Bayesian selection of optimal rules for timing intercourse to conceive by using calendar and mucus

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Objective: To find optimal clinical rules that maximize the probability of conception while limiting the number of intercourse days required.

Design: Multicenter prospective study. Women were followed prospectively while they kept daily records of menstrual bleeding, intercourse, and mucus symptom characteristics. In some cycles, women sought to conceive, whereas in other cycles, they sought to avoid pregnancy.

Setting: Four centers providing services on fertility awareness.

Patient(s): One hundred ninety-one healthy women using the Billings Ovulation Method. Women were invited to enroll by their instructors if they satisfied the entry criteria. We excluded cycles in which mucus was not recorded on a day with intercourse.

Intervention(s): None.

Main Outcome Measure(s): Clinically identified pregnancies. There were 161 clinically identified pregnancies in 2,536 menstrual cycles from 191 women.

Result(s): Our approach relies on a statistical model that relates daily predictors, such as type of mucus symptom, to the day-specific probabilities of conception. By using Bayesian methods to search over a large set of possible clinical rules, focusing on rules based on calendar and mucus, we found that simple rules that are based on days within the midcycle calendar interval that also have the most fertile-type mucus symptom present have high utility.

Conclusion(s): Couples can shorten their time to pregnancy efficiently by timing intercourse on days that the most fertile-type mucus symptom is observed at the vulva. (Fertil Steril® 2007;88:915–24. ©2007 by American Society for Reproductive Medicine.)

Key Words: Bayesian analysis, cervical mucus, conception, decision theory, fertility awareness, natural family planning, time to pregnancy

Couples in Western countries are postponing childbirth to later ages (1), with the reasons for delaying including education, career choice and development, and having a stable relationship. A recent Swedish study showed an intention among college students to delay marriage (2). However, as couples age into their late 30s, there is an increasing concern that they may have difficulty in procreating (1). Couples are often diagnosed as clinically infertile if they fail to conceive within a year of starting an attempt, and many couples worry about their chances of achieving pregnancy even after a few months of attempting.

To shorten the time to pregnancy (TTP) and reduce the risk of being diagnosed as clinically infertile, couples can attempt to prospectively identify the fertile days of the cycle and time intercourse on these days. Because intercourse occurring outside of the 6-day fertile interval that ends on the day of ovulation is unlikely to result in conception (3, 4), couples wishing to time intercourse on highly fecund days must use a method of identifying days occurring before ovulation. Potentially, women may attempt to identify the day of ovulation by using urinary LH surge kits, though these kits can be expensive and may result in both false positives and false negatives, each in ≤9% of cycles (5, 6). In fact, although there has not been a study in which couples using ovulation test kits based on urinary LH are followed prospectively to assess the impact of intentional timing using such an approach on the TTP, there have been studies (e.g., Wilcox et al. [3]) in which urinary LH later is assayed from urine that has been collected from women attempting pregnancy. Dunson et al. (7) show that the day-specific conception probability on different days relative to the urinary LH surge peaked with intercourse occurring 1–2 days before ovulation, with the probability substantially lower on the day of ovulation. Hence, even in cycles in which the true LH surge is accurately detected in urine, kits may miss the most fecund day, which typically precedes ovulation. There are also various devices

available, such as the ClearPlan Easy Fertility Monitor (Unipath Diagnostics Company [8]), which identifies the fertile interval by monitoring of estrogen and LH in the urine. This monitor is promising but remains to be empirically validated by conception rates, and its expense may be a disadvantage (8, 9).

An alternative to kits and devices is to use a simple rule based on self-monitoring of the menstrual cycle and established symptoms of the fertile days, such as vulvar observations of cervical mucus symptom. The use of such rules to identify potentially fecund days forms the basis for natural family planning (NFP) methods to avoid pregnancy (10, 11) and can similarly be used to identify fertile days by couples attempting pregnancy (12). Widely used means of identifying the day of ovulation and the fertile window include calendar calculations (13–17) and fertility charting of mucus symptom observed at the vagina (18–21). A recent European study on symptothermal methods (22) found that rules combining calendar and mucus are somewhat more effective than mucus alone in identifying the beginning of the fertile interval for the purposes of avoiding pregnancy.

Recently, Fehring et al. (23) demonstrated that a particular rule for identifying fertile days prospectively based on mucus characteristics compared favorably with the hormonally identified fertile days that were predicted by the ClearPlan Easy Fertility Monitor. However, data are not yet available for a large sample of couples who use fertility monitors while also collecting daily records of mucus and intercourse. For these reasons, we focus in this article on choosing the best clinical rules for conception based on mucus symptom and calendar.

Wilcox et al. (3) proposed that having intercourse consistently two or three times per week will likely result in one or two acts of intercourse occurring during the fertile window, and this should be sufficient for couples of normal fertility to conceive. However, this approach may be unsatisfactory for couples for whom it is difficult to maintain a schedule of regular intercourse constantly throughout the cycle, or for couples who wish to be certain of timing intercourse correctly; for such couples, it would be better to ensure a high frequency of intercourse during the likely-fertile central window of the cycle close to ovulation. Although data suggest that some regular pattern of intercourse will result in a high per-year probability of conception, the high frequency of intercourse days required consistently throughout the entire cycle over multiple cycles may be unrealistic for many couples. There potentially may be rules identifying fertile days that are yet to be found that require fewer intercourse days without decreasing the pregnancy rate.

There has been recent concern (24) about the generality of results obtained in studies of couples using NFP methods (25, 26). Certainly, without randomization or a comparison group, it is not possible to definitively show that intentional timing of intercourse with NFP methods causes a reduction in TTP. However, our focus is on using the available observational data to search for good rules for timing

intercourse to achieve conception. One hopes that such rules can later be validated in well-designed clinical trials.

Our analysis relies on new data from a multicenter prospective study of Italian users of the Billings Ovulation Method (27), a widely used NFP method based on vulvar observation of mucus symptom. Recent studies of mucus and conception probabilities (21, 28) have used data from the Multinational Fecundability Study (29). Unfortunately, this earlier study only collected mucus information during days in the midcycle, as accepted by the symptothermal method (30). Hence, for most of the cycles, there are many days with missing mucus information early and late in the cycle. In contrast, the new Italian database has complete information on mucus symptom on each day of the cycle for a large number of cycles (2,755 from 193 women, with 177 cycles ending in conceptions that result in clinically detected pregnancies). Women also kept daily records of intercourse and menstrual bleeding. The availability of such complete records for women at risk of pregnancy is a necessity for proper evaluation and comparison of different possible rules.

To select optimal rules, we apply a Bayesian decision theoretic approach in which a utility function is chosen to reward pregnancies and penalize high frequency of intercourse. To relate the cycle day and mucus characteristics to the probability of conception, we use a recently proposed statistical model (31), which generalizes the Barrett and Marshall (32) model to allow for variability among couples in their fertility and predictors of fecundability.

As noted by Barrett and Marshall (32) and by Wilcox et al. (3), it is necessary to use a statistical model to predict the probability of conception in menstrual cycles with multiple acts of intercourse occurring during a potentially fertile phase of the cycle. Earlier investigators have evaluated the theoretical effectiveness of existing rules to avoid conception (e.g., Arevalo et al. [16], Dunson et al. [21]), relying on combining estimates of conception probabilities with data on menstrual cycle characteristics. Colombo (33) compared a list of widely used NFP rules in terms of applicability, acceptability, reliability, and effectiveness, whereas Stanford et al. (12) compared the physiologic basis of a list of different approaches for timing intercourses to achieve pregnancy.

Our goal is not to evaluate a particular rule or set of existing rules but instead to search for new rules that are based exclusively on calendar or on calendar and mucus observations, selecting the best from among the very large number of possible candidates by using innovative Bayesian statistical methods.

MATERIALS AND METHODS
Description of Study Design and Data
These data are drawn from a large study (27) that enrolled 193 women, during 1993–1997, from four Italian centers providing services on fertility awareness using the Billings Ovulation Method (17). Information on the study was provided at