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CLINICAL ARTICLE

Population-based evaluation of the effectiveness of two regimens for emergency contraception☆

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ABSTRACT

Objective: To estimate and compare the effectiveness of the levonorgestrel and Yuzpe regimens for hormonal emergency contraception in routine clinical practice. *Methods:* A retrospective population-based study included women who accessed emergency contraceptives for immediate use prescribed by community pharmacists in British Columbia, Canada, between December 2000 and December 2002. Linked administrative healthcare data were used to discern the timings of menses, unprotected intercourse, and any pregnancy-related health services. A panel of experts evaluated the compatibility of observed pregnancies with the timing of events. The two regimens were compared with statistical adjustments for potential confounding. *Results:* Among 7493 women in the cohort, 4470 (59.7%) received levonorgestrel and 3023 (40.3%) the Yuzpe regimen. There were 99 (2.2%) compatible pregnancies in the levonorgestrel group and 94 (3.1%) in the Yuzpe group ($P = 0.017$). The estimated odds ratio for levonorgestrel compared with the Yuzpe regimen after adjusting for potential confounders was 0.64 (95% confidence interval 0.47–0.87). Against an expected pregnancy rate of approximately 5%, the relative and absolute risk reductions were 56.0% and 2.8%, respectively, for levonorgestrel and 36.7% and 1.8% for the Yuzpe regimen. *Conclusion:* The levonorgestrel regimen is more effective than the Yuzpe regimen in routine use. The data suggest that both regimens are less effective than has been observed in randomized trials.

1. Introduction

Emergency contraceptives can potentially prevent pregnancy after unprotected intercourse. In recent years, 1.5 mg levonorgestrel has been packaged for sale in many high-income countries as a product designated for emergency contraception. However, the product is not available to women in some countries. According to a 2014 statement of the International Consortium for Emergency Contraception [1], 22 countries do not import any product labeled as an emergency contraceptive and have no product marketed specifically for this indication. Even in countries where the levonorgestrel regimen is registered as an emergency contraceptive, the product is not always routinely available [1–3], and might not be available to women in a timely manner.

In countries where no dedicated emergency contraceptive product is available, combined oral contraceptives can be used to recreate the Yuzpe regimen, which was the emergency contraceptive of choice in the 1970s, 1980s, and 1990s. It consists of two doses, each containing 0.1 mg ethinyl estradiol and either 0.5 mg levonorgestrel or 1.0 mg norgestrel, 12 h apart. The International Consortium for Emergency Contraception statement [1] emphasizes the role of the Yuzpe regimen in women without access to contraceptives designated for emergency contraception, and advocates for communication of this information to women and healthcare providers in relevant settings. From an international perspective, the Yuzpe regimen offers critical emergency contraceptive access to these women [1].

In randomized trials comparing the levonorgestrel and Yuzpe regimens [4–6], enrollment was restricted to women with regular menstrual cycles who reportedly had only one act of intercourse within 48 or 72 h of requesting an emergency contraceptive, which might not reflect outcomes in the routine primary-care setting. To date, the effectiveness of the two regimens has not been compared on a large scale under

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conditions of usual care, or among women with regular and irregular menstrual cycles. The objective of the present study was to estimate and compare the effectiveness of the levonorgestrel and Yuzpe regimens under conditions of routine clinical use.

2. Materials and methods

The present retrospective population-based study included women who accessed either the levonorgestrel regimen (various brands, such as Plan B [Paladin Labs, St-Laurent, Canada]) or the Yuzpe emergency contraceptive regimen prescribed by community pharmacists in British Columbia, Canada, between December 1, 2000, and December 31, 2002. This study period was selected because treatment consent forms were required during this period, after which relevant clinical and demographic information was not collected systematically in routine practice. The consent forms included age, the onset of the last menstrual period, the date and time of the index act of unprotected intercourse for which the emergency contraceptive was requested, the trade name and the dispensing date and time of the emergency contraceptive, the pharmacy identification code, and whether the emergency contraceptive was requested for immediate use (after the index intercourse) or advance use (after a future act of intercourse).

De-identified data were obtained from three linkable administrative health data files: PharmaNet (all prescription drug dispensations in British Columbia), Medical Services Plan (physicians' fee-for-service billings for outpatient services), and hospital separation records (services provided in hospital and clinic facilities). The PharmaNet data included the drug name, strength, dosage form, and dispensing date, each woman's local health area code, and the pharmacy's health area code. The Medical Services Plan data included diagnostic codes from the International Classification of Diseases, Ninth Revision, and physician service billing codes [7]. The hospital separation data included the admission date, the separation date, diagnostic codes, and procedure codes listed under the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures [8]. The present research was approved by the University of British Columbia Clinical Research Ethics Board and the Children's and Women's Health Centre Research Ethics Board.

Data for all pharmacist-prescribed emergency contraceptives over the 25-month period were analyzed, excluding prescriptions for advance use. Because the consent forms could not be linked directly to the other data files, each consent form was matched to its corresponding PharmaNet prescription record by four criteria: age, product trade name, dispensing date, and local health area of the dispensing pharmacy. To obtain unambiguous matches, records on each side of the match had to include unique combinations of the four criteria. The study cohort comprised the first prescription for each woman whose PharmaNet record was matched to a consent form.

Pregnancy-related codes within 42 weeks after the dispensing date and abortion-specific codes within 20 weeks were identified. These time windows were anchored on the dispensing date because gestational age could not be accurately determined from the study data. Clinical experts with long-term experience in diagnosing and billing for maternity care services were consulted on relevant administrative codes.

The presence of a pregnancy compatible with the index act of intercourse for which emergency contraceptive was sought (primary outcome) was adjudicated by three experts. Time profiles were used to illustrate the timing of the last menstrual period, intercourse, emergency contraceptive dispensing, and pregnancy-related codes in relation to each other. When an abortion-related code was identified, the facility's policy for service provision was included as a comment on the profile without identifying the facility. The experts were trained using sample time profiles to develop a systematic approach to the adjudication of cases for the presence of compatible pregnancy and induced abortion. After discussing the sample cases and adopting a general approach, each expert adjudicated all cases independently. They then reconvened to discuss cases with discordant adjudication. The experts were masked to the emergency contraceptive regimen throughout the adjudication and discussion process.

Potential confounders related to fertility and/or sexual behavior for which data were available included age [9,10], time to receiving an emergency contraceptive after intercourse [11], income [9], menstrual cycle day of intercourse [10,12], 1-year history of pregnancy [9], 1-year history of any emergency contraceptive dispensation, 5-year history of relevant gynecologic conditions, 1-year history of hormonal contraceptive use, and concurrent hormonal contraceptive use. Canadian census data were used to retrieve the neighborhood income at the dissemination area level [13]. Relevant gynecologic covariates included pelvic inflammatory disease [14], endometriosis [14], ovarian dysfunction [14], ectopic pregnancy [15], infertility, and sterilization.

Compatible pregnancies were enumerated on the basis of the final majority vote of the three experts. Inter-rater agreement of adjudication was measured with the Fleiss κ statistic using SPSS version 15.0 (SPSS, Chicago, IL, USA) and David Nichols' macro [16]. The observed pregnancy rates in the two regimen groups were compared using the χ^2 test in SPSS. $P < 0.05$ (two-sided) was considered statistically significant.

Multivariate logistic regression modeling was used to control for potential confounding, with the selection of variables being guided by prior information about the covariates and by the data [17]. The multivariate model was developed by adding one covariate at a time, beginning with covariates documented elsewhere [10] as clinically important predictors of pregnancy that also had a significant association with pregnancy in the initial univariate analyses. Observations with missing covariate data were excluded. The best model was selected on a balance of model fit (lower Akaike information criterion) and parsimony (fewer variables) to obtain the adjusted odds ratio of pregnancy for the levonorgestrel regimen relative to the Yuzpe regimen.

Continuous variables were included as linear terms unless they displayed a curvilinear relationship with pregnancy, in which case quadratic terms were included with the linear terms based on the results of univariate analyses [17]. Interaction and multicollinearity were assessed as well.

Sensitivity analyses were conducted to evaluate the effect of additional variables and that of alternative model specifications. One modeling strategy was to model each continuous variable as an array of dichotomous categorical variables; another involved curve-smoothing of logistic B-spline regression [18]. Regression modeling was conducted using SAS version 9.2 (SAS Institute, Cary, NC, USA).

To emphasize clinically relevant outcomes, the effectiveness of each regimen was assessed by comparing the observed pregnancy rate and an expected pregnancy rate in both relative and absolute terms [19]. The expected pregnancy rates were estimated using pregnancy probabilities published by Li et al. [12]. The traditional effect measure—the relative risk reduction—was computed as follows: 1 – (observed pregnancy rate/expected pregnancy rate) [19]. We also calculated the absolute risk reduction between the expected and observed pregnancy rates and the number needed to treat (NNT).

3. Results

The study cohort comprised 7493 women (Fig. 1), including 4470 (59.7%) and 3023 (40.3%) women in the levonorgestrel and Yuzpe groups, respectively. Characteristics of the women are shown in Table 1; differences between the two groups were computed with Yuzpe as the comparison group. Intercourse most frequently occurred near mid-cycle and was less frequent near the beginning and end of the cycle (Fig. 2).

The records of 467 (6.2%) of the 7493 women screened positive for pregnancy-related codes. The observed compatible pregnancy rate in the cohort was 2.6% (193 pregnancies among 7493 women), with a high degree of concordance among the three experts' adjudications (Fleiss κ value 0.97). There were 99 (2.2%) compatible pregnancies in the levonorgestrel group and 94 (3.1%) in the Yuzpe group ($P = 0.017$). The unadjusted odds ratio of pregnancy with the levonorgestrel regimen

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