

The Fertile Window from Studies of Conception

Warsaw, october 8, 2005

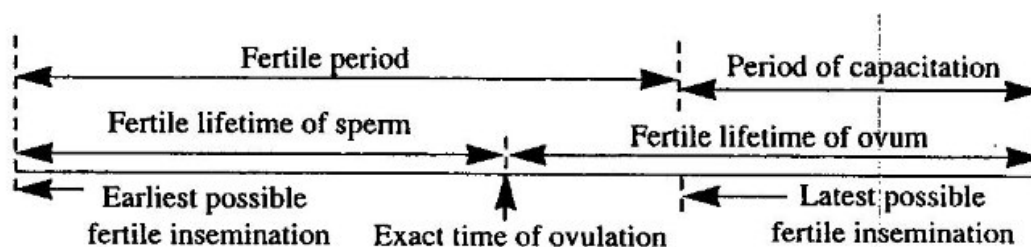
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Biological models and empirical evidence

- In principle, the main factors determining the length of the fertile period have been identified, if not precisely measured. The absolute outer limits of the fertile period are set by the maximal fertile life spans of sperm and egg, that is, by the maximum amount of time either type of gamete can survive in the female reproductive tract and still be capable of taking part in fertilization
- For sperm this life span is measured from the time of ejaculation, for eggs from ovulation

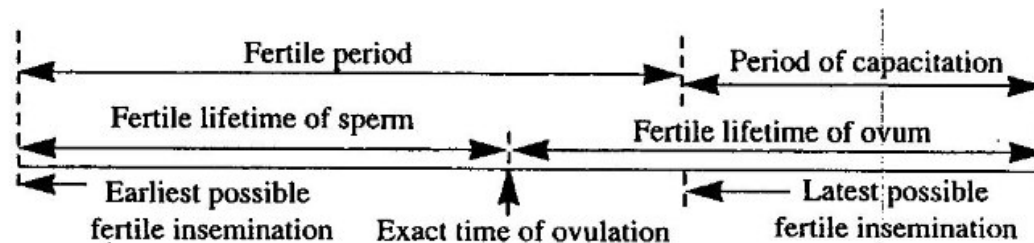


- If sperm can survive no more than T_s days after ejaculation and still be fertile then an insemination occurring more than T_s days before ovulation cannot result in fertilization
- If an egg can survive and be fertilized no more than T_e days after ovulation, no insemination falling more than T_e days after ovulation can result in fertilization.
- Thus we would expect the fertile period to be at most $T_s + T_e$ days long
- With the “complication” of the *sperm capacitation and activation*



Biological models and empirical evidence

- The physiological relations for each woman are known and analyzed, but both location and length of the fertile window depend on the specific characteristics of every woman and vary between women and cycles.





We need data

- In order to have useful indications about a generic cycle of a generic woman we need data on a large number of women describing in detail the entire distribution**
- Then we expect the extension of the fertile window of a new woman to be different from the observed ones**
- In particular, if our aim is to predict the fertile windows for new cycles, the specific interesting characteristics of every single cycle are unknown a priori; therefore we can not identify with enough precision the fertile window for each cycle of every woman, and we need to refer to distributions obtained by using carefully sets of women.**



the available data

- **A short (partial) summary of some data set with relevant information in order to identify the fertile window**
- **EPS data (Early Pregnancy Study)**
 - **221 healthy women from North Carolina (gathered by NIEHS)**
 - **Couples were enrolled at the time they stopped using any form of birth control, and they were planning to conceive.**
 - **Volunteers were mainly white women, college educated. Women were aged 21-42 years, 80% of which were aged 26-35 years.**
 - **Each women collected daily first-morning urine specimens, which were frozen and stored for later analysis. The day of ovulation was defined by measures of oestrogen and progesterone metabolites in urine, the ratio of which decreases abruptly with luteinization of the ovarian follicle. This measure of ovulation corresponds approximately to the urinary luteinizing hormone (LH) peak (Baird, et al. 1991) and to rupture of the ovarian follicle.**
 - **The ovulation day has been detected for 696 cycles from the 221 women**
 - **For detection of pregnancy, they rely on a highly sensitive and specific polyclonal immunoassay to define a sustained rise of intact urinary human chorionic gonadotropin (HCG)**
 - **Women were also asked to record each morning whether or not they had intercourse in the previous 24 h.**



→ the available data

□ **The Barrett and Marshall data**

- **241 British married couples who had at least one child upon entering the study**
- **The couples were recruited upon seeking advice about natural family planning from the Catholic Marriage Advisory Council**
- **Women were aged 21-50 years and 90% were aged 20-39 years**
- **Each women kept daily records of basal body temperature (BBT) which has been used to detect the ovulation day. Women who regularly produced temperature charts that were difficult to interpret were excluded from the study**
- **The rise of BBT has been detected by the 3/6 rule. The ovulation is assigned the day before the rise of BBT**
- **Women recorded also days in which they had intercourse.**
- **The useable data consisted of 2192 cycles from 241 women. Pregnancy was reported in 103 cycles**



→ the available data

□ **Multicentric (European) study - FERTILI**

- **782 couples recruited from 7 European centers (Milan, Verona, Lugano, Dussenldorf, Paris, London, Bruxelles) providing services on fertility awarness and natural family planning + 99 couples from Auckland (New Zealand)**
- **Women were between 18 and 40 years of age, in stable relationship, had at least one menses after the most recent cessation of breastfeeding or delivery, were not currently taking hormonal medication or drugs affecting fertility. In addition, neither partner could have a history of fertility problems and couples were required to not be in the habit of mixing unprotected and protected intercourse.**
- **Women collected demographic data, and they kept daily records of BBT, of cervical mucus (classified in 5 types).**
- **Ovulation days were estimated from the rise in BBT using the 3/6 rule. The peak of the mucus was also collected.**
- **Couples recorded the days during which intercourse and menstrual bleeding occurred**



→ the available data

□ **Italian study – “Billings”**

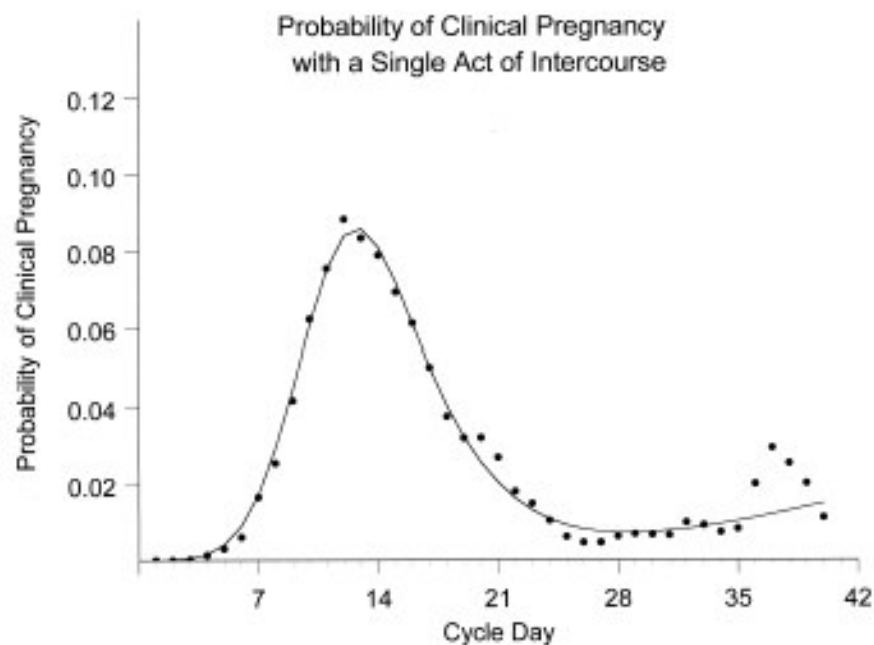
- **193 couples were recruited from 4 Italian centers (Milan, Saluzzo, Parma, Rome)**
- **Women were between 18 and 40 years of age, in stable relationship, had at least one menses after the most recent cessation of breastfeeding or delivery, were not currently taking hormonal medication or drugs affecting fertility. In addition, neither partner could have a history of fertility problems and couples were required to not be in the habit of mixing unprotected and protected intercourse.**
- **Couples were expert in Billings ovulation method of Natural Family Planning**
- **Women collected demographic data, and they kept daily records of cervical mucus (classified by supervisors in 5 types).**
- **Couples recorded the days during which intercourse and menstrual bleeding occurred**



Probabilities of conception

- We can obtain the fertile window by estimating pregnancy probabilities counting forward from the previous menses by referring to the first day of the cycle.
Then we can identify days with positive probabilities. Although this interval is admittedly quite variable (includes the variability on the ovulation day), it is less biased. (EPS data)

- Window: >3 (or 6-24)!



Cycle day	All women	Women with regular cycles	Women with irregular cycles
1	0.000	0.000	0.000
2	0.000	0.000	0.000
3	0.001	0.001	0.000
4	0.002	0.002	0.001
5	0.004	0.004	0.001
6	0.009	0.009	0.002
7	0.017	0.018	0.004
8	0.029	0.032	0.007
9	0.044	0.050	0.011
10	0.061	0.069	0.018
11	0.075	0.085	0.026
12	0.084	0.094	0.035
13	0.086	0.093	0.045
14	0.081	0.085	0.055
15	0.072	0.073	0.061
16	0.061	0.059	0.065
17	0.050	0.047	0.065
18	0.040	0.036	0.062
19	0.032	0.028	0.057
20	0.025	0.021	0.051
21	0.020	0.016	0.044
22	0.016	0.013	0.038
23	0.013	0.010	0.032
24	0.011	0.008	0.027
25	0.009	0.007	0.023
26	0.008	0.006	0.020
27	0.007	0.005	0.017
28	0.007	0.005	0.015
29	0.007	0.005	0.013
30	0.007	0.006	0.012
31	0.008	0.006	0.011
32	0.008	0.007	0.011
33	0.009	0.007	0.011
34	0.009	0.008	0.011
35	0.010	0.009	0.012
36	0.011	0.010	0.013
37	0.012	0.010	0.013
38	0.013	0.011	0.014
39	0.014	0.012	0.014
40	0.015	0.013	0.014



Direct estimates

- Consider **only** cycles with a single act of intercourse in a wide central window
 - Consider **BBT rise** as a marker of ovulation (the same table can be obtained by using other markers)
 - The ratio of instances in which the acts of one day resulted in conception to the total number of acts of intercourse of the same day gave, for that day, an estimate of the probability of conception:

(Multicentric data)

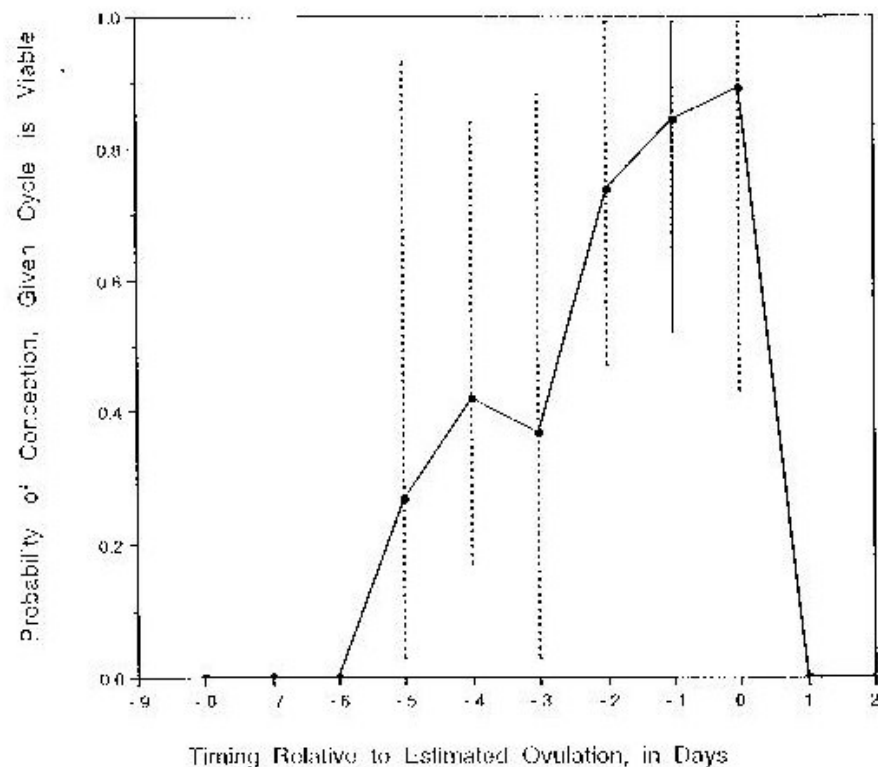
		Distribution of single acts of intercourse in the window												
Cycles		-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	Total
European centres	Conc. cycles	1	1	4	2	9	8	4	5	2	0	4	0	40
	All cycles	265	151	92	55	40	29	26	25	29	35	85	343	1175
	Ratio	0.004	0.007	0.043	0.036	0.225	0.276	0.154	0.200	0.069	0	0.047	0	0.034
All centres	Conc. cycles	1	1	6	5	13	10	12	13	9	2	5	0	77
	All cycles	269	154	97	67	47	35	37	40	46	54	94	348	1288
	Ratio	0.004	0.006	0.062	0.075	0.277	0.286	0.324	0.325	0.196	0.037	0.053	0	0.060

- **Window: (-8; 2)**



Estimates through a statistical model

- Consider all cycles, even with multiple acts of intercourse: it is not possible to attribute conception to a single act
- We need a statistical model to obtain daily conception probabilities by combining information coming from different observed cycles
 - **By referring to a hormone marker of ovulation day (EPS data)**
- **Window: (-6; 1)**



Note: This shows the fitted p_t parameters (see text) for the extended Barrett and Marshall model applied (using maximum likelihood) to the data from the Early Pregnancy Study. The estimate for A , the probability of cycle viability, is 0.37. The vertical dashed lines show estimated 95% confidence intervals, based on the likelihood ratio criterion.

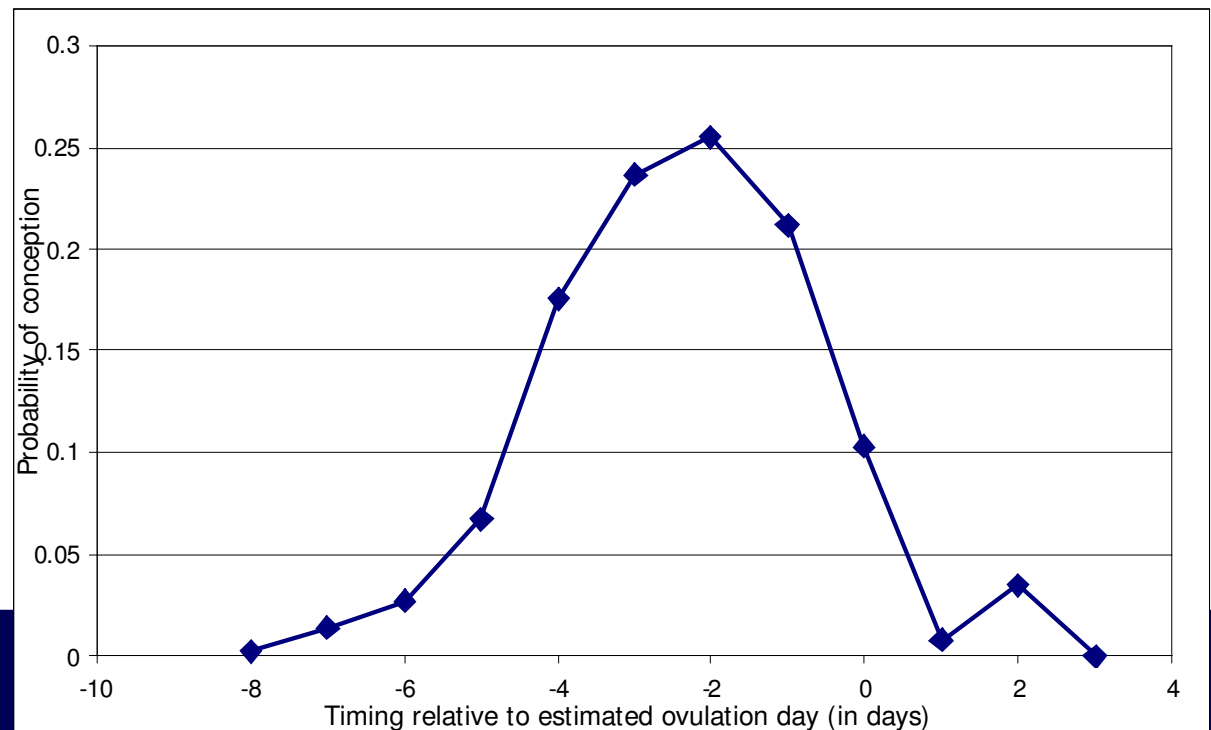


By using a less precise ovulation marker

- Consider all cycles even with multiple acts of intercourse
 - By referring to rise of BBT as an ovulation marker
 - We add a new (and relevant) variability source between cycles and women

(Multicentric data)

□ Window: (-8; 2)



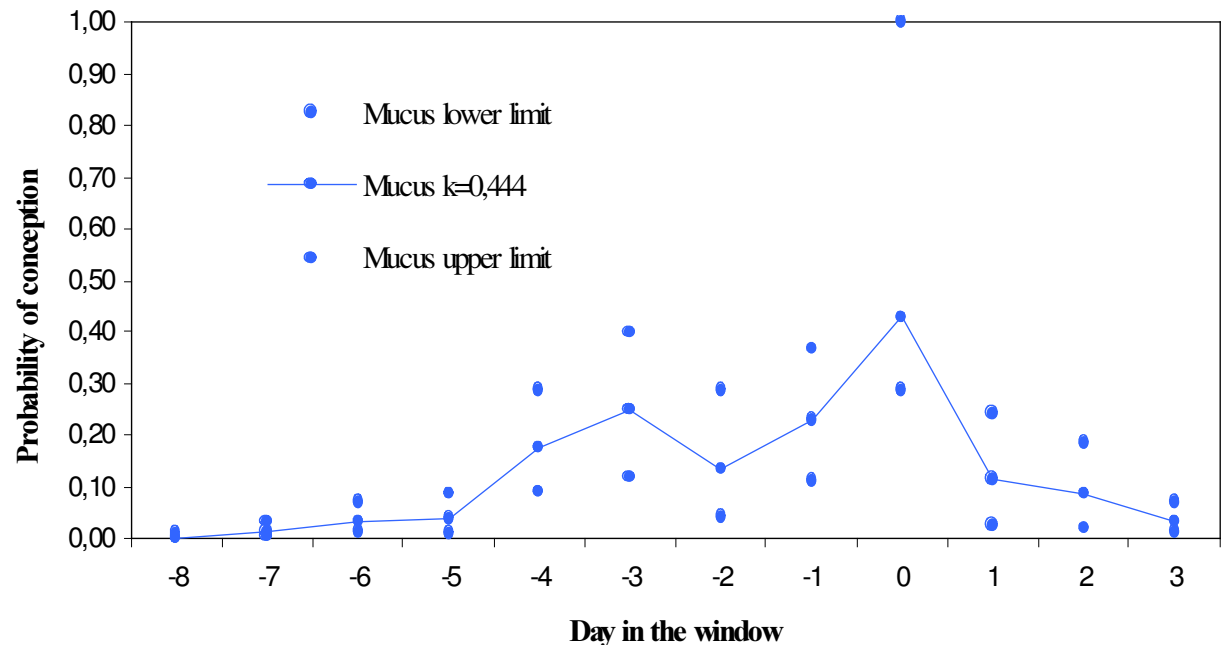


By using a less precise ovulation marker

- Consider all cycles even with multiple acts of intercourse
 - By referring to mucus peak as an ovulation marker
 - We add a new (and relevant) variability source between cycles and women

(Multicentric data)

□ Window: (-8; 3)





By using a less precise ovulation marker

□ A first summary

Intercourse day vs. reference day	Schwartz et al. (1980)	Weinberg et al. (1998)	Wilcox et al. (1998)	Colombo e Masarotto (2000)	Colombo et al. (2004)
Reference	BBT rise	Hormones	Hormones	BBT rise	Mucus peak
-8				0.003	0.000
-7				0.014	0.012
-6				0.027	0.034
-5	0.04	0.100	0.04	0.068	0.035
-4	0.14	0.155	0.13	0.176	0.177
-3	0.20	0.139	0.08	0.237	0.249
-2	0.20	0.274	0.29	0.255	0.136
-1	0.34	0.312	0.27	0.212	0.228
0	0.14	0.331	0.08	0.103	0.429
1	0.07			0.008	0.114
2				0.035	0.085
3					0.033
No. of conception cycles	103	192	144	435	142

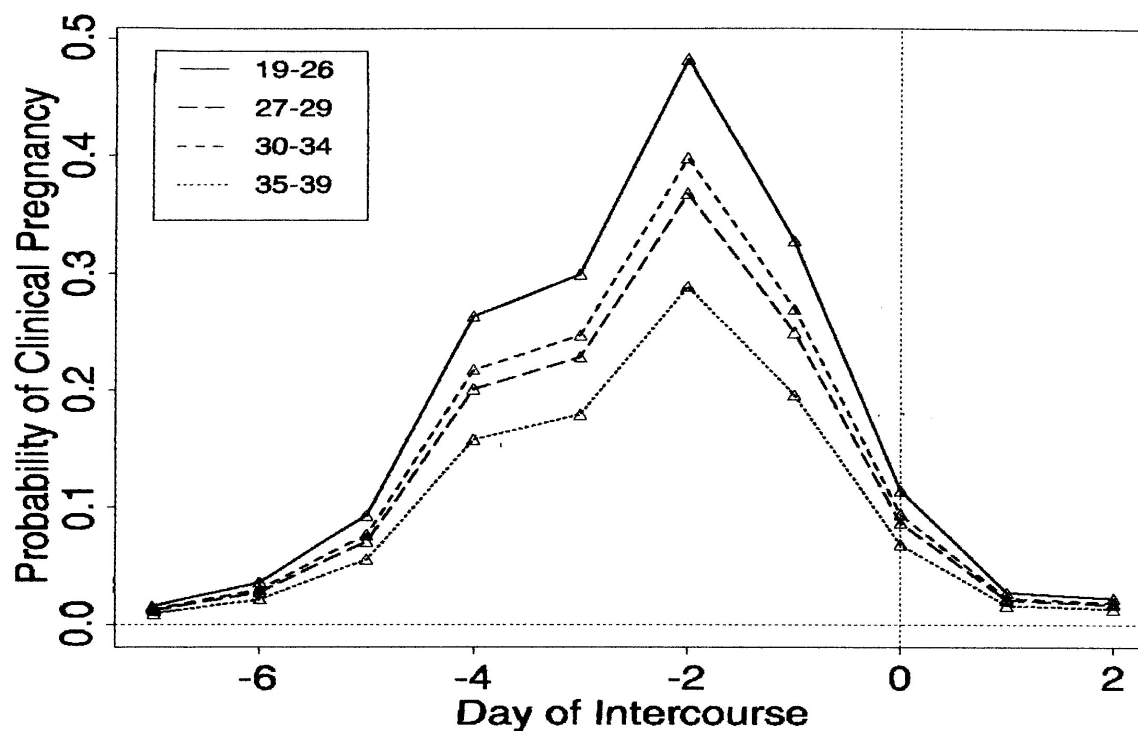


Age of the woman

- Do location and length of the fertile window depend on the age of the woman?

▪ **Daily probability of conception with respect to BBT rise ovulation marker for an average couple with woman of age 19-26, 27-29, 30-34 and 35-39 (433 pregnancies)**

(Multicentric data)



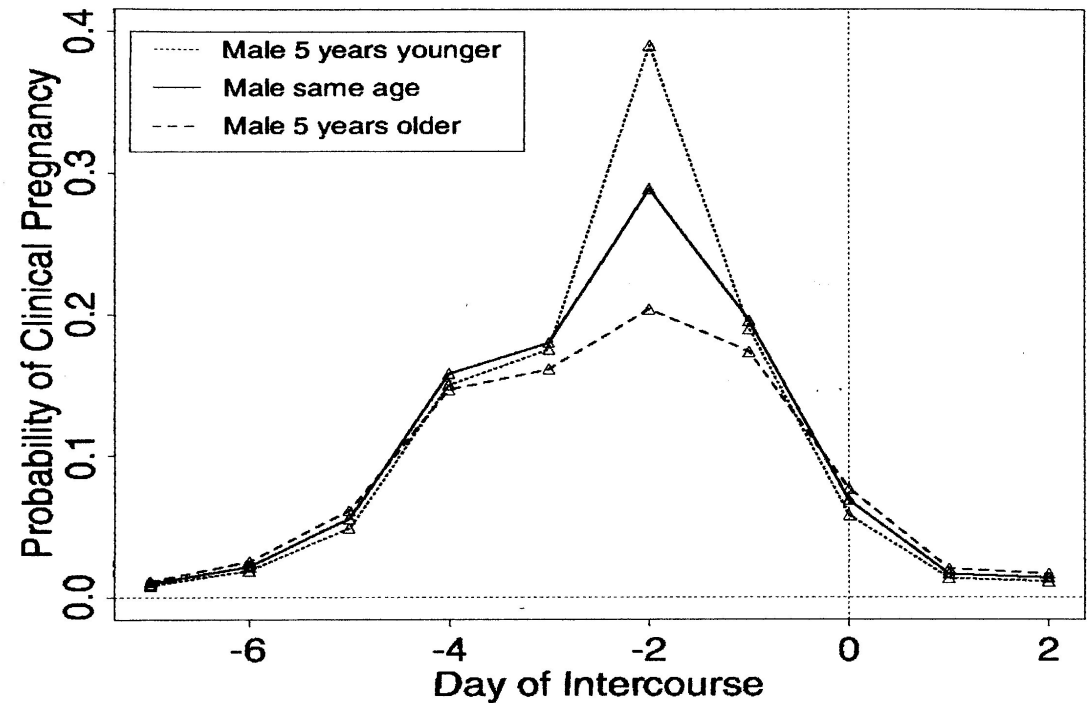


Age of man

- Do location and length of the fertile window depend on the age of the man given the effect of the woman age?

▪ **Daily probability of conception with respect to BBT rise ovulation marker for a couple with woman of age 35-39 and the partner of 5 years younger, of the same age and of 5 years older (additive effect)**

(multicentric data)



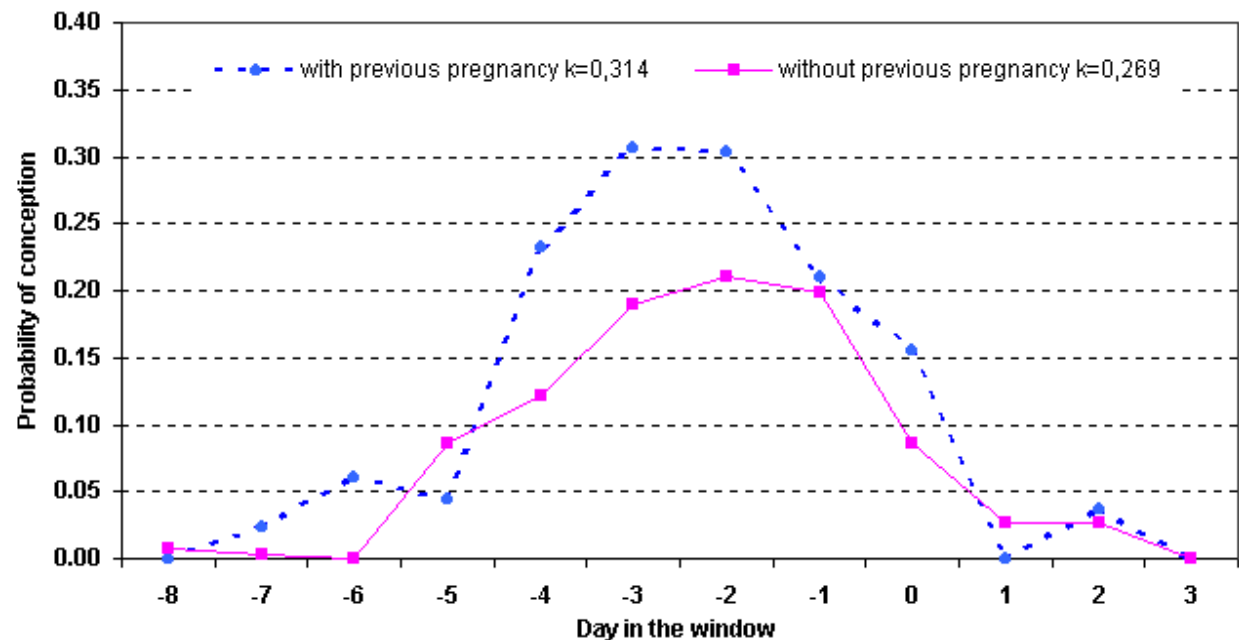


Couples of “proven fertility”

- Are location and length of the fertile window different for women with previous pregnancies?

▪ **Women without previous pregnancies seems to have a fertile window shorter, but this could be influenced by the presence of sterile women**

(multicentric data)





Average length of cycles

- Are location and length of the fertile window different for women with regular cycles?

(EPS data)

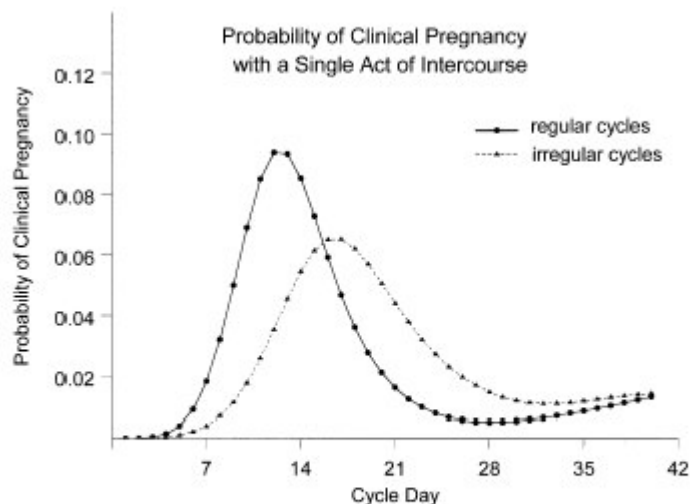


Fig. 2. Probability of clinical pregnancy with one act of intercourse relative to day of the menstrual cycle, for women who reported regular cycles, and for those who reported irregular cycles. (Based on the smoothed distribution of day of ovulation.)

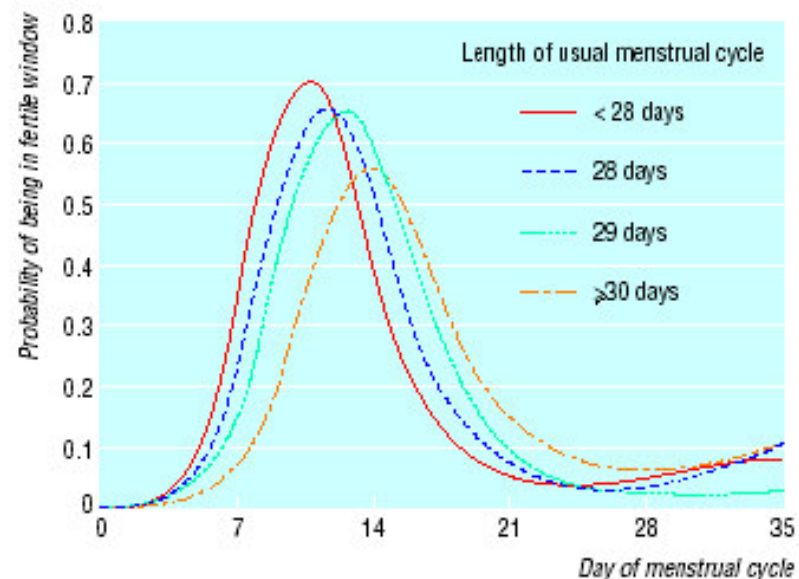


Fig 3 Probability of women with regular cycles being in fertile window, stratified by usual cycle length



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