Predicting conception probabilities using daily mucus records

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Goal

- Investigate the relationship between cervical mucus characteristics on the day of intercourse, as recorded by the woman, and the probability of conception.

- The goal is to evaluate the extent to which cervical mucus characteristics predict the timing of the fertile interval and the day-specific probabilities of conception across the menstrual cycle.

- Data analyzed are from a large prospective Italian study of couples using the Ovulation Method (Previous studies were unable to properly address this question due to under-reporting of intercourse (WHO, 1983; Trussell and Grummer-Strawn, 1991) or to missing mucus data early and late in the cycle (Colombo and Masarotto, 2000)

Mucus classification

- Day 1 of the menstrual cycle was defined by the first day of fresh red bleeding, excluding any previous days with spotting.
- The main outcome measure was clinical conception, defined as an ongoing pregnancy at 60 days from the onset of the last menses. Clinically detected miscarriages were also recorded.
- Cycles were excluded from the analysis as non-informative if there were no reported intercourse acts, excluding days with menstrual bleeding or if there were no mucus recorded on the day of intercourse acts. Out of 2755 cycles of data with 177 conceptions, 2536 cycles from 191 women remained, including 161 conception cycles.
- We had complete mucus records across the cycle.
- Additional details on the study protocol... tomorrow.

Mucus classification

- **Mucus has been coded by women and instructors in 5 classes (we collapsed 4 and 5 in a unique class because of the similarity and the small number)**

Code	*Sensation*	*Appearance*
0	No information	No information
1	No sensation or dry sensation	No mucus nor loss or insubstantial loss
2	Not any more dry sensation	No mucus nor loss or insubstantial loss
3	Damp sensation	Thick, creamy, whitish, yellowish sticky, stringy mucus
4	Wet, liquid sensation	—
5	Wet-slippery sensation	Transparent, ropy, liquid, watery mucus, blood trails

4	Wet sensation

*If during a day there are different observations of the mucus symptom, the coding is determined by the most fertile type

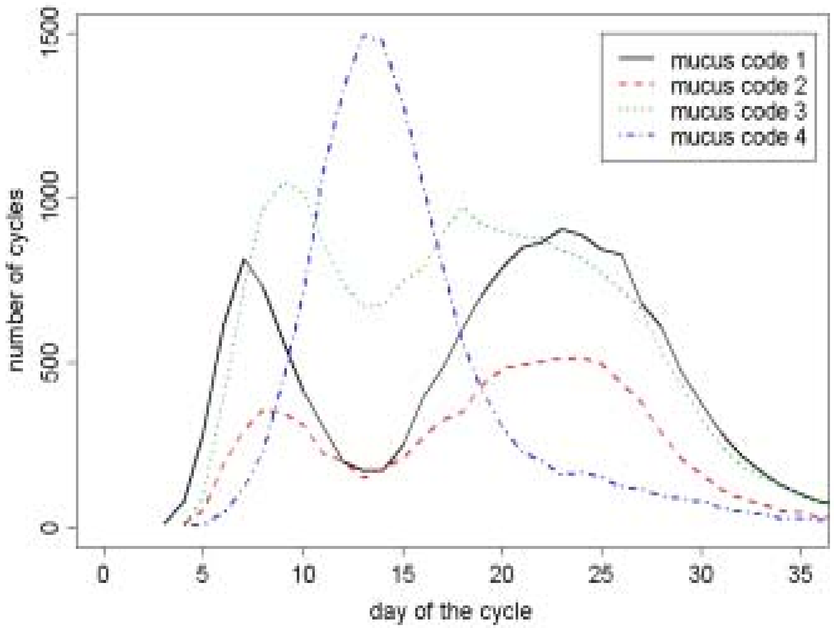
Descriptive statistics

Descriptive statistics of the number of days with each type of mucus

Code	Mean	Median	Interquartile Range	Deviation Standard
1	6.41	5	11	6.35
2	3.56	2	6	4.32
3	8.17	7	8	5.82
4	6.55	6	5	4.04

- Most fertile type mucus (code=4) was recorded for six days on average, a value corresponding to the width of the fertile interval reported by Wilcox et al. (1995) and Dunson et al. (1999).
- The number of days with most fertile type mucus varied considerably for different women, as did the frequency of occurrence of the other mucus sub-types. This high variability may partly reflect differences in the duration of the fertile interval.

Mucus type and day of the cycle



- The picture shows for each day the number of cycles observed in the dataset with each type of mucus
- The probability of observing a particular mucus type depends strongly on the day of the cycle

I. Using only mucus

- We use the Bayesian hierarchical model proposed by Dunson and Stanford (2004)

$$Pr\left(\begin{array}{c}\text{conception in a cycle with}\\ X_{ij}\text{ pattern of intercourse and}\\ \omega_{ijk}\text{ pattern of mucus}\end{array}\right) = 1-\exp\left\{-\xi_i \sum_{k=1}^{K} X_{ijk}\lambda \prod_{h=1}^{\omega_{ijk}-1} \gamma_h\right\}$$

- ξ_i is a couple-specific "random-effect" to accommodate dependence

- λ is a baseline parameter characterizing the distribution of probability of conception (Y_{ij}) for subjects with mucus type 1

- $\gamma_1, \gamma_2, \gamma_3$ quantify the effect on Y_{ij} of increasing the mucus score from 1 to 2, from 2 to 3 and from 3 to 4

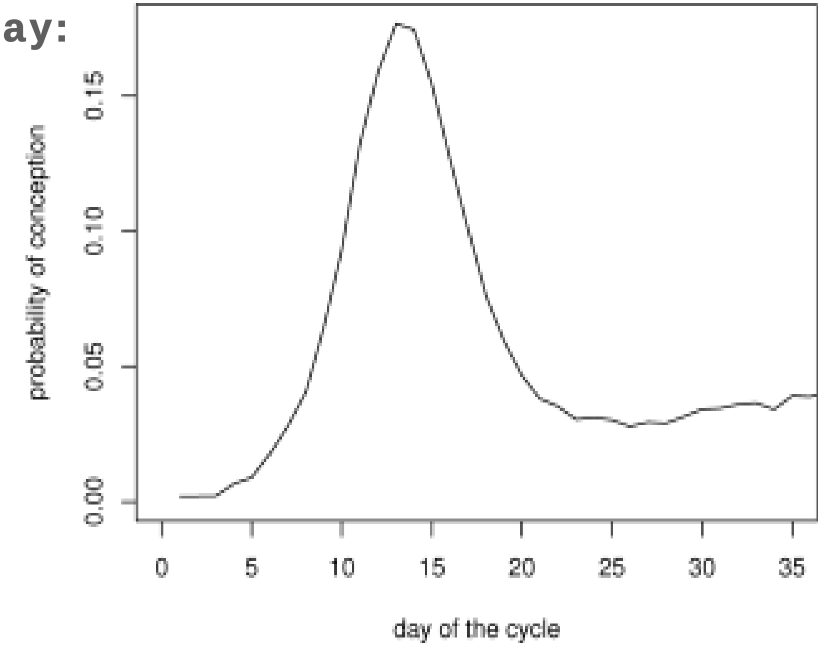
I. Using only mucus

- Bayesian estimates of the probability of conception are obtained
- We assume that pregnancy probabilities do not decrease with increases in the mucus score: $\gamma_h \geq 1$ for h=1, 2, 3
- We accounted for the possibility that mucus has no effect on the pregnancy which correspond to $\gamma_1 = \gamma_2 = \gamma_3 = 1$
- Choice of apriori:
  - For λ: a weakly informative prior distribution → Gamma(a, b), a and b chosen on the basis of Wilcox et al. (1995)
  - For γ_h: we assign probability 0.5 for no mucus effect → P($\gamma_1 = \gamma_2 = \gamma_3 = 1$)=0.5 and the rest is a weakly informative distribution for all the values greater than 1 → truncated Gamma(a_h,b_h)
  - For ξ_i: a weakly informative prior distribution → Gamma(ν^{-1},ν^{-1})

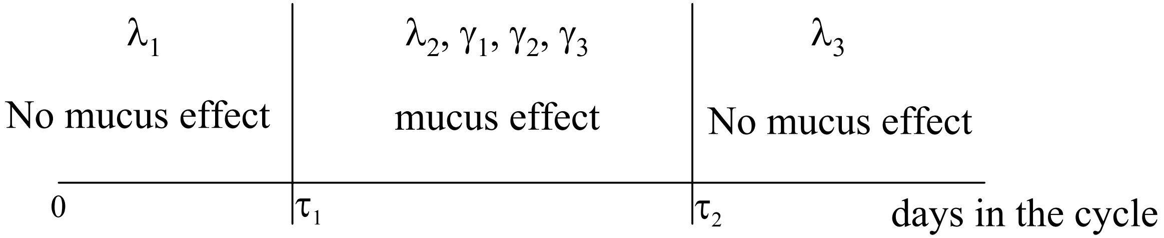
I. Estimated probability of conception for each day

- Aposteriori distribution are obtained using a MCMC method
- By combining the estimated probabilities of conception according to mucus type on the day of intercourse with the observed frequencies of the different mucus types on different days of the cycle, we estimated the marginal probability of conception on each cycle day:

Mucus type	Probability of conception		
	Mean	SD	95% Interval
1	0.0033	0.0021	0.0006 - 0.0088
2	0.0125	0.0058	0.0038 - 0.0262
3	0.0248	0.0084	0.0120 - 0.0448
4	0.2858	0.0418	0.2083 - 0.3713



II. Using mucus and calendar



- we use the Dunson and Stanford (2004) model

$$Pr\left(\begin{array}{c}\text{conception in a cycle with}\\ X_{ij}\ \text{pattern of intercourse and}\\ \omega_{ijk}\ \text{pattern of mucus}\end{array}\right) = 1 - \exp\left\{-\xi_i \sum_{k=1}^{K} X_{ijk}\lambda_t \prod_{h=1}^{\omega_{ijk}-1} \gamma_h\right\}$$

- ξ_i is a woman-specific “random-effect” to accommodate dependence
- $\lambda_1, \lambda_2, \lambda_3,$ are baseline parameters characterizing the distribution of Y_{ij} for all subjects in the first interval, for subjects with mucus type 1 for the second interval and for all subjects in the third interval
- $\gamma_1, \gamma_2, \gamma_3$ quantify the effect of increasing the mucus score from 1 to 2, from 2 to 3 and from 3 to 4

II. Using mucus and calendar

- Bayesian estimates of the probability of conception are obtained using as apriori

$$\left\{\prod_{i=1}^{n}\mathcal{G}(\xi_i;\nu^{-1},\nu^{-1})\right\}\mathcal{G}(\nu;c_1,c_2)\left\{\prod_{t=1}^{3}\mathcal{G}(\lambda_t;a_{0k},b_{0k})\right\}\left\{\prod_{h=1}^{3}\mathrm{I}_1\text{-}\mathcal{G}_{[1,\infty)}(\gamma_h;\pi_{0h},a_h,b_h)\right\}$$

- The estimated probabilities are

		Probability of conception		
Time interval	Mucus type	Mean	SD	95% Interval
$\leq \tau_1$		0.0017	0.0053	0.0000 - 0.0191
$(\tau_1, \tau_2]$	1	0.0103	0.0063	0.0014 - 0.0258
	2	0.0381	0.0170	0.0115 - 0.0764
	3	0.0643	0.0216	0.0316 - 0.1189
	4	0.4077	0.0520	0.3059 - 0.5094
$> \tau_2$		0.0004	0.0014	0.0000 - 0.0048

Parameter	Mode	Mean	SD
τ_1	5	5.96	1.16
τ_2	20	20.92	1.03

Other works/ongoing work

- Choosing the best rule for timing intercourse using calendar and mucus data (with D. Dunson)
  We define a loss function incorporating both pregnancy risk and abstinence days and look for an "optimal" rule among a simple class

- Cervical mucus symptom and daily fecundability: First results from a new data base (with B. Colombo, A. Mion, K. Passarin). Using the peak of mucus as indicator of the ovulation we estimate day specific probabilities for each type of mucus with reference to the peak day. We used a likelihood approach in a Schwartz – type model

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II. Exercise: An optimal rule

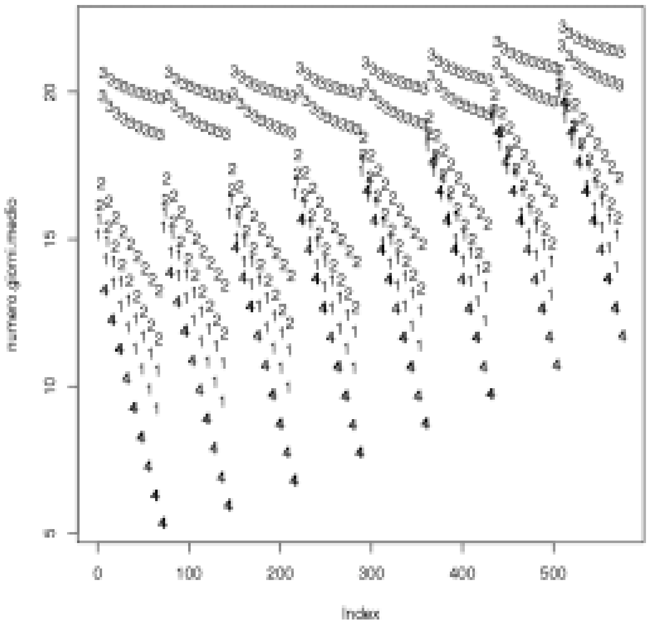
- Looking for a "rule" to avoid conception let us define a loss function:

$$E\{P|R\} = \int_{\theta} E\{P|R,\theta\}\pi(\theta|y)d(\theta)$$

- $R=\{\psi_1, \psi_2, A\}$ is the rule:
  - ✓ before ψ_1 and after ψ_2 intercourse acts are "safe"
  - ✓ Between ψ_1 and ψ_2 are "safe" days with mucus type less than h in the last day or with mucus type less then h for the last 2 days.
  - ✓ When "safe" different patterns of intercourse acts can be tested: every day or in 1/3 of days
- $\theta=\{\lambda_1, \lambda_2, \lambda_3, \gamma_1, \gamma_2, \gamma_3, \tau_1, \tau_2, \nu\}$ is the vector of all the parameters of the model
- Fix a maximum value B for the loss function

II. An optimal rule

- Some sketch of results:
  - ✓ **If** $B=0.01$ **the best rule is** $R=\{\psi_1=12, \psi_2=17, A=$ intercourse every day of mucus type at most equal 1$\}$**:** **maximum 6 days of abstension**
  - ✓ **If** $B=0.005$ **the best rule is** $R=\{\psi_1=10, \psi_2=18, A=$ intercourse every day of mucus type at most equal 4$\}$**:** **maximum 9 days of abstension**
  - ✓ **If** $B=0.001$ **the best rule is** $R=\{\psi_1=6, \psi_2=24, A=$ intercourse every day of mucus type at most equal 4$\}$**:** **maximum 19 days of abstension**



III. Mucus and peak day as ovulation marker

- **Schwartz model in relation with each type of daily observed mucus.**

$$P_j = k \cdot P_{f,j} = k \cdot \left[1 - \prod_i \left(1 + \exp\left(\delta_i + \beta M_{ij}\right)\right)^{-X_{ij}} \right]$$

- ✓ $P_{f,j}$ is the probability of fertilization in cycle *j* of a fertilizable ovule.
- ✓ $M_{ij}=(M0_{ij}, M2_{ij}, M3_{ij}, M4_{ij})^T$ is the vector of dummy variables which indicates the presence of different mucus codes (0,2,3,4, and 1 is the reference code) for a specific day i within a cycle j.
- ✓ We assumed for the fertilization probability α_i a logit relation $\mathrm{logit}(\alpha_i) = \delta_i + \beta M_{ij}$
- ✓ δ_i is the effect on the probability of fertilization depending on the specific position of day i
- ✓ $\beta = (\beta_0, \beta_2, \beta_3, \beta_4)$ $(h = 0, 2, 3, 4)$ is the effect on the probability of fertilization in the logit scale due to the presence of mucus of code h.
- ✓ The parameters estimation can be obtained through standard maximum likelihood procedures.

III. Estimates

Parameter	Estimate	Lower – Upper 90% Interval	Parameter	Estimate	Lower – Upper 90% Interval	$\exp\{\beta_h\}$
δ_{-8}	-26.62	(-∞, -4.975)	δ_1	-2.84	(-4.625,-1.228)	
δ_{-7}	-4.82	(-6.604, -3.434)	δ_2	-2.97	(-4.676, -1.426)	
δ_{-6}	-3.73	(-5.077, -2.574)	δ_3	-4.06	(-5.568, -2.790)	
δ_{-5}	-4.04	(-5.808, -2.571)	k	0.495	(0.378, 1)	
δ_{-4}	-1.75	(-3.318, -0.343)	β_0	1.727	(-1.014, 3.571)	5.624
δ_{-3}	-1.62	(-3.537, 0.927)	β_2	1.733	(0.468, 3.223)	5.658
δ_{-2}	-2.62	(-4.496, -0.731)	β_3	1.885	(0.892, 3.080)	6.586
δ_{-1}	-1.90	(-3.729, 0.507)	β_4	1.517	(0.228, 2.976)	4.559
δ_0	0.25	(-2.797, +∞)				

III. Probabilities of conception

- Estimated daily probabilities of conception with respect to the peak day