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Original research article

Effect of obesity on the effectiveness of hormonal contraceptives: an individual participant data meta-analysis

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Abstract

Objective: The objective of this investigation was to assess the potential effect of obesity on the effectiveness of hormonal contraceptives (HCs).
Study Design: A meta-analysis was conducted using individual participant data directly from the Phase 3 clinical trials of combination oral contraceptives (COCs) rather than extracting summary data from literature. Trials selected were reviewed by the US Food and Drug Administration (FDA) between 2000 and 2012, conducted in North America, had more than six 28-day cycle equivalents of exposure, and had readily retrievable participant-level data. Contraceptive effectiveness was measured by the Pearl Index (PI: the number of pregnancies per 100 woman-years) in women aged 18–35 at risk of unintended pregnancy. The incidence rate ratio (IRR), a ratio of PIs for obese women (defined as body mass index [BMI] ≥ 30 kg/m^2) compared to non-obese women (BMI < 30 kg/m^2) was calculated. A Cox proportional-hazard regression model with fixed and random-effects were used to estimate hazard ratios (HRs) for unintended pregnancy in obese women compared to non-obese women.
Results: Seven clinical trials with COCs (N=14,024: 2707 obese and 11,317 non-obese women) met the inclusion criteria for the meta-analysis. The PI for each trial varied: 2.05–5.08 for obese and 1.84–3.80 for non-obese women. The pooled PI estimated using direct weighted average method was 3.14 (95% CI: 2.33–4.22) for obese and 2.53 (95% CI: 1.88–3.41) for non-obese women. The pooled IRRs estimated using direct weighted average and Mantel–Haenszel adjustment methods were comparable: 1.37 (95% CI: 1.02–1.84) and 1.43 (95% CI: 1.07–1.92), respectively. The overall HR of 1.44 (95% CI: 1.06–1.95; p=.018) in the meta-analysis suggested a 44% higher pregnancy rate during COC use for obese women after adjusting for age and race.
Implications Statement: Obesity may increase the risk of unintended pregnancy in women using COCs; more data on obese women from ongoing and future Phase 3 clinical trials are necessary to allow further evaluation of this topic.
Conclusions: Results of this meta-analysis suggest that obese women may have a higher pregnancy rate during COC use compared to non-obese women. Future analysis should assess differences in pharmacodynamics or compliance that could potentially account for the observed difference in unintended pregnancy rates.
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Keywords: Obesity; Body mass index; Contraceptive effectiveness; Meta-analysis; Hazard ratio

1. Introduction

In 2006–2008, 43 million women were at risk of unintended pregnancy (fertile and sexually active) among the 62 million US women at their reproductive ages (15–44 years) [1]. Nearly 90% of those at-risk women used at least one contraceptive method.[1] The leading method among reversible contraceptives is use of combination oral contraceptives (COCs) [2,3]. The proportion of unintended pregnancies has remained unchanged at about 50% since 2001, costing over $11 billion annually [4,5].

According to data from 2009–2010, over 30% of women in the US aged 20–39 were obese (defined as body mass index [BMI] ≥ 30 kg/m^2) [6]. Despite this high prevalence,

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obese women have generally been excluded from clinical trials of hormonal contraceptives (HCs), and the effect of obesity on the effectiveness of HCs remains unclear. Increased body size and metabolic changes may lead to decreased HC effectiveness through the impact on bioavailability, hepatic or renal clearance and volume of distribution of contraceptive hormones [7]. However, one study reported that there were no significant differences in volume of HC distribution between the BMI groups [8]. The influence of altered pharmacokinetics (PK) on pharmacodynamics (PD) is unclear. In particular, for contraceptive hormones in COCs, high inter- and intra-individual variability is observed with regard to the impact of obesity on PK [9]. The objective of this investigation was to better understand the potential impact of obesity on the effectiveness of COCs.

A recent PK study with a COC found substantial and comparable ovarian suppression, a PD outcome commonly evaluated for HCs, among compliant users (15 obese [BMI: 30.0–39.9], 15 normal-weight [BMI: 19.0–24.9]) regardless of BMI category [10]. Although area under the concentration curve and maximum concentration of ethinyl estradiol (EE) were significantly decreased, no difference was observed in levonorgestrel (LNG) levels. Obese and normal-weight women had similar follicular development, endogenous EE levels, Hoogland scores and bleeding patterns. The authors concluded that likelihood of ovulation did not differ in the two groups.

Clinical trials have shown that overweight has decreased effectiveness in two extended release non-COC regimens, the patch, norelgestromin (NGMN)/EE transdermal delivery system, and the implant, etonogestrel. The current product labels of these two products state that there is a potential decrease in their effectiveness in women with higher body weight (BW), above 198 lb for the patch and above 130% of ideal weight for the implant, respectively [11,12]. In addition, some Phase 3 clinical trials with emergency contraceptives suggested an increased risk of unintended pregnancy among obese women [13,14], while a meta-analysis of the World Health Organization (WHO) studies for emergency contraceptives containing LNG showed no trend for a reduced efficacy with increasing BW/BMI [15]. In contrast, a recent systematic review suggested that COCs may be less effective in overweight and obese women [16]. Post-marketing observational studies reported an inverse association between obesity and effectiveness of COC use in the US, but not in European women [17,18]. The European Society of Contraception recently recommended to promote the use of HCs regardless of women's weight, but noted increased risks of unplanned pregnancy and venous thromboembolism associated with overweight or obese women [19].

Public access to participant-level data in Phase 3 clinical trials submitted to the US Food and Drug Administration (FDA) is limited. To our knowledge, no individual participant data (IPD) meta-analysis has been conducted using Phase 3 clinical trials across various New Drug Applications (NDAs) of COCs. Unlike a traditional meta-analysis that extracts aggregate data from publications, an IPD meta-analysis involves re-analysis of original IPD in each trial [20,21]. The IPD meta-analysis allows verification of the quality of data and the appropriateness of the analyses, and produces more reliable results [22]. The analysis also adjusts for participants' baseline characteristics and tests for interactions across subgroups at the participant-level [23,24].

2. Materials and methods

2.1. Analysis sample

Fig. 1 depicts the process of sample selection. Twenty-six NDAs of HCs reviewed in 2000–2012 were identified and located in the FDA database. NDAs of HC submitted for indications other than prevention of pregnancy such as treatment of premenstrual dysphoric disorder (PMDD), acne or to raise folate concentrations were excluded. When multiple dose levels of the same combination of progestin/estrogen were studied, only the NDA with the lowest dose formula was included, which should be most sensitive to detect the effect of obesity, if any. A typical HC clinical trial was a multicenter, open-label, non-comparative study; however, when there was a comparator arm, only the study drug arm was included. Sponsors' protocols and inclusion criteria for Phase 3 clinical trials with HCs for prevention of pregnancy were generally comparable, enrolling women aged 18–49 at risk of pregnancy for a 1-year (thirteen 28-day cycles) treatment period.

A Phase 3 clinical trial was eligible for the meta-analysis if it was conducted in North America, was of acceptable quality per the FDA's review with respect to adequate pregnancy recording, assessment of conception during the treatment period, and provision of back-up contraceptive use, its IPD were retrievable in readily analyzable data format (SAS xpt. file), its sample size was ≥ 200 subjects and obese sample size was $\geq 10\%$ of the analysis sample or ≥ 100 subjects, and its observation period was longer than six HC cycles. Women in the pregnancy intent-to-treat (PITT) cohort consisting of women aged 18–35 were eligible for inclusion in the IPD meta-analysis if BMI, age and race were known.

2.2. Definition of variables

The outcome variable was an unintended pregnancy confirmed by a urine or serum pregnancy test (1: pregnant, 0: not pregnant) that was conceived during HC use or within 7 days after the last HC administration. Initial assessment found no trend in effect of BMI (kg/m^2, continuous) on pregnancy rate; thus, the explanatory variable BMI was dichotomized (1: BMI $\geq 30\ kg/m^2$ [obese]), 0: BMI $< 30\ kg/m^2$ [non-obese]) based on the WHO classification [25]. Evaluable duration of HC use was the total number of 28-day HC cycles in which no other contraceptive method, including condom,