Effects of Sexual Intercourse Patterns in Time to Pregnancy Studies

Joseph B. Stanford¹ and David B. Dunson²

¹ Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT.
² Biostatistics Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC.

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Time to pregnancy, typically defined as the number of menstrual cycles required to achieve a clinical pregnancy, is widely used as a measure of couple fecundity in epidemiologic studies. Time to pregnancy studies seldom utilize detailed data on the timing and frequency of sexual intercourse and the timing of ovulation. However, the simulated models in this paper illustrate that intercourse behavior can have a large impact on time to pregnancy and, likewise, on fecundability ratios, especially under conditions of low intercourse frequency or low fecundity. Because intercourse patterns in the menstrual cycles may vary substantially among groups, it is important to consider the effects of sexual behavior. Where relevant and feasible, an assessment should be made of the timing and frequency of intercourse relative to ovulation. Day-specific probabilities of pregnancy can be used to account for the effects of intercourse patterns. Depending on the research hypothesis, intercourse patterns may be considered as a potential confounder, mediator, or outcome.

coitus; confounding factors (epidemiology); fertility; fertilization

Abbreviation: TTP, time to pregnancy.

In the study of factors predictive of human fecundity, such as environmental exposures, the most widely used epidemiologic design is the time to pregnancy (TTP) study (1–3). The purpose of this paper is to model the relation between different patterns of sexual intercourse (including both frequency and timing of intercourse) and time to pregnancy. Through the simulation of different patterns of sexual intercourse within the fecund window of the menstrual cycle, we model the effects of sexual intercourse patterns on mean time to pregnancy and fecundability.

TTP is usually measured prospectively or retrospectively as the number of menstrual cycles (or months) of noncontracepting intercourse until the occurrence of pregnancy (defined clinically or biologically). TTP has been used to study the effects of many exposures on human fecundity in both men and women (4–15). TTP is widely considered to be the preferred measure of fecundity for epidemiologic studies (16–18).

Studying TTP retrospectively is feasible, and study participants have been shown to have good recall (19, 20). Retrospective studies have the advantage of clearly identified sampling frames and high external generalizability. They are generally much less expensive to implement than prospective designs. Properly designed, they can include couples that do not conceive (18). However, they are limited in their ability to assess many exposures and, particularly, the timing of exposures (21).

Prospective TTP studies also have a number of advantages. These include more accessible and precisely timed assessments of exposures and covariates, as well as their changes over time (16, 17). Most prospective studies have been limited to couples that are explicitly planning pregnancy, raising concerns about the impact of excluding unplanned pregnancies. Questions remain about how much difference there is between planned and unplanned pregnancies, from the standpoint of assessing fecundity (22). It is
possible to design a sampling frame for a prospective study that includes couples that are not planning pregnancy (23). Prospective studies can capture early pregnancy outcomes, including early pregnancy loss and spontaneous abortion (24–26). In addition, with prospective data collection, one can obtain information on predictors of fecundity that may be less reliable or unavailable in retrospective studies, such as menstrual cycle characteristics (23, 27, 28), the timing of ovulation and intercourse within the cycle (29, 30), semen quality (31), cervical mucus characteristics (32, 33), and hormones (34). For example, recalled questionnaire data on the frequency of intercourse are probably less reliable than daily intercourse diaries (35). Concerns with prospective studies include the generalizability of volunteer-based samples and maintaining adequate retention. Methodological discussions of the strengths and weaknesses of retrospective and prospective TTP studies have been published (18, 21, 22, 36).

A direct counterpart to TTP is fecundability or the per menstrual cycle probability of conception. Fecundability is mathematically related to TTP, and it can likewise be studied prospectively or retrospectively (37–39).

Women can conceive only during a short interval of the menstrual cycle, and the probability of conception conditional on sexual intercourse varies from day to day within this fecund window (29, 30, 40). Therefore, intercourse timing and frequency affect TTP and fecundability (1, 41–43). Adjusting for the impact of intercourse behavior is important, even when the interest focuses on exposure effects, because different subgroups of the population may have different frequencies of intercourse (44–46).

Because the relation between intercourse frequency and the probability of conception is highly nonlinear (even on the logistic scale), it is not appropriate to simply include frequency as a continuous variable in a regression model (43, 47). For example, an intercourse frequency of zero implies a zero probability of conception within a given menstrual cycle, but the presence of other parameters in a regression model implies a nonzero probability of conception even if intercourse is absent. At the other extreme, there is little marginal difference in conception probability of increasing frequency of intercourse beyond every 2 days. Some TTP studies have adjusted for an overall measure of frequency of intercourse, using a set of categorical variables (8, 13, 14, 48).

Even if intercourse frequency is precisely measured, this does not eliminate the potential for confounding of TTP by sexual behavior, because couples may differ in the timing of intercourse during the menstrual cycle. Although the overall frequency of intercourse may be the same per month, there may be times during the menstrual cycle when couples may be more or less likely to have intercourse. Many couples informally use calendar calculations to guide decisions about when to have intercourse or when to use barrier contraception, according to their current intentions to achieve or avoid pregnancy (49). In addition, some couples use menstrual cycle symptoms, basal body temperature, or urine luteinizing hormone kits (49–51). The prevalence and nature of such practices are likely to vary among different socioeconomic groups, as is the general knowledge of the days of the menstrual cycle when the probability of conception is high. Although demographic surveys have included questions on the knowledge of the “fertile window,” we are unaware of any instances where such questions have been used to assess differences in such knowledge among groups in TTP studies (52).

A recent study demonstrated a 24 percent increase in intercourse frequency during the fecund window in women who had undergone tubal ligation or were preventing pregnancy by an intrauterine device (53). There is a clear evolutionary advantage to increased libido in the fecund window, in terms of reproductive efficiency. Thus, intercourse patterns could be considered not only as a potential confounder for time to pregnancy but also as an intermediary component of a path to fertility, or as another marker of reproductive function. Cyclic libido competes with social and cultural influences in determining patterns of sexual intercourse. An increase of intercourse during the fecund window may be more prominent in ethnic and cultural groups in which intercourse is likely to be initiated by the female (54). Prospectively collected daily records of intercourse could address various hypotheses regarding patterns of intercourse behavior as outcomes, intermediaries, or confounders in time to pregnancy (55). For example, it has been shown that apparent TTP may depend on the differential persistence of different couples of different ages in attempting to conceive (56). By analogy, it is possible that patterns of intercourse, corresponding to the intensity of attempting to conceive or the knowledge about fertility, may also differ by age or other characteristics.

Interest in the relation of sexual behavior to fecundity has led to the development of models of day-specific probabilities of pregnancy (30, 38–40). We now give an overview of the methodological aspects of day-specific probabilities of pregnancy; describe a model to assess the relations among day-specific probabilities, intercourse patterns, and TTP; illustrate this model with a series of simulations; and discuss the implications of the results for studies of TTP.

DAY-SPECIFIC PROBABILITIES OF PREGNANCY

In its simplest formulation, a day-specific probability of pregnancy is the probability of conception (measured clinically or biochemically) in the theoretical case that intercourse occurs just once on a given day within the fecund window. The concept of day-specific probabilities of pregnancy gives a measure of fecundity that is adjusted for the frequency and timing of noncontracepting intercourse, because conception is conditional upon the occurrence of intercourse on any specific day. Day-specific probabilities of pregnancy can be used to assess the effects of exposures, biologic factors, and demographic factors on human fecundity. This approach has been used to assess the effects of caffeine (57), recent use of oral contraceptives (30), and female and male age (46) on fecundity. As summarized recently, several models have been developed and applied to data from several prospective studies of conception and pregnancy (29, 30, 32, 38, 58).

A detailed review of methodological issues in the study of day-specific probabilities of pregnancy has been provided
elsewhere (59). Briefly, data for the analysis of day-specific probabilities of pregnancy are a daily diary of intercourse and use of contraception, a marker for the day of ovulation (optional; discussed further later in this paper), and an indicator of conception (biochemical or clinical). Because most couples have more than one act of intercourse during the potentially fertile days of the menstrual cycle, conception typically cannot be attributed to a single act of intercourse, and it is necessary to use a statistical model to estimate the day-specific probabilities of pregnancy (60). The most commonly used approach, the Schwartz model, assumes that sperm from different intercourse acts compete independently to fertilize the ovum (39). It is expressed as follows:

$$P_{ij} = pr(conception|X; A, p) = A(1 - \Pi_k(1 - p_k)^{X_{ik}}),$$

where $P_{ij}$ is the probability of conception for couple $i$ in cycle $j$, $k$ is the day in the cycle relative to ovulation ($k = 0$ on the day of ovulation), $X_{ik}$ is an indicator variable that equals 1 if intercourse occurred on day $k$ and 0 otherwise, and $A\pi_k$ is the probability of conception in a cycle with intercourse only on day $k$. The parameter $A$, cycle viability, is meant to measure all male and female factors influencing the probability of conception in a given cycle other than the timing of intercourse: It measures the biologic capacity for conception in a cycle. The effect of the occurrence of intercourse on a specific day is represented by the day-specific parameter, $p_k$. Enhancements of the Schwartz model have been proposed, including methods to model exposure effects (60–62) and unexplained differences among couples in their fecundity (62, 63). Statistical power and estimation efficiency can be improved by specifying assumptions about trends in the day-specific probabilities within the fecund window that are biologically plausible and consistent with unconstrained analyses (57). The Schwartz model can also be simplified by the removal of the cycle viability factor, allowing cycle viability to be modeled implicitly within the day-specific probabilities, thus improving the efficiency of parameter estimation (64).

The classic study reporting day-specific probabilities of conception was published in 1995 by Wilcox et al. (29). A later analysis of these same data, based on clinically defined pregnancies, found that the day-specific probability of conception is very low outside a 6-day window ending on the day of ovulation, and it is highest 2 days prior to ovulation (40, 65). More recently, an analysis of a larger European data set confirmed this pattern and showed substantial variation in the day-specific probabilities by age and substantial unexplained residual heterogeneity among couples in their day-specific probabilities (46).

The European fecundability study was based on 782 couples who kept daily diaries of intercourse, vaginal mucus discharge, and basal body temperature. Couples were potentially interested in conceiving sometime during the study period but were not necessarily planning pregnancy. The day of ovulation was estimated as the last day of hypothermia. There were 5,390 cycles and 434 pregnancies (30). We have summarized relevant day-specific probabilities of conception from this data set in table 1, illustrating the spectrum of fecundity associated with age (46). The major difference between age groups is in the overall cycle viability (parameter $A$); whether the smaller differences attributable to $p_k$ represent true differences in the nature of the fecund window across age groups is unknown.

**MODELING POTENTIAL EFFECTS OF INTERCOURSE PATTERNS**

It is clear from previous studies of the day-specific probabilities of conception that intercourse timing within the fertile window has a large impact on fecundability. However, to relate the day-specific probabilities to the time to pregnancy distribution, it is necessary to specify values for the frequency of intercourse on different days within the fecund window.

Specifically, letting $\pi_k$ denote the probability of intercourse on day $k$, Dunson (55) showed that the marginal probability of conception in a menstrual cycle, integrating the frequency of intercourse and timing of intercourse: It measures the biologic capacity for conception in a cycle. The effect of the occurrence of intercourse on a specific day is represented by the day-specific parameter, $p_k$. Enhancements of the Schwartz model have been proposed, including methods to model exposure effects (60–62) and unexplained differences among couples in their fecundity (62, 63). Statistical power and estimation efficiency can be improved by specifying assumptions about trends in the day-specific probabilities within the fecund window that are biologically plausible and consistent with unconstrained analyses (57). The Schwartz model can also be simplified by the removal of the cycle viability factor, allowing cycle viability to be modeled implicitly within the day-specific probabilities, thus improving the efficiency of parameter estimation (64).

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Specifically, letting $\pi_k$ denote the probability of intercourse on day $k$, Dunson (55) showed that the marginal probability of conception in a menstrual cycle, integrating out the intercourse timing and frequency and under the simplifying assumption that acts of intercourse occur independently, can be expressed as follows:

$$P = pr(conception|A, p, \pi) = A(1 - \Pi_k(1 - \pi_kp_k)).$$

Assuming that the intercourse probabilities, but not the actual timing and frequency of intercourse, are constant from cycle to cycle, and letting $T$ denote the random variable

<table>
<thead>
<tr>
<th>Table 1. Summary of day-specific probabilities of pregnancy from a multicenter European fecundability study, by age group*</th>
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<tbody>
<tr>
<td>Estimated day-specific probabilities of pregnancy</td>
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<tr>
<td>19–26 years</td>
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<td>---------------------------------------------------------------</td>
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<tr>
<td>A (cycle viability)</td>
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<td>$A \times p_k$ day $-8$</td>
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<td>$A \times p_k$ day $-1$</td>
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<td>$A \times p_k$ day 0 (ovulation)</td>
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<td>$A \times p_k$ day $+1$</td>
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<td>$A \times p_k$ day $+2$</td>
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* Information from Dunson et al. (Hum Reprod 2002;17:1399–403) (46).

† $A \times p_k$ denotes the probability of pregnancy from intercourse on a single day within the fecund window. The isolated day-specific parameter, $p_k$, can be obtained by dividing by $A$. For example, the $p_k$ for day $-2$ is $0.5336/0.5336 = 1$ for the women aged 19–26 years and is likewise 0.2901/0.2901 = 1 for the women aged 35–39 years. When there are multiple acts of intercourse in the fecund window, the “Schwartz model” is used to separate the cycle-level parameter $A$ from the day-specific parameter $p_k$, as shown in the equations in the text.
representing the number of menstrual cycles until conception, we have
\[
\Pr(T = t) = P(1 - P)^{t-1}
\]
= probability of conceiving in the \(r\)th menstrual cycle.

Therefore, because this equation represents a geometric distribution for TTP, the mean TTP is \(1/P\), which is a simple expression of the parameters \(A\), \(p\), and \(\pi\).

We used these equations to illustrate the effect of intercourse behavior on mean TTP. We generated simulations based on several systematic variations, focusing on the effect of intercourse timing across a range of values for the overall frequency of intercourse and for the underlying biologic fecundity of the couples. For all simulations, we calculated time to pregnancy distributions for three different patterns of intercourse timing: pattern 1, probabilities of intercourse proportional to the day-specific pregnancy probabilities \((\pi_t \propto p_t)\); pattern 2, constant probabilities of intercourse \((\pi_t = \text{constant})\) for all days in the fecund window; and pattern 3, probabilities of intercourse proportional to one minus the day-specific pregnancy probabilities \((\pi_t \propto (1 - p_t))\). For each pattern, we fixed the average daily frequency of intercourse within the fecund window in order to distinguish the effects of the pattern from the effects of the frequency on TTP. By including intercourse frequency as a covariate in TTP models, researchers implicitly assume that the daily intercourse probabilities are constant in the fecund window, as in pattern 2. In the presence of a midcycle rise in libido, intercourse patterns may tend toward pattern 1 (53, 66). In addition, couples who are using physiologic signs to identify their fertility will be more likely to exhibit pattern 1 (30, 32, 33). Pattern 3 represents the opposite extreme from pattern 1, where couples would seek to not have intercourse during days of higher fertility, a scenario for couples who seek to avoid or perhaps are ambivalent about pregnancy. We chose this range of patterns to represent a full range of different behavioral patterns that couples may follow, independent of the overall frequency of intercourse in the fecund window. Our models are based on the simplifying assumptions that no couples are sterile and that both the distribution of couple-specific fecundability and the mean fecundability do not differ among groups with different intercourse patterns.

We first conducted simulations systematically, varying the overall frequency of intercourse within the fecund window for couples with high fecundity, as represented by the day-specific probabilities estimated for women aged 19–26 years in the European fecundity study (table 1). Mean TTP values for different frequencies and patterns of intercourse are plotted in figure 1. We repeated this exercise for couples with low fecundity, as represented by the day-specific probabilities estimated for women aged 35–39 years in the European study (figure 2). In addition, we conducted simulations holding the average daily frequency of intercourse constant at 0.25 (or 1.75 times per week), while systematically varying cycle viability over a range of 0.1–0.5 (figure 3). The low end of this range is relevant for couples with impaired fecundity, e.g., due to an adverse exposure effect.

As expected, the model demonstrates in figures 1 and 2 that increasing the mean frequency of intercourse decreases the mean time to pregnancy in a nonlinear fashion, with the decreasing marginal effects on reducing TTP at higher mean frequencies of intercourse. However, it is also clear that, even with a constant overall frequency of intercourse in the fecund window, there can be substantial effects of the timing of intercourse. For example, couples with higher fecundity (figure 1) and an overall daily intercourse probability of 0.28 (or twice per week), the mean TTPs for the three
Patterns of intercourse are 1.9, 3.0, and 4.9 cycles for patterns 1, 2, and 3, respectively. The relative effect of intercourse patterns is more pronounced at lower overall frequencies of intercourse. For figure 1, the fecundability ratio of pattern 1 to pattern 2 is 1.6 at an intercourse frequency of 0.28 and 2.0 at an intercourse frequency of 0.1. For figure 2, the fecundability ratio of pattern 1 to pattern 2 is 1.4 at an intercourse frequency of 0.28 and 1.7 at an intercourse frequency of 0.1.

The effect of intercourse patterns at various levels of fecundity (cycle viability) is illustrated in figure 3. Here, the fecundability ratio remains constant, 1.7 for pattern 1 compared with pattern 2, but the absolute difference in TTP varies. For example, with a cycle viability of 0.3, the difference in mean TTP between pattern 1 and pattern 2 is 2.3 months, whereas with a cycle viability of 0.1, it is 6.8 months. In relation to environmental exposures that may impair fecundity, the potential for interaction of timing of intercourse and TTP at low fecundity is of particular interest.

RECOMMENDATIONS FOR PROSPECTIVE TIME TO PREGNANCY STUDIES

Our analysis shows that variations in the timing, as well as the frequency, of intercourse may affect TTP. Day-specific probabilities of pregnancy can yield estimates of fecundity that are adjusted for sexual behavior. At present, it is unknown to what extent differences in patterns of intercourse may exist among groups defined by various exposures and to what extent these patterns might be correlated with (and therefore partially adjusted for) measured demographic factors, largely because the necessary data are seldom collected in TTP studies. Determining the extent of these potential confounding effects in actual studies will require collecting the requisite data and completing the analysis of day-specific conception probabilities. Our simulations indicate that there is a potential for confounding of results of TTP studies if sexual behavior relative to the fecund window is not carefully considered in the analysis. Therefore, we believe that adjustments for intercourse patterns should be made when possible. At present, the methods to do this are available for prospective TTP studies.

Obstacles to considering the patterns of intercourse in prospective studies have included concerns about the burden for couples to collect daily data for intercourse, including concerns about enrollment and retention rates. In addition, there are concerns about the logistic burden and cost of obtaining a marker of ovulation, and there is a lack of familiarity with statistical methods for analysis of day-specific conception probabilities.

A recent review of prospective TTP studies illustrates that such studies are probably more feasible than generally supposed (22). Prospective designs with daily diaries have had cohorts with good compliance enrolled from community volunteers (22, 23, 29, 30), clinic-based samples (67), samples drawn from industry (26, 68), and community-based samples (69).

The analysis of day-specific probabilities of pregnancy requires a measure of the day of ovulation. The current “gold standard” for assessing the day of ovulation is daily urine collection. However, there are also other approaches that are less costly, that are simpler to use, and that yield satisfactory estimates of the day of ovulation. These include the measure of daily basal body temperature (which can be measured and stored with commercially available electronic devices), simple home-based measurement of urinary hormones based on a commercially available fertility monitor, or the observation of vaginal discharge of mucus, which is easily learned by women, requires no devices, and has an accuracy similar to that of basal body temperature (32, 70–72). Each of these approaches has been used or is being used in fertility or TTP studies (58). The latter two approaches have an additional advantage of providing women with information that is useful to help them achieve pregnancy, recognizing that this information may in itself affect the couples’ intercourse patterns (73).

Recently developed methods have made it possible to adjust for the timing of intercourse relative to the first day (74–76) or the last day of the menstrual cycle (or length of the previous cycle for conception cycles) (77, 78), without any other marker of ovulation. If available, daily information from vaginal discharge of mucus can provide additional information regarding the probability of conception, even without a direct marker of ovulation (79–81). It is not yet clear how much the precision in estimating the day-specific probabilities differs with or without a direct marker of ovulation. Alternatively, it is possible to collect the information needed for day-specific probabilities of conception for a subset of cycles and to use this information to generalize to a larger data set of cycles without this information (55).

RECOMMENDATIONS FOR RETROSPECTIVE TIME TO PREGNANCY STUDIES

Obtaining evidence that patterns of intercourse are similar among groups with different levels of exposure in retrospective TTP studies can provide reassurance that it is not
necessary to assess intercourse behavior to obtain valid results in some studies (21). An assumption of similarity of intercourse patterns is most robust where there are a relatively high fecundity and overall frequency of intercourse, or where the groups are similar in terms of demographic and cultural characteristics that may be associated with sexual behavior. Additional reassurance of similarity can be derived from using standard demographic questions to assess knowledge and beliefs about the fertile window (52). There are increased challenges with studies that seek to assess cultural and regional differences, including a greater potential for variability in sexual behavior (36).

However, it is also possible that methods could be developed to assess frequency and timing of intercourse in retrospective TTP studies. This could include the development and validation of tools to collect such information retrospectively or, perhaps, the application of prospectively collected behavioral data from groups similar to those under study. An integrated approach would be a combined design in which retrospective information is collected while also following women who are currently attempting prospectively. The intercourse diaries from the prospective data can be used as a validation subset with methods such as those proposed by Dunson (55). Given the importance and strengths of the retrospective TTP design in the considerations of feasibility and generalizability, such method development should be encouraged.

CONCLUSION

Having demonstrated differences in TTP based on intercourse patterns that include both frequency and timing of intercourse, we conclude that it is valuable to obtain data that will facilitate an analysis of day-specific probabilities of conception, to the extent possible within a specific study. For more background, we recommend several methodological papers as a starting point (22, 58, 59, 65, 78, 82). In addition, the forms for the classic North Carolina study are available on the Web at http://dir.niehs.nih.gov/direb/studies/eps/home.htm.

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