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

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available, such as the ClearPlan Easy Fertility Monitor (Uni-path 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
the participating centers, and women were invited to enroll by their instructors if they satisfied the entry criteria, which included the following: experienced in use of the Billings Method, married or in a stable relationship, between 18 and 40 years of age, had at least one menses after cessation of breastfeeding or after delivery, not taking hormonal medication or drugs affecting fertility, and no known permanent infertility or illnesses that might cause subfertility in neither partner. The women in the study were selected to not be currently using condoms or other methods of contraception. If they started using such methods during the study, the relevant cycles were excluded. In fact, only 33 of 193 women had used hormonal contraception before entering the study, with only 1 woman stopping use within 3 months of the first cycle in the study. The protocol was approved by the institutional review board of Fondazione Lanza (Padua, Italy).

At enrollment, the women were given a questionnaire to obtain demographic and reproductive history information. The women then were followed prospectively as they collected detailed daily records of vulvar observations of the mucus symptom and recorded the days during which intercourse and menstrual bleeding occurred. Because women enrolled were followed for an arbitrary portion of their reproductive lives, they included a mixture of avoiders and achievers, with intention status possibly changing across cycles from the same woman, but no direct information was collected on pregnancy intention in each cycle.

The Ovulation Method is based on self-observation of characteristic changes of vulvar sensation and cervical mucus during the cycle. The estrogen rise from a ripening follicle in each menstrual cycle stimulates cervical production of fluid mucus and indicates the beginning of fertility. Vulvar observations by women correlate well with the hydration and related biophysical characteristics of cervical mucus, and a fertile type of mucus is necessary for sperm survival and transport (34–36). Further, changes in mucus hydration increase as ovulation approaches and immediately decrease thereafter (17, 37). The peak of the mucus symptom (that is, the last day of fluid mucus and/or slippery sensation) correlates closely with the day of ovulation and allows recognition of the end of the fertile window (23, 38).

The women had received training at the study centers on how to identify different types of sensation and mucus and were experienced in the use of the method. Teachers classified each day of the cycle according to a five-point scale according to the type of mucus symptom described by the women. As discussed in Colombo et al. (27), the two most fertile types of mucus score are very similar clinically. Therefore, we collapsed these into one category, resulting in the following four-point scale: [1] dry; [2] a humid or damp feeling; [3] thick, creamy, elastic, whitish moist mucus; and [4] slippery, stretchy, watery, clear mucus. Higher scores indicate higher levels of estrogenic-type mucus and hence conditions more conducive to sperm survival and transport.

It is difficult to formally evaluate the reliability of the reported mucus classification and intercourse records. In fact, there have been some previous NFP studies in which intercourse was underreported because only the intercourse acts closest to the mucus peak were recorded (e.g., World Health Organization [39], Trussel and Grummer-Strawn [40]). However, the women enrolled in our study were in the habit of routinely recording mucus symptoms and intercourse on a daily chart. In addition, women were informed about the aims of the study and about the importance of recording every intercourse act. They understood that carefully recording this information would lead to more reliable study results, which would potentially help them personally. In addition, a teacher was responsible for the women, monitoring their data collection and checking in to verify that they had recorded the daily information.

Day 1 of the menstrual cycle was defined as the 1st day of fresh red bleeding, excluding any previous days with spotting. A conception was assumed in the presence of a pregnancy ongoing at 60 days from the onset of the last menses, or when, before that term, a miscarriage was clinically detected. A detailed description of the study protocol is available (27).

Bayesian Statistical Analysis

Most statistical models for relating daily records of intercourse to the probability of conception require a conventional indicator of ovulation day, such as rise of temperature, mucus peak, or hormonal observations, for each cycle under consideration (31, 41–46). Unfortunately, such models require anovulatory cycles and cycles with no clear indicator of ovulation to be discarded, possibly biasing estimation. In addition, there can be problems with measurement error in indicators of ovulation day (21, 46, 47). To allow a missing ovulation day in the model, Dominik et al. (48) extended the day-specific conception model of Zhou and Weinberg (41). Dominik and Chen (49) later modified this approach to model a per-cycle day pregnancy curve, avoiding reliance on potentially error-prone imputation of the unknown ovulation day. A drawback of these models is that they do not account explicitly for heterogeneity among couples in their pregnancy probabilities, instead using a variance adjustment method. Hence, because less-fecund couples may contribute more cycles to a data set, the resulting pregnancy probabilities will be biased downward. For these reasons, we use a different model that does not require information on timing of intercourse relative to ovulation, instead relying only on the cycle day and mucus characteristics, but that introduces a woman-specific random effect to accommodate between-cycle dependency that is caused by women who contribute multiple cycles of data.

This model generalizes the model applied by Scarpa et al. (50) to incorporate information on cycle day and mucus on days other than the intercourse course. In particular, considering that intercourse has a significant probability of resulting in conception only if it occurs in a midcycle 6-day fertile interval (3, 4), we divide the cycle into three temporal windows: [1] an early infertile window during which mucus score is not
considered; [2] a midcycle, potentially fecund window during which a daily 1–4 categorization of mucus can have a time-varying effect on the probability of conception; and [3] a late infertile window during which mucus score is again not considered. In focusing on simple rules that prospectively identify days of the cycle with high fecundability, we rely on a daily mucus score on days within a known midcycle interval. Peak mucus may sometimes occur outside this interval, or there may be other mucus score 4 days early or late in the cycle that is informative of fertility. However, using such information adds to the complexity of the rules considered and is unlikely to improve the prediction of highly fecund days.

Our statistical model does not include an abstinence effect. Although sperm concentration and motility increase in the 1–2 days after ejaculation (e.g., Lunenfeld et al. [51]), the magnitude of the improvement in semen parameters caused by an additional day of abstinence does not appear sufficient to result in a significant increase in the day-specific conception probability (41).

The model that we use allows day-specific conception probabilities to depend nonparametrically on the 1–4 daily categorization of mucus score type. In Bayesian models, parameters are considered to be random variables, which are assigned prior distributions that quantify the state of knowledge about the parameters before examination of the current data. These prior distributions are then updated by using data from the study to obtain posterior distributions quantifying the current uncertainty in the parameters. The process of updating relies on Markov chain Monte Carlo algorithms to implement the high-dimensional integration, which is required. Our Markov chain Monte Carlo algorithm is based on a simple modification of the approach of Dunson and Stanford (31) and is closely related to stochastic search algorithms for subset selection of genes in microarray experiments and other applications.

Identifying an Optimal Rule

We do not rely on conception probabilities obtained by plugging in point estimates of fecundability parameters into a statistical model (as in Arevalo et al. [16]), because this strategy potentially can give misleading results by ignoring estimation uncertainty. Instead, we follow a formal Bayesian decision-theoretic approach, relying on Markov chain Monte Carlo methods to remove the unknown parameters by integrating them out. This is performed by estimating the posterior probabilities associated with different parameters’ values and using these probabilities as weights in estimating the expected utility of a rule, as presented in detail by Scarpa and Dunson (52). By using computer simulations, we estimate expected utilities for a wide class of rules, assuming perfect use to assess theoretical effectiveness. Rules are then compared on the basis of their expected utilities, incorporating a reward for pregnancy probability and a penalty for intercourse frequency.

The rule utility function is the sum of two components: [1] the predictive probability of conceiving in a cycle conditional on the pattern of intercourse allowed by the rule and [2] a penalty for the number of prescribed intercourse days. We consider a range of values for this penalty and focus on rules prescribing intercourse on certain days within a midcycle interval, including [1] every day, [2] on days with mucus score >1, [3] on days with mucus score >2, [4] on days with mucus score >3, [5] on days with mucus score >1 on that day or the day before, [6] on days with mucus score >2 on that day or the day before, and [7] on days with mucus score >3 on that day or the day before.

We allowed the last day of the first interval of the cycle to vary between 5 and 12, and the last day of the second interval, to vary between 17 and 25, resulting in 504 different rules. For each rule, we estimated the probability of conception. To apply each rule and to define the intercourse days, the observed mucus patterns of the data from the Italian study are used for the rules based on mucus. Couples often do not strictly follow a rule, so in evaluating rules, we considered different patterns of intercourse acts for prescribed days (for instance, we allow intercourse every prescribed day or only on half of them), and we assume that intercourse occurs on either 1/7 or 0/7 of the days outside of the midcycle interval. For each rule, the average number of extra days of intercourse required by the rule also was estimated.

We did not stratify by a woman’s usual cycle length, age, or reproductive history. Although the statistical method easily can accommodate such information in obtaining individualized optimal rules for women having particular characteristics, it becomes much more complicated to present and disseminate this information to couples. Hence, we focused on optimal selection of rules for couples overall.

RESULTS

When one focuses on menstrual cycles with complete records of mucus score and excludes cycles in which mucus was not recorded on a day with intercourse, in our entire data set (2,755 cycles of 193 women with 177 pregnancies), there are 2,536 menstrual cycles from 191 women, with 161 of these cycles (from 132 women) ending in a clinical pregnancy. Table 1 presents some simple summaries of the demographic characteristics of the 191 women who produced the cycles of data analyzed, and Table 2 shows the average number of days per cycle with each type of mucus for women in different age groups. Although the number of days with the most fertile-type mucus (mucus score of 4) declines somewhat with age (all women in the study are between 18 and 40 y of age), this trend is modest. There are, however, clear differences in mucus according to a woman’s reproductive history. As shown in Table 3, as the number of prior pregnancies increases, the number of days with no secretions (mucus score of 1) decreases. The median length of the observed nonconception cycles is 28 days, with range between 18 and 76 days (first quantile, 27 d; third quantile, 31 d; mean, 29.33 d; SD, 4.98 d).
We first estimated the timing of the midcycle interval. In fitting the Bayesian model, priors were chosen to assign high probability to a wide range of plausible values, with equal probability assigned to each model. The posterior mean (Bayesian estimate updating prior information with information in the data) for the last day of the first interval is 6, and the 95% credible interval (Bayesian equivalent of a confidence interval) ranges between days 5 and 8. For the last day of the second interval, the posterior mean is 21, and the 95% credible interval is between days 19 and 23. These results are consistent with the interval between days 6 and 21 being considered to involve a high probability of fertile days, as presented by Wilcox et al. (53), and also are similar to the fixed fertile window of days 8–19 that were chosen for a fixed calendar calculation method (16) that was suggested to women with cycle lengths between 26 and 32 days. We also obtained posterior distributions for the day-specific probabilities of conception given a single act of intercourse in the cycle, occurring in one of the three phases. For intercourse acts in the second phase, we stratify by the type of mucus on the intercourse day.

Consistent with earlier analysis of these data and two other data sets (28, 50, 54), mucus score does an excellent job of predicting the conception probabilities. In the midcycle interval, the probability is quite low for days with no secretions (0.01) and with a mucus score of 2 (0.038) or 3 (0.064) but then increases dramatically to 0.41 on days with most fertile-type mucus. These differences are all statistically significant, having posterior probabilities for no difference of <.05. On days in the first and third phase, the probability of conception is essentially zero (0.002 and 0.0004). Given these estimates, mucus characteristics early and late in the menstrual cycle are unlikely to be very informative about conception probabilities.

Table 4 presents the results of the optimal rules, assuming that a normal couple has intercourse only when required by the rule in the midcycle interval and never within the other intervals. The first line presents the optimal rule and the corresponding integrated utility function, initially considered to be simply the probability of conception without an explicit penalty for intercourse days. This figure allows one to identify the pregnancy probability and the relative number of intercourse days associated with each rule. To choose an optimal rule, it is necessary to weigh the pregnancy probability against the number of intercourse days required. To formalize this tradeoff, we estimated the integrated utility function with different penalties, resulting in progressively reduced numbers of days on which intercourse is prescribed, while still maximizing the probability of conception.

The remaining rows of Table 4 present results for progressively reduced numbers of prescribed intercourse days. For a very limited number of prescribed intercourse days (mean, 2.42 d per cycle), the optimal rule suggests intercourse between cycle days 13 and 17 on days with a mucus score of 4. For an intermediate number of 9 prescribed days

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**TABLE 1**

Descriptive statistics of the couples in the study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Median</th>
<th>Interquartile range</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female partner’s age</td>
<td>29.95</td>
<td>30</td>
<td>6</td>
<td>4.15</td>
</tr>
<tr>
<td>Male partner’s age</td>
<td>32.64</td>
<td>32</td>
<td>6</td>
<td>4.76</td>
</tr>
<tr>
<td>Previous pregnancies</td>
<td>0.99</td>
<td>1</td>
<td>2</td>
<td>1.17</td>
</tr>
<tr>
<td>No. of cycles for woman</td>
<td>13.28</td>
<td>9</td>
<td>14</td>
<td>12.66</td>
</tr>
</tbody>
</table>


**TABLE 2**

Descriptive statistics of the number of days per menstrual cycle with each type of mucus for women in different age groups (means, with SD in parentheses).

<table>
<thead>
<tr>
<th>Type of mucus</th>
<th>Age (y) interval</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>No. of cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(20, 26)</td>
<td>5.74 (6.27)</td>
<td>3.52 (4.56)</td>
<td>9.38 (6.55)</td>
<td>6.02 (4.26)</td>
<td>612</td>
</tr>
<tr>
<td></td>
<td>(26, 29)</td>
<td>7.46 (6.62)</td>
<td>3.60 (4.27)</td>
<td>7.98 (6.04)</td>
<td>5.04 (2.94)</td>
<td>597</td>
</tr>
<tr>
<td></td>
<td>(29, 34)</td>
<td>6.65 (6.33)</td>
<td>3.44 (4.41)</td>
<td>7.75 (5.30)</td>
<td>4.99 (2.45)</td>
<td>928</td>
</tr>
<tr>
<td></td>
<td>(34, 40)</td>
<td>6.07 (5.90)</td>
<td>3.94 (3.70)</td>
<td>7.25 (4.80)</td>
<td>4.72 (2.78)</td>
<td>381</td>
</tr>
</tbody>
</table>

per cycle, the optimal rule suggests intercourse between cycle
days 10 and 18 on days with any fertile type of mucus. Fi-
nally, for couples desiring an intermediate number of pre-
scribed intercourse days, an average of 3.9 days per cycle,
the optimal rule suggests intercourse in the interval between
cycle days 13 to 17 on days with a mucus score of 3 or 4.

By using the probabilities of conception estimated by the
model, we simulated a distribution of the TTP (the number
of cycles of attempts needed by a couple to conceive) for
couples following each of the optimal rules obtained with
different penalties. Table 4 also presents some estimated
percentiles of these distributions.

Table 5 presents results for couples that have intercourse
once per week during the first and third intervals (mostly non-
fertile) of the cycle, in addition to the intercourse prescribed
by the rules to try to conceive. For high and low levels of pre-
scribed intercourse frequency, the choice of the optimal rule
is the same as in the previous case (with no intercourse in the
mostly nonfertile first and third intervals), but the results for
a medium frequency of intercourse are slightly different. In
particular, for a prescribed intercourse frequency of an aver-
age of 4.45 days per cycle, the optimal rule recommends in-
tercourse within the cycle day 13 to 17 interval on days with
a mucus score of >1, whereas for couples not having any in-
tercourse outside the prescribed window, a slightly higher
number of prescribed intercourse days (5 d) recommends in-
tercourse in the same cycle day 13 to 17 interval without re-
gard to mucus score. Overall, having additional intercourse
occasionally in the mostly nonfertile first and third intervals
raises the cycle probability of conception slightly, all else be-
ing equal. We estimated that the median waiting time for
a couple having intercourse on one seventh of the days of a cy-
cle without regard for timing or mucus characteristics is
about four cycles. For couples using the optimal rule pro-
posed (Table 5), this time is decreased to one to two cycles.

We also considered the case in which couples do not
strictly follow the rule but instead have intercourse on half

<table>
<thead>
<tr>
<th>Previous pregnancies</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>No. of cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8.02 (6.78)</td>
<td>3.56 (4.55)</td>
<td>7.64 (6.13)</td>
<td>5.15 (3.58)</td>
<td>943</td>
</tr>
<tr>
<td>1</td>
<td>6.06 (6.42)</td>
<td>3.19 (4.56)</td>
<td>9.42 (6.64)</td>
<td>5.28 (3.34)</td>
<td>508</td>
</tr>
<tr>
<td>2</td>
<td>6.38 (5.92)</td>
<td>3.00 (3.66)</td>
<td>8.23 (5.03)</td>
<td>5.12 (2.51)</td>
<td>645</td>
</tr>
<tr>
<td>≥3</td>
<td>3.85 (4.78)</td>
<td>4.74 (4.15)</td>
<td>7.86 (4.87)</td>
<td>5.50 (2.93)</td>
<td>440</td>
</tr>
</tbody>
</table>

Table 3

Descriptive statistics of the number of days per menstrual cycle with each type of mucus according to
the number of previous pregnancies reported by the woman (means, with SD in parentheses).

<table>
<thead>
<tr>
<th>Rule parameters</th>
<th>Cycle probability of conception</th>
<th>Mean no. of prescribed intercourse days</th>
<th>Cycles to pregnancy by percentile (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penalty</td>
<td>Midcycle interval start</td>
<td>Midcycle interval end</td>
<td>Mucus type</td>
</tr>
<tr>
<td>0</td>
<td>6</td>
<td>25</td>
<td>No</td>
</tr>
<tr>
<td>0.01</td>
<td>10</td>
<td>18</td>
<td>No</td>
</tr>
<tr>
<td>0.05</td>
<td>13</td>
<td>17</td>
<td>No</td>
</tr>
<tr>
<td>0.07</td>
<td>13</td>
<td>17</td>
<td>3, 4</td>
</tr>
<tr>
<td>0.1</td>
<td>13</td>
<td>17</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: Each row is related to a different penalty, expressed in terms of the decrease in pregnancy probability that one is
willing to face in exchange for each additional abstinence day. The last three columns describe some relevant percentile
of the distribution (obtained by simulation) of the number of cycles until conception for couples who use each optimal
rule.
of the recommended days. Table 6 presents the optimal rules for different penalties, along with percentiles of the TTP distribution. Here, mucus is less important in choosing the optimal rule, and the midcycle interval is enlarged.

**DISCUSSION**

This article used a Bayesian decision-theoretic approach to search for optimal rules for timing intercourse to achieve conception. We first considered a biologically based model of the day-specific probabilities of conception in the menstrual cycle, incorporating information on timing and vulvar observation of cervical mucus score. Estimating the parameters in this model by using Bayesian methods applied to a new Italian database, we found that conception probabilities were effectively 0 outside of a midcycle interval starting on day 7 and ending on day 20. Within this midcycle interval, there was a dramatic increase in the probability of conception with increases in a 1–4 mucus score.

The day-specific probability of conception on a day with most-fertile type mucus is 40 times higher than that on a day with no noticeable mucus score. Although these initial results clearly implied that rules based on both calendar and mucus may perform well in predicting fertile days, we proceeded to conduct a systematic search to choose from among the enormous number of specific rules. By using a Bayesian approach, we found that simple rules that are based on increasing the frequency of intercourse on days within a midcycle interval having a mucus score at or above a threshold on a 1–4 scale have high theoretical effectiveness.

The optimal width of the midcycle interval and choice of threshold depend on the extent to which a couple is willing to face a modest decrease in conception probability in exchange for a lower frequency of intercourse. In particular, for couples strictly following the rule, placing a high penalty on additional intercourse days, the optimal rule prescribes intercourse between cycle days 13 and 17, only when there is most-fertile type mucus (mucus score, 4). The average number of required intercourse days is 2.42, and the predicted conception probability in a cycle for couples following this rule is 0.35, which gives a median waiting time of about three cycles.

We estimate, using the same data and the same model, that a couple having intercourse on one seventh of the days of a cycle without regard for timing or mucus characteristics has a median waiting time of about four cycles. Optimally utilizing information on calendar and mucus, while assuming an intercourse frequency of one seventh of days not recommended by the rule, the median TTP decreases to one to two cycles, with a waiting time of one cycle obtained if a low penalty on the number of intercourse days is assumed. These results are for couples who have biologic fecundity comparable to that of the sample of women in this study. The impact on TTP of intentionally timing intercourse using optimal rules will be less for more fecund couples (couples who have a higher than average probability of conception in a generic cycle when following the same pattern of intercourse) but substantially higher for low-fecundity couples.

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**TABLE 5**

Optimal rules, utility function, and probabilities of conception for couples who strictly follow the proposed rules: intercourse on each day identified by each rule in the midcycle interval and on 1/7th of days in the other intervals.

<table>
<thead>
<tr>
<th>Penalty</th>
<th>Midcycle interval start</th>
<th>Midcycle interval end</th>
<th>Mucus type</th>
<th>Cycle probability of conception</th>
<th>Mean no. of prescribed intercourse days</th>
<th>Cycles to pregnancy, by percentile (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6</td>
<td>25</td>
<td>No</td>
<td>0.668</td>
<td>20.00</td>
<td>1 2 3</td>
</tr>
<tr>
<td>0.01</td>
<td>10</td>
<td>18</td>
<td>No</td>
<td>0.654</td>
<td>9.00</td>
<td>1 2 3</td>
</tr>
<tr>
<td>0.03</td>
<td>12</td>
<td>17</td>
<td>No</td>
<td>0.605</td>
<td>6.00</td>
<td>1 2 4</td>
</tr>
<tr>
<td>0.05</td>
<td>13</td>
<td>17</td>
<td>2, 3, 4</td>
<td>0.546</td>
<td>4.45</td>
<td>2 3 7</td>
</tr>
<tr>
<td>0.1</td>
<td>13</td>
<td>17</td>
<td>3, 4</td>
<td>0.452</td>
<td>2.79</td>
<td>2 4 11</td>
</tr>
</tbody>
</table>

Note: Each row is related to a different penalty, expressed in terms of the decrease in pregnancy probability that one is willing to face in exchange for each additional abstinence day. The last three columns describe some relevant percentile of the distribution (obtained by simulation) of the number of cycles until conception for couples who use each optimal rule.

The identification of wet, slippery, stretchy or clear mucus, characterizing most-fertile type mucus, is very useful for couples wanting to shorten their TTP, achieving conception without requiring a high intercourse frequency. However, for couples who have intercourse on average every other day during the fertile window and occasionally during the rest of the cycle, calendar rules are sufficient, and mucus identification does not give any additional benefit.

Given the high degree of heterogeneity in biological fecundability and the degree of control that couples exercise over their procreation, it is impossible to obtain a truly representative sample of a modern population. The women currently using an NFP method are not necessarily representative of the general population of women attempting pregnancy. However, this is also true of other designs, which recruit a convenience sample of couples interested in conceiving. It is reassuring that the day-specific conception probability estimates follow a similar pattern to those reported in previous studies, including Wilcox et al. (55).

Given the nature of our sample, our results apply directly to couples with normal or high-normal fecundity and to cycles of median length of 28–29 days. However, Stanford et al. (12) argue that charting of vaginal discharge should be taken as a first step for couples having some difficulty achieving in a timely manner and for women with a history of irregular or infrequent cycles. This charting can serve to identify days with high conception probabilities, while also being diagnostic of sources of reproductive dysfunction. Correct classification of mucus requires some education of the women; at the beginning of our study, a teacher followed each woman, with the training then allowing women to identify easily the most-fertile type of mucus.

Our short median waiting time (around 1 or 2 cycles) for healthy couples using optimal rules suggests that one can potentially shorten the time required to diagnose infertility by having women chart discharge while using optimal rules for timing intercourse (calendar or mucus, depending on frequency of intercourse) to achieve conception. Hilgers (56) suggested that with timed intercourse, a diagnosis of infertility can be established in 6 months, and Gnoth et al. (57) suggested that after 6 months of intercourse with fertility-focused rules, a medical evaluation is appropriate.

Unsuccessful timed intercourse is diagnostic of the need for additional medical evaluation and intervention. The accepted approach is to allow younger couples with no historical risks for infertility ≤1 year before recommending an initial evaluation for infertility (58). Our results appear to confirm what already has been suggested by others (56, 57), which is that this interval could be shortened with

<table>
<thead>
<tr>
<th>Rule parameters</th>
<th>Cycles to pregnancy, by percentile (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Penalty 1/7th of days</td>
</tr>
<tr>
<td></td>
<td>Midcycle interval start</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
</tr>
</tbody>
</table>

Note: Each row is related to a different penalty, expressed in terms of the decrease in pregnancy probability that one is willing to face in exchange for each additional abstinence day. The last three columns describe some relevant percentile of the distribution (obtained by simulation) of the number of cycles until conception for couples who use each optimal rule.

**TABLE 6**

Optimal rules, utility function, and probability of conception for couples who have intercourse 1/2 of the days identified by each rule in the midcycle interval, and either never or 1/7 of the days in the other intervals.

documentation of appropriately timed intercourse based exclusively on calendar, or on calendar and mucus, independently of the peak day.

In future work, it will be useful to consider personalized rules that incorporate information such as age of the woman, hormone data obtained from fertility monitors, lengths of previous menstrual cycles, or even number of cycles attempting.

Potentially, there may be certain rules that work well for some couples but not for others. For example, the optimal midcycle interval may vary depending on whether a woman has long or short cycles and how regular they are. Also, mucus types can have different effects on the probability of conception in different women and in different cycles of the same woman. Incorporating such woman-specific information into the rule selection process should improve the performance of the rule, and potentially software could be developed that outputs the optimal rule when a user inputs personal cycle history, age, and other characteristics, such as desired intercourse frequency.

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REFERENCES