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Review

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 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

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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