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# Body mass index does not affect the efficacy or bleeding profile during use of an ultra-low-dose combined oral contraceptive☆,☆☆

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## Abstract

**Objectives:** Safe and effective contraceptive options for obese women are becoming more important due to the obesity epidemic within the United States. This study evaluated the impact of body mass index (BMI) on efficacy, safety and bleeding patterns during use of an ultra-low-dose combined oral contraceptive (COC).

**Study Design:** Data are from a Phase 3 clinical efficacy and safety study of an ultra-low-dose COC containing 1.0-mg norethindrone acetate and 10-mcg ethinyl estradiol. Pearl Indices, adverse events and bleeding profile were calculated for BMI ranges of <25, 25–30 and >30 kg/m$^2$.

**Results:** Of the 1581 participants included in the analysis, 28.3% were overweight, and 18.0% were obese. For women aged 18–45 years, the Pearl Indices were 2.49, 2.32 and 1.89 for women with a BMI <25, 25–30 and >30 kg/m$^2$, respectively. The ultra-low dose of ethinyl estradiol did not impact scheduled bleeding or intensity of bleeding, but we observed a slight decline in amenorrhea and slight increase in unscheduled bleeding in obese women compared with other BMI categories.

**Conclusions:** Our analysis of an ultra-low-dose COC did not find clinically important differences in contraceptive failure rates, adverse events or bleeding profile with increasing BMI.

**Implications:** Our analysis of an ultra-low ethinyl estradiol dose COC did not find clinically important differences in contraceptive failure rates, adverse events or bleeding profile with increasing BMI. An ultra-low-dose COC provides another safe and effective contraceptive option for obese women.



*Keywords:* Oral contraceptive; Obesity; Weight; Ethinyl estradiol; Norethindrone acetate

## 1. Introduction

Sixty-six percent of adult women aged 20 years or older in the United States are classified as overweight, with 36.5% classified as obese [1]. Assisting women in making the selection of a safe and effective contraceptive option can be challenging for healthcare providers. As the incidence of obesity increases, understanding the efficacy and potential risks of combined oral contraceptives (COCs) with increasing BMI is extremely important. Obese women are almost twofold likely as normal-weight women to experience a venous thromboembolism, and obese women using COCs are more likely to experience a venous thromboembolism than obese women who are not users [2,3]. Pregnancy and delivery, however, represent a greater risk of thromboembolism than use of COC [4,5]. Therefore, preventing unplanned pregnancy in obese females is very important due to the associated pregnancy comorbidities and complications [5–7].

The estrogen component of COCs is specifically associated with cerebrovascular complications, thromboembolic incidents and myocardial infarction [8]. The risk of thrombotic stroke and myocardial infarction in women

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increases with age and is important in the consideration of COC [9]. There was a small difference in the risk of stroke and myocardial infarction between COC users of 30–40-mcg and 20-mcg ethinyl estradiol (EE), but BMI was not reported [9]. Estrogen doses have decreased in modern COCs without affecting overall efficacy [10], their efficacy is primarily controlled by the progestin component and the estrogen component primarily controls irregular (unscheduled) endometrial bleeding. Further improvements in efficacy and bleeding control of low-dose estrogen COCs have been demonstrated by decreasing the hormone-free interval [11]. There is one ultra-low-dose COC available that contains 10-mcg EE and has a 24/2/2 dosing regimen with 24 days of active pills, followed by 2 days 10-mcg EE, and another 2 days of inactive (hormone-free) ferrous fumarate tablets (Lo Loestrin® Fe, Actavis Pharma, Inc., Parsippany, NJ, USA).

We conducted a post-hoc analysis of the previously published Phase 3 study of the ultra-low-dose COC [12] to examine efficacy, safety and the bleeding profile by body mass index (BMI) category [normal weight (BMI, ≤24.9), overweight (BMI, 25–29.9) and obese (BMI, >30)]. Previously published analyses evaluating the impact of increasing BMI on COCs have focused on COCs with higher estrogen doses (≥20 mcg) and have primarily examined the effects on efficacy.

## 2. Materials and methods

A complete description of the Phase 3, open-label, uncontrolled, multicenter study of an ultra-low-dose COC regimen has been previously reported [12]. The study population included heterosexually active women aged 18–45 years with a BMI (calculated as weight (kg)/[height (m)]$^2$) ≤35, a negative serum pregnancy test and a willingness to use the study drug as the only method of contraception. Serum and urine pregnancy tests were performed at Visits 1 and 8; urine pregnancy tests were performed at interim visits. Pregnancy tests also were performed if a patient missed a scheduled bleed. The current post-hoc analysis of efficacy, safety and bleeding profile was performed based on BMI (range, 15.7–38.3) of <25 kg/m$^2$ (normal-weight), 25–29 kg/m$^2$ (overweight) and >30 kg/m$^2$ (obese) in order to evaluate any changes related to body weight and height. Women with BMI >35 were excluded, although five women with BMI >35 were inadvertently enrolled and included in our analysis. In the original efficacy trial [12], women with BMI >35 were excluded to avoid biasing the study group with women who might have greater predisposition toward anovulatory menstrual cycles with an inherent lower chance of conceiving and potentially overestimating the contraceptive efficacy of the studied COC.

The treatment regimen for each 28-day pill cycle was one oral tablet containing 1.0-mg norethindrone acetate and 10-mcg EE daily for 24 days followed by one oral 10-mcg EE tablet daily for 2 days followed by one ferrous fumarate tablet on each of the final 2 days. Number of reported pills taken by each patient was determined from returned blister packs.

Bleeding data were determined by patient diary. A scheduled bleeding episode was defined as the first bleeding episode starting 4 days before the last day of active drug intake during a treatment cycle and 3 days after beginning treatment in the next treatment cycle [12]. All other bleeding (spotting) days and episodes were counted as unscheduled bleeding or spotting days and episodes. Presence and intensity of expected, scheduled withdrawal bleeding were scored in a diary as: 0=*none*, 1=*lighter than normal*, 2=*normal* or 3=*heavier than usual*. The intensity of the unexpected, unscheduled bleeding (spotting) episode was defined as the maximum intensity of the bleeding (spotting) days, in which 1=*light*, 2=*normal* and 3=*heavy*. Amenorrhea was defined as complete absence of all bleeding or spotting (scheduled and unscheduled) during a cycle. Further details may be found in the supplementary appendix.

## 3. Results

There were 1581 participants in the modified intent-to-treat population, 18–45 years of age, included in the analysis. Of these, 53.7% were normal-weight, 28.3% overweight and 18.0% obese. Baseline demographics and patient characteristics (Table 1) were similar between groups with respect to age and smoking status. Although the number of obese women enrolled was lower than the number of normal-weight or overweight women, we observed a trend toward more Black women and new COC users in the obese group. Dropout rate (40–43%) was similar across BMI groups, as was the percentage of women who completed two cycles (78–80%) in the larger treated population with BMI data ($N$=1657).

Examination of returned blister packs indicated that the average number of reported pills taken per cycle out of a possible 28, of which two were considered placebo, was similar between the BMI categories. Women with BMI <25 kg/m$^2$ ($n$=849) and 25–30 kg/m$^2$ ($n$=448) took an average of 26.2 pills per cycle, while women with BMI >30 kg/m$^2$ ($n$=284) took an average of 25.8 pills per cycle.

A total of 28 pregnancies occurred in 12,312 at-risk cycles in women 18–35 years old and in 15,596 at-risk cycles in women 18–45 years old (Table 2). Based on the Pearl Index, women with higher BMI did not have decreased efficacy. For women aged 18–35 years, the Pearl Indices were 3.06, 3.04 and 2.5 for women with a BMI <25, 25–30 and >30 kg/m$^2$, respectively. For women aged 18–45 years, the Pearl Indices were 2.49, 2.32 and 1.89 for women with a BMI <25, 25–30 and >30 kg/m$^2$, respectively. No pregnancies occurred in 3759 at-risk cycles in women 36–45 years at time of enrollment.

The percentage of participants with scheduled bleeding decreased during the study. Scheduled bleeding was highest