

Cervical mucus symptom and daily fecundability

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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))



Primary purpose of the study

- ❑ Predicting the fertile phase in a woman's menstrual cycle using cervical mucus symptom (CMS).
- ❑ The knowledge of the characteristics of this marker and his relationship with intercourse behaviour allow to identify levels of daily fecundability.
- ❑ Previous studies relating mucus information to fecundability (World Health Organization 1983) were limited by underreporting of intercourse (Trussell and Grummer-Strawn 1990)
- ❑ Other studies collecting detailed information on the timing of intercourse relative to a marker of ovulation, either did not collect any information on mucus (Barrett and Marshall 1969, Wilcox et al. 1995) or do not have large enough sample sizes for detailed analysis (Stanford, Smith and Dunson 2003).
- ❑ There was a clear need for the establishment of a new more reliable data base



Billings method

- ❑ The Billings Ovulation Method (Billings and Westmore 1998) relies on daily observations of the CMS throughout all of the cycle, that is, on the characteristics of the mucus as it appears at the vagina and the assessment of the associated sensation produced at the level of the vulva
- ❑ In describing her observations a woman makes use of words which seem appropriate to her but which are also understandable to her natural family planning teacher
- ❑ Her interpretation of the CMS is recorded on a chart usually by use of descriptive adjectives, conventional signs, or coloured stamps and the estimated day of the 'Peak Symptom' (the last day of observations of fertile-type mucus) is marked.



Billings method

□ the method divides a cycle into sections

- ✓ The days of the menses are considered potentially fertile since it is not possible to identify the CMS
- ✓ After the period, a possible infertile preovulatory phase may occur
- ✓ Two possible (depend from the woman) so-called *basic infertile patterns* (BIP) occur during the days following the period:
 - The most common is characterised by a sensation of dryness and by absence of mucus. This pattern can usually be identified by the woman already from her first cycle of observation (dry BIP).
 - The second is characterised by damp sensation and/or continuous mucus discharge: it is identified as an unchanging mucus pattern (u.m. BIP). The characteristics of sensation, appearance and consistency of discharge remain in this instance steadily unchanged day after day, cycle after cycle. A suitable number of cycles (generally three) will be necessary to learn to recognise this BIP.
- ✓ Any time the characteristics of the CMS becomes different from those typical for a specific BIP, it is considered that a *fertile phase* is beginning.



Billings method

- *mucus peak*: “The last day of the cycle during which at least one characteristics of high fertility in mucus type has been observed or felt, considering characteristics of high fertility a wet sensation and/or the observation of slippery, transparent, liquid or watery mucus, or of blood trails. Moreover, this day must be preceded by an adequate growth in sensation and appearance of mucus characteristics, which should also show afterwards a clear change to the less fertile”
- Ovulation is expected within two days after the peak: this can then be used as a reference for the determination of the end of the fertile phase.
- When in a cycle no peak is detected, it is not possible to judge if and when ovulation did occur and, therefore, to identify a *postovulatory infertile phase*.



Target population - sample

- ❑ **Prospective cohort study approved by the Institutional Review Board of Fondazione Lanza (Padua, Italy)**
- ❑ **Co-ordination of the study was made in the Department of Statistical Sciences of the University of Padua (prof. Bernardo Colombo)**
- ❑ **The study entry criteria for the subjects were:**
 - ✓ the woman was experienced in the use of the Billings Ovulation Method;
 - ✓ the woman was married or in a stable relationship;
 - ✓ the woman was between 18th and 40th birthday at admission;
 - ✓ the woman had at least one menses after cessation of breastfeeding or after delivery (or miscarriage);
 - ✓ the woman was not taking hormonal medication or drugs affecting fertility
 - ✓ Neither partner could be permanently infertile and both had to be free from any illness that might cause sub-fertility.
 - ✓ It was strictly required that couples did not have the habit of mixing unprotected with protected intercourse.

Women were excluded if any one of these criteria was not fulfilled.



Target population - sample

- **Co-operation of 4 Italian centres providing services on the Billings ovulation method**

Centre	City	Principal investigator
Centro Lombardo Metodo Billings-CLOMB	Milan	Mrs. Medua Boioni
Centro Piemontese Metodo Billings, CEPIMB	Saluzzo	Mrs. Lorella Miretti, RN
Associazione Metodo Billings Emilia-Romagna, AMBER	Parma	Sr. Erika Bucher
Centro Studi e Ricerche Regolazione Naturale della Fertilità	Rome	Mrs. Elena Giacchi, MD

- **During the years 1993-97 were recruited 193 women**
- **A few subjects had kept long series of past own observations. So long as it satisfied all the criteria of the programmed protocol, also this little piece of information was utilized in the construction of the data base.**



Target population - sample

- **At entry into the study, the following information was collected:**
 - month and year of birth of the woman and of her partner;
 - number of previous pregnancies, if any;
 - date of the last delivery (or miscarriage) and of the end of breastfeeding, if relevant;
 - date of last contraceptive pill taken, if relevant;
 - date of marriage and sex of the baby born.

- **In each menstrual cycle, the subject was asked to record on a chart**
 - the days of the period and of any disturbances (illness, broken sleep, etc).
 - her Cervical Mucus Symptom daily
 - daily every act of intercourse together with specification whether it was unprotected or protected (barrier methods, withdrawal,...)

Cycles in which even a single act of protected intercourse or a simple genital contact occurred were excluded from the analysis.



Target population - sample

- ❑ *A menstrual cycle* was defined as the interval from the beginning of one period of vaginal bleeding until the commencement of the next.
- ❑ Day 1 of the menstrual cycle was defined by the first day of fresh red bleeding, excluding any previous days with spotting.
- ❑ *A pregnancy* was assumed in the presence of amenorrhoea continuing at 60 days from the onset of the last menses, or when, before that term, a miscarriage was clinically detected.
- ❑ 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.



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)

<i>Code</i>	<i>Sensation</i>	<i>Appearance</i>
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

Centres	N. of women	N. of entries	N. of cycles	N. of detected pregnancies	At any entry			
					Age of women		Age of men	
					mean	s.d.	mean	s.d.
Milan	50	70	909	45	27.9	3.34	31.2	4.39
Parma	98	114	1,060	92	27.3	3.39	30.0	4.14
Saluzzo	17	22	267	16	28.9	4.56	32.5	4.69
Rome	28	36	519	24	31.8	3.22	34.3	4.88
All	193	242	2,755	177	28.3	3.77	31.2	4.58



Descriptive statistics

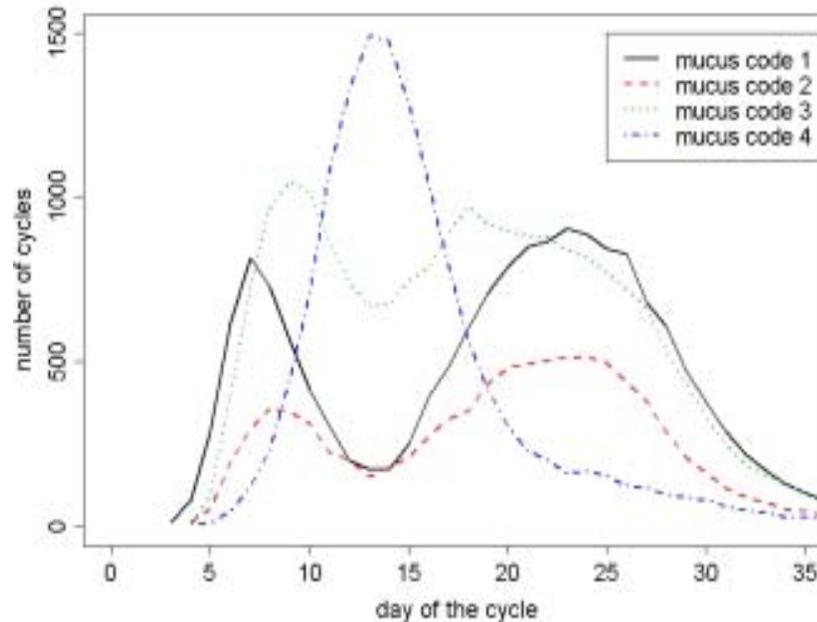
Descriptive statistics of the number of days with each type of mucus

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



Dunson and Stanford model (2004)

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

$$\Pr(Y_{ij}=1 \mid \xi_i, \mathbf{X}_{ij}, \mathbf{U}_{ij}) = 1 - \prod_k (1 - p_{ijk})^{X_{ijk}}$$

$$p_{ijk} = 1 - \exp\{-\xi_i \exp(\mathbf{u}_{ijk} \mathbf{b})\}$$

$$f(\xi_i) = \text{Gamma}(v^{-1}, v^{-1})$$

p_{ijk} = day-specific probability in cycle i,j on day k

ξ_i = fecundability multiplier for couple i

Generalization of Barrett and Marshall model



I. Using only mucus

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

- ξ_i is a woman-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 \rightarrow 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 $\rightarrow P(\gamma_1 = \gamma_2 = \gamma_3 = 1) = 0.5$ and the rest is a weakly informative distribution for all the values greater than 1 \rightarrow Gamma(a_h, b_h)
 - For ξ_i : a weakly informative prior distribution \rightarrow Gamma(v^{-1}, v^{-1})



I. Estimated probability of conception for each day

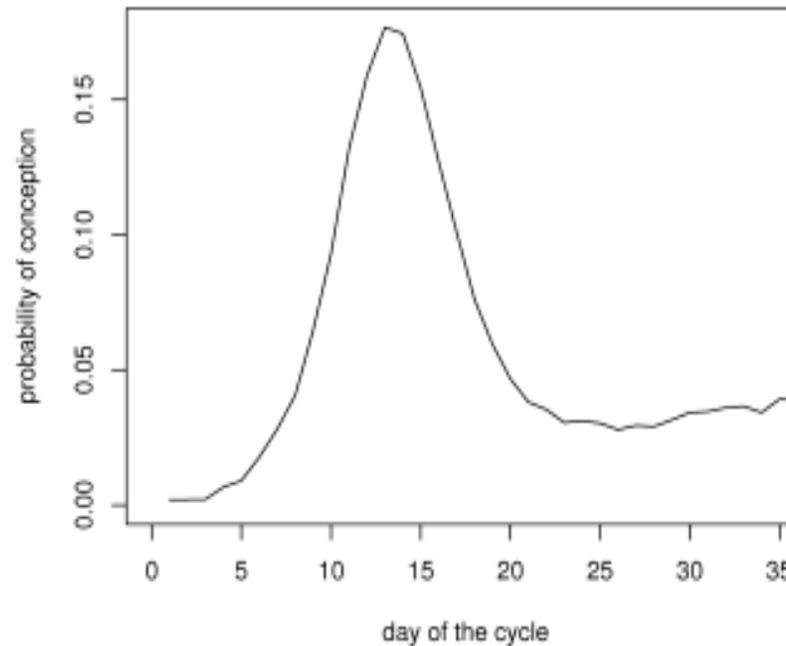
- Aposteriori distribution are obtained using a MCMC method

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



I. Estimated probability of conception for each day

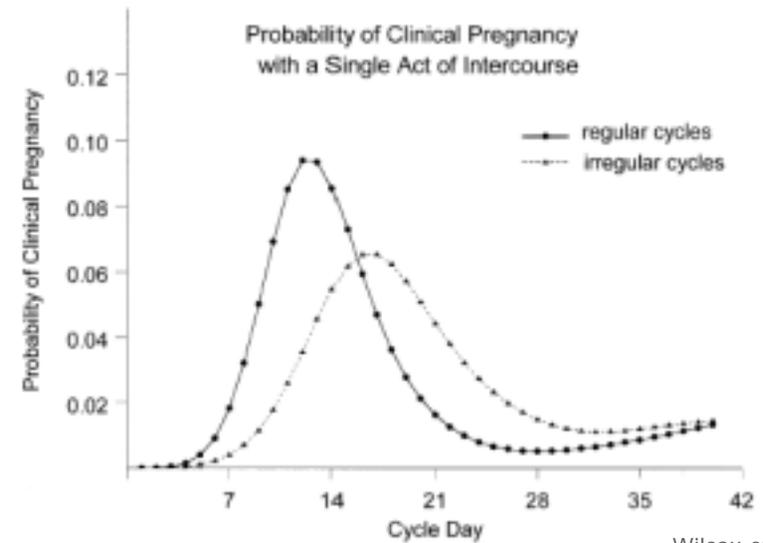
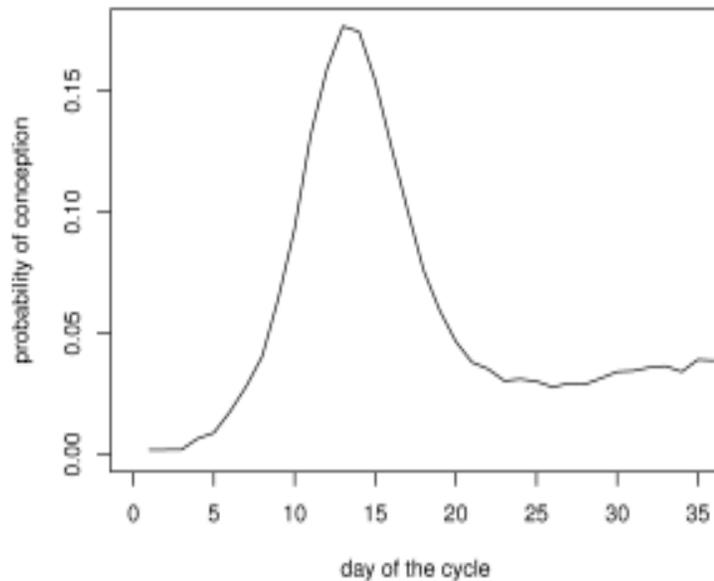
- By combining the estimated probabilities of conception according to mucus type on the day of intercourse with the observed frequencies of the different mucus types on different days of the cycle, we estimated the marginal probability of conception on each cycle day:





I. Estimated probability of conception for each day

- Similar to the relation reported by Wilcox et al. (2001) using day specific probabilities relative to a hormonal marker of ovulation day



Wilcox et al. (2001)

- The higher peak in our estimates likely reflects the fact that mucus type contributes additional information about the conception probability beyond marking the fertile interval



I. Biological interpretation

- ❑ **Results consistent with the known role of estrogenic cervical mucus in marking the fertile interval and in regulating sperm survival and transport to the ovum.**
- ❑ **The strength of the association between type of mucus on the day of intercourse and the probability of conception suggests that secretions may be even more important biologically than previously believed.**
- ❑ **Given that reliable information on mucus can be collected non-invasively by a woman without need for expensive devices or clinic visits, cervical mucus monitoring should play an increasing role in assessing a womens' fertility, both clinically and in epidemiologic studies.**
- ❑ **The four point scale for classifying mucus was designed to be both simple for women to use and highly predictive of the type and amount of mucus:**
 - ✓ most-fertile type mucus (mucus type 4) has characteristics of estrogenic-type mucus, and hence intercourse on days with most-fertile type mucus should have much higher conception probabilities than intercourse on days with less fertile-type secretions.
 - ✓ the probability of conception is almost 100 times higher when intercourse occurs on a day with most fertile-type mucus instead of a day with no secretions.



I. Clinical guidelines

- **Our data suggest that self-monitoring of cervical mucus secretions to identify days with most fertile-type mucus should be a highly effective approach for selecting days with high conception probabilities.**
- **Advantages of this approach over ovulation-detection kits, include**
 - (1) lower cost: monitoring of mucus requires only minimal training and no special equipment;**
 - (2) greater efficacy: most fertile-type mucus secretions typically appear early in the fertile interval and occur during the most fertile days while ovulation-detection kits typically miss the most fertile days;**
 - (3) collecting mucus data provides additional information on ovarian function which can be used to diagnosis possible causes of infertility.**

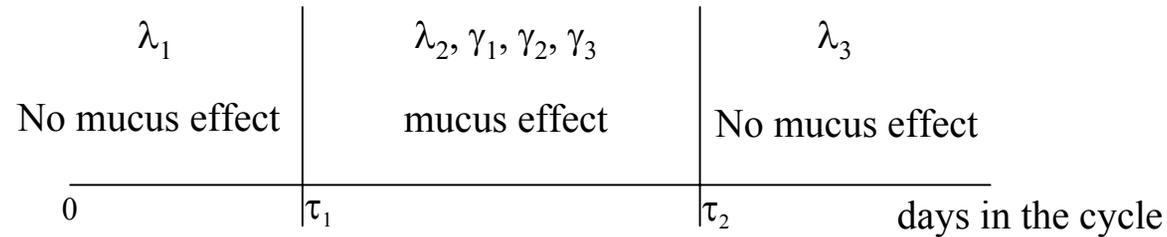


I. Advice to couples

- ❑ On days of the menstrual cycle with a wet sensation in the vagina and mucus discharge that appears transparent, ropy, liquid or watery (type=4), non-contraceptive intercourse is much more likely to result in conception compared with days with no mucus or thick, creamy mucus.
- ❑ By timing intercourse on such days, couples wishing to conceive can enhance the probability of conception and reduce time to pregnancy.



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

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

- The estimated probabilities are

Time interval	Mucus type	Probability of conception		
		Mean	SD	95% Interval
$< \tau_1$		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



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 than h for the last 2 days.
- ✓ When “safe” different patterns of intercourse acts can be tested: every day or in 1/3 of days

- $\theta = \{\lambda_1, \lambda_2, \lambda_3, \gamma_1, \gamma_2, \gamma_3, \tau_1, \tau_2, v\}$ 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**

$R=\{\psi_1=12, \psi_2=17, A=\text{intercourse every day of mucus type at most equal } 1\}$:
maximum 6 days of abstension

✓ **If $B=0.005$ the best rule is**

$R=\{\psi_1=10, \psi_2=18, A=\text{intercourse every day of mucus type at most equal } 4\}$:
maximum 9 days of abstension

✓ **If $B=0.001$ the best rule is**

$R=\{\psi_1=6, \psi_2=24, A=\text{intercourse every day of mucus type at most equal } 4\}$:
maximum 19 days of abstension



III. Mucus and peak day as ovulation marker

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

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

- ✓ P_{fj} 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 $\text{logit}(\alpha_i) = \delta_i + \beta M_{ij}$
- ✓ 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.



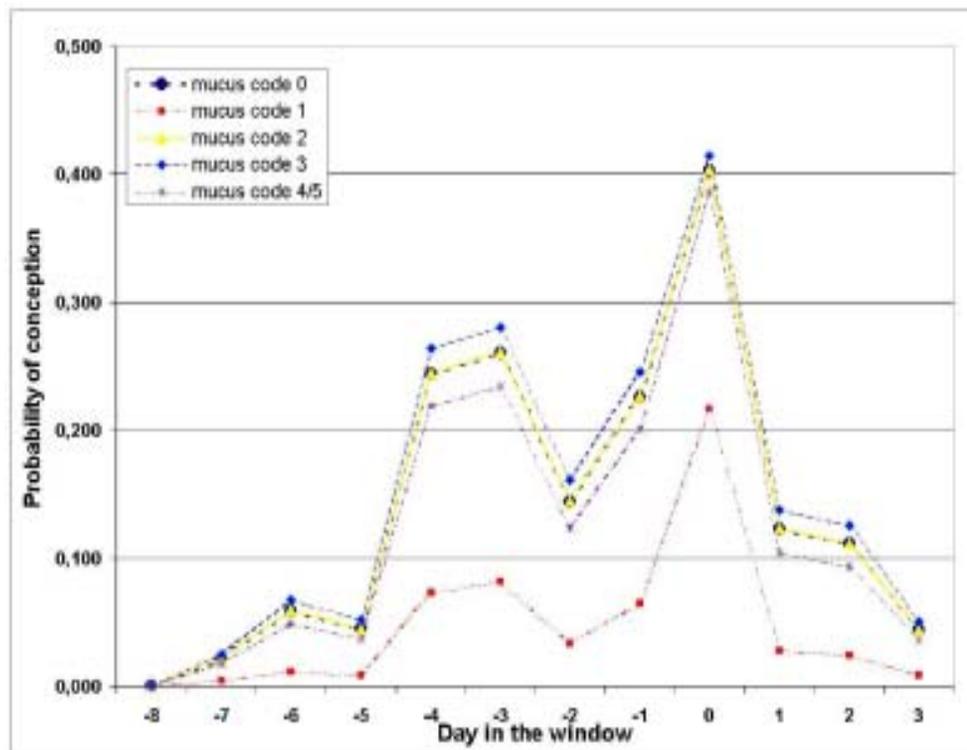
III. Estimates

Parameter	Estimate	Lower – Upper 90% Interval	Parameter	Estimate	Lower – Upper 90% Interval	$\exp \{ \beta_h \}$
δ_{-8}	-26.62	$(-\infty, -4.975)$	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	$(-2.797, +\infty)$				



III. Probabilities of conception

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





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Analysis done

- Passarin Katia (1998), Old and new fecundability estimates and their applications (italian), Laurea Thesis, Facoltà di Scienze Statistiche, University of Padua
- Colombo B., Mion A., Passarin K., Scarpa B. (2004) Cervical mucus symptom and daily fecundability: First results from a new data base, Working Paper, Department of Statistical Sciences, University of Padua, N.2/2004
http://wp.stat.unipd.it/2004_2.pdf
Submitted to *Demographic Research*
- Scarpa B., Dunson D.B. (2004) Mucus on the day of intercourse predicts conception, *in progress*
- Scarpa B., Dunson D.B. (2004) Choosing the Best Rule for Timing Intercourse Using Calendar and Mucus Data, *in progress*
- Colombo B., France J. (2004) Timing of intercouses end sex of new born, *in progress*



Metodologic issues

Problems on study design

- Mucus codification
- Strong participation of the couples on the purposes of the study
- First period of data collection (selection of a nonrandom sample)

Problems on data analysis

- Small numbers of cycles and of conceptions are not useful
- Schwartz (and others) model need much more data



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