A new method for estimating the effectiveness of emergency contraception that accounts for variation in timing of ovulation and previous cycle length

Rafael T. Mikolajczyk, M.D.[a] *and Joseph B. Stanford, M.D.*[b]

[a] Department of Public Health Medicine, School of Public Health, University of Bielefeld, Bielefeld, Germany; and [b] Department of Family and Preventive Medicine, University of Utah, Salt Lake City, Utah

Objective: To develop a new method for estimating the effectiveness of emergency contraception (EC) by using information about previous menstrual cycle length, accounting for the variation in the day of ovulation within the menstrual cycle, and comparing the validity of the new and previous methods.
Method(s): Secondary analysis of a data set with a biological marker of ovulation and its distribution in the cycle. Based on a sample of cycles with known length and a known biological marker of ovulation, we simulated trials of predetermined EC effectiveness and then calculated estimates of EC effectiveness based on old and new methods.
Result(s): Under some conditions, all methods produced biased estimates of effectiveness with simulated trials, especially when the actual effectiveness was low. The systematic bias was minimized with the new method. The new method was robust with regard to the distribution of the day of intercourse in women presenting for EC.
Conclusion(s): Future studies of EC effectiveness should consider both the uncertainty in predicting the day of ovulation and previous cycle length. Our estimates of daily fecundity should be replicated with other data sets. (Fertil Steril® 2005;83:1764–70. ©2005 by American Society for Reproductive Medicine.)

Key Words: Emergency contraception, effectiveness, cycle length, ovulation detection

There is a strong and increasing interest in hormonal emergency contraception (EC) as a component of social policy to reduce unintended pregnancy (1). Several clinical trials have been performed to assess the effectiveness of EC, but for ethical reasons a placebo-controlled trial has never been conducted. The effectiveness of EC is estimated indirectly as the reduction in expected pregnancies, i.e., 1 − (the number of observed pregnancies divided by the number of expected pregnancies). Most reports have focused on the issue of identifying all pregnancies observed in a study, but the equally important problem of accurately estimating the expected number of pregnancies has received less attention. Because actual substantial fecundity is restricted to approximately 5–6 days of the menstrual cycle (2, 3), the timing of intercourse within the menstrual cycle has a strong impact on expected pregnancies. Some clinical studies of effectiveness have used either hormonal status (4, 5) or ultrasound to assess the daily fecundity for each act of intercourse in the study (6, 7), but the study samples were relatively small and the reliability of these markers has yet to be established. Information about the beginning date of the current menstrual cycle and the usual length of previous cycles are most commonly used as proxy indicator of the 5–6 day fecund window in clinical studies of EC, and are the most feasible method in large trials.

Established methods used to estimate expected pregnancies have estimated the day of ovulation based on previous cycle length without adequately accounting for variability in the exact day of ovulation (8–11) or have accounted for variability in the exact day of ovulation while discarding information on the subject's previous cycle length (12, 13). The validity and comparability of these two methods has not been studied formally.

The purposes of this study are to propose a new method to estimate effectiveness of EC, accounting both for variation in the timing of ovulation and the length of previous menstrual cycles, and to compare the estimates derived from this new method with estimates from current methods. For comparison of the methods, we used simulated trials of predetermined EC effectiveness.

MATERIALS AND METHODS

Previous Methods for Estimating EC Effectiveness

Estimates accounting for the timing of intercourse within the cycle were first used by Dixon et al. (8), who designated the day of ovulation as "usual cycle length −14," thus incorporating information about previous cycle length. They used estimates of daily fecundity derived from three studies: two of users of natural family planning in Britain and Switzerland (14, 15) and one from artificial inseminations (16), with

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Reprint requests: Rafael T. Mikolajczyk, M.D., Department of Public Health Medicine, School of Public Health, University of Bielefeld, P.O. Box 100131, D-33501 Bielefeld, Germany (FAX: +49-521-1062968; E-mail: rmikolajczyk@uni-bielefeld.de).

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the day of ovulation determined in all cases by basal body temperature. In an attempt to account for variability in the timing of ovulation, they also used an arbitrary distribution of daily fecundity around the estimated ovulation. In this article, we refer to this approach as the Dixon method.

Trussell et al. initially used the Dixon method (9), but later discarded the arbitrary distribution of daily fecundity around the estimated ovulation and adopted daily fecundity estimates from the previously used British study of natural family planning users (14), as well as new estimates from a North Carolina study of fecundity and early pregnancy loss, which identified the day of ovulation by urinary hormonal metabolites (3, 10, 11, 17). They concluded that the most relevant estimates were from pooled estimates from the two studies. They included only pregnancies that were detected clinically by delayed menstruation. In this article, we refer to this approach as the Trussell method.

In a more recent article, Trussell et al. (13) used daily estimates for consecutive cycle days, referenced to the first day of menses, calculated for an average woman with regular cycles in the North Carolina sample. This approach accounts for the variability in the timing of ovulation, but does not include information about cycle length from previous cycles for an individual woman. Because the estimates of daily fecundity for this approach were developed by Wilcox et al. (12) from the North Carolina study, we refer to it in this article as the Wilcox method.

New Method for Estimating EC Effectiveness, Accounting for Both Variation in Ovulation Timing and Previous Cycle Length

To develop a set of estimates of daily fecundity that would account for variation in both ovulation timing and previous cycle length, we used data from a recently published study of natural family planning users that included information on the length of consecutive cycles, a biological marker of ovulation, and an associated set of daily fecundity estimates (18). The biomarker used was the peak mucus day, defined as the last day of vulvar discharge with highly fertile characteristics. There were 725 cycles from 125 women who had information available from 6 serial cycles without pregnancy (25 cycles had missing data for the mucus peak day). The estimates of daily fecundity around the peak day were combined with the distribution of the peak day in reference to the last day of the cycle, resulting in a set of estimates of daily fecundity referenced to the last day of the cycle. In defining the fecund window for these estimates, we set the estimates from intercourse that occurred less than 9 days before the last day of the cycle to zero (to allow adequate time for implantation), and also excluded early probabilities of $<.001$. This resulted in a cutoff for the beginning of the fecund window of 22 days before the last day of the cycle. This yielded a 14-day fecund window of days 10 to 23, counting backward from the last day before subsequent menses.

Standardization of Baseline Fecundity of the Sample

Two sources of variation are used in estimating expected pregnancies. The first is the distribution of daily fecundity, which has been discussed previously. The second is the baseline fecundity of the sample, representing the reproductive potential of the sample. If the baseline fecundity of the group of women for which EC is tested differs from the baseline fecundity of the women from whom the estimates of daily fecundity are derived, the number of expected pregnancies may be biased (either up or down). Some differences in previous estimates of EC effectiveness in different studies are a result of using different reference populations, with different baseline fecundity. Because all EC effectiveness trials have been limited to participants who reported a single act of intercourse within a designated fecund window of the menstrual cycle, the overall fecundity of the sample can be thought of as the area under the curve for daily fecundity or simply the sum of daily fecundity estimates over the entire fecund window. To address this issue, we standardized all estimates of daily fecundity to the baseline fecundity calculated by Dunson et al. (2) from the North Carolina study. The adjustment factor for the standardized Dixon estimates of daily fecundity is 0.815, and the adjustment factor for the standardized Trussell estimates is 0.740. Because the Wilcox method described previously is based on the North Carolina sample, its total fecundity is already the same as that of the standardized Dixon and Trussell methods. The adjustment factor for our own sample was 0.703. We compared simulations with and without the adjustment factors.

Simulated Trials of EC Used to Compare Methods for Estimating EC Effectiveness

We simulated trials of EC with actual known effectiveness specified at 50% and 75%. We used the database from the study by Stanford et al. (18) to obtain sequences of 6 cycles for 125 women. The sixth cycle ($n = 120$ cycles; the peak day was unavailable in 5 cycles) was used as the index cycle for simulated EC administration. The prediction of cycle length, and therefore the estimated day of ovulation and associated daily fecundity, was made based on several alternative scenarios: [1] the last preceding cycle, [2] a mean cycle length from the five preceding cycles, or [3] a fixed assumption of a 28-day cycle for all women. The 28-day fixed assumption represents a scenario of completely noninformative reporting by women based on idealized instead of actual cycle length. The median cycle length for the index cycles, the previous cycle, and the 5 previous cycles was 29 in each case; 90% of the cycles were between 24 and 40 days, 24 and 38 days, and 25 and 36 days, respectively. We assumed that EC had a fixed effectiveness of 50% or 75% regardless of which day within the fecund window it was administered. Further, we assumed no delay in EC administration or, equivalently, that the delay would not alter its effectiveness. We assumed that only one act of intercourse occurred during a defined exposure frame of the cycle defined by the first day of the menstrual flow, with the act of

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