, loss to follow-up and sample size and power. For secondary data analyses, we assessed quality based on these factors in the original studies as well as how the secondary data analysis was conducted. Due to the heterogeneity of study designs and overlapping data, we did not compute summary measures.

3. Results

This search identified 605 articles of which four articles met our inclusion criteria [12–15]. All four articles reported on secondary analyses that pooled data from six clinical trials. Three analyses included study participants from the United States, United Kingdom and Ireland using data from three overlapping studies, and the fourth analysis included study participants from over 14 countries using data from three additional studies (Table 1). One analysis pooled data from two randomized controlled trials (RCTs) that examined risk of pregnancy for both LNG and UPA formulations of emergency contraceptive (EC) [12]. A second analysis pooled data from the same two RCTs and examined the LNG data to further assess the relationships between pregnancy and weight or BMI [14]. The third analysis pooled data from a clinical trial of UPA in addition to the same data from the UPA arm of one of the RCTs included in the first two pooled analyses [13]. A fourth analysis pooled data from three RCTs and examined pregnancy risk among LNG ECP users [15]. We did not identify any studies that examined risk of pregnancy by weight or BMI for combined ECPs. We also did not identify any studies that reported on adverse events of ECPs by weight or BMI.

In the first pooled analysis by Glasier et al. [12], which included two studies of women randomized to receive either LNG or UPA formulations of ECPs, BMI was identified as the risk factor with the most highly significant impact on the risk of pregnancy after ECP use [16,17]. Further unprotected intercourse within the same cycle and conception probabilities based on the timing of unprotected intercourse within a cycle were also significant risk factors for EC failure. Both individual studies had adequate randomization and concealment and used a primary efficacy study population for analyses, meaning that women had to receive EC and their pregnancy status at follow-up was known, with exclusions for pregnancies determined to have occurred before EC was taken or long after EC was taken. BMI was categorized as normal/underweight (BMI<25 kg/m^2), overweight (BMI= 25–29.9

kg/m^2) and obese (BMI≥30 kg/m^2). When compared with normal/underweight women, the risk of pregnancy for obese women following either EC treatment was more than three times as great [odds ratio (OR) 3.60; 95% confidence interval (CI), 1.96–6.53; p<.0001]. When comparing obese women to overweight women, however, the OR for risk of pregnancy was attenuated (OR 1.53; 95% CI, 0.75–2.95). While the point estimate for the risk of pregnancy among obese women who took UPA was higher(2.6%; 95% CI, 1.2–5.6) than the risk among normal/underweight women (1.1%; 95% CI, 0.6–1.9), the difference was not significant (OR 2.62; 95% CI, 0.89–7.00). Among those who took LNG, however, obese women had a greater risk of pregnancy than that of normal/underweight women (5.8% versus 1.3%, respectively, OR 4.41; 95% CI,2.05–9.44; p=.0002). Weight (kg) was also found to be a significant risk factor for pregnancy (p<.0001); the specific weight categories that were analyzed were not reported.

Kapp et al. [14] took the same pooled data from Glasier et al. [12] and further examined the relationship between pregnancy and weight or BMI among women in the LNG arms of the two studies, using several statistical approaches. The distribution of both weight and BMI was significantly different between the women who became pregnant and those who did not. There was a significant increasing trend between pregnancy rates and increasing weight and BMI categories. In multivariable models, adjusted for further unprotected intercourse, conception probability and study effect, the relationship between pregnancy rate and weight was significant (p=.0003). A cubic spline model was used to determine at approximately what weight or BMI the pregnancy rate rose to 6% — the expected pregnancy rate for a women not using contraception — and was found to be around 80 kg. A steep incline in pregnancy rates was observed between 70 and 80 kg, as pregnancy rates rose from 2% to near 6%. Women weighing b75 kg with various BMI levels were determined to still have a low pregnancy rate of 2%, and BMI overall did not provide information over and above body weight.

The third analysis [13] pooled data from two Phase III trials (one of which was also included in the Glasier et al.[12] UPA pooled analysis) to compare proportions of women taking UPA who became pregnant across several demographic and medical characteristics [13,17,18]. The only variables found to have a significant impact on risk of pregnancy were subsequent acts of unprotected intercourse and BMI or weight. One trial included a single arm of women taking UPA and the other trial adequately randomized and blinded women to either LNG or UPA treatment. Primary efficacy populations of women taking UPA from both studies were used for the analysis, thus excluding those with preexisting pregnancies or pregnancies that occurred from further unprotected acts and women lost to follow-up. BMI was categorized into nonobese with BMI<30 kg/m^2 and obese with BMI≥30 kg/m^2. Obese women had a 2-fold increase in the risk of pregnancy after taking UPA compared with nonobese women (OR 2.1; 95% CI, 1.0–4.3; p=.04) after UPA use. A similar OR was found when women were stratified by weight categories of >85 kg and ≤85 kg (OR2.2; 95% CI, 1.1–4.6; p=.03).

Finally, the most recently published analysis [15] pooled data from three multinational RCTs and examined the risk of pregnancy among women taking LNG ECPs within 72 h after a single act of unprotected intercourse [15,19–21]. These three individual RCTs had adequate

randomization and concealment and also used a primary efficacy study population for analyses, meaning that women had to receive EC and their pregnancy status at follow-up was known, with exclusions for pregnancies that occurred before EC was taken or long after EC was taken. Authors calculated crude pregnancy risk by BMI (kg/m^2) and body weight (kg) and did not find significant increases in crude pregnancy risk as factor category increased; BMI ranged from 13.84 to 51.2 kg/m^2 and body weight ranged from 30 to 130 kg. Logistic regression was performed with pregnancy as the outcome and included both BMI and body weight as continuous variables, interaction terms, both cubic and quadratic BMI and body weight terms and other covariates (i.e. continent, treatment delay, expected probability of pregnancy and age). At a given BMI unit, body weight was not associated with increasing odds of pregnancy. At a given body weight, point estimates for OR generally increased with increasing BMI; however, CIs grew wide and overlapped.

4. Discussion

We identified four secondary data analyses that examined the effects of obesity on effectiveness of ECPs; two examined UPA and three included LNG formulations. Obese women using LNG as EC in two analyses using the same primary data from two trials had a 4.4-fold increased risk of pregnancy compared with normal/underweight women [12] and rates of pregnancy increased dramatically between 75 kg and 80 kg [14]. A third analysis examining risk of pregnancy among women using LNG ECPs found no significant increases in risk with increasing body weight or BMI [15]. For UPA, two analyses reported an approximate 2-fold increased risk of pregnancy among obese women, though CIs were wide [12,13]. The magnitude of effect was slightly lower in the second study (2.1 [13] and 2.6 [12], respectively) and of borderline insignificance, which may have been due to differences in sample size between the two studies or due to the use of different comparison groups — obese compared with normal/underweight women [12] and obese compared with nonobese women [13]. Pregnancy rates were 1.7% and 1.9% among all women in these two analyses.

According to estimates by Trussell et al. [22], the overall expected risk of pregnancy after unprotected intercourse without EC treatment is 5.6%. For obese women who took LNG, the observed risk in one analysis was 5.8%, suggesting that LNG may not be effective for obese women [12]. This was further examined in the Kapp analysis where the risk of pregnancy did increase with increasing weight and BMI categories and was found to be around 6% at approximately 80 kg [14]. This increased risk of pregnancy was not found in a third analysis that included data from three other RCTs; crude pregnancy risk in this analysis ranged from 0.6% to 1.9% as BMIs ranged from 13.8 to 51.2 kg/m^2 [15]. We assessed this analysis as poor quality given the inclusion of both body weight and BMI in the model, as well as the small sample size divided into several BMI categories, leading to wide CIs and insignificant associations between BMI or weight and pregnancies. The study population included a much broader group of women from 14 countries and with a lower distribution of BMI than the study population for the Glasier and Kapp analyses. In addition, the modeling strategies used by the different analyses precluded direct comparisons of the results across studies. In contrast, the observed risk of pregnancy among obese women taking UPA was 2.6% or 3.1% in the two analyses, less than the expected risk of pregnancy without taking EC [12,13].

No data on adverse events in relation to weight or BMI were identified. One of the pooled analyses reported on adverse events in the overall study population; of the four serious adverse events reported (seizure, urinary tract infection, contact lens-related corneal ulcer and case of dizziness), none were common complications or comorbidities of obesity such as venous thromboembolism or cardiovascular events and only dizziness was considered possibly related to UPA intake [13].

There are several limitations to this body of evidence, and the four analyses were considered to be of poor to fair quality. These pooled analyses were all secondary data analyses and none of the studies were designed to assess the effect of BMI or weight on EC effectiveness. One consequence of this was that both weight and height were measured by self-report in some of the studies [12,14,17] or methods for assessing weight and height were not clearly reported [13,15]. Women tend to underestimate weight and overestimate height [23], which would have underestimated the effects of BMI on ECP effectiveness for the studies in this review. Given that these analyses all included RCTs evaluating effectiveness, samples included efficacy populations that excluded loss to follow-up, preexisting pregnancies and either excluded women with multiple unprotected acts of intercourse or adjusted for this in the analyses. Three of four analyses included overlapping data. While three individual studies examined UPA, one of these studies was included in both pooled analyses and thus calculating pooled estimates for UPA from all three studies was not possible for this review [17]. Two analyses used the same LNG data from two trials [12,14]; while these data are overrepresented in this review, the two different approaches for each analysis together provide useful information to assess the effect of BMI on ECP effectiveness as well as information assessing the effect of increasing weight on LNG effectiveness. All individual studies included in these analyses had small numbers of EC failures and had small numbers of overweight or obese women, which may have resulted in a lack of power to observe a statistically significant effect of obesity on UPA effectiveness in one analysis [12], LNG in another analysis [15] and an overall lack of precision in the estimates.

While data are limited and of poor to fair quality, one study found obese women experience an increased risk of pregnancy of about 4-fold after use of LNG ECP compared with normal weight women and the risk is comparable to that for a women not using any contraception at approximately 80 kg. While one analysis did not find an increased risk of pregnancy among obese women using LNG ECPs, the adjusted model including both body weight and BMI could not be similarly interpreted as the other secondary analyses for LNG ECPs. A recent pharmacokinetic study demonstrates a 50% lower maximum serum LNG concentration among women with BMI ≥ 30 kg/m^2 compared with

BMI<25 kg/m^2 taking 1.5 mg LNG and similar concentrations between obese women taking 3 mg LNG compared with obese women taking 1.5 mg LNG [24]. While this supports biological plausibility of increased EC failures among obese women taking LNG ECPs, primary clinical data are needed. Obese women who use UPA ECP may also experience a two-fold increased risk of pregnancy compared with normal/underweight or nonobese women; however, the differences in these two studies did not reach statistical significance, and again primary clinical data are needed to further investigate an association between obesity and UPA failures. While there are no identified safety concerns associated with ECP

use among women with obesity, pregnancy among obese women may increase risk for some pregnancy complications [25] indicating a need for EC should an obese women be exposed to pregnancy risk after unprotected intercourse or contraceptive failure.

It should be noted that pregnancy rates observed in these ECP studies are all much greater than the 0.14% pregnancy rate following copper IUD insertion as EC [26]. While studies have not examined whether the efficacy of copper IUD for EC is different for obese women, this method of long-acting reversible contraception is safe for women with obesity [9,27,28]. Counseling about the effectiveness of the full range of emergency contraception options is imperative for all women at risk for unintended pregnancy, including those with obesity, in order for them to understand their options, to receive advanced supplies of emergency contraception and to understand how to access an emergency copper IUD if desired.

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Table 1

Evidence for safety and effectiveness of ECPs among obese women

Author, Year, Location, Funding Source	Study Design	Population, Intervention	BMI/Weight Categories	Outcome	Results	Strengths	Weaknesses	Grade
Glasieretal. 2011 [12] UK, Ireland and United States Source of funding not reported; original studies funded by HRA Pharma and Federal funds from the National Institute of Child Health and Human Development, National Institutes of Health, Clinical Contraceptive Trials Network under Contract Numbers N01-HD-6–3261 and N01-HD-9–3297 through 3303 and, in part, by National Institutes of Health General Clinic Research Center Grants MO1RR000056 at the University of Pittsburgh and M01RR00096 at New York University.	Secondary analysis using data from metaanalysis of 2 RCTs [16,17]	*N*=3445 women, who received EC and had known pregnancy status after EC treatment RCT 1 [16]: 1672 women presenting for EC within 72 h of UPI randomized to 2dosesof0.75mgLNG 12 h apart or single-dose 50 mg CDB-2914 (nonmicronized formulation of UPA), double-blinded, noninferiority trial RCT 2 [17]: 2221 women presenting for EC within 120 h of UPI randomized to single dose of 30 mg UPA or 1.5 mg LNG, single-blinded (participants masked), noninferiority trial	Obese: BMI ≥ 30 kg/m^2 (*n*=469) Overweight: BMI 25–29.9 kg/m^2 (*n*=744) Normal/underweight: BMI<25 kg/m^2 (*n*=2232) Also examined the association of weight with pregnancy risk	Risk of pregnancy (as measured by urine pregnancy test 1 week after time of expected menses after EC treatment)	60 pregnancies (1.7%) Any EC (LNG or UPA): OR 3.60; 95% CI, 1.96–6.53 for obese women compared with normal/ underweight women LNG only: OR 4.41; 95% CI, 2.05–9.44 for obese women compared with normal/ underweight women UPA only: OR 2.62; 95% CI 0.89–7.00 for obese women compared with normal/ underweight women Similar findings with weight alone and risk of pregnancy	Data from RCTs with large sample sizes, adequate randomization, one double-blinded and one single-blinded Trend of increasing pregnancy risk as BMI increases is seen	Small number of pregnancies, which decreased power, especially in UPA group Small number of women in obese group BMI data were self-reported by participants in one study [17]	I, Fair, Direct
Kappetal., 2015 [14] UK, Ireland and United States HRA Pharma; original studies funded as above	Secondary analysis using LNG data from metaanalysis of 2 RCTs [16,17]	*N*= 1731 women, who received LNG EC and had known pregnancy status after EC treatment RCT 1 [16]: 773 women presenting for EC within 72 h of UPI randomized to 2 doses of 0.75 mg LNG 12 h apart, double-blinded, noninferiority trial comparing LNG with UPA RCT 2 [17]: 958 women presenting for EC within 120 h of UPI randomized to single	Weight: <55kg 55–65 kg 65–75 kg 75–85 kg ≥85kg BMI: <20 20–25 25–30 30–35 ≥35	Comparison of body weight and BMI according to pregnancy status (as measured by urine pregnancy test 1 week after time of expected	The weight and BMI distributions among women found to be pregnant compared with not pregnant was significantly different Increasing trend was significant for differences in estimated	Data from RCTs with large sample sizes, adequate randomization, one double-blinded and one single-blinded	Small number of pregnancies, which decreased power Small number of women in obese group BMI data were self-reported by participants in one study [17]	I, Fair, Direct

Author, Year, Location, Funding Source	Study Design	Population, Intervention	BMI/Weight Categories	Outcome	Results	Strengths	Weaknesses	Grade
		dose of 1.5 mg LNG, single-blinded (participants masked), noninferiority trial comparing LNG with UPA		menses after EC treatment) Relationship between pregnancy and weight or BMI Effect ofweight or BMI on pregnancy rates using logistic regression and cubic spline logistic regression	pregnancy rates by weight categories and BMI categories Multivariate model examining pregnancy risk and weight while adjusting for further UPI, conception probability and study effect was significant (p=. 0003) Cubic spline model demonstrates predicted probability of pregnancy increases from 2% at 70 kg to 6% at 80 kg, which is similar to estimated probability without contraception Women with weight <75 kg of various BMI values have pregnancy rates below 2%			
Gemzell-Danielsson, et al., 2015 [15] Multinational Gedoen Richter; original studies funded by UNDP/ UNFPA/WHO/ World Bank Special Program of Research, Development and Research Training in Human Reproduction	Pooled analysis using LNGdata from 3 RCTs	*N*=5863 women who received LNG for EC treatment within 72 h of single act UPI and had known pregnancy status after EC treatment RCT 1 [19]: 1001 women in 14 countries randomized to two doses of 0.75 mg LNG within 72 h of UPI RCT 2 [20]: 1379 women in 10 countries randomized to single-dose 1.5 mg LNG and 1377 women randomized to two doses 0.75 mg LNG RCT 3 [21]: 1512 women from multiple centers in Nigeria randomized to single-dose LNG and 1510 women randomized to two doses 0.75 mg LNG	BMI: 13.84–18.0 (*n*=406) 18.03–25.0 (*n*=4158) 25.01–29.9 (*n*= 1039) 30–34.9 (*n*=202) 35.0–51.2 (*n*=54) Weight: 30–54 kg (*n*=2008) 55–64 kg (*n*=2168) 65–74 kg (*n*= 1180) 75–84 kg (*n*=399) 85–130 kg (*n*= 104) For logistic regression, BMI and weight were represented in same model as continuous variables	Pregnancy (as measured by urine pregnancy test 1 week after time of expected menses after EC treatment if no normal menses in two trials; pregnancy test or ultrasound at 1 week if no normal menses in third trial)	56 pregnancies (1.0%) OR (95% CI) for pregnancy at BMI and body weight (BW) compared with BMI 22.5 and BW 60 kg: BMI/BW 18/60: 2.98(0.39–22.6) 25/50: 5.17(1.03–25.9) 25/70: 0.5 (0.19–1.31) 30/55: 13.7 (2.14, 87.2) 30/70: 1.32(0.23–7.41)	Data from 3 double-blinded RCTs with large sample sizes, adequate randomization, height and weight measured in at least one study and 2 studies with multinational populations For logistic regression, *n*=51 (3 pregnant) excluded for missing data	Small number of pregnancies, which decreased power Small number of obese women Special subgroup of 60 women from Nigerian study exceptionally short for their weight represented 1% of study sample, but	I, Poor, Direct

Author, Year, Location, Funding Source	Study Design	Population, Intervention	BMI/Weight Categories	Outcome	Results	Strengths	Weaknesses	Grade
					40/70: 12.5 (0.12–1339)	Adjusted model included continent, treatment delay, expected probability of pregnancy and age	6.8% of pregnancies Only one model reported which included both BMI and weight	
Moreau and Trussell, 2012 [13] United States, UK and Ireland HRA Pharma, Eunice Kennedy Shriver National Institute of Child Health and Human Development grant for Infrastructure for Population Research at Princeton University	Pooled analysis of two Phase III trials [17,18]	*N*=2173 women who received UPA for EC treatment and had known pregnancy status after treatment Trial 1 [18]: Single-arm open label study of 1241 women presenting for EC 48–120 h after UPI [18] given single-dose 30 mg UPA Trial 2 [17]:: RCT of 2221 women presenting for EC within 120 h of UPI randomized to single dose of30mgUPAor 1.5 mg LNG, single-blinded (participants masked)	Obese: BMI>30 kg/m^2 (*n*=351) Nonobese: BMI ≤ 30 (*n*=1830) Weight>85kg (*n*=298) Weight≤ 85 kg (*n*=1883)	Risk of pregnancy (as measured by urine pregnancy test 1 week after time of expected menses after EC treatment)	41 pregnancies (1.9%) OR 2.1; 95% CI, 1.0–4.3; p=.04 for obese women compared with nonobese women OR 2.2; 95% CI, 1.1–4.6; p=.03 for women weighing > 85 kg compared with women weighing ≤85 kg	UPA given up to 120 h from UPI Large study samples Adequate randomization of the RCT, single-blinded	Small number of pregnancies BMI not further categorized beyond obese and nonobese BMI data were self-reported by participants in at least one study	I, Fair, Direct

UPI: unprotected intercourse.

LNG: levonorgestrel.

EC: emergency contraception

UPA: ulipristal acetate.