Recruitment bias in studies of semen and other factors affecting pregnancy rates in fertile men

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BACKGROUND: Recruitment bias is possible in population studies of semen quality because few men volunteer. We examine differences between Australian couples with natural conceptions who agreed or declined to participate in such a study.

METHODS: Women pregnant between 16 and 32 weeks gestation participating in a retrospective time to pregnancy (TTP) study were each requested to recruit their eligible (on the basis of age, place of his birth and of his mother’s birth) male partner to complete additional questionnaires, have a physical examination and provide blood and two semen samples.

RESULTS: From 2061 women who completed the TTP questionnaire (response rate, 98%) there were 928 eligible male partners of whom 225 (24%) were responders. There were significant socio-demographic and self-reported exposure differences between responders and non-responders in particular, female professional occupation, knowledge of the fertile phase, pelvic inflammatory disease, non-smoker at time of conception and wine consumption per week were more frequent in the responders. There was no evidence of a bias for the subfertile being more likely to volunteer for the study. Mean TTP for planned pregnancies for responders and non-responders were 3.3 and 3.8 cycles ($P = 0.319$), respectively, and the cycle specific pregnancy rates were not significantly different after covariate adjustment by Cox regression.

CONCLUSIONS: The present study confirms that participation rates are low in studies of semen quality. Although the expected higher participation of subfertile couples was not confirmed, there remains considerable potential for bias and other problems that could invalidate this type of study.

Key words: fertile men / semen quality / time to pregnancy / bias

Introduction

There is concern that male fertility is declining. Studies to assess trends in male fertility are difficult; few men volunteer for studies of semen quality, and previous experience indicates that volunteers disproportionately represent those who are concerned about their fertility, either because of previous testicular disorders or suspected infertility (Handelsman, 1997; Larsen et al., 1998; Cohn et al., 2002). This is evident in several studies which have shown that men who provide semen were more likely to have had a history of infertility and urogenital disease, lower fertility and unfavorable pregnancy outcomes (e.g. miscarriages, ectopic pregnancies, terminations and stillbirths) in their female partners than men who refuse (Larsen et al., 1998; Eustache et al., 2004; Muller et al., 2004; Toft et al., 2005). Some authors have suggested testosterone levels could be used to check selection bias with men with abnormal testicular function participating in this type of study (Mullard et al. 1999). However, this is not apparent in a larger study among young men (Andersen et al. 2000a, b). The World Health Organization (WHO) Special Program of Research, Development and Research Training in Human Reproduction developed a study ‘Sentinel Surveillance of Semen Quality and Time to Pregnancy’ to test whether human fertility is changing in different regions of the world (Stewart et al., 2001). The WHO study was specifically designed to address the shortcomings and criticisms of previous studies which attempted to establish if there were temporal changes in human fertility and male reproductive characteristics. The aim of the WHO surveillance study was to perform sequential cross-sectional studies of currently pregnant women and their partners at 3 year time intervals to determine whether fertility and semen quality are decreasing with time. The basic study design combined a retrospective time to pregnancy (TTP) study with a cross-sectional study of semen quality. The main strength of the WHO study was...
that it was designed to measure the effects of possible selection bias created by an expected low response rate by men to the semen study. The strength of the study design to be able to do this lies in the fact that all pregnant women were asked to complete the TTP questionnaire in a face to face interview at the time when they were first approached about the study. A high response rate was expected for this, allowing direct comparison of the questionnaire information for the eligible couples who declined to participate and the eligible couples who agreed. The main problem with other studies that have examined selection bias is that information was only available in a proportion of the subjects who refused to provide semen (Eustache et al., 2004; Muller et al., 2004; Toft et al., 2005). By contrast, in the present study, due to the high response rate by women to the TTP questionnaire, information was available for almost all the eligible subjects who refused to provide semen, thus permitting a thorough analysis of selection bias. We examined differences in characteristics between the two groups, and tested the hypothesis that less fertile women who take longer to conceive and have characteristics between the two groups, and tested the hypothesis.

**Materials and Methods**

**Study population**

Women pregnant between 16 and 32 weeks gestation who attended either the antenatal clinic at The Royal Women’s Hospital (RWH) or private obstetric practices, for routine management of pregnancy and childbirth in Melbourne, Australia between January 2000 and December 2002, were approached in the waiting areas and asked to complete the WHO TTP questionnaire. If the current pregnancy was a natural conception and if their partner was eligible (18–50 years, and both he and his mother were born in Australia), he was invited to participate in a more detailed evaluation. This included a physical examination, two semen analyses, measurement of reproductive hormones in blood and the completion of additional questionnaires. For this study, we defined those couples in whom the male participated as ‘responders’ and those who were eligible to participate but did not as ‘non-responders’. All women and men gave written informed consent. The RWH Research and Ethics Committee approved the project.

**TTP questionnaire**

The development and validation of the TTP questionnaire has been described in detail (Stewart et al., 2001). In brief, the questionnaire for women elicited information on socio-demographic factors, contraceptive use, health, pregnancy and reproductive history, height, weight, body mass index (BMI) and lifestyle factors such as smoking and illicit drug use around the time of conception. Women were asked about noxious exposures that she or her partner may have been exposed to around the time of conception. Specifically, the women were asked whether they were involved in any activities in which they were exposed to chemicals, pesticides, herbicides, paint thinners, photographic chemicals or any other noxious agents not otherwise specified. If they answered YES to being exposed they were then asked to recall the noxious agents to which they had been exposed. The exposures listed by the participants could be classified into 10 broad categories these were: pesticides, solvents and degreasers, unspecified work-related exposures, photographic chemicals, petro-chemicals, asbestos, X-rays, radioactive material, gases and non-specific chemicals.

Occupations were classified according to nine major groups as detailed in the ‘Australian Standard Classification of Occupations’ (ASCO) compiled by the Australian Bureau of Statistics. Pregnancies were classified as planned if the couple were actively trying to conceive, or unplanned if the couple were using contraception at the time of conception, or were not using contraception but had no desire to conceive.

**Statistical analysis**

To estimate the number of cycles it took each woman to achieve her current pregnancy (TTP), the time in days between the reference date (year and month when the woman was first exposed to the risk of conception) and the last normal menstrual period preceding the pregnancy was calculated. This was then converted to the number of cycles by dividing by the woman’s mean cycle length and adding an additional cycle to account for the cycle in which conception occurred (Weinberg et al., 1993). Periods of sexual abstinence of 1 month or longer which occurred within this time were subtracted, but such abstinence was not common (n = 113).

Sensitivity analyses were performed to explore the extent to which findings change by including or excluding unplanned pregnancies (Weinberg et al., 1994; Joffe, 1997). This involved running two additional separate analyses: one in which unplanned pregnancies are included in the analysis (by assigning them to pregnant at time zero) and one in which TTP values of zero and one are excluded (Weinberg et al., 1994; Joffe et al., 2005). The reason for also excluding first-cycle conceptions is to eliminate potential ‘wantedness bias’, where women whose pregnancies are unplanned may change their feelings towards the pregnancy and report it as planned even though it was unplanned or had occurred as a result of contraceptive failure. These women tend to report their TTP as one (Weinberg et al., 1994).

The Wilcoxon rank sum test was used to assess the significance of differences between the results of responders and non-responders for continuous variables such as age, BMI and TTP. Cointal frequency was analyzed per month. Last method of contraception before the conception was either natural (withdrawal and rhythm), barrier (IUD, condoms and diaphragm) or hormonal (oral contraceptive pill and depot medroxyprogesterone acetate (Depo-Provera)). Chi squared tests were performed on cross-tabulations. Correlations between characteristics were examined by Spearman’s rho (p) test. Logistic regression analysis was used to find the factors that were independently significantly associated with participation. Life table pregnancy rate curves for responders and non-responders were calculated and the significance of differences between life-tables assessed by log rank tests. Cox regression analysis was used to allow for differences between the two groups in factors affecting pregnancy rates. A discrete time Cox model was used (Armitage et al., 2002). Various approaches were applied to inclusion of potential covariates in the models: including all factors, including only those known or hypothesized to affect participation regardless of statistical significance, including only those which changed the odds or hazard ratio for participation by more than 10% or including only those with P-values less than 0.25 or 0.05.

**Results**

**Participation**

Of the 2100 women approached, 2061 agreed to complete the WHO TTP questionnaire (response rate, 98%). Those who declined to be interviewed (2%) did so for various reasons, with tiredness by far the most common. None refused to be interviewed because the questionnaire was seen to be intrusive or too sensitive. From 2061 couples
who completed the WHO TTP questionnaire there were 928 eligible males of whom 225 (24%) were responders.

**Differences in characteristics between responders and non-responders**

Responders were more likely to be tertiary educated and have a ‘professional’ occupation as classified by the ASCO. Female partners of responders were more likely than those of non-responders to be employed, be non-smokers at the time of conception, report a diagnosis of pelvic inflammatory disease (PID), and/or claim to have knowledge of the fertile phase and to have timed intercourse to the fertile phase. Both female and male responders were slightly but significantly older than non-responders. There was a significant difference between responders and non-responders with respect to the number of standard glasses of wine consumed per week around the time of conception: female responders on average consumed more glasses of wine per week than non-responders. Interestingly, there was also a significant difference in the reporting of female exposure to noxious agents: responders 18%, non-responders 13%. There were a number of significant correlations among the factors that were found to be statistically significantly different between the responders and non-responders (these are presented in Supplementary Table A1). Only diagnosed PID did not correlate significantly with any other variable. Multiple logistic regression analysis of the data in Table I showed only: female occupation classified as ‘professional’ (positive), female smoked at time of conception (negative), female knowledge of the fertile phase (positive), self-reported diagnosed PID (positive) and female wine consumption per week (positive), were independently significantly associated with participation (Table II). Male age and female self-reported exposure were just excluded from the final model as not significant ($P$-values 0.062 and 0.086, respectively).

**Time to pregnancy**

In the present study, 82% ($n = 185$) of responders and 78% ($n = 551$) of non-responders had planned pregnancies. The frequency of unplanned pregnancies in responders and non-responders was not significantly different. Table III shows the mean TTP (both in cycles and months) for all pregnancies, planned pregnancies only and excluding cycles zero and one conceptions. The mean TTP (either in cycles or months) was not significantly different between responders and non-responders when the analysis included all pregnancies (unplanned pregnancies were included as pregnant at time zero) or planned pregnancies only. However, when cycles zero and one were omitted to check for wantonedness bias there was a significant difference ($P < 0.05$) in the mean TTP (both in cycles and months) between responders and non-responders, with non-responders taking longer to conceive than responders. Figures 1 and 2 show the life table pregnancy rate curves for all pregnancies and for planned pregnancies in responders and non-responders up to the end of 13 cycles. Similar results were found for life table pregnancy rate curves based on months. The life table curves in Fig. 1 cross, and the test for departure from the proportional hazards assumption is not significant ($P = 0.092$).

Including participation in various Cox models based on all pregnancies, planned pregnancies only, excluding cycles zero and one conceptions and truncating the results to pregnancies within the first six cycles and applying various approaches to inclusion of covariates did not change the model and participation remained not significant. The results for models including all known or potential factors affecting pregnancy rates irrespective of statistical significance are summarized in Table IV. Similar results were found when TTP was analyzed in months.

**Discussion**

The present study confirms that participation is low in studies of semen quality. There was no evidence that less fertile women who had a longer TTP were more likely to have their partners participate in the semen study. However, the 95%CI of the covariate adjusted hazard ratio remains relatively wide (0.9–1.2) and some difference in fertility remains possible. A number of factors were significantly different between the responders and non-responders but many were interrelated. Only one characteristic (diagnosed PID) was not significantly correlated with any other characteristic. In cases where significant correlations exist between one characteristic and two or more characteristics which are themselves correlated, the associations may not reflect an independent association between a characteristic with each of the correlated variables. As shown in Table II only a few factors independently affected participation.

**Participation in semen quality studies**

The participation rate in the present male study was low, at 24%. However, this was to be expected as previous experience indicates that compliance is low in studies of semen quality in men from the general community (Handelsman, 1997; Larsen et al., 1998). For example, Andersen and colleagues (2000a, b) have reported striking differences in participation rates between two protocols offered to young men in Denmark. When the protocol required a physical examination and the provision of a blood and semen sample it was found that only 16–19% of eligible men agreed whereas, 79% agreed when the only requirement was a blood sample. Even though the participation rate in the present study was low, it was typical of the participation rates reported for other studies of semen in partners of pregnant women, and substantially higher than that reported for prospective studies of men whose mothers were part of pregnancy cohort studies which they had enrolled in during their pregnancy with their son (Cohn et al., 2003; Muller et al., 2004; Toft et al., 2005; Tsarev et al., 2005; Iwamoto et al., 2006). Higher participation rates (>48%) have been reported in studies of men whose mothers were part of pregnancy cohort studies which they had enrolled in during their pregnancy with their son (Cohn et al., 2002; Ramlaus-Hansen et al., 2007). In the present study, responders were not remunerated for their participation. However, a study has shown that financial compensation did not influence the participation rate (Eustache et al., 2004).

The main concern about low participation in studies of semen quality is that it may lead to selection biases that may threaten the validity of studies and limit generalization of the findings. In the present study, we were able to assess evidence of selection bias because of the experimental design to obtain data from most pregnant women and then to compare results for the expected low response rate part of the study involving the male volunteers. A feasibility study
showed that response rates to this questionnaire were high (>90%) (Stewart et al., 2001). The actual response rate by women to the TTP questionnaire in the present study was even higher (98%). Other studies of partners of pregnant women that have examined selection bias had a lower participation rate in the TTP analysis, which limits the generalizability of the findings (Eustache et al., 2004;
in these studies are that data to compare TTP in responders and non-responders was only available for 12–78% of the subjects originally approached to participate in the studies (Table V). The significance of this low response is that differences in TTP and other characteristics cannot be assessed in the high proportions of the eligible subjects who declined to participate and biases may not be detected.
Table IV  Participation as a factor in univariate and multivariate Cox models based on TTP in cycles including: all pregnancies, planned pregnancies only and excluding cycles zero and one conceptions A, and pregnancies after six cycles censored B

<table>
<thead>
<tr>
<th>Cox model</th>
<th>All pregnancies (n = 928)</th>
<th>Planned pregnancies only (n = 736)</th>
<th>Excluding cycles zero and one conceptions (n = 450)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) All pregnancies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariate hazard ratio (95% CI)</td>
<td>1.04 (0.89–1.21)</td>
<td>1.10 (0.93–1.30)</td>
<td>1.18 (0.95–1.46)</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI)*</td>
<td>1.03 (0.88–1.21)</td>
<td>1.05 (0.88–1.24)</td>
<td>1.11 (0.89–1.39)</td>
</tr>
<tr>
<td>(B) Pregnancies after six cycles censored</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariate hazard ratio (95% CI)</td>
<td>1.04 (0.88–1.22)</td>
<td>1.06 (0.88–1.27)</td>
<td>1.15 (0.90–1.47)</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI)*</td>
<td>1.03 (0.88–1.21)</td>
<td>1.10 (0.91–1.31)</td>
<td>1.19 (0.94–1.52)</td>
</tr>
</tbody>
</table>

*Adjusted for male age, marital status, number of live births, male employed, female tertiary educated, female age >34 years, last method of contraception before the conception, daily coitus, illicit drug use, previous gynaecological operations, alcohol consumption per week and female BMI >34.

Table V  Studies of semen analysis in partners of pregnant women that have examined recruitment bias for long TTP

<table>
<thead>
<tr>
<th>First author</th>
<th>Country</th>
<th>Total population</th>
<th>TTP data available</th>
<th>Semen data available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eustache et al. (2004)</td>
<td>France</td>
<td>1318</td>
<td>598 (45%)</td>
<td>208 (16%)</td>
</tr>
<tr>
<td>Muller et al. (2004)</td>
<td>France</td>
<td>2581</td>
<td>1007 (39%)</td>
<td>331 (13%)</td>
</tr>
<tr>
<td>Toft et al. (2005)</td>
<td>Poland</td>
<td>690</td>
<td>376 (54%)</td>
<td>198 (28%)</td>
</tr>
<tr>
<td></td>
<td>Ukraine</td>
<td>2478</td>
<td>307 (12%)</td>
<td>208 (8%)</td>
</tr>
<tr>
<td></td>
<td>Greenland</td>
<td>665</td>
<td>520 (78%)</td>
<td>201 (30%)</td>
</tr>
</tbody>
</table>

Factors related to participation

Only female occupation classified as ‘professional’, female smoker at time of conception, female knowledge of the fertile phase, self-reported diagnosed PID and wine consumption per week were found to be independently significantly associated with participation. Female occupation classified as ‘professional’ seemed to be the best indicator of socio-economic status (SES). Our finding that responders were more likely to have their occupation classified as ‘professional’ is consistent with other reports (Eustache et al., 2004). Our correlation analysis showed that diagnosed PID was not significantly correlated with any other variable, suggesting an independent association. The finding that responders were more likely to have diagnosed PID suggests that either there may have been some self-selection with respect to poor reproductive health, or that responders were just more likely to report it. However, the higher frequency of PID in responders is more likely to be a singularity in the data and therefore be a fortuitous finding because only 3% of responders and 1% of non-responders reported diagnosed PID. In the French multi-centre study, it was shown that female partners of men who provided semen were more likely to have experienced unfavorable pregnancy outcomes (i.e. miscarriages, ectopic pregnancies, terminations and stillbirths) than the partners of those who only completed the questionnaires (Muller et al., 2004). In the study by Eustache and colleagues (2004) a higher proportion of men who provided semen were found to have had a history of urogenital disease such as cryptorchidism, sexually transmissible infections (gonorrhea and Chlamydia) and varicocele. In the present study, it was also found that partners of responders were more likely to claim knowledge of the fertile phase. This finding is only partly related to responders being better educated than non-responders as the analysis shows knowledge of the fertile phase, while correlated with several markers of SES, remains a significant independent factor associated with participation. Similar results were found with responders being more likely to be non-smokers at time of conception and consume more wine per week. Other semen quality studies have shown that participants are less likely to be smokers than non-participants. For example, in the French multi-centre study, participants were more likely to be non-smokers than those who refused participation entirely (Muller et al., 2004). Other studies have shown socio-demographic status to be related to drinking habits. Wine drinkers are generally better educated and have a higher income than beer, spirit or non-drinkers (Klatsky et al., 1990; McCann et al., 2003; Kerr et al., 2004; Nielsen et al., 2004; Mortensen et al., 2005). Although our study confirms the significant correlation between wine consumption and several markers of SES, there is still perhaps surprisingly, an independent effect. This may be worth further study.

The fact that women who did not smoke about the time of conception were more likely to participate in this type of study is an important difference that could invalidate epidemiological studies of TTP. For example it could affect a study on smoking and male fertility, because male partners of non-smokers are also less likely to smoke. Disproportionate recruitment of subjects who do not smoke would reduce the power of a study to detect as statistically significant an adverse effect of smoking on testicular function.
We also found people of higher SES are more likely to participate in this type of study and more likely to report exposures, however, it is possible that these are not really relevant to TTP. In contrast, people from lower SES groups who could be more heavily exposed, by not taking part in the studies would reduce statistical power to detect adverse effects.

**Are women with a longer TTP more likely to have their partners participate in the semen quality study?**

The likelihood of self-selection bias is of particular concern for studies of semen quality which rely on volunteers, specifically subjects who participate because of concern about their fertility (Handelsman, 1997). This was evident in a Danish occupational study where it was shown that men who agreed to provide semen were more likely to have had a history of infertility (Larsen et al., 1998). Also in the French center, a higher proportion of subjects with long TTP was found in those who provided semen (Eustache et al., 2004). This was not found in other reports (Swan et al., 2003; Muller et al., 2004). However, as discussed above these studies have significant limitations. In the present study this question could be assessed directly because of the high recruitment rate of pregnant women.

We performed extensive analyses to determine if there was any evidence of lower fertility in the responders, but could not find none. The mean TTP and life table curves (based on either cycles or months) were not significantly lower in the responders than in the non-responders. There was a slightly higher proportion of subjects from the non-responder group with unplanned pregnancies. The pregnancy rates for planned pregnancies were slightly higher in the responders and became statistically significant if cycle one was omitted. This may be explained if unplanned pregnancies tend to occur more often among more fertile couples, a larger proportion of the highly fertile will be lost from the planned pregnancy group of non-responders than for the responders and the pregnancy rates will tend to appear higher in the latter.

Regression modeling used various approaches to the inclusion of covariates (e.g. those known or hypothesized to affect participation regardless of statistical significance, only those which changed the odds or hazard ratio for participation by more than 10% or only those with $P$-values <0.25 or 0.05) but responders never had significantly lower pregnancy rates than non-responders. The assumption of proportional hazards was challenged by the life table curves crossing and the $P$-value for proportional hazards being 0.09 thus the interpretation of the modeling needs to be guarded. However, it is unlikely any adjustment would show lower pregnancy rates in the responders. In fact there was a trend for responders to have a shorter TTP than non-responders. The failure to find a bias towards subfertility in the responders is likely to be attributed to the design of our study as only couples who had conceived an ongoing pregnancy were included. Therefore concerns about fertility are not likely to be common in the couples. However, if the general population were sampled the over-representation of the subfertile in the participants in a semen quality study would be more likely as those with concerns about fertility take the opportunity to have a free evaluation for infertility (Handelsman, 1997; Larsen et al., 1998; Cohn et al., 2002).

**Study strengths and weaknesses**

A possible weakness in the present study, and in other studies that have examined selection bias based on partners of pregnant women, is the inclusion of only fertile couples. Excluding infertile couples and medically assisted pregnancies may limit the ability to detect a difference in the probability of pregnancy between responders and non-responders. As previously mentioned, infertile couples are more likely to volunteer for this type of study as it allows those who have concerns about their fertility the opportunity to have a free infertility evaluation. The main strength of the present study was that it was specifically designed to measure the effects of possible selection bias created by an expected low response rate by men to the semen study. A high response rate (98%) by women to the TTP questionnaire was expected and this allowed for a thorough analysis of selection bias in the semen study as questionnaire information could be compared on the majority of eligible male subjects who agreed and declined to participate in the semen study. In other studies however such detailed information has not been available on such a high proportion of subjects who refused to provide semen (Eustache et al., 2004; Muller et al., 2004; Toft et al., 2005).

**Conclusions**

This study was specifically designed to measure bias associated with the low response rate expected in a semen analysis study in fertile couples who conceived without medical assistance. Although there was no evidence that women who had a longer TTP were more likely to have their partners participate in the semen quality study, there were some statistically significant differences in characteristics between responders and non-responders, particularly for socio-demographics and exposures which need to be considered when using and interpreting retrospective TTP studies.

**Supplementary data**

Supplementary data are available at http://humrep.oxfordjournals.org/.

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