Time to pregnancy as a correlate of fecundity: differential persistence in trying to become pregnant as a source of bias

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Background Subfecundity is a frequent and often serious problem and it is important to identify its preventable determinants and to monitor fecundity over time. Since follow-up studies are difficult and expensive to conduct, time to pregnancy (TTP) in pregnant women is often used as a surrogate measure of fecundity. TTP data can be retrieved at low costs and they need no valid population registry as a source for sampling. While TTP may serve as a valid surrogate measure in many situations, its validity rests upon a number of assumptions. We have analysed one of these overlooked assumptions, the importance of persistence in trying to become pregnant.

Methods By means of computer simulations we estimated bias caused by differences in persistence in pregnancy attempts. We investigated whether the assumptions made in the simulation were realistic by using empirical data from a European study.

Results The mean waiting time to pregnancy and other estimates of subfecundity (or infertility) strongly depend upon the persistence of couples in pursuing a pregnancy. We show that even moderate changes in the planning behaviour considerably modify the waiting time distribution. Empirical data confirm that persistence in trying to become pregnant is age-related.

Conclusions Persistence in pregnancy attempts affects outcome measures of subfecundity in studies based upon TTP in pregnant women. It is likely that the length of time during which couples keep trying to become pregnant is influenced by a number of factors which would probably change over time or be different between populations to be compared.

Keywords Time-to-pregnancy, fecundity, epidemiology, bias

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Fecundity determines the expected length of time from starting unprotected intercourse till conception (TTP) and, to properly estimate fecundity, complete follow-up after a well-defined starting time is needed, or a modified case-cohort design has to be used. Follow-up studies are, however, expensive and difficult to perform since pregnancy planners are few at any given point in time in most populations. For this reason TTP measures in pregnant women are often used since these women are easy to identify due to their frequent contacts with the health care system, and most of them are able to recall TTP accurately. These TTP measures have been extensively used in internal comparisons and to identify risk factors or changes in fecundity over time. We examine the effect of incomplete follow-up on TTP measures, that is, when couples do not pursue the desire to have a child with a similar persistence in the groups to be compared. No published research has been devoted to examine this type of bias before.

In principle, comparable persistence in trying to become pregnant between regions and over time is required for a monitoring system to provide unbiased results based upon TTP measures, which is a strong assumption. This study provides a tool to estimate how crucial this assumption may be for detecting geographical and temporal variations in fecundity based upon pregnancy samples.

We observed that older women on average conceived faster than younger women in pregnancy-based TTP studies, while the opposite was seen when using survey data including unsuccessful waiting times. We analyse if a differential persistence in the pregnancy attempt according to age could be a possible explanation.
**Methods**

We used different scenarios applied to simulated populations as well as calculated estimates under simplified conditions in order to estimate the direction and magnitude of the bias related to differential persistence in pregnancy attempts. The simulated models have the following characteristics:

1. Couples are divided into different sub-populations, which may be seen as representing different age groups, geographical areas, time periods or exposure groups.
2. Each couple is assigned a probability of conception per cycle ($p$), which for convenience follows a Gaussian distribution. The mean probability varies in different simulations together with the pattern of giving up the pregnancy attempt. Fecundability remains the same for each couple throughout follow-up (up to 36 cycles or months).
3. The giving up process takes place from a given cycle ($s$) onward, and among all couples who have not conceived, a fraction ($r$) is eliminated at each cycle from the population trying. Thus, the population of pregnancy planners declines over time from cycle $s$ to the end of follow-up.

We used the following outcome measures:

1. **Mean TTP** (average number of cycles taken to conceive within each group).
2. The proportion of couples who conceived within 6 and within 12 months.

Simulations are not needed if all couples within each subgroup are given the same fecundability. A closed formula is then available to identify the determinants of the mean TTP in populations with different patterns of giving up (see Appendix).

Data from The European Studies of Infertility and Subfecundity\(^9\) are used to illustrate TTP measures in pregnancy samples and the pattern of stopping a pregnancy attempt according to age in data with censored waiting times. The empirical data on persistence in pregnancy attempts were obtained from a population-based survey on fecundity in Europe.\(^10\) Kaplan-Meier estimates were calculated by censoring waiting times at the time of conception or interview.

**Results**

**Simulations**

Table 1 presents results from several simulations including 10 000 couples in each simulation. The table shows that different patterns of giving up a pregnancy attempt in themselves change the TTP distribution, as well as the relative measures of subfecundity. The earlier couples start giving up and the higher the proportion giving up, the lower the mean TTP values become, and the higher the relative effect measures.

Figure 1 shows the histogram of TTP in two different mixtures of the simulations and in women from the pregnancy-based samples of The European Studies of Infertility and Subfecundity’ in Denmark and Northern Italy who conceived.
within 36 months. The distribution of TTP for Denmark is similar to the modelled one, while that for Northern Italy differs substantially. Since the simulations assumed regular cycles and that all women started trying at the beginning of a cycle, while women in the study reported the number of months they required to conceive, the two distributions are not entirely comparable. Possibly, in Northern Italy there was a stronger phenomenon of digit preference in reporting TTP, and the question about ‘planning a pregnancy’ may have been interpreted differently.

Table 2 shows the TTP distribution from the above mentioned empirical data. In both regions women above median age...
apparently conceived faster. From the data displayed in Table 2 the ratio between older and younger women in Denmark can be computed: 12% more of older Danish women conceived within the first month, 7% more within 6 months, and 2% more within 12 months, compared with younger women. For the Italian data the corresponding figures were 6%, –1%, and 3%, respectively. Similar differences could be reproduced in the simulations by letting older women more often leave the group of pregnancy planners in spite of the fact that fecundity was set at identical values in the two groups. The Danish results (in terms of ratios between the older and younger age groups) could, e.g. be reproduced with a fecundity of 0.19 and letting the younger group start giving up from the tenth cycle with a 3.5% rate per cycle while older couples started giving up from the fifth cycle with a 7% rate per cycle. The results for Northern Italy could be reproduced in the model if we assumed a fecundity of 0.18 and let the younger group start giving up from the sixth cycle with a rate of 1.3% as opposed to the fourth cycle with a 4% rate for the older group. The proposed model provides many possible ways to obtain ratios similar to those seen in Table 2, even if fertility declines with age.

Figure 2 shows that, when data including censored waiting times are examined, older women tended to give up a pregnancy attempt after a shorter period of trying, and this tendency differed between the two regions. In Denmark older age was a substantial determinant of giving up. In Italy, on the other hand, no differential persistence by age was seen up to 24 months of waiting time. The giving up phenomenon was not age-dependent in the first attempt to become pregnant, while it was markedly more so in the following attempts (data not shown).

Discussion

We showed that studies based upon TTP are vulnerable to bias related to differential compliance in pregnancy planning. Relative effect measures could be biased up to 20% under realistic circumstances.

The wish to continue a pregnancy attempt may differ over time, between populations, or between subgroups defined according to a given determinant. Obviously, a change of partner or a divorce usually terminates a pregnancy attempt. Such events are probably rare shortly after the beginning of a waiting time to pregnancy, but will be more frequent over longer waiting times. Changes in income, housing and job situations could play a role. The importance of these potential determinants of duration of the pregnancy attempt will partly depend upon the prior desire to have a child, which may be a function of parity and age.

Whether the described source of bias actually explains the observation of a shorter TTP among older women in pregnancy-based samples is not known, but it is a possible explanation and, as shown in Figure 1, differential persistence does exist. The older the couple, the more difficult it may be to make room for a pregnancy, and many will have children already. Longer TTP in young couples could, of course, also be due to a declining fecundity for younger birth cohorts.11,12

It should be well accepted that TTP does not provide estimates of fecundity. Still, it may be a useful measure for identifying determinants of subfecundity,4,13,14 if these determinants have no impact on the persistence in trying to become pregnant. Caution is especially needed when TTP are compared over long time periods since time in itself is likely to change both proximal and distal determinants in pregnancy planning behaviour.

In affluent societies with low fertility and good opportunities for treatment, an increasing persistency in trying to achieve a pregnancy is probably to be expected, and this may lead to an increase in TTP, even if fecundity remains unchanged over time.

In this paper we have used simple TTP measures rather than analysing the waiting time by survival techniques since in pregnancy-based TTP studies only censored observations are available.

A monitoring system based upon TTP may be too prone to bias to produce valid results, especially over longer time periods and when comparing different populations. The difference in TTP between the Danish and Italian regions may partly be explained by differences in persistence in attempting pregnancy, as shown in Figure 1. Experience shows, however, that most determinants of subfecundity usually are detectable in TTP.
studies. In the future, researchers should try to incorporate information on some of the known determinants of the wish to pursue a pregnancy attempt.

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Appendix

If all couples are set to the same fecundity (p) within a sub-population, the mean TTP can be derived from a formula, which is furthermore simplified when virtually all couples become pregnant when trying throughout the duration of follow-up (m cycles, so that (1 – p)^m is almost 0).

Formula (8) shows that the mean TTP is a function of fecundity and of the compliance to pregnancy planning (how early couples start giving up and how many do so). When giving up occurs, the mean TTP decreases. If, e.g. older couples more easily give up a pregnancy attempt, the remaining couples will have a lower mean TTP even without differences in the underlying fecundity distribution in the compared groups. The TTP could still appear to be lower even if fecundity in older women is reduced. If a large proportion of couples only persists in trying to become pregnant for a few months, the resulting mean TTP will overestimate fecundity.

In case all women keep trying for the duration of the follow-up, the mean TTP is given by:

\[
\text{mean TTP} = \frac{\sum_{i=1}^{m} [i(q)^{i-1}]}{\sum_{i=1}^{m} q^{i-1}}
\]

Where q = (1 – p);
\[p = \text{fecundity and}
\]
\[m = \text{duration of follow-up}
\]

In general, we have that

\[\sum_{i=1}^{m} q^{i} = (q - q^{m+1})/(1 - q) = f(q)
\]

and

\[\sum_{i=1}^{m} i q^{i-1} = (1 - q^{m})/(1 - q) = [f(q)]/q
\]

So,

\[\sum_{i=1}^{m} i(q)^{i-1} = [f'(q)]
\]
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Expression (1) is then equivalent to:

$$\text{(5) mean TTP} = \frac{[f'(q)]}{[f(q)]/q}$$

which becomes, after expanding (5) by computing the derivative:

$$\text{(6) mean TTP} = \frac{1 - q^m [1 + m(1 - q)]}{(1 - q)(1 - q^m)} \approx 1/(1 - q) \quad (\text{if } m \text{ very large or } q \text{ small enough to approximate 0 at power } m: \text{ e.g. } q < 0.82 \text{ when } m = 36)$$

In case a fraction of the women give up trying, the mean TTP is given by a more complicated expression:

$$\text{(7) mean TTP} = \frac{\sum_{i=1}^{(s-1)} [i(q)^{i-1}] + t^{1-s} \sum_{i=s}^{m} [i(qt)^{i-1}]}{\sum_{i=1}^{(s-1)} (q)^{i-1} + t^{1-s} \sum_{i=s}^{m} (qt)^{i-1}}$$

$s = \text{month in which giving up starts for a fraction } (r) \text{ of the couples}$
$t = (1 - r); \tau = \text{rate of giving up per cycle}$
$q = (1 - p); p = \text{fecundity}$
$m = \text{total number of months of follow-up}$

Expression (7) can also be written, by following analogous steps as in (2) and (3), in the following way:

$$\text{(8) mean TTP} = \frac{[[s - 1]q^s - sq^{s-1} + 1]/(1 - q^s)] + [t^{1-s} [[(qt)^{s-1}(s - sqt + qt)] - [(qt)^{m}(m - mqt + 1)]]/(1 - qt)^2]}{[(1 - q^{s-1})/(1 - q)] + [t^{1-s} [(qt)^{s-1} - (qt)^{m}]/(1 - qt)]}$$

When $m$ is large or $(qt)$ is small enough as to approximate 0 when at power $m$, the formula can be simplified to:

$$\text{(9) mean TTP} = \frac{[[s - 1]q^s - sq^{s-1} + 1]/(1 - q^s)] + [t^{1-s} [(qt)^{s-1}(s - sqt + qt)]/(1 - qt)^2]}{[(1 - q^{s-1})/(1 - q)] + [t^{1-s}(qt)^{s-1}]/(1 - qt)]}$$