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Contraception 91 (2015) 97 – 104

Contraception

Original research article

Effect of body weight and BMI on the efficacy of levonorgestrel emergency contraception☆,☆☆

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Received 25 July 2014; revised 29 October 2014; accepted 2 November 2014

Abstract

Objectives: To further evaluate the effect of weight and body mass index (BMI) on the efficacy of levonorgestrel emergency contraception.
Methods: Data from two large, multicenter, randomized controlled trials designed to assess emergency contraceptive efficacy were pooled to evaluate the effect of weight and BMI on pregnancy rates among women who received levonorgestrel. Descriptive methods (comparison of means and distributions according to pregnancy status and pregnancy rates across weight and BMI categories) as well as cubic spline modeling were used to describe the relationship between pregnancy risk and weight/BMI.
Results: The analysis population comprised 1731 women, among whom 38 pregnancies were reported. Women for whom levonorgestrel was not effective in preventing pregnancy had a significantly higher mean body weight and BMI than women who did not become pregnant (76.7 vs. 66.4 kg, $p<.0001$; 28.1 vs. 24.6 kg/m^2, $p<.0001$). The estimated pregnancy rate increased significantly from 1.4% [95% confidence interval (CI): 0.5%–3.0%] among the group of women weighing 65–75 kg to 6.4% (95% CI: 3.1%–11.5%) and 5.7% (95% CI: 2.9%–10.0%) in the 75–85 kg and >85 kg groups, respectively. Statistical modeling demonstrated a steep increase in pregnancy risk starting from a weight near 70–75 kg to reach a risk of pregnancy of 6% or greater around 80 kg. Similar results were obtained for statistical modeling of BMI as well as when the two studies were analyzed individually.
Conclusions: All analyses showed a significant drop in the efficacy of levonorgestrel emergency contraception with increasing body weight, with pregnancy risk in the higher weight categories similar to expected rates in the absence of contraception. Like body weight, increasing BMI was highly correlated with increased pregnancy risk.

Keywords: Emergency contraception; Hormonal contraception; Levonorgestrel; Efficacy; Body weight; Body mass index

1. Introduction

Levonorgestrel (LNG) is a well-established and widely used treatment to prevent pregnancy after an act of intercourse which was unprotected or inadequately protected by a contraceptive method. LNG at a dose of 1.5 mg was registered as an emergency contraceptive based on the results of World Health Organization-sponsored clinical trials conducted primarily in the developing world [1,2]. Since first becoming available 15 years ago, LNG has become available without prescription in most countries around the world given its well-characterized safety profile and the importance of intake as soon as possible after unprotected intercourse.

Ulipristal acetate (UPA) was developed more recently as a novel emergency contraceptive. In the course of the UPA development program, a series of large-scale prospective clinical efficacy trials were conducted in the United States and Europe, two of which included a LNG comparator arm. Such randomized controlled trials thereby provide data on the efficacy of LNG in a contemporary Western population. In comparison with previous studies [1,2] in which LNG was estimated to prevent at least 80% of expected pregnancies [85% (95% confidence interval [CI]), 74%–93%] and 80% [95% CI, 71.2%–85.6%], respectively), in these two trials, LNG prevented 69% (95% CI, 46%–82%) and 52.2% (95%

☆ Funding was provided by HRA Pharma.
☆☆ Conflict of interest: all authors are employed or contracted by HRA Pharma.
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http://dx.doi.org/10.1016/j.contraception.2014.11.001
0010-7824/

CI, 25.1%–69.5%) of expected pregnancies, suggesting a lower effectiveness rate of LNG than in previous reports. Similarly, a recent study, which utilized hormonal measurements of the fertile window rather than relying on presumptive menstrual data, estimated an effectiveness of LNG for emergency contraception (EC) of 68% [3].

The question of whether body mass index (BMI) or weight might influence the efficacy of EC was first raised in a 2011 analysis that examined prognostic factors for risk of pregnancy using the same pooled database [4] and showed that LNG when taken for EC among overweight or obese women had decreased efficacy in preventing pregnancy. The relationship was highly statistically significant, similar to that seen with established risk factors such as further unprotected intercourse and intercourse during the fertile window (conception probability). Before this publication, increased weight/BMI had not been previously described as negatively impacting the emergency contraceptive effect of LNG.

As such findings have important implications for the counseling and clinical management of women seeking and using EC, we performed further statistical analyses of this data set [4] to thoroughly describe the relationship between LNG efficacy (pregnancy rate) and body weight/BMI.

2. Materials and methods

Data from the two randomized controlled trials with a LNG comparator arm that were carried out in the course of the development of UPA were pooled [5,6] to increase the overall sample size and maximize the ability to detect any effect of body weight on pregnancy rates. The first study [5] enrolled women from seven investigational sites in the United States, and the second [6] included women from 35 investigational sites in the United Kingdom (10 sites), Ireland (1 site) and the United States (24 sites). Both studies were designed to demonstrate the noninferiority of UPA treatment compared with LNG among healthy women seeking EC after unprotected intercourse (defined by lack of contraceptive use, condom breakage or other barrier method failure). Inclusion criteria for both studies were unrestricted in terms of body weight and BMI; however, to be eligible, women had to report a history of regular menstrual cycles (24–35 days long), a negative pregnancy test at enrollment and no current or recent use of hormonal contraception. Follow-up was scheduled approximately 1 week following the next expected menstrual period, at which time systematic urine pregnancy testing was performed.

The two studies had a similar design with three key exceptions: the time window for EC intake following unprotected intercourse, the LNG dosing regimen and the manner in which weight and height were reported. In the Creinin study, unprotected intercourse must have taken place within 72 h of seeking EC, while this timeframe was increased to within 120 h in the Glasier study. The LNG dosing regimen used was two doses of 0.75 mg LNG taken 12 h apart in the Creinin study and 1.5 mg in one dose in the Glasier study. The two LNG dosing regimens have been shown in the literature to have similar effectiveness in a head-to-head clinical efficacy comparison [2]. Finally, body weight and height were measured in the Creinin study and self-reported in the Glasier study.

The analyses were conducted on the primary efficacy evaluable populations as specified in each study protocol. This population corresponds to women who received LNG, had a known efficacy outcome (pregnancy status) and whose pregnancy did not precede drug intake. The efficacy evaluable population as defined in the Glasier study included women aged ≤ 35 years, while the Creinin study's efficacy evaluable population included women aged >35 years. We compared the two data sets for demographic homogeneity and assessed for interaction between studies. Additionally, we assessed for any correlation between possible confounding factors previously described in this data set [4] and in the literature and as prognostic factors for treatment failure (conception probability calculated according to Trussell et al. [7], and further acts of unprotected intercourse after intake). Conception probability for the study population was calculated using the cycle day of intercourse relative to the expected ovulation for each woman enrolled [7,8].

To assess the effect of weight and BMI on pregnancy rates, several complementary analyses were performed. The first statistical analysis compared the weight and BMI of women found to be pregnant versus those who were not pregnant following LNG treatment. The second analysis estimated the pregnancy rate in five prespecified classes of weight and BMI. The first two methods were not adjusted for major confounding factors (study effect, further unprotected intercourse and conception probability), but the relationship between the variables and the weight or BMI was estimated (e.g., correlation between conception probability and weight).

A logistic model including known confounding factors (study, further unprotected intercourse, conception probability) and the dichotomization factor (high vs. low weight and BMI) while maximizing the R^2 of the model was retained to provide the best description of data assuming a stepwise relationship. Finally, cubic spline logistic regression modeling was performed to create a smoothing of the shape of the unadjusted relationship between weight/BMI and pregnancy rates [9]. This method utilizes five predictions of the pregnancy rates corresponding to five percentiles (the first, third, fifth, seventh and ninth deciles) of the distribution of the data.

3. Results

The primary efficacy evaluable populations from the two studies included 1731 women randomized to receive LNG, among whom 38 pregnancies were reported. The pregnancy rate was 1.7% ($n=13$) and 2.6 % ($n=25$) in the Creinin and