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Daily Fecundability: First Results from a New Data Base

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on Behalf of the Menstrual Cycle Fecundability Study Group [Note 1]

Abstract

This multicentre study has produced a database of 7017 menstrual cycles contributed by 881 women. It provides improved knowledge on length and location of the "fertile window" (identified as of up to 12 days duration) and the pattern and level of daily conception probability. The day of ovulation was identified in each cycle from records of basal body temperature and mucus symptoms. By referencing days of intercourse to the surrogate ovulation markers, estimates of daily fecundability were computed either directly or by the Schwartz model, both for single and multiple acts of intercourse in the fertile window. The relationship between coital pattern and fecundability has been explored. Univariate analysis underlines the significant link with fecundability only of the woman's reproductive history.

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1. Introduction

In healthy non-contracepting sexually active couples fecundability, probability of conceiving a pregnancy during a menstrual cycle [Gini 1924, Gini 1928], depends on behaviour as well as physiology. Spermatozoa with the capability of fertilising the egg must already be present in the woman's reproductive tract at the time the egg is released at ovulation or must arrive there soon after. Number and timing of acts of intercourse in the cycle are an important factor. The width of the "fertile" window around ovulation, that is the number of days during which intercourse has a non-zero probability of resulting in conception, is uncertain. Widely diverging figures have been proposed in the literature, ranging from less than two to more than ten days [Glass and Grebenik 1954, Potter 1961, James 1963, Marshall 1967, Lachenbruch 1967, Glasser and Lachenbruch 1968, Barrett and Marshall 1969, Barrett 1971, Loevner 1976, Vollman 1977, Schwartz et al 1979, Trussell 1979, Schwartz, MacDonald, and Heuchel 1980, Royston 1982, Bongaarts and Potter 1983, World Health Organization 1983, World Health Organization 1985, Potter and Millman 1985, Bremme 1991, Weinberg, Gladen, and Wilcox 1994, Trussell 1996, Masarotto and Romualdi 1997, Weinberg et al 1998, Wilcox, Weinberg, and Baird 1998, Sinai, Jennings, and Arévalo 1999, Dunson et al 1999]. These estimates depend on data analysed, on conjectures accepted, on evaluations made with different approaches. Precise information on the pattern of daily fecundability and the width and location of the associated fertile interval in the menstrual cycle is of interest to both the biologist and the demographer. For the purpose of fertility regulation, the information is essential to those couples attempting to avoid pregnancy and those trying to achieve this end through appropriate timing of intercourse. The need for a large menstrual cycle data base, including a high number of conception cycles, for the purpose of clarifying various points of interest for basic knowledge and applications, has been repeatedly emphasised [Schwartz, MacDonald, and Heuchel 1980, James 1981, Potter and Millman 1986, Royston 1991, Royston and Ferreira 1999].

This paper introduces the results of an exercise performed in this direction with the co-operative collaboration of a group of organised centres giving advice to subjects interested in learning about the fertile phase of the woman and the use of a Natural Family Planning method to avoid or achieve pregnancies. To reach the planned target number of pregnancies (about 500) with a prospective design in a reasonable amount of time, the participation of several centres was necessary. In the following is given a summary description of the common protocol adopted and of the whole study design. We also describe the characteristics of the study subjects and centres and present preliminary analytical results. These results give special attention to covariates linked with the magnitude and pattern in the daily conception probabilities. They are compared with previous estimates from the literature. Mention is also made on ongoing lines of research opened by the available database.

2. Materials and Methods

2.1 Study Design and Population

The investigation was planned as a prospective cohort study conducted to determine the daily probability of conception among healthy subjects. The research protocol was reviewed and approved by the Institutional Review Boards of Fondazione Lanza (Padua, Italy) and Georgetown University (Washington D.C., U.S.A.). The study was co-ordinated from the Department of Statistical Sciences of the University of Padua (Padua, Italy).

From 1992 through 1996, 782 women were recruited with the collaboration of seven European centres (Milan, Verona, Lugano, Düsseldorf, Paris, London and Brussels) providing services on fertility awareness and natural family planning. The entry criteria for the subjects were: women experienced in use of a Natural Family Planning method; married or in a stable relationship; between 18th and 40th birthday at admission; having at least had one menses after cessation of breastfeeding or after delivery; not currently 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, e. g., endocrine disorders. It was also required that couples did not have the habit of mixing incidences of unprotected and protected intercourse. Women were excluded if any one of the previous criteria was not fulfilled.

Data from an additional 99 subjects were also included retrospectively in view of their relevance to the aims of the study. These data came from a prospective investigation carried out in Auckland, New Zealand, in 1979-85 into the relationship between the interval from intercourse to fertilisation and the sex of the baby conceived. In this study recruitment was made from couples of proven fertility who were contemplating a further pregnancy. For the purpose of timing intercourse, these couples were instructed on how to recognise the fertile period of the menstrual cycle and anticipate ovulation from changes in cervical mucus. The woman partner also recorded her basal body temperature each day. The study design restricted the couples to only one act of intercourse during the fertile phase of the cycle [France et al 1984, France et al 1992]. This requirement, not respected in a few instances, was the probable cause of subjects frequently dropping out of the study if they had not achieved a pregnancy after 3-4 cycles of trying. The resulting short observational period of sexually active non-conception cycles is a plausible source of positive bias in the estimate of the level of daily fecundability in the present study. Therefore, while the Auckland data is of significant value to other aspects of the study, only results from the seven European centres have been used in determining daily probabilities of conception.

A description of the centres, with the names of the local principal investigators, is given in [Note 1].

2.2 Data Collection

In each centre the local principal investigator instructed selected natural family planning teachers about the purpose and the requirements of the study. After completing the instruction phase, the teachers screened and selected the subjects for admission into the study. A woman satisfying all the inclusion criteria was enrolled only after having given written informed consent. In order to ensure complete subject anonymity and confidentiality, each subject was assigned a study number and only the teacher maintained a personal relationship with the subject. The mutual trust established in this relationship was essential to maintaining the collection of quality reliable data of a sensitive personal nature, which encompassed sexual behaviour.

All the charts were periodically sent to the Department of Statistics at the University of Padua, where uniform evaluation for all cases of the recorded basal body temperature (BBT), taken on awakening in the morning before engaging in any activity, was conducted. Coding of mucus typology, in accordance with agreed common rules, was done in the local centres.

2.3 Study Factors

At entry into the study, the following information was collected: the month and year of birth of the woman and of her partner; the number of previous pregnancies, if any; the date of her last delivery (or miscarriage) and of the end of breastfeeding, if relevant; the date of last oral contraceptive pill taken, if any. Subsequently, after the collection of data had begun, it was decided to add the date of marriage for married couples and the sex of any baby conceived and born during the period of the study. This latter information is available for a large proportion of subjects.

In each menstrual cycle the woman was asked to record on a chart the days of her period and of any disturbance such as illness, broken sleep. She was asked to also record her basal body temperature on the chart for as many days as necessary to determine a clear post-ovulatory rise. She was further asked to observe and chart her cervical mucus symptoms daily during the cycle, and to record every episode of coitus, with specification of whether it was unprotected or protected (barrier methods, withdrawal, …). Cycles in which even a single act of protected intercourse or of simple genital contact occurred were excluded from the analysis. The reliability of the information recorded of acts of intercourse was checked by the teacher in discussion with subjects at the end of each cycle. The importance of continuing to keep the record chart when subjects were trying to conceive a pregnancy was emphasised.

Charts were regularly collected by the teacher concerned. Following review at the local centre and scoring of the cervical mucus symptoms according to the common rules agreed for the study (Table 1), the charts were sent to the co-ordinating investigators in Padua for processing and entry into the data base [Note 2].

2.4 Definitions

A menstrual cycle was characteristically defined as the interval in days from the beginning of one period of vaginal bleeding until the commencement of the next, where day 1 was the first day of fresh red bleeding, excluding any preceding days with spotting.

The “three over six rule” was used to determine the BBT shift, defined as follows: the first time in the cycle that three temperatures were recorded all of which were above the level of the immediately preceding six daily temperature recordings. Such a rule has been shown to perform well in predicting the start of the infertile period following ovulation [Marshall 1968]. Exceptions to the rule were permitted: a) if there was one “spike” temperature among the six at the lower level (a spike temperature was defined as a temperature which was 0.2 centigrades or more above both its immediate neighbouring temperatures); b) or, in a cycle in which the impact of illness or other disturbances could be discounted, if there were at least six lower temperatures recorded before the upward shift. In analyses in which the BBT rise was used as a conventional indicator for timing ovulation, the last day of lower temperatures was designated as day 0, the “BBT reference day”, to which all preceding and following days were scaled according to their distance by integer numbers.

The cervical mucus peak day was defined as the last day with best quality mucus, in a specific cycle of the woman, by sensation or appearance, known retrospectively. This peak day was taken as “Mucus reference day” and identified as day 0.

A conception was assumed in the presence of a pregnancy going on at 60 days from the onset of the last menses or when before that term a miscarriage was clinically detected.

2.5 Statistical Analysis

All the following statistical analyses, performed in the Department of Statistical Sciences, at the University of Padua, were limited to cycles in which ovulation occurred, or at least appeared to occur, and BBT reference day and/or mucus reference day was identified.

We first chose the window of potential fertility to be the series of days relative to the identified day of ovulation such that a cycle without intercourse during these days never resulted in a pregnancy. Daily estimates of probability of conception (a simple division: day by day, number of pregnancies/number of acts of intercourse) were then calculated using cycles with only one intercourse during the putative window. Since the act responsible for conception was unknown in cycles with more than one act of intercourse in the fertile interval, a more sophisticated procedure was needed to estimate globally the daily fecundability in the general case with one or more than one act of intercourse in the window. For this purpose the Schwartz model [Schwartz, MacDonald, and Heuchel 1980] (see [2.5.1]), which is an extension of the one suggested by Barrett and Marshall [Barrett and Marshall 1969], was used. For each cycle, the probability of no conception is the probability the cycle is not viable plus the probability the cycle is viable and none of the intercourse acts result in successful fertilisation and survival to detection.

Inference was based on the likelihood: (i) parameter estimates were obtained by maximum likelihood, (ii) confidence intervals were then computed for each parameter of interest using the profile log-likelihood [Clayton and Hills 1993] and (iii) likelihood ratio tests were used to assess the significance of selected covariates.

Descriptive analysis was performed using SAS (see http://www.sas.com). R (http://www.r-project.org) was used to fit the Schwartz et al. model to the data. Functions and scripts are available upon request from the authors.

2.5.1 The Schwartz Model [Schwartz, MacDonald, and Heuchel 1980]

For each cycle, the observed outcome (conception/non conception) can be modelled as a Bernoulli random variable with parameter (the probability of success, i.e., the fecundability) that depends on the number and timing of the intercourse events.

Schwartz et al. [Schwartz, MacDonald, and Heuchel 1980] write fecundability as the product of three probabilities:

$$\text{fecundability} = \mathrm{P} = \mathrm{P_0} \cdot \mathrm{P_f} \cdot \mathrm{P_v}$$

where $\mathrm{P_0} = \mathrm{pr}(\text{that a fertilizable ovule is produced})$

$\mathrm{P_f} = \mathrm{pr}(\text{that the ovule is fertilized} \mid \text{fertilizable ovule})$

$\mathrm{P_v} = \mathrm{pr}(\text{that the conceptus stays alive for at least six weeks} \mid \text{fertilized ovule})$

To link $\mathrm{P_f}$ to the locations of the acts of intercourse, Schwartz et al. assume, following Barrett and Marshall [Barrett and Marshall 1969], that (i) different intercourse events have independent effects on the outcome and (ii) the probability of conception following intercourse only on day *i* (defined relative to the reference day [2.4]), $\mathrm{P_{f,i}}$ say, is constant between couples and cycles.

Then, fecundability can be written as

$$\mathrm{P} = k \cdot \mathrm{P_f} = k \cdot \left[1 - \prod_i \left(1 - \mathrm{P_{f,i}}\right)^{x_i}\right]$$

where *k*, called the cycle viability, denotes the product $\mathrm{P_0} \cdot \mathrm{P}_v$, while

$$x_i = \begin{cases} 1 & \text{presence of intercourse in the i th day} \\ 0 & \text{otherwise} \end{cases}.$$

3. Results

3.1 Overview of the Sample

The characteristics of the 881 subjects enrolled in the various centres and of the 7017 considered cycles, with their outcomes, are summarised in Tables 2, 3, and 4. The number of subjects and contributed cycles varied markedly between centres and consequently, in order to obtain meaningful fecundability patterns from the analysis, some aggregation of data was made. In most analyses the data from Auckland were kept separate from those of the European centres owing to their specific features mentioned in [2.1] having an impact on the level of fecundability.

The average age of women in the study population was close to 29 years and was relatively similar at each centre (Table 2). The proportions of women of proven fertility and of those with past use of hormonal contraception are, however, very different among the centres. For the European centres overall, the percentage of women with at least one previous pregnancy was only 44.6% (range for centres: 30.8 - 73.1) while only 30.1% (range for centres: 11.4 - 56.2) had ever used hormonal contraception in the past (Table 2).

For these same centres, Table 3 underlines the high frequency of cases (96.4%) in which, when enough information was available, the described procedure allowed the BBT shift to be determined. However, when at least some information on temperature was recorded, in further 6.1% of the cycles the reference day could not be identified due to missing information on critical days, and in 1.6% due to disturbing illness. The proportion of cycles with determination – in similar conditions- of the mucus reference day is a little lower (94.1), owing to the particularly low percentage of the Paris subgroup. At that centre, in local usage, mucus symptoms are taken into consideration mainly for identification of the beginning of the “fertile” phase. The 575 detected pregnancies listed according to centres in Table 3 include both those continuing at 60 days from the onset of the last menses and the 49 clinically recognised miscarriages of the same period (also listed).

The figures of Table 4 -5591 cycles with BBT reference day (Table 4a) and 5928 with mucus reference day (Table 4b)- are linked with a conventional determination of the post-ovulatory phases starting after the respective reference days. They give an impression of a remarkable homogeneity between centres. The length of the phase after the peak mucus day in the various centres parallels similar results obtained in the WHO [World Health Organization 1983] study on the ovulation method. As expected, the length of the preovulatory phase shows a relative variability higher than that of the postovulatory one: e.g., for the European aggregate the coefficient of variation (4.74/16.7) is 25.7% in the first vs. 16.2% in the second.

It has to be noted that the two samples - with information on BBT and/or mucus - coincide in a sizeable proportion of cycles (5390 in the combined European group, 232 in Auckland: in the two sets of data both surrogate markers of ovulation were determined in about 80% of the cycles). On average, the peak mucus symptom occurred 0.31 days (S.d. 1.82) before the last low temperature day in the European group (0.30 with S.d. 1.83 when the Auckland data were included).

The database can also be used in various forms to study the behaviour of the subjects. Table 5, showing the decline in the frequency of intercourse with the increasing age of each of the partners, provides an example. Three points have to be considered: the number of men above 40 is rather small; in conception cycles only acts of intercourse up to the 29th day of the cycle were counted; for obvious reasons, the data are for European centres only. The trend with age, evaluated through the arithmetic average (preferred to the median for sake of better evidence), and the higher coefficient of variation in non-conception cycles (61.3% vs. 49.7%), both support the reliability of the data collected. The small variations between the male and the female findings reflect differences in the number of subjects in the various classes and on the whole. For female partners, over all age groups, the median number of recorded acts of intercourse (10th, 90th percentiles) is equal to 6 days (3,11) in the conception cycles and to 4 (1,8) in the non-conception cycles.

Table 6 lists the distribution of 5390 cycles according to the interval in days between the two markers of ovulation (BBT reference day minus mucus reference day). We know already - from [3.1] - the value of the average distance between those days. There is some translation between the two reference terms, which -though small - can influence the comparative distributions of cycles, and of intercourse episodes and pregnancies allocated to the various days of the respective fecundability window. In the majority (62.4%) of the cycles the two markers are within ± one day and the difference is greater than ± two days in 17% of the cycles. This suggests that estimates of day-specific pregnancy probabilities should not depend greatly on which marker is used for ovulation. However, we cannot rule out possible overestimation of the fertile interval relative to BBT or mucus reference day compared with the width of the fertile interval relative to the true day of ovulation. Although efforts were made to rule out errors in documentation of BBT or cervical mucus, measurement errors can result due to unavoidable biological variability. In future work, such measurement errors could be assessed and corrected using recently developed statistical methodology [Dunson and Weinberg 2000, Dunson et al in press].

3.2 Fertility Windows: Direct Estimates of Fecundability

In order to find windows of fertility - around the BBT or the mucus reference day - to be used for estimates of daily fecundability, an exploratory analysis was made, changing width and location of chosen windows. For each reference marker, it was found that, when no intercourse episodes were ascertained in a 12-day window, no pregnancy was recorded. Eight among the 12 days preceded the day 0 and three came afterwards.

Then, direct estimates of daily fecundability were computed inside these windows. In this initial determination, only cycles with a single act of intercourse in a window were selected. 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. The results are presented in Table 7 for the combined European centres (top section) and with inclusion of Auckland for all centres (bottom section). The differences in the number of cycles between the bottom and the top grouping give the contribution from Auckland. The two sets of probabilities are very different, particularly when the impact of the Auckland data, in terms of number of conception cycles, is relevant: direct estimates obtained for this site are on the average about double those of the European ones. It is worth mentioning that no one of the almost 350 intercourse episodes of the third day of the high BBT gave rise to a conception. And also that Auckland conforms to the other centres concerning the width of the window, which might be shorter, even when due account is taken of the smaller sample size.

A similar exercise was performed, with data only from European centres, with the aim of obtaining more precise fecundability estimates by increasing the number of contributing cycles through use of a smaller window, in which the probability of having single intercourse episodes is increased. Cycles, however, were eliminated from consideration in which, while only a single act of intercourse occurred in the shorter window, conception might have been due (though certainly with a small probability) not to that coital act but to intercourse episodes falling outside the window. From this point of view, were considered relevant, for cycles having intercourse on day -6, the three days -9, -8, -7, reduced to two (-8, -7) for cycles with intercourse on day -5, and to one (-7) in cycles with intercourse on day -4. Similarly, were excluded from the analysis cycles with intercourse on day +2. The elaboration was extended to evaluate a parallel window around the mucus reference day. The results for both analyses are shown in Table 8. In absolute terms, the main differences between the two sets of probability are observed on days -3 and 0. Considering - besides random errors and the small shift in BBT versus mucus - that the two aggregates of cycles are different, the estimates of fecundability, daily and total, appear in good agreement. Worthy of attention is the finding that the peak mucus day is not the one with maximum fecundability. In each aggregate, the four days preceding the reference day are the most relevant for cycle fecundability.

3.3 Estimates through a Model

In the presence of multiple acts of intercourse during the fertile interval of a cycle, the probability of conception due to a single act on any day cannot be estimated directly. One has to make use of a model whose computed coefficients may lead to an evaluation of daily fecundability. For this purpose, in the following, estimates of day by day conception probabilities are obtained through the application of the Schwartz model [Schwartz, MacDonald, and Heuchel 1980], summarised in [2.5.1]. This model has been repeatedly used in the literature, and by that it allows comparisons with other experiences.

The model estimates of daily fecundability for the European subjects are presented in Table 9, with confidence intervals obtained through the profile maximum likelihood [Clayton and Hills 1993], at the 90% level. The chosen windows are those already seen. The two sets of data have a different composition, but once again they underline in both cases the significance of higher rates in the four days preceding the respective reference day.

In Figure 1, the daily estimates relative to each of the two markers of ovulation are presented. These estimates are based on the 5390 cycles from the European centres for which both reference days are available. There is a total of only 386 pregnancies, since for 48 there is information only on the peak mucus day, for 49 only on BBT shift, and nothing in 4 instances. The given confidence intervals are at the 90% level. Several points may be mentioned: a) in the two sets of estimates, though the total number of cycles is the same, the number of those with at least one intercourse episode in the window differs: 2917 for BBT and 2843 for mucus, respectively. This difference will have an effect, though small, on the respective areas under the curve; b) one has to remember the mentioned average distance between the two reference days and its possible effects (see para 7 of [3.1]); c) the estimates based on the mucus symptom conform less well to a bell shaped pattern as observed with the BBT window; d) the dip at day -3 found through the mucus symptom repeats what seen in the data set of Table 9 and also in the direct estimates of Table 8: a point deserving further elaboration.

It appears that the BBT reference day may be a slightly better (i.e. less error prone) marker of ovulation day, since the estimates, compared with those around the mucus reference day, are higher on the days of peak fertility (i.e. days -3 to -1) and lower on the days towards the edge of the window.

In Table 10 the results for the 12 days BBT window are compared with fecundability estimates reported from five other similar studies. A few notes will clarify the limits of these comparisons. The discrepancies between the different sets of probabilities can be attributed - apart from random errors- to different characteristics of the subjects, to distinct procedures followed in determining the ovulation reference day and to the inclusion or exclusion of early miscarriage in the counted pregnancies. The probabilities reported by Schwartz et al. [Schwartz et al 1979] are direct estimates from single donor artificial inseminations per cycle by donors. The data by Weinberg et al. [Weinberg et al 1998] and by Wilcox et al. [Wilcox, Weinberg, and Baird 1998] come from recruitment from the general population of subjects wanting to achieve a pregnancy. In the other two studies, the information was collected in centres providing services on fertility awareness and natural fertility regulation. Weinberg et al [Weinberg et al 1998] were able to include through assay of hCG very early pregnancies losses, otherwise undetected by clinical diagnoses. In the same set of pregnancies, Wilcox et al. [Wilcox, Weinberg, and Baird 1998] considered only those clinically diagnosed, that is events more similar to those considered in the present aggregate of European centres. In the other studies there were no important differences in the recording of pregnancies. In conception cycles with multiple acts of intercourse in the "fertile" window, Bremme [Bremme 1991] chose to assign pregnancy to the intercourse which occurred closest in time prior to or coinciding with the presumed day of “ovulation”: a procedure leading to a bias which increased fecundability rates as the “ovulation” day was approached. For the probabilities computed in Weinberg et al [Weinberg et al 1998] and in Wilcox et al. [Wilcox, Weinberg, and Baird 1998] ovulation day (i.e. day 0) was identified using the decline in the ratio of oestrogen to progesterone metabolites in the urine that accompanies luteinization of the ovarian follicle [Baird et al 1991]. This steroid based marker should be less error-prone than markers on BBT or mucus, but should not deviate systematically from the last day of low temperature used in the other studies, as in the present data base. Apart from Bremme and Schwartz et al [Schwartz et al 1979], the other four sets of estimates were based on the Schwartz model [2.5.1].

Figure 2 shows a graphical comparison of the pattern of conception probabilities in the BBT window for four subgroups (centres or combinations of centres) and for the whole European experience. The results for the Auckland subjects clearly differ from those of the other instances. The other three subgroups consisted of the Verona centre, Milan aggregated with Lugano because of similarity of NFP teaching content and method, and the four remaining European centres combined because of their small sample sizes. The homogeneity of the fecundability data between the three European subsets is striking. The maximum likelihood ratio test of significance of the differences between the three European subsets gives $p>0.10$. The merging of their records in a unique European group appears reasonable: this will form the basis of all subsequent analyses on the level of fecundability

Figures 3, 4 and 5 focus on the link between three covariates pertaining to the female subjects and fecundability in the window around the BBT reference day. The covariates evaluated are: the reproductive history of the woman, by comparing subjects with and without a previous pregnancy (Figure 3); the woman's age, by dividing the subjects into three age groups, 18-24 yrs (103 subjects), 25-34 yrs (596), and 35-39yrs (83; Figure 4); and past use or non use of oral contraception (Figure 5). The difference in the level of fecundability of the women of proven fertility versus the unproven group is very significant ($p = 0.014$). In the group with unproven fertility, though the subjects obviously believed they were fertile, their number would include some with undiagnosed infertility or sub-fertility as in the general population. Furthermore, at least in one Italian centre, subjects may have been included in the study who were seeking help in achieving a pregnancy after a prolonged experience of failure. No marked differences in fecundability rates were observed in the three age groups ($p>0.10$), though the sample sizes in the younger and older groups are relatively small. When the subjects were divided into those below and those above the median age (29 years), again no significant difference in fecundability was found between the two groups ($p>0.10$, data not shown). Similarly, no significant differences ($p>0.10$) are seen in the daily fecundability when comparisons are made between past use or no previous use of oral contraception. It should be noted, however, that the number of women having used this method of contraception in the three cycles preceding their entry into the study is extremely low (3.0%).

Two further results pertaining to the cycles are presented in Figures 6 and 7. Figure 6 is based on the data of Table 6. The whole set of cycles is divided into three groups according to the time difference between the BBT reference day and the peak mucus day: group 1, negative difference (1569 cycles, 29.1% of the total); group 2, difference equal to 0 and 1 days (2553, 47.4%); group 3, greater than 1 day (1268, 23.5%). For each of the three derived sub-sets the Figure shows the pattern of estimated daily conception probabilities. Attention is drawn to the sub-set in which the two reference points (almost) coincide, and therefore should support each other as giving a rather good approximate indication on the time of ovulation. The pattern of conception probabilities appears very concentrated, falling after a continuous rise extending over five days, with a maximum at day –2, approaching zero at both extremes (see also Wilcox et al. [Wilcox, Weinberg, and Baird 1998]). The pattern is somewhat similar in group 3, though more elevated at beginning of the ascending part and then falling abruptly on day zero, remaining then at this level. When the peak mucus day occurs after the BBT reference day (group 1) the probability pattern is very irregular with two maxima (on day -3 and day 0). The difference between the three sets of probabilities is very significant (p=0.020).

Figure 7 illustrates the pattern of daily fecundability for two different subsets of cycles, one with the window around the BBT shift (3175 cycles with at least one intercourse in the window, 434 pregnancies) and the other with the window around the mucus reference day (3265 cycles, 435 pregnancies). The two subsets are each further divided according to the length of the conventional follicular phase of the cycles, <16 days and > = 16 days The very different shape of the two derived patterns of fecundability is highly significant (p=0.003 for BBT, p<0.001 for mucus). The differences in probability levels on, say, day –4 depending on the said length is very strong. Evidently the distance -4 does not have the same meaning for all cycles: as does the distance at day zero, though with inverse relationship in the probabilities of the two subsets. The evidence is the same for both BBT and mucus which tends to exclude systematic errors in the identification of the reference days as an explanation. There is a biological foundation for such a result or does this serve as a hint to consider more stable the positioning of ovulation in the cycle and more variable that of the conventional surrogate indicators?

4. Discussion

The startling variety of suggestions concerning the width of the “fertile window” found in the literature depends in part from conceptual approaches adopted. To try and measure the window summing lifetime of sperm and ovum -less the time needed for capacitation of spermatozoa -is a deductive theoretical solution. But when, instead of a single cycle, a mixture of cycles of a group of women is considered, due account has to be taken of the biological variability of both patterns and its interaction. When trying to make evaluations starting from aggregates of distinct empirical experiences, one should be sure that the single cases record real facts uniformly and homogeneously, without the impact of confounding factors. According to Potter and Millmann [Potter and Millman 1985], the lines of research followed to clarify the point can be grouped into two categories. In the first one, assumptions are made on mean fecundability and average coital pattern: a chosen model allows us to estimate the length of the fertile period assuring compatibility between the two. In the second, starting from estimated daily probabilities, given a certain coital pattern, the fecundability in a cycle is derived.

The procedure followed in this exercise falls into this second class. That is, it starts from and deals with aggregations of distinct ascertained facts. One aspect of the documentation that has been collected needs to be stressed here: that is, its reliability about type and timing of what is essential for the study of fecundability, the acts of intercourse. This has been assured by the long experience of the co-operating centres, an agreed rigorous protocol, the follow up of the ongoing work through periodical meetings of the Principal Investigators, the scrupulous screening of the forms arriving at the co-ordinating centre.

At the same time, the main weakness of the information has to be underlined: the reliance on the surrogate indicators of the true day of ovulation, the BBT shift and the peak mucus day. The distribution of deviations between these markers and the true ovulation day is poorly known (see, e.g. [Hilgers, Abraham, and Cavanagh 1978, Hilgers and Bailey 1980, France 1982, Guida et al 1999]). Several recent studies have obtained estimates of error in BBT reference day. There have been small validation studies and Dunson et al. [Dunson et al 1999] present estimates. These studies suggest that most cycles have errors of less than ± one day. A major challenge is to try to obtain correct measures of daily fecundability, possibly using the methods of Dunson and Weinberg [Dunson and Weinberg 2000] and Dunson et al. [Dunson et al in press]. Furthermore, while ovulation is practically instantaneous, we have only information on the level of days.

The Schwartz et al. [Schwartz, MacDonald, and Heuchel 1980] model (see [2.5.1]) chosen has its merits: it rests on appealing biological hypotheses, and in general fits well the data. But it has weaknesses: it is based on rather simplistic assumptions; with high frequency of intercourse it tends to underestimate observed fecundability; the parameter k, supposed to measure the so-called cycle viability, is not independent from the pattern of intercourse episodes. But it is not the place, here, to enter into a thorough discussion of comparative evaluation of advantages and disadvantages of different proposed or conceivable models, or of other approaches to the desired estimation.

These words of caution do not detract significance for applications from the main results of the study in the area of fertility regulation. Couples attempting pregnancy should maximise their intercourse frequency during the four days preceding the first upward shift of the basal body temperature or the peak mucus day. In both distinct sets of cycles the maximum level of conception probabilities is achieved in the second day before the reference point: 0.255 in the window around BBT reference day and 0.203 in the other case. Couples wanting to avoid pregnancy are informed that the unsafe period might be extended up to 11-12 days. The computed confidence intervals may help to qualify the situation obtaining at the two extremes of the window, where the probabilities of conception are very low. In both sets, eight days before the reference point the estimated probability is 0.003, which means, approximately, a pregnancy every 26 years: but the computed upper confidence limits reach 0.011. Obviously, these conclusions are drawn from *a posteriori* observation, but concerning the determination of the beginning of the pre-menstrual infertile phase they provide sufficient information. For other purposes, needing day to day decisions, apart from some observations currently possible - as a first evidence of the mucus symptom -, it would be advantageous to be able to make reliable forecasts. For this sake, an improvement of usual calendar methods through a sequential procedure using updated accumulated observations made on preceding cycles might prove useful.

The results obtained are of interest also from a demographic point of view. Contraception has an obvious impact as a confounding factor on the link between so-called natural and actual fertility of a population. The said results make clear how behaviour together with physiology has an influence on natural fertility. What matters is not only frequency of coitions, but also their allocation to the different days of the fertile interval. The maximum daily fecundability estimated in the BBT window is .255 (Table 9) which corresponds to an average number of 3.92 cycles needed for obtaining a pregnancy, while after one year (roughly 13 cycles) 2.2% subjects remain without success. Couples with at least three acts of intercourse in the same window –roughly representing those attempting a pregnancy- reach a proportion of .227 conception cycles on the whole. This corresponds to 4.41 cycles for a pregnancy and 3.5% of failures in a year.

After the elaboration for the whole data set, some covariates are taken into consideration, one by one: centres, reproductive history and age of the women, and previous use of oral contraception. Homogeneity was observed among three sets of European populations both in pattern and level of conception probabilities and in the extension of the fertile window. Auckland shows the same pattern but a significantly higher level of probabilities. Similar results are reached in the other elaboration on the European set, with a clear difference in the level of daily fecundability only according to previous reproductive experience. Attention should be drawn, however, on the upper age limit of 40 years for the women, the lack of standardisation with respect to the reproductive history of the woman and the decline of k with increasing age. The interrelations between covariates -for instance between age and reproductive history of the women- show that for the distinct evaluation of the impact of various factors, a multivariate analysis approach is needed. A consideration of heterogeneity between units due to unobservable phenomena has to be added to this. The study design is rather complex, hierarchical and multilevel. Considering the women subjects, there are days in a cycle, cycles in a woman, women in a centre, various centres. At each level there is involvement of specific covariates and there is unobservable heterogeneity between the units. Furthermore, there is a confounding factor, the age of the partner.

If one wants - particularly in view of more efficient applications in the field of fertility regulation - to try to make clusterization of subjects, the results by cycle shown in Figures 6 and 7 suggest that longitudinal analyses of consecutive cycles within women are needed to characterise them. Also, longitudinal analysis of cycles might prove useful in clarifying the impact of physiology and behaviour on the outcomes: a rather intriguing area of study since at every step the event -number and allocation of acts of intercourse- may change.

These examples show that the database presented in this paper offers possibilities of investigation along several lines of research.

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Notes

1. The Study Group Investigators were: Michele Barbato, M.D., Centro Ambrosiano Metodi Naturali, Milan, Italy, Priscilla Coppieters, M.D., Fédération Francophone pour le Planning Familial Naturel, Couple-Amour-Fécondité, Brussels, Belgium, John France, PhD., DSc., Research Center in Reproductive Medicine, Department of Obstetrics and Gynaecology, University of Auckland School of Medicine, Auckland, New Zealand, Sandro Girotto, M.D., Istituto per l'Educazione alla Sessualità e alla Fertilità (INER – Verona), Verona, Italy, Christian Gnoth, M.D., Natürliche Familien Planung, Frauenklinik, University of Düsseldorf, Germany, Jane Knight, R.N., Fertility UK, London, United Kingdom, Lucia Rovelli, Centro Metodi Naturali di Lugano, Lugano, Switzerland, Cathérine Renard Denis, Centre de Liaison des Equipes de Recherche, Paris, France, and General Coordinators: Bernardo Colombo, Emer. Prof., and Guido Masarotto, Prof., Dipartimento di Scienze Statistiche, Università degli Studi, Padua, Italy.
2. An example of a menstrual cycle record chart received in the coordinating centre of Padua. The cross on the date indicates the peak mucus day.

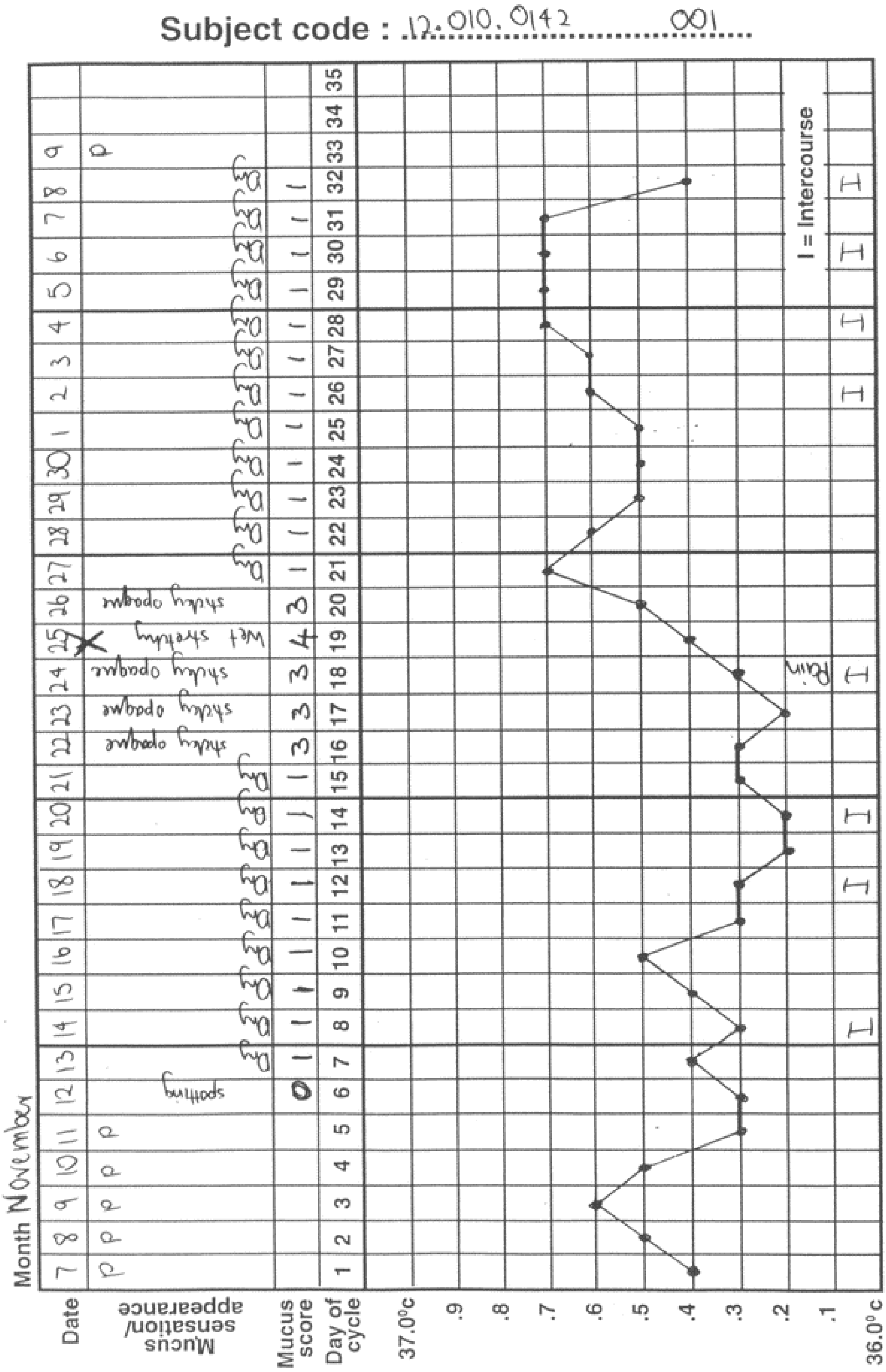
Subject code : 12.010.0142 001
Month November
Date
Mucus sensation/ appearance
Mucus score
Day of cycle
37.0°c
36.0°c
I = Intercourse

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Table 1:
Classification and codification of mucus symptoms.*

Code of mucus type	Feeling	Appearance of mucus
0	No information	No information
1	Dry, rough and itchy feeling or nothing felt	Nothing seen, no mucus
2	Damp feeling	Nothing seen, no mucus
3	Damp feeling	Mucus is thick, creamy, whitish, yellowish, not stretchy/elastic, sticky
4	Wet, slippery, smooth feeling	Mucus is transparent, like raw egg white, stretchy/elastic, liquid, watery, reddish (with some blood)

* If there are different mucus observations on one day, the most fertile characteristic of the mucus observed determines the classification.

Table 2:
Characteristics of women and men participating in the exercise.

Centres	No. of women	Age of women Mean	(Sd)	Age of men Mean	(Sd)	No. of women with at least one past pregnancy	(% of women)	No. of women with past use of hormonal contra-ception	(% of women)
Verona	214	28.6	(3.54)	30.7	(4.16)	66	(30.8)	63	(29.4)
Milan	272	28.7	(3.56)	31.3	(4.73)	109	(40.1)	31	(11.4)
Lugano	13	29.3	(4.50)	32.1	(3.99)	5	(38.5)	4	(30.8)
Paris	104	29.3	(4.52)	31.4	(5.42)	76	(73.1)	38	(36.5)
Düsseldorf	105	28.2	(4.48)	30.4	(4.86)	44	(41.9)	59	(56.2)
London	45	31.6	(4.68)	34.0	(4.60)	29	(64.4)	24	(53.3)
Brussels	29	29.7	(4.52)	31.6	(3.78)	20	(69.0)	16	(55.2)
Total European	782	28.9	(4.00)	31.2	(4.70)	349	(44.6)	235	(30.1)
Auckland	99	29.9	(3.13)	32.3	(3.87)	96	(97.0)	34	(34.3)

Table 3:
Characteristics of cycles and their outcomes

Centres	No. of cycles	No. of cycles with identification of BBT reference day	(% of cycles*)	Mucus reference day	(% of cycles†)	No. of cycles with at least one coition in the window‡	No. of detected pregnancies	(% of cycles)	No. of miscarriages	(% of pregnancies)
Verona	1279	1133	(97.9)	1246	(98.3)	827	171	(13.4)	11	(6.4)
Milan	3288	2840	(95.4)	3051	(95.8)	1351	151	(4.6)	20	(13.2)
Lugano	57	56	(98.2)	57	(100)	48	13	(22.8)	0	(0)
Paris	787	680	(95.8)	576	(74.0)	340	63	(8.0)	5	(7.9)
Düsseldorf	654	615	(97.8)	650	(99.4)	257	41	(6.3)	3	(7.3)
London	320	250	(95.8)	272	(96.1)	181	30	(9.4)	5	(16.7)
Brussels	339	286	(99.0)	314	(95.2)	171	18	(5.3)	3	(16.7)
Total European	6724	5860	(96.4)	6166	(94.1)	3175	487	(7.2)	47	(9.7)
Auckland	293	238	(94.8)	285	(97.3)	215	88	(30.0)	2	(2.3)

* The percentage is the proportion of cycles with the identified rise in the BBT over the cycles with enough information on the BBT

† The percentage is the proportion of cycles with the identified peak of the mucus over the cycles with enough information on the mucus

‡ Window around the last day of hypothermia

Table 4:
Characteristics of non conception cycles with identification of reference days.

a) With BBT reference day*

Centres	No. of cycles	Total length of cycles		Duration of phases			
				Preovulatory		Postovulatory	
		Mean	(S.d.)	Mean	(S.d.)	Mean	(S.d.)
Verona	982	29.0	(5.04)	16.4	(5.01)	12.6	(2.09)
Milan	2711	29.1	(3.89)	16.7	(3.93)	12.4	(2.09)
Lugano	44	27.2	(2.24)	14.7	(2.73)	12.5	(2.19)
Paris	620	29.3	(4.92)	17.1	(4.91)	12.2	(1.08)
Düsseldorf	574	28.3	(3.73)	16.3	(3.68)	12.0	(1.89)
London	224	29.8	(4.68)	17.2	(4.56)	12.5	(2.46)
Brussels	271	28.7	(3.63)	16.3	(3.74)	12.4	(1.94)
Total European	5426	29.0	(4.26)	16.6	(4.26)	12.4	(2.07)
Auckland	165	29.5	(4.37)	16.7	(4.64)	12.8	(2.36)

b) With mucus reference day*

Centres	No. of cycles	Total length of cycles		Duration of phases			
				Preovulatory		Postovulatory	
		Mean	(S.d.)	Mean	(S.d.)	Mean	(S.d.)
Verona	1084	29.1	5.04	15.6	4.91	13.4	2.22
Milan	2913	29.1	3.95	16.6	3.93	12.5	2.07
Lugano	44	27.2	2.24	14.2	2.48	13.0	2.19
Paris	534	29.2	5.01	16.9	5.12	12.3	2.04
Düsseldorf	610	28.3	3.69	15.9	3.52	12.4	2.01
London	245	29.3	4.29	17.4	4.04	11.9	2.54
Brussels	301	28.6	3.56	15.2	3.68	13.4	2.07
Total European	5731	29.0	4.25	16.3	4.23	12.7	2.16
Auckland	197	29.0	4.16	16.2	4.21	12.8	2.43

* Conventionally: Preovulatory phase = until the last day of hypothermia or, respectively, the peak mucus day, included; Postovulatory phase = the remaining part of the cycle.

Table 5:
Average number of acts of intercourse per cycle (European centres)

Age classes (years)	Intercourse of women in				Intercourse of men* in			
	Conception cycles†		Non conception cycles		Conception cycles†		Non conception cycles	
	Mean	(S.d.)	Mean	(S.d..)	Mean	(S.d.)	Mean	(S.d.)
18-24	7.1	(3.19)	5.2	(3.10)	7.4	(3.86)	5.7	(3.47)
25-29	6.5	(3.08)	4.9	(2.82)	6.6	(3.17)	5.1	(3.08)
30-34	5.5	(3.03)	4.2	(2.73)	6.0	(3.00)	4.3	(2.54)
35-39	5.1	(2.30)	3.7.	(1.96)	5.3	(2.65)	4.0	(2.52)
≥40					5.6	(2.62)	4.2	(2.19)
Total	6.2	(3.08)	4.5	(2.76)				

* There are 34 cycles in which the man's age is missing
† In conception cycles, only the first 29 days since the onset of the menses are taken into consideration.

Table 6:
Distribution of cycles according to the distance between the reference days in 5390 cases in which both days have been identified (European centres).*

Distance in days	Number of Cycles	Percent	Number of pregnancies
-9	1	0.0	0
-8	1	0.0	0
-7	1	0.0	0
-6	10	0.2	0
-5	16	0.3	1
-4	108	2.0	5
-3	203	3.8	15
-2	420	7.8	26
-1	809	15.0	56
0	1434	26.6	97
1	1119	20.8	80
2	692	12.8	58
3	356	6.6	29
4	170	3.2	13
5	33	0.6	4
6	14	0.3	2
7	1	0.0	0
8	1	0.0	0
9	0	0.0	0
10	1	0.0	0
Total	5390	100	386

* The distance is the difference: day of last low BBT minus mucus reference day.

Table 7:
Direct estimation of fecundability in the window [-8,3] around the BBT reference day for the European centres and all the centres.

		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

Table 8:
Direct "adjusted" estimation of fecundability in the window [-6,1] around the reference day (European centres).

Reference		Distribution of single acts of intercourse in the window								
		-6	-5	-4	-3	-2	-1	0	1	Total
	Conc. cycles	3	2	11	12	10	10	4	2	54
BBT	All cycles	90	59	50	45	41	54	59	60	458
	Ratio	0.033	0.034	0.220	0.267	0.244	0.185	0.068	0.033	0.118
	Conc. cycles	4	4	11	8	10	13	6	6	62
Mucus	All cycles	86	71	59	43	42	50	52	80	483
	Ratio	0.047	0.056	0.186	0.186	0.238	0.260	0.115	0.075	0.128

Table 9:
Daily estimates in cycles with one or more acts of intercourse in the windows
(European centres; Schwartz et al. model [see 2.5.1])

	BBT reference day		Mucus reference day	
Intercourse day vs reference day	Probability of conception	Lower-Upper 90% Confidence Interval L U	Probability of conception	Lower-Upper 90% Confidence Interval L U
-8	0.003	0.000 - 0.011	0.003	0.000 - 0.011
-7	0.014	0.003 - 0.035	0.000	0.000 - 0.004
-6	0.027	0.013 - 0.049	0.045	0.026 - 0.071
-5	0.068	0.037 - 0.108	0.078	0.046 - 0.118
-4	0.176	0.124 - 0.236	0.181	0.131 - 0.238
-3	0.237	0.179 - 0.277	0.114	0.068 - 0.173
-2	0.255	0.193 - 0.277	0.203	0.145 - 0.270
-1	0.212	0.157 - 0.272	0.177	0.126 - 0.237
0	0.103	0.059 - 0.155	0.135	0.089 - 0.192
1	0.008	0.000 - 0.046	0.067	0.035 - 0.109
2	0.035	0.016 - 0.060	0.020	0.005 - 0.049
3	0.000	0.000 - 0.003	0.005	0.000 - 0.015
No. of cycles	3175		3265	
No. of pregnancies	434		435	
k	0.277		0.301	

Table 10:
Comparison of estimates of daily probability of conception

Intercourse day vs. reference day	Schwartz et al [1979]	Schwartz, MacDonald, and Heuchel [1980]	Bremme, [Bremme 1991]	Weinberg et al [1998]	Wilcox, Weinberg, and Baird [1998]	European centres
-8						0.003
-7			<0.005			0.014
-6			0.018			0.027
-5		0.04	0.076	0.100	0.04	0.068
-4	0.08	0.14	0.100	0.155	0.13	0.176
-3	0.20	0.20	0.152	0.139	0.08	0.237
-2	0.13	0.20	0.235	0.274	0.29	0.255
-1	0.21	0.34	0.270	0.312	0.27	0.212
0	0.15	0.14	0.331	0.331	0.08	0.103
1	0.11	0.07	0.065			0.008
2	0.09					0.035
No. of conception cycles	631*	103†	109	192‡	144§	434§§

* After at least 21 days of hypothermia. The "zero" point is the last day of hypothermia, following [Vincent 1964].

† Pregnancies of at least six weeks duration in a given cycle.

‡ Of which 48 (25%) early losses within six weeks and 15 clinical spontaneous abortions after six weeks from the onset of the last menses

§ The same set of data as in ‡, but excluding the 48 early losses (i.e. within 6 weeks of LMP). The probabilities used to generate the figure in [Wilcox, Weinberg, and Baird 1998] were kindly provided by Dr. David Dunson.

§§ Ongoing at 60 days from the onset of the last menses, included clinically diagnosed abortions in this period (window around BBT reference day).

Figure 1:
Daily fecundability in cycles with both BBT and mucus reference day (day 0), with 90% confidence intervals. European centres.

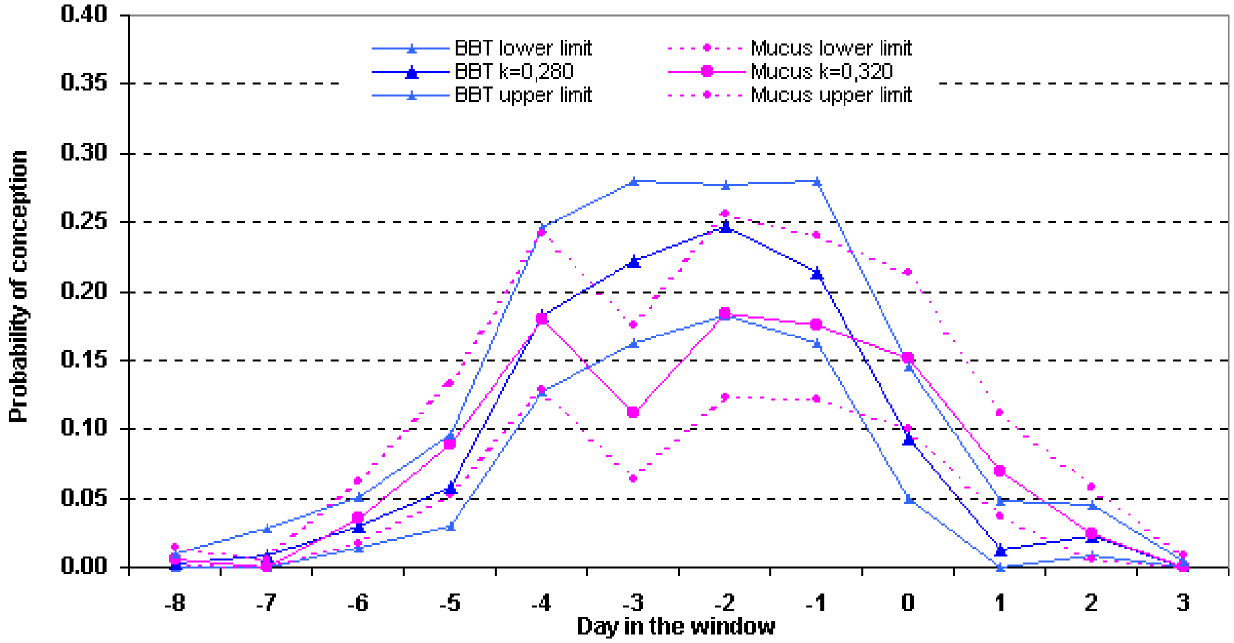

Figure 2:
Daily fecundability around the BBT reference day. Various subgroups.

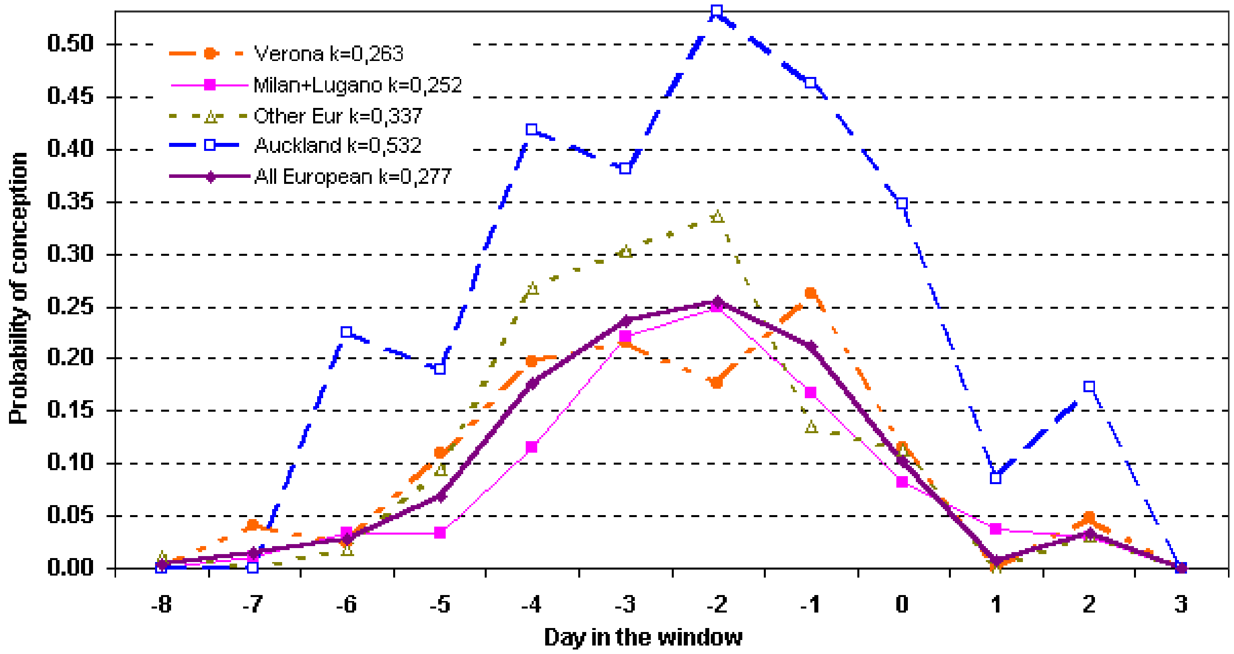

Figure 3:
Daily fecundability around the BBT reference day for women with or without previous pregnancies. European centres.

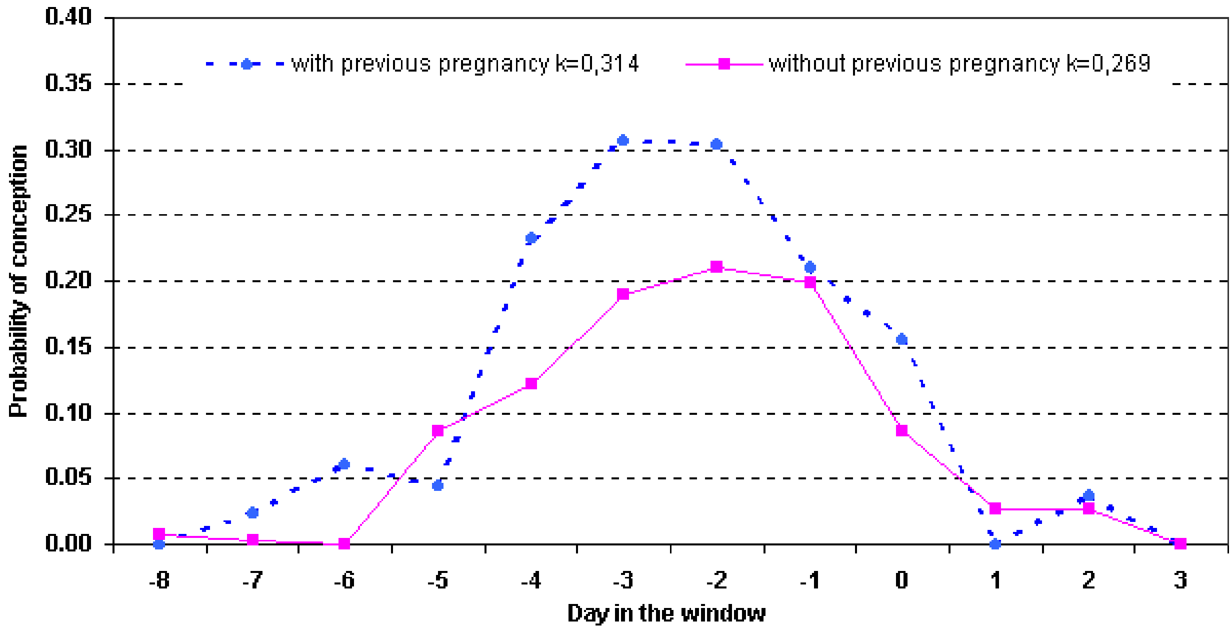

Figure 4:
Daily fecundability around BBT reference day by age classes (18-24 years, 25-34, 35-39) of women. European centres.

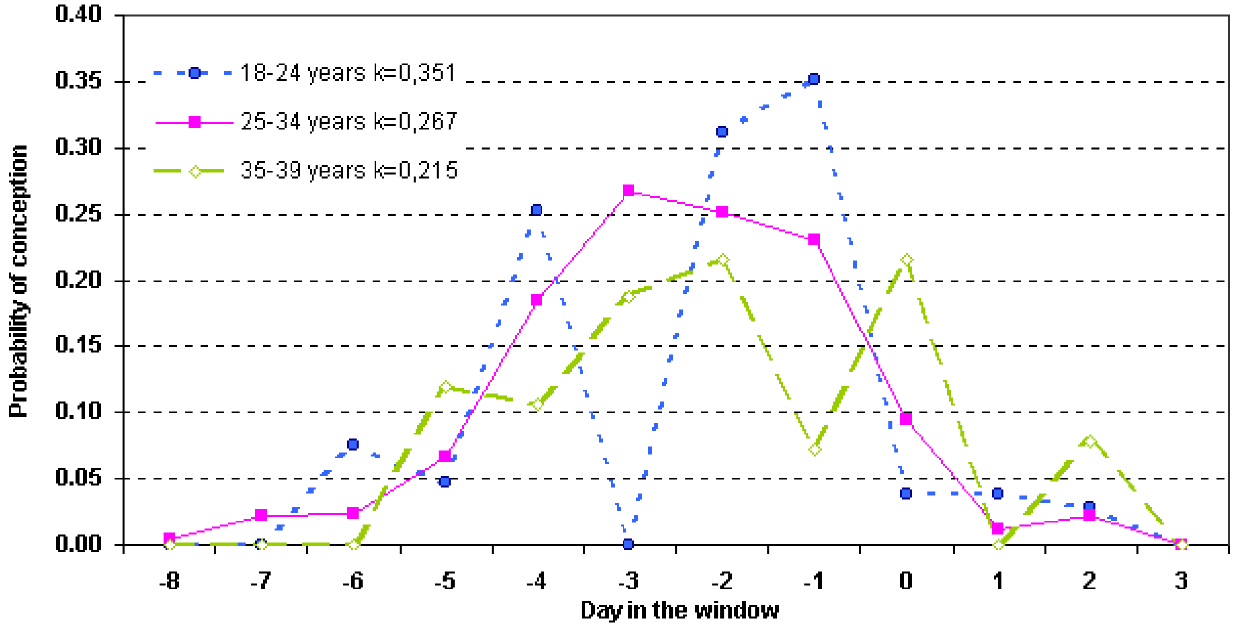

Figure 5:
Daily fecundability around BBT reference day according to the past use or no use of oral contraception. European centres.

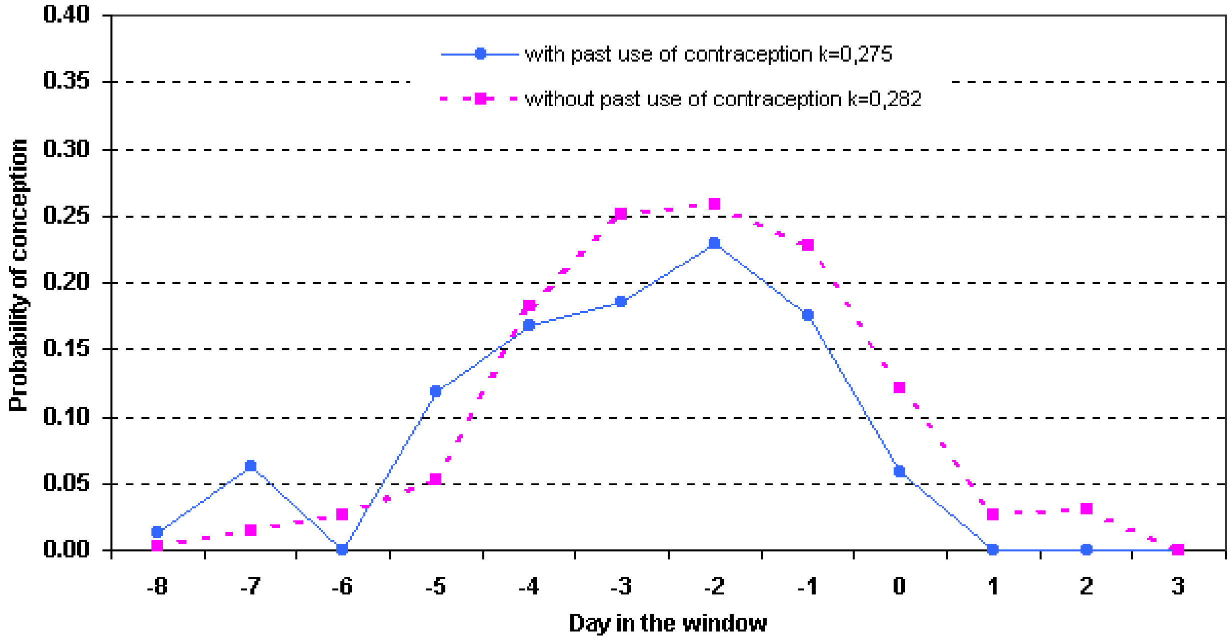

Figure 6:
Daily fecundability around BBT reference day according to the distance "BBT minus mucus reference day" (distance equal to 0 or 1 days, higher than 1 day, negative). European centres.

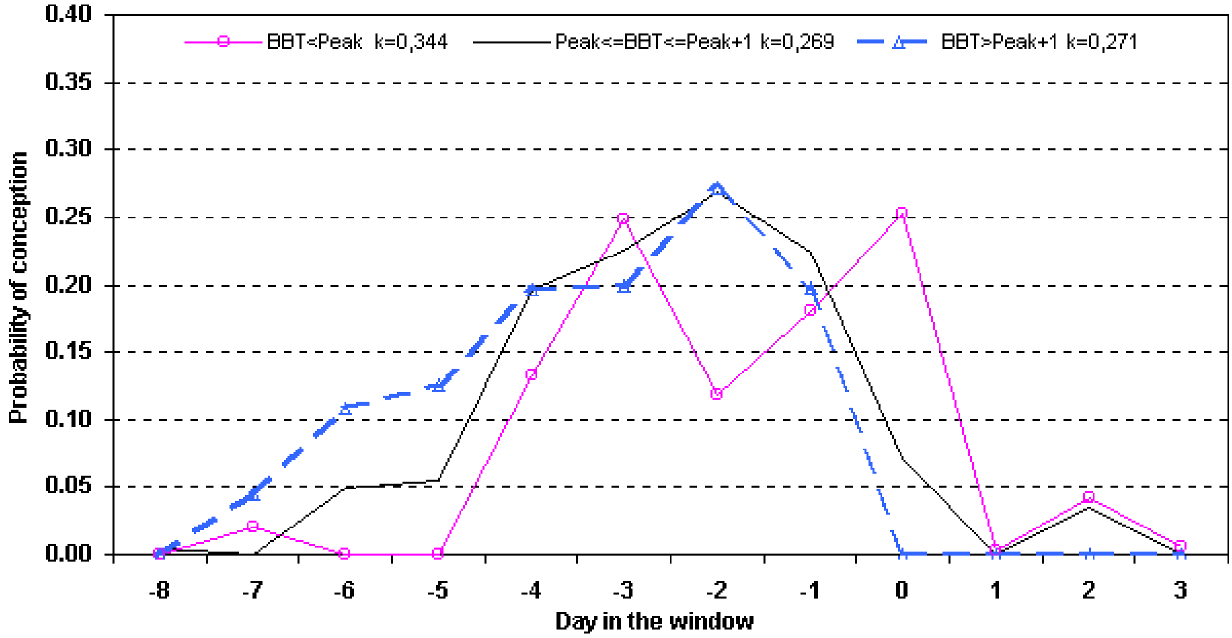

Figure 7:
Daily fecundability around BBT or mucus reference days according to the length of the respective conventional preovulatory phase (<16 days, ≥16 days). European centres.