Optimal rules for timing intercourse to achieve pregnancy

Bruno Scarpa and David Dunson

Dipartimento di Statistica ed Economia Applicate
Università di Pavia

Biostatistics Branch,
National Institute of Environmental Health Sciences
U.S. National Institutes of Health

7 settembre 2006

Motivations

- Couples attempting pregnancy often become increasingly concerned as the months pass without a positive pregnancy test, pressing their clinicians
- Even in the absence of known causes of infertility, couples may be recommended for assisted reproductive therapy (ART) before the attempt time exceeds a year. But ART procedures can be extremely costly and may convey an increased risk of adverse outcomes
- For couples who could otherwise not conceive naturally, ART provides a valuable option. However, data suggest that most couples who do not conceive within the first year of attempting could conceive naturally if attempting for longer (Bongaarts, 1975; Dunson, Baird, Colombo 2004)
- The statistical explanation is that there is a high degree of **heterogeneity** among couples in their fecundability
- This heterogeneity leads to a highly skewed time to pregnancy distribution. As the attempt time increases, the distribution of fecundability among couples still at risk will increasingly concentrate on low values. However, since the proportion of sterile couples is very low (e.g., 1-3%) (Trussell and Wilson 1985), most couples not conceiving by a year are fecund

The fertile window

- Methods for **intentionally timing intercourse** during the most fertile days of the menstrual cycle provide a valuable alternative to couples concerned about a long time to pregnancy
- Numerous rules have been proposed based on self-monitoring of the menstrual cycle and symptoms of the fertile days (Stanford, White and Hatasaka 2003)
- Most rules are based on the identification of the ovulation day and the **fertile window** around it
- Methods of identifying the day of ovulation and the fertile window include basal body temperature, calendar calculations, serial ovarian ultrasound, monitoring of hormones in urine, monitoring of salivary electrolytes, and fertility charting of vaginal discharge...

In practice

- It is unclear which one of the available rules is the best available option
- Given that there has been no systematic search for optimal rules among the huge number of possibilities, there may be other rules yet to be defined that perform better than those proposed
- A good rule for intercourse behavior is one that
  - maximizes the probability of conception in a menstrual cycle,
  - minimizes the required days of intercourse
- Although there are not many individuals who would characterize a high intercourse frequency as a *loss* (!), most would agree that it is appealing to limit the number of days on which intercourse is *required*.
  Requiring intercourse on specific days may be stressful for many couples

Steps of our work

1. Accurately model day-specific fecundability across the menstrual cycle, allowing for heterogeneity with measured and unmeasured predictors.
   We also need to relate cycle day and biomarkers, such as basal body temperature and characteristics of vulvar secretions, to the day-specific probabilities of conception

Steps of our work

1. Accurately model day-specific fecundability across the menstrual cycle, allowing for heterogeneity with measured and unmeasured predictors.
   We also need to relate cycle day and biomarkers, such as basal body temperature and characteristics of vulvar secretions, to the day-specific probabilities of conception
2. Given intercourse on particular days of the cycle having particular biomarker levels, one can obtain a cycle-specific probability of conception. Depending on the rule being used, the intercourse days will be altered, resulting in an altered conception probability
   Our goal is to choose "good" rules for timing intercourse on the basis of cycle day and the time-varying biomarker for couples attempting conception.

An Italian Study

- We focus on data from a new Italian study of users of the Billing's Ovulation method of natural family planning (Colombo et al. 2006)
- 2536 menstrual cycles from 191 women have been collected, with 161 of these cycles (from 132 women) ending in a clinical pregnancy
- The participants collected detailed daily records of vulvar observations of the cervical mucus symptom, and recorded the days during which intercourse and menstrual bleeding occurred.
- Each day of the cycles has been classified according to the type of mucus symptom described by women
  1. dry
  2. a humid or damp feeling
  3. thick, creamy, elastic, whitish moist mucus symptom
  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. Therefore, the conception probability is expected to increase monotonically with mucus score

Biological aspects

- Suppose that data are collected from n couples, with couple i contributing n_i cycles $(i = 1, \ldots, n)$
- For cycle j from couple i, let $\mathbf{v}_{ij} = (v_{ij1}, \ldots, v_{ijD_{ij}})'$ be a vector of intercourse indicators,

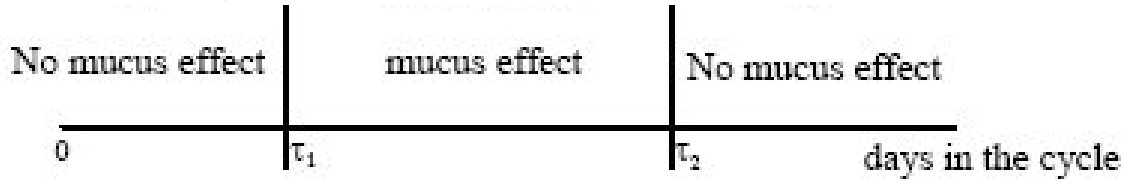
$$v_{ijd} = \begin{cases} 1 & \text{if there was intercourse on day } d \\ 0 & \text{otherwise} \end{cases}$$

and $y_{ij} = 1$ indicate conception

$$y_{ij} = \begin{cases} 1 & \text{if a conception is observed on cycle } j \\ 0 & \text{otherwise} \end{cases}$$

- An intercourse act can result in conception only if it occurs in a mid-cycle window ending on the day of ovulation
- Thus, time-varying predictors impact the probability of conception only when one or more acts of non-contracepting intercourse occur during the fertile interval

- We divide each cycle into three windows:



  The τ_1 and τ_2 are treated as unknown, but constant across cycles (for simplicity and identifiability).
- First, suppose that only daily intercourse records over the cycle are available to predict conception (no biomarkers available)
- Clearly, if we allow distinct probabilities for each day, there are too many parameters to be estimated (without incorporation of strong prior information)
- To reduce dimensionality, we assign a different baseline parameter for each of the three intervals l_1, l_2, l_{3ij}

Baseline Model

- Our baseline model for the probability of conception is

$$P\{y_{ij} = 1 \,|\, \xi_i, \mathbf{v}_{ij}\} = 1 - \prod_{d=1}^{D_{ij}} (1 - p_{id})^{v_{ijd}}$$

$$p_{id} = 1 - \exp\left\{ -\xi_i \sum_{t=1}^{3} \lambda_t 1_{(d \in I_{tij})} \right\}$$

where

- p_{id} is the day-specific probability of conception given intercourse on only day d,
- $I_{1ij} = I_1$ and $I_{2ij} = I_2$,
- λ_t $(t = 1, 2, 3)$ is the window-specific baseline parameter, and
- ξ_i is a couple-specific random-effect measuring the ith couple's biologic fecundity, with $\xi_i < 1$ representing low fecundity, $\xi_i = 1$ for typical fecundity, and $\xi_i > 1$ for above average fecundity

- The model may be rewritten as

$$P\{y_{ij} = 1 \,|\, \xi_i, \mathbf{v}_{ij}\} = 1 - \exp\left\{-\xi_i \sum_{t=1}^{3} \sum_{d \in I_{tij}} v_{ijd} \lambda_t\right\},$$

- To allow fecundity to vary continuously in the population, we let

$$\xi_i \sim \mathcal{G}\left(\nu^{-1}, \nu^{-1}\right)$$

where $\mathcal{G}(a, b)$ denotes the gamma density with mean a/b and variance a/b^2, so that $\nu = \text{var}(\xi_i)$

Extension: covariates

- Consider now the case in which a $D_{ij} \times q$ time-varying covariate matrix for cycle j from couple i, is available: $\mathbf{M}_{ij} = [\mathbf{m}'_{ij1}, \ldots, \mathbf{m}'_{ijD_{ij}}]'$.
- A parsimonious extention model would allow the day-specific probabilities in the mid-cycle interval to vary by a multiplicative factor depending on the level of the predictors on the day of intercourse

$$P\{y_{ij} = 1 \,|\, \xi_i, \mathbf{v}_{ij}, \mathbf{M}_{ij}\} = 1 - \exp\left\{ -\xi_i \sum_{t=1}^{3} \sum_{d \in I_{tij}} v_{ijd} \lambda_t \exp\left\{ (\mathbf{m}'_{ijd}\beta) 1_{(d \in I_2)} \right\} \right\},$$

  where β is a vector of regression coefficients
- We focus on a single M-level day specific categorical predictor (mucus effect) $w_{ijd} \in 1, 2, \ldots, M$, corresponding to the covariate matrix having rows $\mathbf{m}_{ijd} = [1_{(w_{ijd}=2)}, 1_{(w_{ijd}=3)}, \ldots, 1_{(w_{ijd}=M)})]'$, for $d = 1, 2, \ldots, D_{ij}$
- We assign each day d from cycle i, j to one of $K = M + 2$ categories

$$C_{ijd} = \begin{cases} 1 & \text{se } d \in I_1, \\ w_{ijd} + 1 & \text{se } d \in I_2, \\ K & \text{se } d \in I_{3ij}. \end{cases}$$

- Let $x_{ijk} = \sum_{d=1}^{D_{ij}} 1_{(C_{ijd}=k)} v_{ijd}$ denote the number of days in the jth cycle of couple i that have reported intercourse and that are in the kth category $(k = 1, \ldots, K)$, with $\mathbf{x}_{ij} = (x_{ij1}, \ldots, x_{ijK})'$
- The probability of conception is expressed as

$$P\{y_{ij} = 1 \,|\xi_i, \mathbf{x}_{ij}, \mathbf{M}_{ij}\} = 1 - \exp\left\{-\xi_i \sum_{k=1}^{K} x_{ijk}\lambda_k\right\},$$

where

  - $\lambda_1, \lambda_2, \lambda_K$ are the baseline parameters characterizing the probabilities of conception in the three intervals
  - $\lambda_k = \exp(\beta_{k-2})$ per $k = 3, \ldots, K-1$ allow changes from λ_2 across categories of the time-varying predictor

Comments on the model

- We assume that the biomarker data and the random effects will not be altered by changing the intercourse data through targeted intercourse.
- By estimating the couple specific random-effect ξ_i, this model allows for the unobserved etherogeneity among couples
- We obtain the marginal probability of conception integrating out the couple-specific random-effect ξ_i. A simple closed form is available:

$$\Pr(y_{ij} = 1 \mid \mathbf{x}_{ij}, \mathbf{M}_{ij}) = 1 - \left(1 + \nu \sum_{k=1}^{K} x_{ijk}\lambda_k\right)^{1/\nu}$$

.

MCMC algorithm for posterior computation

- Our model has an equivalent representation as an underlying Poisson variable model, with

$$y_{ij} = 1_{\left(\sum_{k=1}^{K} Z_{ijk} > 0\right)}$$

and Z_{ijk} conditionally-independent Poisson latent variables with mean $E(Z_{ijk}) = \xi_i \, x_{ijk} \, \lambda_k$. *Full conditional* posterior distributions are then easily obtained for each of the parameters and latent variables.

- Conditionally conjugate priors are chosen for each of the parameters:
  - discrete uniform priors for τ_1 and τ_2
  - gamma priors for $\lambda_1, \lambda_2, \lambda_K, \nu^{-1}$
  - a mixture of a point mass at one (with probability π) and a gamma density, possibly truncated below or above by one, for the $\gamma_m = \lambda_{m+1}/\lambda_m$ $(m = 1, \ldots, M-1)$
    These parameters quantify the effect of increasing, in I_2, the categorical predictor by one unit from m to $m+1$

- This parameterization allows for selecting predictors of the day-specific conception probability and may improve efficiency by incorporating constraints on the values of the multiplicative increments $\{\gamma_k\}$
- For example, focusing on ordered categorical predictors, if the covariate has a potentially beneficial impact on the probability of conception and an adverse effect can be ruled out *a priori*, then the constraint $\gamma_k \geq 1$ would be appropriate, and included in the prior by truncating below by one the gamma distribution in the mixture

Application to the Italian Study

- The time-varying marker is chosen as the 1-4 mucus score: we obtain $K = 6$ categories for the model.
- We choose a diffuse prior for the baseline parameters $\lambda_1, \lambda_2, \lambda_6$ by letting $a_{0k} = b_{0k} = 0.01, k = 1, 2, 6$ as parameters of the gamma distribution $\mathcal{G}(\lambda_k; a_{0k}, b_{0k})$.
- It is reasonable to assume that the probabilities are nondecreasing with increases in the mucus score for days of the second interval. We let $\pi_{0h} = 0.5^{1/3}$ for $h = 1, 2, 3$ and $a_h = b_h = 0.01, h = 1, \ldots, 3$ to allow a high degree of uncertainty in the values of γ_h under the alternative hypothesis
- We choose $c_1 = 1$ and $c_2 = 2$ to specify a weakly informative prior for the frailty variance ν.
- We let τ_1 vary uniformly within $[5, 12]$, and τ_2 within $[17, 25]$.
- We ran the MCMC algorithm for 12800 iterations, discarding the first 500 iterations as a *burn-in*
- Convergence was rapid and mixing was excellent, and these burn-in and collection intervals were deemed sufficient

Estimate of parameters

Posterior summaries of the parameters are

Parameter	Mode	Mean	Median	SD	95% Credible Interval
τ_1	5	5.96525	5.0000	1.1653	[5, 8]
τ_2	21	20.92396	21.0000	1.0284	[19, 23]
λ_1		0.00178	0.0000	0.0055	[0.00, 0.02]
λ_2		0.01052	0.0093	0.0065	[0.001, 0.027]
γ_1		6.66306	3.8479	11.1830	[1.20, 37.01]
γ_2		2.12287	1.6683	1.4273	[1.00, 6.11]
γ_3		14.27453	13.3324	5.8750	[5.71, 28.88]
λ_6		0.00042	0.0000	0.0014	[0.000, 0.005]
ν		1.82630	1.8016	0.3492	[1.20,2.58]

Conception probabilities estimate

Summary of Posterior Distributions for the 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 type of mucus on the intercourse day.

Category			Probability of conception		
k	Time interval	Mucus Type	Mean	SD	Credible Interval
1	$\leq \tau_1$		0.0017	0.0053	0.0000 - 0.0191
2	$(\tau_1, \tau_2]$	1	0.0103	0.0063	0.0014 - 0.0258
3		2	0.0381	0.0170	0.0115 - 0.0764
4		3	0.0643	0.0216	0.0316 - 0.1189
5		4	0.4077	0.0520	0.3059 - 0.5094
6	$> \tau_2$		0.0004	0.0014	0.0000 - 0.0048

A "good" rule

- Our goal is to choose "good" rules for timing intercourse for couples attempting conception
- We want to suggest intercourse in days predicted as most fertiles on the basis of
  1. cycle day from the beginning of the cycle
  2. time-varying biomarker (mucus, hormons, environmental expositions,...)
- A "good" rule is one which
  1. is simple to apply
  2. shortens the time to pregnancy
  3. while limiting the number of days on which intercourse is prescribed

Our Approach

- First we choose a list of simple rules as potential candidates
- We then specify a utility function, which rewards a high conception probability while penalizing number of prescribed intercourse acts
- Because this utility function necessarily involves many unknown parameters, we follow the approach of calculating the expected posterior utility averaged across the posterior distribution of the unknown parameters (DeGroot 1970; Berger 1985)
- The Bayes optimal rule among those considered is then the one with the highest expected utility

The Utility Function

- We define a set $\mathcal{R}$ of rules under consideration. For each day of the cycle, rule $R \in \mathcal{R}$ either recommends
  - that the couple has intercourse on that day
  - or else leaves the decision up to the couple's desire
- There may be a large number of rules, even when one focuses on simple rules based on calendar and the history of a single biomarker
- The utility function for a rule $R \in \mathcal{R}$ is defined as follows:

$$u_\delta(\theta, R, \mathbf{M}) = \Pr(y = 1|\theta, \mathbf{M}, R) - \delta B(\mathbf{M}, R),$$

where

  - $\Pr(y = 1|\theta, \mathbf{M}, R)$ is the probability of conception given parameters θ, biomarker data $\mathbf{M}$ and rule R,
  - $B(\mathbf{M}, R)$ is the number of days of required intercourse recommended by rule R given biomarker data $\mathbf{M}$, and
  - δ is a known penalty. It quantifies the decrease in pregnancy probability one is willing to face in exchange for one less day of required intercourse

Bayes optimal rule

For a new couple $i = n + 1$ wanting to limit their time to conception without knowledge of their biomarker data, the Bayes optimal rule is

$$\begin{aligned} R^* &= \arg\max_{R \in \mathcal{R}} U_\delta(R) \qquad \text{con} \\ U_\delta(R) &= \int u_\delta(\theta, R, \mathbf{M})\, \pi(\theta \,|\, \text{data})\, \pi(\mathbf{M} \,|\, \text{data})\, d\theta\, d\mathbf{M} dp(\theta|\mathbf{y}) \end{aligned}$$

where

- $\pi(\theta \,|\, \text{data})$ is the posterior distribution of the parameters in model given the data, and
- $\pi(\mathbf{M} \,|\, \text{data})$ is the posterior predictive distribution of the marker data $\mathbf{M}$ for a new subject

A wide class of rules

- We focus on rules based on calendar and mucus
- Rules prescribing intercourse on days within a mid-cycle window, between $\phi_1 + 1$ and ϕ_2 allowing
  - ϕ_1 to vary between 5 and 12
  - ϕ_1 to vary between 17 and 25
- Within this mid-cycle window we require intercourse
  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 day before
  6. on days with mucus score > 2 on that day or day before
  7. on days with mucus score > 3 on that day or day before
- We then obtain 504 different rules

Different patterns of intercourse acts

For each rule, we considered different patterns of intercourse acts

- For the first and the third interval we suppose that couples
  1. never have intercourse
  2. have intercourse on 1/7 of days, randomly chosen
- In the mid-cycle window we suppose that couples either
  1. strictly follow the rule, having intercourse every day required or
  2. choose randomly one half of the prescribed days
- By crossing the described possibilities we obtain four scenarios for which we evaluate the optimal rule

- For each scenario we consider the utility function with a range of values for the penalty coefficient δ
- We choose B_R in the utility function to be the average number of intercourse days that each rule prescribes, while other intercourse acts during the cycle decided by the couple are not considered as a loss

Results for the Optimal Rule Search

Optimal rules and utility function for couples that strictly follow the proposed rule.
Intercourse every day required by the rule in the mid-cycle interval and 1/7th of days in the others intervals

	Rule parameters			Utility function		
δ	Interval Start $\phi_1 + 1$	Interval End ϕ_2	Mucus type	Prob. of conc.	Number of prescribed intercourse days	$\hat{U}_\delta(R)$
0	6	25	no	0.688	20.00	0.688
0.003	8	21	no	0.683	14.00	0.641
0.01	10	18	no	0.654	9.00	0.564
0.03	12	17	no	0.605	6.00	0.425
0.05	13	17	2, 3, 4	0.546	4.45	0.323
0.055	13	17	3, 4	0.525	4.05	0.302
0.1	13	17	4	0.452	2.79	0.173

Results for the Optimal Rule Search

Percentiles from the distribution of the probabilities of conception for the optimal rules for couples strictly following the rule

	Percentile							Cycles to pregnancy percentile		
δ	0.05	0.10	0.25	0.50	0.75	0.90	0.95	50%	75%	90%
0	0.51	0.59	0.66	0.72	0.76	0.78	0.80	1	2	3
0.01	0.45	0.55	0.64	0.69	0.74	0.76	0.77	1	2	3
0.03	0.24	0.45	0.57	0.64	0.71	0.74	0.74	1	2	4
0.05	0.12	0.23	0.47	0.59	0.68	0.71	0.72	2	3	7
0.1	0.03	0.07	0.42	0.55	0.63	0.68	0.69	2	4	11

Bruno Scarpa
bruno.scarpa@unipv.it
Dipartimento di Statistica ed Economia Applicate
Università di Pavia

http://www.unipv.it/dipstea/wp/24.pdf