Time to pregnancy: results of the German prospective study and impact on the management of infertility

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BACKGROUND: The likelihood of spontaneous conception in subsequent cycles is important for a balanced management of infertility. Previous studies on time to pregnancy are mostly retrospective and biased because of exclusion of truly infertile couples. The study aim was to present a non-parametric estimation of cumulative probabilities of conception (CPC) in natural family planning (NFP) users illustrating an ideal of human fertility potential. METHODS: A total of 346 women was observed who used NFP methods to conceive from their first cycle onwards. The couples practising NFP make optimal use of their fertility potential by timed intercourse. The CPC were estimated for the total group and for couples who finally conceived by calculating Kaplan-Meier survival rates. RESULTS: A total of 310 pregnancies occurred among the 346 women; the remaining 36 women (10.4%) did not conceive. Estimated CPC for the total group (_n_ = 340 women) at one, three, six and 12 cycle(s) were 38, 68, 81 and 92% respectively. For those who finally conceived (truly fertile couples, _n_ = 304 women), the respective pregnancy rates were 42, 75, 88 and 98% respectively. Although the numbers of couples in both groups were similar, the impact of age on time to conception, as judged by the Wilcoxon test, was less in the truly fertile than in the total group. CONCLUSIONS: Most couples conceive within six cycles with timed intercourse. Thereafter, every second couple is probably either subfertile or infertile. CPC decline with age because heterogeneity in fecundity increases. In the subgroup of truly fertile couples, an age-dependent decline in CPC is statistically less obvious because of high homogeneity, even with advancing age.

Keywords: cumulative probability of conception/management of infertility/natural family planning/survival rates/time to pregnancy

Introduction

The likelihood of conception in subsequent cycles is of major interest to clinicians and epidemiologists to measure human fertility and to balance the management of infertility, thereby avoiding over- and under-treatment. Recent literature contains very little prospective data on time to pregnancy (TTP) (Wilcox _et al._, 1988; Hilgers _et al._, 1992). One group examined fertility rates and pregnancy wastage prospectively in 200 presumably fertile couples trying for pregnancy over 12 menstrual cycles (Zinaman _et al._, 1996). These authors observed a maximal conception rate of ~30% per cycle and a cumulative pregnancy rate of 82% after 12 menstrual cycles. More recent studies (Juul _et al._, 1999; 2000; Jensen _et al._, 2001) only recorded TTP retrospectively among pregnant women using questionnaires to measure, for example, couple fertility by assessing exposures related to semen quality, age or environment. Although their observation of a 12-months pregnancy rate of ~80% was similar to that reported by others

(e.g. Zinaman _et al._, 1996), their study design did not estimate real fecundity, due mainly to the fact that infertile couples were excluded (Jensen _et al._, 2000). Therefore, effects on the proportion of truly infertile couples, which is of major importance, cannot be assessed (Baird _et al._, 1986). Another disadvantage is the possible inaccuracy because at long-term recall, TTP may sometimes only be estimated roughly by couples completing the questionnaire. It is known from cited previous studies that most couples are likely to conceive early. Therefore, for validity of data, the precise shift from contraception to reproduction is very important. Although validation studies of TTP recall exist (Joffe _et al._, 1993), some doubts remain. Thus, prospective studies are urgently needed.

Reproductive behaviour in western society has changed dramatically during the past two decades. Twenty years of contraception may precede a first pregnancy; therefore, age effects on fertility are of extreme importance. An age-related decline in the fertility of couples was previously documented

for daily probabilities of conception (Dunson *et al.*, 2002). Much more appropriate and informative are the age effects on couples' cumulative chances of conceiving.

In general, subfertility is defined as the inability to conceive within 12 months of unprotected intercourse. Cumulative pregnancy prospects over cycles with fertility-focused intercourse may be better than the usual dichotomous, simplified definition of fertile-subfertile with a failure to become pregnant during a 12-month period. The aim is to present a non-parametric estimation of cumulative probabilities of conception (CPC) in natural family planning (NFP) users, thereby illustrating an ideal of human fertility potential. These cumulative pregnancy prospects will probably help to decide whether sufficient exposure to the chance of conception has taken place, when to start a routine infertility investigation, and how to avoid a premature resort to assisted-reproduction techniques (ART) with their associated risks, especially in patients unsuccessfully practising a method of NFP to achieve a pregnancy.

For more than 15 years, a long-term prospective cohort study on the use of NFP has been conducted in Germany (Freundl *et al.*, 1988; 1993; Frank-Herrmann *et al.*, 1991; 1997). In Germany the use of symptothermal is recommended which has been proven to be the most efficient and reliable method of NFP (The European Natural Family Planning Study Groups, 1993; 1999). The double-check variation of the STM consists of recording the main symptoms of fertility: basal body temperature (BBT) and cervical mucus pattern and the application of calculation rules. The fertility awareness part of the STM focuses mainly on cervical mucus monitoring, which correlates very closely with rising estrogen levels and onset of the fertile period. The peak day (last day of highly fertile mucus) is a reliable indicator of very near-ovulation. The BBT rise indicates the beginning of the luteal phase and the end of the fertile period. This cycle monitoring by self-observation allows reliable ovulation detection (Freundl *et al.*, 1984; Gnoth *et al.*, 1996; Dunson *et al.*, 1999) and location of the fertile window within the cycle for either avoiding or achieving pregnancy. Generally, recent fertility studies on users of NFP (e.g. Colombo and Masarotto, 2000; Dunson *et al.*, 2001; 2002), are based on a fairly ideal sample of upper-class couples with high compliance and close follow-up by the study centre. The participants of this study practising NFP to achieve a pregnancy make optimal use of their fertility potential by accurate detection of the fertile window in their menstrual cycles and an above-average knowledge on reproductive basics such as optimal time and interval of intercourse.

The present study estimates CPC over time for a cohort of couples using NFP to conceive from their first cycle onwards. To the present authors' knowledge, this is the largest prospective study conducted to date on CPC and time to pregnancy in terms of participants and pregnancies.

Materials and methods

Data collection

The study was conducted in accordance with the principles of the Declaration of Helsinki. All participating women were instructed by

experienced NFP teachers during the first 3–6 months of study participation until reliability in using the fertility awareness part of the STM was reached. The couples entered this study voluntarily after providing their informed consent. Several standardized questionnaires were completed in order to record all relevant data concerning parity, medical (especially obstetric) history, socioeconomic and demographic backgrounds and finally—when they ceased participation—the reasons for dropping out. By the end of March 2001, a total of 31,498 NFP cycle charts from 1357 women using the STM had been collected in the authors' database. This database (NFPDAT version 1.0) is based on Microsoft Access® (Gnoth *et al.*, 1999), and guarantees maximum data quality by utilizing more than 200 validated error formulae and an automatic request for follow-up on participants, at least every 3 months. Among all participants, there were 346 couples who switched from contraception [NFP or oral contraceptives (~20%)] to reproduction using the STM for fertility-focused intercourse. For only a few of the former users of oral contraceptives (OC), the first cycles using the STM were also their first trying for pregnancy, as most had initially avoided pregnancy with the STM.

The 346 women were observed from their first cycle onwards in which they tried to conceive. Pregnancy was assessed by either ultrasound, positive pregnancy test or a luteal phase longer than 18 days. In both of the latter cases, only later-confirmed clinical pregnancies (live birth, ectopic implantation or clinical abortion) were included in the analyses.

Inclusion and exclusion criteria

The use of NFP is not bound to a regular cycle pattern (Frank-Herrmann *et al.*, 1991), as it is often implicitly maintained. On the contrary, women trying to conceive use the advantages of NFP for fertility-focused intercourse (fertility awareness), especially in cases of irregular cycles or after discontinuation of oral contraceptives (Gnoth *et al.*, 2002a).

During the early stages of the study, all women trying for pregnancy with the help of the fertility awareness part of the STM were included. Later before data were processed using the Statistical Analysis System (SAS) package to ensure unbiased analyses, some couples with previous fertility problems were also excluded in addition to those women taking hormonal medication or drugs that might affect fertility. One women requested fertility treatment during the course of this study and was excluded thereafter. After cessation of OC, only ovulatory cycles were included and any woman with more than three subsequent anovulatory cycles was excluded. Some women re-entered the study after breastfeeding or abortion. Hence, only women trying for a first pregnancy under the conditions of the study (which may not be necessarily the first pregnancy for the couple) were included in the analysis. Prior to every cycle, the family planning intention had to be indicated on the cycle sheet, and the women were asked to mark every episode of intercourse on the cycle sheet. Only cycles with at least one episode of unprotected intercourse in the fertile window were taken into account. Cycles with exclusively protected or no intercourse in the fertile phase were excluded. As all of the couples in this study had intercourse on the fertile days in most cycles, any major effect of coital pattern on estimation of cumulative probabilities of conception could be excluded. Only 3% of the cycles had to be excluded because of missing intercourse, or intercourse only outside the fertile window. In three couples, there was a longer pause with absolutely no intercourse up to 7 months, probably with an interim change in the family planning intention which was unreported.

Six women among those who finally conceived [truly fertile (TF) couples; see below] were completely excluded from the analysis of cumulative probabilities of conception because some cycles were completely missing and no information on episodes of intercourse

Table I. Cumulative probability of conception (CPC) for all couples and the truly fertile subgroup of women who finally conceived

Patient group	No. of cycle			
	1	3	6	12
All couples[a]	0.38 (0.026)	0.68 (0.026)	0.81 (0.022)	0.92 (0.017)
Truly fertile couples[b]	0.42 (0.028)	0.75 (0.025)	0.88 (0.018)	0.98 (0.009)

Values in parentheses are SEM.
[a]$n = 340$; six couples excluded due to inaccurate time to pregnancy.
[b]$n = 304$ couples; six couples excluded due to inaccurate time to pregnancy.

(exposure to pregnancy) was available, though a conception cycle was submitted later which led to inaccurate TTP.

Statistical methods and analysis

Statistical analyses were performed using the SAS package, version 8. On the basis of previous studies, the analysis was based on two *a priori* hypotheses that pregnancy rates decline with age in all couples and in TF couples. Hence, in addition to the usual exploratory analyses, *t*-tests, χ^2-tests for categorical data, Wilcoxon test and Log-rank test for conception probabilities based on Kaplan–Meier survival rates were also performed. The statistical method of Kaplan–Meier specifically allows for estimations of 'real CPC' without under- or overestimation, especially if some women were censored for reasons other than conception. Cumulative probability curves were computed from these estimates as '1 – survival rate', which provides distribution functions for the respective variables 'time to pregnancy' and 'time to drop-out', with a cut-off at 21 months observation because of the small numbers remaining. All analyses were carried out for the whole group, and separately for those who finally conceived (TF couples). Control was applied for the influence of confounding factors of major importance such as age, parity, educational level and socio-economic status.

Results

In total, 310 pregnancies (TF) occurred among 346 women during a maximum of 29 cycles of observation [mean 3.56 ± 4.03 (SD) for a total of 1208 cycles observed]. During this period, 36 women did not conceive [probably infertile (PI), 10.4%]. The mean number of cycles observed in the PI group until drop-out was 7.83 ± 5.43 (range 1–20) cycles. The mean age of all women ($n = 343$) was 29.0 ± 3.6 (range 20–44) years. There was no statistically significant difference in age between those women who finally succeeded or failed to conceive (TF 28.5 ± 3.5 years; $n = 309$; PI 28.9 ± 3.0 years; $n = 34$). The mean age of all men ($n = 333$) was 31.6 ± 5.5 years, and a significant difference ($P = 0.027$) was seen in the men's age in couples who either finally conceived (TF 31.4 ± 5.6 years; $n = 297$) or failed to conceive (PI 33.6 ± 5.3 years; $n = 36$) during the observation period.

Most of the couples were married, and ~60% of the women had a high-school or university degree. Approximately 50% of the women were housewives, and ~50% were working; 82% were Roman-Catholic.

Some 52% of the TF-group and 31% of the PI-group reported on a prior pregnancy before participating in the study ($P < 0.001$). As stated above, some women re-entered the study after live-birth or abortion. To avoid a possible bias in the statistical estimations, all couples were observed only for their first pregnancy under the conditions of the study. Hence, this 'first study-pregnancy' was not necessarily the first pregnancy of the couple.

Cumulative probabilities of conception

The estimated CPC for the whole group and for the TF group are shown in Table I and Figures 1 and 2. Only data from 340 of 346 women were included in this analysis. The TTP of six women from the TF group (now $n = 304$) was inaccurate because some cycles were completely missed (no information on exposure to pregnancy), although a conception cycle was submitted later, thereby leading to an inaccurate TTP.

A total of 8% of all participating women failed to conceive within 12 cycles of fertility-focused intercourse, and were deemed subfertile according to current clinical opinion (which expects an ~80% overall conception rate within 12 months). For ~30% of the women this was a secondary infertility.

By analysing CPC for the whole group (including subfertile and truly infertile couples), and then for the subgroup of those who finally conceived (TF couples) separately, very large sub-groups (81 and 88% respectively) were identified of clearly highly fertile couples who conceived quite early within six cycles with timed intercourse. Approximately 20% of all couples, and only ~10% of finally conceiving couples (TF), did not conceive within six cycles. Consequently, among those women who did not become pregnant after six cycles with timed intercourse, almost every second couple may be regarded as subfertile or probably infertile (PI) according to current clinical definitions.

Fertility was not artificially overestimated due to the early drop-out of those women who did not become pregnant. The distribution function computed from the survival curve of cycles for those who did not conceive (PI) was significantly lower than for those who finally became pregnant (TF) (Figure 2). The mean participation time (observed cycles) was statistically longer for the PI group (7.83 ± 5.43 cycles) than the TF group (3.05 ± 3.52 cycles) ($P < 0.001$; Wilcoxon and Log-Rank tests). Among the PI group, 30 women stopped sending data to the research units and withdrew from the study; however, they continued with NFP to achieve pregnancy. Information obtained via the NFP investigators suggested that some women were disappointed because conception did not occur as early as expected. Five women were lost to follow-up, and one woman finally stopped attempting to conceive.

A statistically significant ($P = 0.0371$; Wilcoxon test for survival rates) age-related decrease in CPC was seen for all
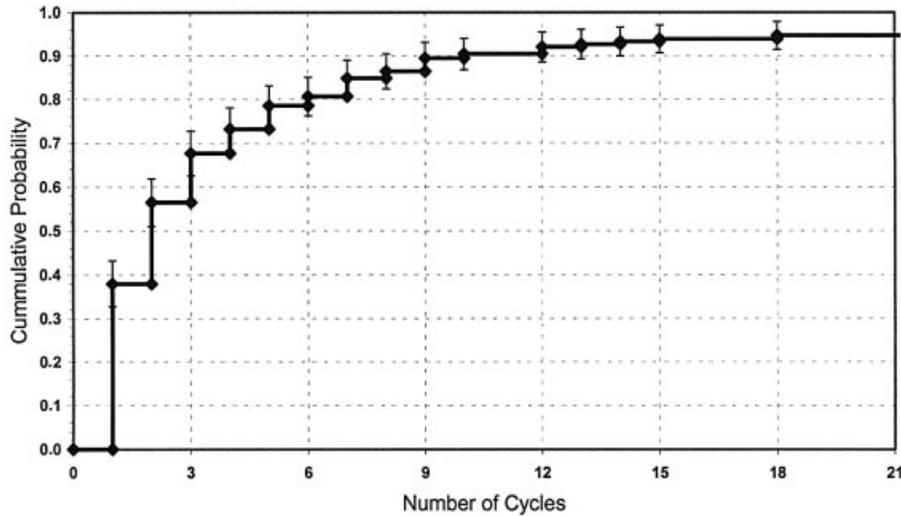
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Figure 1. Cumulative probability distribution of conception over time [number of cycles with fertility-focused intercourse; time to pregnancy (TTP)] calculated from the Kaplan-Meier survival function (*n* = 340 couples, six excluded because of inaccurate TTP, censored for non-conception).
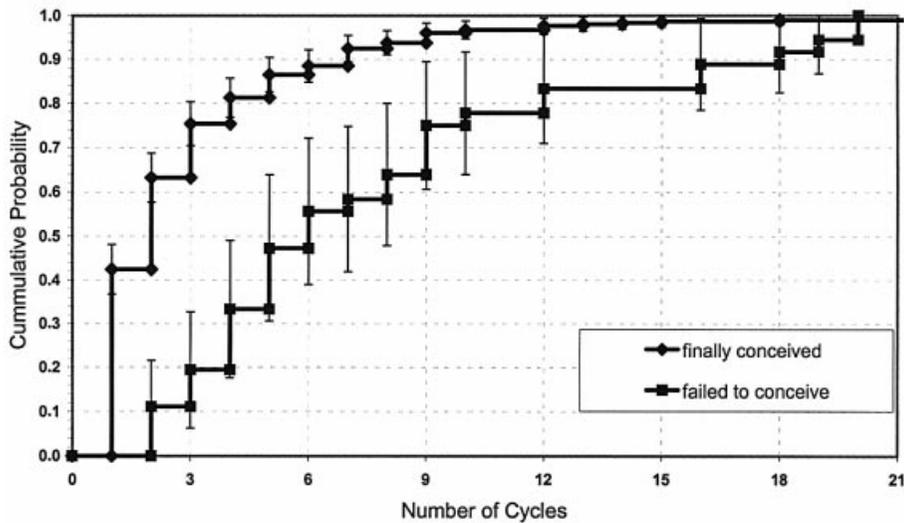

Figure 2. Cumulative exit rate from study calculated from the Kaplan-Meier survival function for couples who finally conceived [diamonds: truly fertile (TF); *n* = 304, TTP] and those who failed to conceive [square: probably infertile (PI); *n* = 36, time to drop-out] during the observation period. Wilcoxon and Log-rank test: *P* < 0.001.

couples (including subfertile and truly infertile couples) (Figure 3). The data for cycle 1 complied with data for daily probabilities of conception (Dunson *et al.*, 2002). On examining the final cycle of observation, high prospects of conception were found (~90%, maximum of 29 cycles observed) in all age categories except for women aged >35 years (73%), mainly due to low numbers of participants. The estimated overall CPC was seen to decrease with age, but the final cumulative prospects were high and not significantly different [–2Log (Log-rank): *P* = 0.0534].

In women who finally became pregnant (TF), the results were less obvious (Figure 4), and although cycle fecundity seemed to decrease with age, the cumulative pregnancy rates were not statistically different. Neither the Log-rank-test (*P* = 0.199), Wilcoxon test (*P* = 0.066) nor –2Log (Log-rank)

test (*P* = 0.170) revealed any difference for the different sections of the survival curve. After 12 cycles, all women reached an estimated plateau of 90–98% pregnancy rate. Thus, in this rather ideal sample of TF couples, age *per se* was not associated with any statistically significant reduction in CPC and decreased final pregnancy prospects.

Discussion

In this prospective study on CPC, a total of 310 pregnancies was observed among 346 women using NFP methods for timing of intercourse. Previous prospective studies on CPC have been much smaller in terms of participant and pregnancy numbers (Wilcox *et al.*, 1988; Hilgers *et al.*, 1992; Zinaman *et al.*, 1996), and have also reported a longer average time to
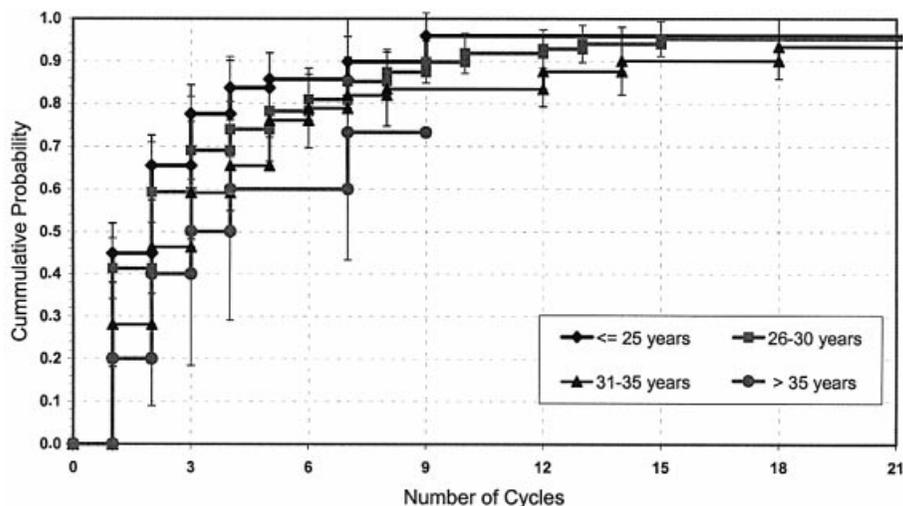
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Figure 3. Cumulative probability distribution of conception for all couples in different age categories (<25 years, $n = 58$; 26–30 years, $n = 189$; 31–35 years, $n = 82$; ≥35 years, $n = 10$) over time calculated from Kaplan-Meier survival functions [$n = 339$; seven couples excluded due to inaccurate TTP ($n = 6$) or woman's age not indicated ($n = 1$)].

Figure 4. Cumulative probability distribution of conception for truly fertile couples in different age categories (<25 years, $n = 55$; 26–30 years, $n = 168$; 31–35 years, $n = 71$; ≥35 years, $n = 9$) over time calculated from Kaplan-Meier survival functions [$n = 303$; seven couples excluded due to inaccurate TTP ($n = 6$) or woman's age not indicated ($n = 1$)].
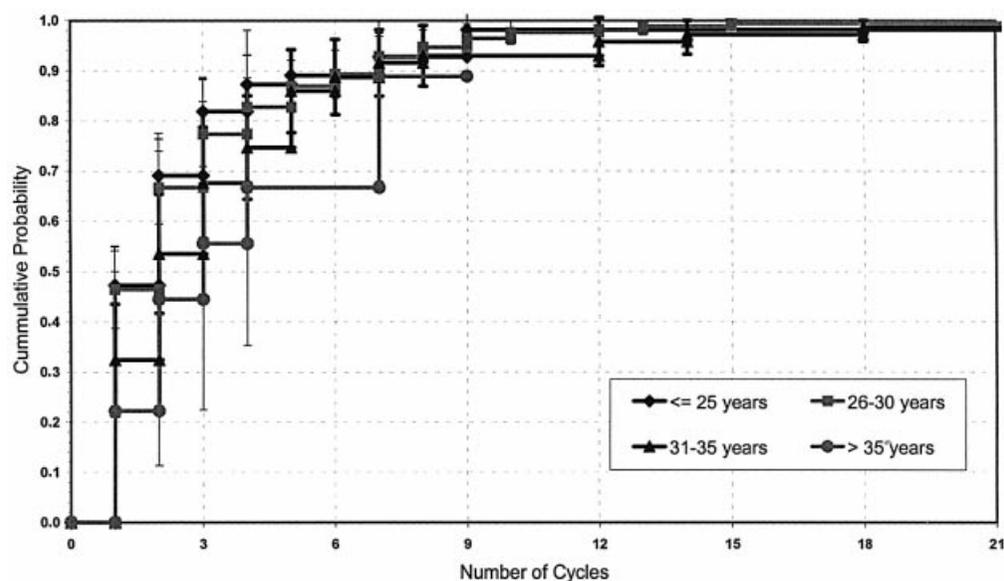
pregnancy and a lower pregnancy rate at the 6- and 12-month periods. More recent studies have been mostly retrospective (Juul *et al*., 1999; 2000; Joffe, 2000; Jensen *et al*., 2001), but may be biased due to long-term recall of TTP and exclusion of truly infertile couples (Jensen *et al*., 2000). Nevertheless, the CPC of the present 'total' group (including subfertile and PI couples) at the 12-month period was comparable with that reported by others. The important advantage of this prospective study is the information it provides about the precise shift of contraception to reproduction, the long-term design (maximum 29 cycles of observation), and the power of the statistical method (Kaplan-Meier) used to minimize an artificial over-estimation of fertility due to early drop-out of women who did not conceive. In addition, the mean number of cycles of

observation for those women who did not conceive was significantly greater then for those who finally became pregnant. In contrast to previous reports (Dunson and Weinberg, 2000; Dunson *et al*., 2002), a non-parametric model was preferred to assess fertility rates in the present study, mainly because presently there was no parametric model available which would describe with sufficient precision the entire process of fertility and its changes. This suggests that estimating CPC by monitoring survival functions and related probability distribution functions, as in the present study, is more accurate than using a parametric model.

Although the upper-class population of the present study may not be representative of the general population in Europe, the authors are unaware of any study linking social status to

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variability of fertility. In Germany in 1999, the mean age of women at their first birth was 28.83 years, and this was comparable with the present study population. The influence of factors such as age (late first pregnancy), coital patterns or genital infections in different social classes on fertility is unknown, and indeed some of these effects might neutralize each other (e.g. higher age in upper-class groups and probable higher rate of genital infection in lower-class groups). It is known from previous studies (Frank *et al.*, 1985; Frank-Herrmann *et al.*, 1991) that the STM also provides effective contraception in so-called 'lower-class' couples; hence, it could be expected that the results obtained might be generalized to other populations in developed countries.

Users of NFP may represent a somewhat ideal sample, as they make optimal use of their fertility potential by accurate detection of the fertile window in their menstrual cycles and an above-average knowledge of reproductive basics such as optimal time and interval of intercourse. Nevertheless, it is known from the authors that Internet-based counselling of couples with infertility problems (www.meinkinderwunsch.de) that increasing numbers of women are practising natural methods before, and also in parallel with, infertility therapy. Hence, it is hoped that the results of the present study will aid those who counsel couples (e.g. prior to specialized infertility therapy, general practitioner, general gynaecologist) and direct them towards further steps of diagnosis and possible reference to a specialized centre. Moreover, these data may also help specialists to decide whether sufficient exposure to the chance of conception has occurred, as well as when to start further infertility investigation and resort to ART, especially in cases of unexplained infertility.

All participating women were trained and instructed by experienced NFP teachers in parallel with their study participation (1–6 months) until autonomy and reliability in using NFP was reached. About 20% of women switched from OC to the STM, and in only a few of the former OC users was their first cycle using STM also their first cycle in attempting pregnancy. This was due to the fact that in the past, most former OC users initially avoided pregnancy by using the STM. Hence, there was no difference in the correct location of the fertile window for experienced NFP users and absolute beginners, as has been shown previously (Frank-Herrmann *et al.*, 1991; 1997) when NFP was used as an effective method of contraception.

In the present study, most couples attempting pregnancy had intercourse in the fertile window in almost every cycle, from the first cycle until conception or drop-out. The couples were obliged to record on the cycle sheet every episode of intercourse was recorded, and only 3% of cycles were excluded due to missed intercourse or intercourse only outside the fertile window. Three couples reported a longer pause, with no intercourse for up to 7 months, most likely with an interim change in their family planning intention. Therefore, before conducting the first analysis the decision was made to include only those cycles with prior documented family planning intention, and also those with unprotected intercourse at least once in the fertile window, the reason being that the aim was to

propose NFP as a tool for diagnostic assessment of 'infertile' couples (see below).

About 80% of the couples conceived in the first six cycles when using the fertility awareness part of the STM with fertility-focused intercourse. These numbers partly confirm the data obtained from earlier and larger retrospective studies (Bonde *et al.*, 1998; Juul *et al.*, 1999; 2000; Joffe, 2000; Jensen *et al.*, 2001), though a higher final cumulative probability of conception within 12 cycles was found. As expected, some 10.4% of women did not conceive within all observed cycles. For those who finally conceived, only 2% of the pregnancies occurred later than 12 cycles.

In another well-designed, prospective study (Bonde *et al.*, 1998), cumulative pregnancy probabilities of almost 60% were obtained after six menstrual cycles. The higher CPC value compared with all cited studies accounts for the effects of information on the fertile period and of repeated timed intercourse. The effect of timed intercourse on pregnancy rates of women, with optimal use of their fertility potential, was also recently emphasized by others (Stanford *et al.*, 2002).

These findings highlight the existence of a huge group of highly fertile couples who conceive quite early within six cycles with timed intercourse. About 20% of all couples, and only 10% of finally conceiving couples (TF), will not be successful within six cycles (see Table I). These TF couples represent an ideal homogeneous group without any infertility problems and, using a ~30% monthly chance of conception, they will achieve a pregnancy rate of almost 90% in six cycles, based on the formula:

Probability of conception within 6 months = $1 - (1 -$ monthly probability of conception$)^6$, which is precisely the relationship confirmed by the results of the present study.

Taking into account the results of the overall conception rates for all couples, among whom ~20% do not conceive in six cycles and ~10% do not conceive in 12 cycles, almost every second couple is probably subfertile or infertile after six unsuccessful cycles with timed intercourse. Thus, it is possible to suggest a new threshold such that, after six unsuccessful cycles with fertility-focused intercourse (the ideal exposure to pregnancy) prior to the first visit or during the following months, clinicians in primary care must assume subfertility or, in rare cases absolute infertility (such as tubal pathology or azoospermia), in almost every second case. In the present authors' opinion, this justifies an early and basic infertility work-up in these individual cases; in individual cases, the waiting time should not be extended to 12 cycles, before starting basic infertility work-up to avoid possible under-treatment of infertility later.

Couples with a good prognosis (unexplained infertility, no tubal affection, no oligoamenorrhoea, no oligoasthenozoospermia and no signs of reduced ovarian reserve; Navot *et al.*, 1987; Seifer *et al.*, 1997; Scheffer *et al.*, 1999), and/or no suspicion of endometriosis, should be advised to wait as they have a reasonably good chance (>60%) of conceiving spontaneously during the next 36 months (Collins *et al.*, 1995; Snick *et al.*, 1997; Glazener *et al.*, 2000; Glazener and Ford, 2002; Gnoth *et al.*, 2002b). During this period, self-monitoring with NFP methods may be all that is necessary. However, it is

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sometimes difficult to get patients with infertility problems to wait unless they are given detailed information about their prognosis, the proposed pattern (and difficulties) of investigation and treatment, as well as alternative ways of becoming parents (Schmidt, 1998).

An advanced infertility work-up which includes laparoscopy and hysteroscopy, endocrinological tests, in-vitro tests of sperm–cervical mucus interactions together with consultation with a reproductive gynaecologist and andrologist as well as ART, should be offered to couples with poor prognosis and more than 12 unsuccessful cycles with timed intercourse. They may benefit from an early resort to ART because in this case they are superior to expectant management (Evers *et al.*, 1998). This balanced management avoids unreasonable early interventions such as IVF as first-line treatment (Karande *et al.*, 1999), which may represent over-treatment and expose women to medical complications (e.g. multiple pregnancies and ovarian hyperstimulation syndrome) and unnecessary expense. It also avoids late interventions which may represent infertility under-treatment.

As expected, CPC was found to decrease with advancing female age in all couples. Indeed, previous reports on daily fecundability (Dunson *et al.*, 2002) showed a decline for women in their late 20s as well as for men in their late 30s. In that study, 105 of the 782 participants were from a long-term study on NFP in Germany, and most had used the STM for contraception such that acts of unprotected intercourse were often located in border regions of the fertile window. Intercourse on days with the highest pregnancy prospect was somewhat under-represented. This mixture of pregnancy avoiders (predominantly) and achievers influenced coital pattern and may have affected the calculations of fertility. Another possible bias in the study was an overestimation of fertility due to the non-exclusion of participants who re-entered the study after breastfeeding or abortion.

Cumulative pregnancy rates in natural cycles are much more appropriate for assessing age-related effects than are daily pregnancy probabilities (te Velde *et al.*, 2000). In the present study, all women had intercourse on the most fertile days of the cycle, thereby reducing any influence of coital pattern on fertility estimation. As expected, the CPC decreases significantly with age for all couples, and the final estimated pregnancy prospect is high (about 90%), except for women aged >35 years. However, the proportion of women falling into this age category is too small to prove (statistically) a significant decline in fertility. In the separately analysed, ideal subgroup of TF couples, the CPC did not differ significantly among the different age groups. Methodically, even when heavy censoring is employed (as in the present study), a Kaplan-Meier approach allows the analysis of non-censored subjects (i.e. TF couples) to calculate a distribution function of the numbers of cycles from the survival function, as those who failed to conceive (i.e. censored) were observed for a significantly longer period than the finally successful couples (i.e. non-censored) ($P < 0.001$; Wilcoxon and Log-rank test). Thus, for this ideal sample of TF couples, the effect of age on the decline in fertility was less obvious because of their high homogeneity with advancing age. Unfortunately, no information is available on the rate of ongoing pregnancies and live births in all cases. As the incidence of abortions is higher in older women, an outcome measure of live births would provide additional—and probably more solid—information in terms of an age-related birth rate. Consequently, it is difficult to draw final conclusions based on these findings.

With increasing age, there is an increasing proportion of couples with infertility problems, and this is related mainly to the woman. Although some fertility problems are associated with age (e.g. reduced ovarian reserve), they depend mainly on individual factors (te Velde and Pearson, 2002) that cause increasing heterogeneity in fecundity with age. In the present study, the inter-quartile range in cumulative probability of conception for women aged between 31 and 35 years extended from 28 to 76%, while for women aged >35 years it extended from 20 to 100%. It is this increased heterogeneity due to an increasing proportion of truly subfertile and infertile women which accounts for an age-related decrease in fertility, lowering the average for the whole group, and giving the illusion of a gradual age-related effect. The small differences in overall CPC between the age groups of <30 years account for a broad plateau of relatively high fertility in most couples, and a subsequent rapidly increasing infertility with a small plateau of highly fertile couples of greater age. The significant difference ($P = 0.0371$) between these groups is mainly due to the influence of women aged >35 years. In view of the effects of age on CPC for all and TF couples, the findings of the present study suggest that in this homogeneous setting a woman's fertility most likely does not decline gradually with advancing age. This stresses the importance of an early basic infertility investigation for probably subfertile or infertile couples in order to detect individual factors associated with a poor prognosis of achieving spontaneous conception, regardless of age. It is of interest to note that there was a significant association with men's age among TF couples; this confirms the data published by others (Dunson *et al.*, 2002) and forms the basis for future investigations.

Last—but not least—NFP methods are widely used by women. Two European multicentre studies (The European Natural Family Planning Study Groups, 1993; 1999; Colombo and Masarotto, 2000) have shown that the NFP centres in Europe are now well structured to carry out prospective studies to measure a couple's fertility by assessing exposures related to semen quality, age or environment.

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