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

Vivian W.Y. Leung, Judith A. Soon, Larry D. Lynda, Carlo A. Marra, Marc Levine

Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada
Centre for Health Evaluation and Outcomes Sciences, Providence Health Research Institute, Vancouver, BC, Canada
School of Pharmacy, Memorial University, St. John’s, NL, Canada

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.

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outcomes in the routine primary-care setting. To date, the effectiveness of the two regimens has not been compared on a large scale under 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 $\kappa$ 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 $\chi^2$ 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 $\kappa$ 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 compared with the Yuzpe regimen was 0.71 (95% confidence interval [CI] 0.53–0.94). In multivariate regression analysis, the age and the cycle day of intercourse were added to the model with quadratic terms. After adjustment for potential confounders in the most parsimonious model with the best fit, the risk of pregnancy with the levonorgestrel regimen was 36% lower relative to the Yuzpe regimen (odds ratio 0.64, 95% CI 0.47–0.87). Additional variables did not improve the model fit substantially, and there was no evidence of interaction or multicollinearity between covariates. Therefore, the final model included the regimen type, age, and cycle day of intercourse for the 6683 women (89.2% of the cohort) whose age and cycle day of intercourse were known. In sensitivity analyses, alternative strategies for modeling age and the cycle day of intercourse produced results similar to polynomial regression.

The effectiveness of the two regimens was estimated and calculated in a number of ways to illustrate their comparative effectiveness (Table 2). Against the estimated expected pregnancy rate of 5.0% in the levonorgestrel group, the relative risk reduction was 56.0%, the absolute risk reduction was 2.8%, and accordingly the NNT was 56 to prevent one pregnancy was 36. For the Yuzpe regimen, the relative risk reduction was 36.7%, the absolute risk reduction was 1.8%, and the NNT was 56.

4. Discussion

In the present population-based study, the observed pregnancy rates were 2.2% and 3.1% in the levonorgestrel and Yuzpe groups, respectively. The adjusted odds ratio of pregnancy was approximately 0.64, indicating that levonorgestrel is more effective than is the Yuzpe regimen under conditions of routine use.

In a review published in 2012 [19], the average pregnancy rates were 1.7% (95% CI 1.2–2.2%) and 2.0% (95% CI 1.5–2.5%) in studies of women treated with levonorgestrel or the Yuzpe regimen, respectively. The two regimens have been compared in randomized trials [4–6]. The first [4] involved 880 women and found pregnancy rates of 2.4% (95% CI 0.8%–4.1%) and 2.7% (95% CI 1.0%–4.1%) in the levonorgestrel and Yuzpe groups, respectively, after excluding women who had subsequent acts of intercourse. A very small trial [6] of 122 women observed pregnancy rates of 0% and 8.3% in the levonorgestrel and Yuzpe groups, respectively. The largest randomized trial ($n = 1955$) [5] observed pregnancy rates of 1.0% (95% CI 0.5%–1.9%) and 2.9% (95% CI 1.9%–4.1%) in the levonorgestrel and Yuzpe groups, respectively, after excluding women who were pregnant at enrollment (risk ratio 0.36, 95% CI 0.17–0.73). The significant association between regimen type and risk of pregnancy in the present cohort study is consistent with the results of the WHO trial [5]. However, the point estimates of the regimen-specific pregnancy rates in the present study were higher, possibly because women who request emergency contraceptives under routine practice conditions (compared with those in a clinical trial) have more acts of unprotected intercourse before and/or after the index act for which the emergency contraceptive is requested.

Levonorgestrel is better tolerated than is the Yuzpe regimen [4,5], and despite its higher cost, it has, over the past decade, become regarded as the oral emergency contraceptive of choice in many countries. The present study provides further evidence that the levonorgestrel regimen should continue to be preferred when a choice needs to be made between the two regimens during routine care. Nevertheless, because access to emergency contraception is currently limited to the equivalent of the Yuzpe regimen in some low-income countries [13], it is important to recognize that it is less effective than the levonorgestrel regimen.

On the basis of the WHO trial [5], the levonorgestrel regimen has been widely reported to be 85% effective [20,21]; however, evidence indicates that the baseline (expected) pregnancy rates used to derive effectiveness in that trial and in other studies were overestimated [22–24]. We selected the data by Li et al. [12] from a North Carolina study group for estimating the expected pregnancy rates because the women in that study had no known subfecundity, the method used by the North Carolina group adjusted for variability in the day of ovulation, and it did not require information about the women’s cycle length [25]. The expected pregnancy rate in the present cohort was estimated to be 5%, which is slightly higher than the reported rate of 3.9% among 20 437...
The effectiveness of emergency contraceptives is typically presented as a relative reduction in pregnancy risk [19]. However, it is becoming more common in general to report absolute treatment effects, which are more clinically meaningful and less susceptible to misinterpretation than relative risk reduction [19]. The present study showed that, with an expected pregnancy rate of approximately 5%, the absolute reduction of pregnancy risk was only 2–3%. This magnitude of effect is probably surprising to those who have anticipated greater effectiveness on the basis of earlier reports of substantial relative risk reductions [19].

The present study was limited by the use of administrative data from only one geographic region. Some pregnancies might not have been documented (e.g., if women had left the province). However, the number of missed pregnancies in the levonorgestrel group would have to be substantially more than in the Yuzpe group to affect the association of treatment with pregnancy. It is possible that the experts misclassified nonpregnant cases as pregnant and vice versa. However, because the experts were masked to the regimen, any outcome misclassification would probably have been non-differential between the two groups. As in other cohort studies, the present multivariate analysis included only measured covariates. Residual confounding stemming from unmeasured confounders (e.g., body mass index) and/or inadequately controlled confounding could have contributed to the observed difference between the two regimens. However, the observed findings are unlikely to be explained entirely by confounding because the magnitude of any association of confounders with the regimen type and with pregnancy would have to be so strong as to be clinically implausible to nullify the effect of the levonorgestrel regimen. In view of the strength of association between the regimen type and pregnancy after adjustment for imbalances in the measured covariates, the levonorgestrel regimen was deemed to be the more effective of the two. Thus, levonorgestrel should be the preferred regimen where it is available.

Postmarketing comparative effectiveness research is important for evaluating medications under real-world usage conditions [27]. In the present study of almost 7500 women, the levonorgestrel regimen was more effective than the Yuzpe regimen. Against an expected pregnancy rate of approximately 5%, the absolute reduction in the pregnancy rate was only 2–3%. More effective approaches, including regular contraception and other forms of emergency contraception such as intrauterine devices and ulipristal acetate, should be considered and personalized according to each woman’s preferences. As has been recommended, levonorgestrel and other methods should be made more widely available, along with education of women and healthcare providers.

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**Conflict of interest**

The authors have no conflicts of interest.

**References**


