Reproductive History and Mortality of fertile and subfertile men

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Abstract

In one of the first studies ever on the subject we have reported a higher lifetime mortality rate for subfertile and sterile men without co-morbidity over all age groups in comparison to fertile men. The objective of this retrospective cohort study is to explore the association between male fertility and life time mortality. Little is known from literature reviews and own research about eventual biological mechanisms behind these mortality differentials. Here we go on reporting on a survey of surviving subjects and proxys on life time morbidity and reproductive biography details which may give additional information. Databases are general and semen parameters of 1408 patients attending the andrological service at Marburg University Hospital in 1949 and later and data from a core interview with 973 survivors and a proxy interview with 435 surviving family members. Results may indicate a protective effect of cohabiting with children (own/foster/adopted/step) for subfertile men.

Introduction

Male infertility is a frequent problem with a complex aetiology. In many industrialized countries about 15% of all couples trying to become pregnant are infertile giving a waiting time of 12 month.[I]

Although the research on reproductive health gains in importance, one third of the aetiology of fertility disorders remains unclear. Particularly with regard to the hypothesis of declining sperm quality in Western countries[II] and the debate on the testicular dysgenesis syndrome[III] the research on determinants of reproductive failures is receiving increasing attention. Thus there are a lot of studies which investigate the relationship between risk factors and male infertility. In most of them infertility is referred to as a multifactorial disease and the research interest is on investigating risk factors causing infertility.

Whereas most studies are concerned with the causes of male infertility, there are only a few studies which investigate the outcomes of male infertility on morbidity and/or mortality[IV] Based on the results of a previous published studies[v] in which surprisingly a higher mortality risk was found for subfertile men without a specific co-morbidity or previous disease in comparison to fertile men over all age groups (see Figure 1), the target of the current study is to investigate that association between fertility and mortality on an extended database by linking information from medical records on semen parameters with interview data to provide additional and detailed information for explaining that association.

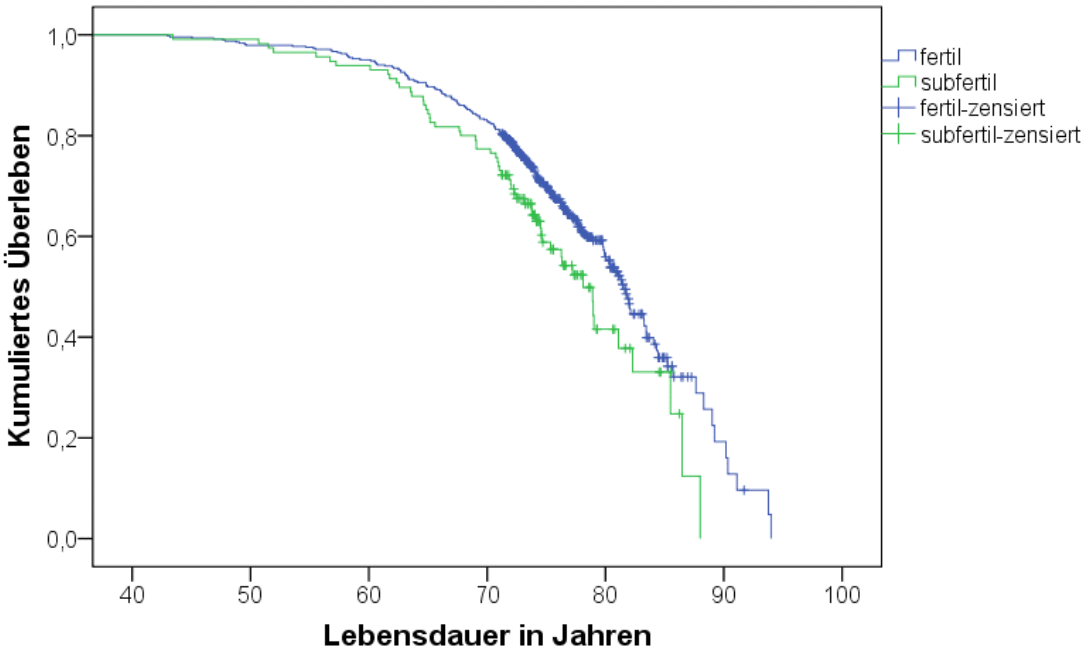

Figure 1: Survival functions of fertile and subfertile men; early natal cohort (In: Seydel H Überlebenszeit und Todesursachen fertiler und subfertiler Männer, Diss. Marburg 2010 (p. 77)

Conceptional Framework

Objectives

As a plausible biological mechanism for the higher mortality and shorter life span could not be found by literature review yet, we consider the following possibilities:

- a specific comorbidity or specific noxious agents with unfavourable influences on the spermatogenesis were already existing at the time of medical examination for a number of cases with subnormal sperm findings but were not diagnosed or documented (confounder);
- men with subnormal sperm findings had a different life course: because of the higher prevalence of childlessness more unstable partnerships and a more risky behavior (drift);

- intact fertility is per se a life prolonging specific disposition (direct specific causation);
- intact fertility is – because of a more frequent successful reproduction - a life prolonging specific disposition (indirect specific causation).

Hypotheses

To explain which of the possibilities come into question, we do not only consider the cumulative mortality in dependence of fertility status but also

- the life time morbidity of the survivor and the deceased cases and
- the reproductive biography of these cases: fertility disorders do not exclude reproduction as well as intact fertility is only one of many conditions of actual reproduction.

For this reason we want to test the following hypotheses:

1. The morbidity profile of infertile men is different from that of fertile men.
2. The prevalence of morbidity of infertile men is different from that of fertile men. The latter will be rarely and less (critically) ill.
3. Fertility and fecundity interact with morbidity: by the same fertility status childless men will have a higher morbidity risk and/or a different morbidity as men with children.
4. Fertility and fecundity interact with mortality: by the same fertility status childless men will have a higher mortality risk as men with children.
5. The life course trajectory has an impact on morbidity/mortality. Stresses and strains in marriage/partnership in consequence of fertility disorders are the real cause.

In our study we conceptualize fertility not as a typical andrological disease for which risk factors should be identified but rather as a risk factor or exposure variable for male life time mortality.

In this context we refer to the term exposure as a ”contact of an individual with an agent through any medium or environment”[V] Applying exposure to external and internal agents, fertility status can be understood as both: a biologic agent in the body (disorders of the spermatogenesis) and a social agent - an incriminatory event in the live time.

Thus, by investigating the association between fertility and life time mortality direct and indirect effects of involuntary childlessness on male mortality should be distinguished. In the first case infertility can

be considered as a disease per se with objective physical symptoms (abnormal semen characteristics) which manifest in higher morbidity and higher mortality risk. As an example we can take studies on the association between semen characteristics and testicular cancer in which a higher risk of testicular cancer could be found for men with abnormal semen characteristics.[VI]

In the second case infertility can be referred to as a stressful life event for the men involved and thus have negative indirect implications on morbidity/mortality by influencing other areas of life associated with ill health. In this context the investigation of the life course of patients after infertility diagnosis is of great importance. Aspects like reproductive biography (type of infertility - primary and secondary-paternity and their alternative forms), partnership history (marital status), life time morbidity and health related behaviour should be taken into consideration by exploring the relationship between fertility status and mortality.

Data and Research Methods

Data

Database are medical records of 2296 men in couples with fertility problems who had a semen analysis done at the fertility and sterility office of the department of andrology at the University Hospital in Marburg during 1949 and 1995 and which were born before 1942.

After applying excluding criteria like being born after 31st December 1941, having foreign citizenship, missing values in sperm parameters and pre-existing diseases to assure that at the time of medical examination impairment of spermatogenesis was not the consequence of an existing disease, we have a sample size of 1408 cases, for which the vital status through the registration office could be found out. Thereof 973 cases are still alive and 435 cases are already deceased.

To provide additional information explaining the association between sperm concentration and lifetime mortality a core interview with expected 973 living cases and an exit interview with expected 435 surviving family members of deceased cases is conducted on the basis of pretested standardized questionnaire to survey information on general health status, history of diseases, health related behaviour and family and partnership history etc.

Methods

1. The Estimation of Odds Ratios

In a first step we want to estimate the Odds for fertile and subfertile men according their risks in morbidity. For locating the overestimation of the truth OR therefore two different methods are used for approximating the KI.

Approximative KI of Woolf (1955)

$$KI(OR)=\left[OR_{est} \cdot \exp\left\{ \pm u_{1-\alpha/2} \cdot \sqrt{\frac{1}{n_{11}}+\frac{1}{n_{10}}+\frac{1}{n_{01}}+\frac{1}{n_{00}}} \right\} \right] \quad (1)$$

if estimation is incumbent on Gaussian distribution.

In using the difference of two Logits this interval is also called as Logit-Limits. The most disadvantage of Woolf's approximation is that in cases with small cell frequencies it can be excepted that the estimation for KI leads to biases results.

Alternative in context to small epidemiological studies it is possible to use the asymptotic KI of Miettinen (1976). This method is a combination of the approximation of χ^2 and the quadratic approximation of log Odds Ratios

$$KI_{Miettinen}(OR) := \left[OR_{est}^{1 \pm \frac{u_{1-\alpha/2}}{\sqrt{\chi^2}}} \right] \quad (2)$$

Under the assumption of Odds Ratios = 1 or ≈ 1 the KI of small epidemiological studies can be used for the estimation of Relative Risks.

2. Adjusting age-specific effect as confounder

For generating successive regression models it is indispensable to test the data set on homogeneity. We can suppose diversely likelihoods or Odds for fertility and morbidity status because of different age-specific composition. To avoid a confounding effected overestimation of the truth association it is common to use the Mantel-Haensel-Estimator. Our probands are divided in two different age groups.

$$OR_{est} = \sum_{k=1}^{l} W_k \cdot OR_{est}, \text{ then } W_k := \frac{\frac{n_{10k} \cdot n_{01k}}{n_{\bullet\bullet k}}}{\sum_{k'=1}^{l} \frac{n_{10k'} \cdot n_{01k'}}{n_{\bullet\bullet k'}}}, k = 1,...,l. \quad (3)$$

The stratified analysis is suited because of the adjustments for confounding. The Mantel-Haensel-Estimator is a weighted mean of the estimators for every stratum. The weights are the approximation for the reciprocal of the variances of the estimator $OR_{est.}$

Under the hypothesis H_0 Odds Ratio =1 is OR_{est_ko} a combined estimator of the stratified results for the common OR following the χ^2 statistics

$$\text{with } X^2_{\text{Hom-1}} = \sum_{k=1}^{l} \frac{(\ln(OR_{estk}) - \ln(OR_{est\_kombj}))^2}{\text{Var}(\ln(OR_{estk}))})$$
$$\text{then Var}\,(\ln(OR_{estk})) = \left(\frac{1}{n_{11k}} + \frac{1}{n_{10k}} + \frac{1}{n_{01k}} + \frac{1}{n_{00k}}\right) = vk^{-1}, k = 1,...l. \quad (4)$$

By comparing the quadratic differences of log Odds-Ratio-Estimator (observed) in the strata to the combined estimator (expected in case of homogeneity) their distance is purposed to be small in case of homogeneous strata. Following to our context if the distance of the observed Odds for the younger and older cohort and the expected combined Odds containing both subgroups is very small then the strata will be homogeneous.

Then follow χ^2_{Hom-1} with hypothesis H_0 χ^2- distributed with (l-1) degree of Freedom, the decision (1-α) has to be denied, if

$$\chi^2_{Hom-1} > \chi^2_{t-1;1-\alpha}$$

After the test-statistics on homogeneity are already done we want to focus on the generation of four logistic models. To avoid inconsistent results we use age-standardized variables for fertility and morbidity status because both are affected by events and changes over the life course.

Not only the age-specific variation in fertility and morbidity has to be examined, the fertility and morbidity status also might have changed according the cohorts. Hence we are also generating dummies for cohorts to control the cohort-specific variation for our regressors.

$$\text{logit}(P) = a + b_1 \cdot X^{(1)} + b_2 \cdot X^{(2)} + b_3 \cdot X^{(3)},\ X^{(1)}\ X^{(2)}\ X^{(3)} = 0,1 \quad (4)$$

P - probality for being infertile/fertile with interval (0,1)

OR_1- $\exp(b_1)$

OR_2- $\exp(b_2)$

OR_3- $\exp(b_3)$

$X^{(1)}$ = 1, if cohort, cohort1; 0 if cohort, not cohort 1
$X^{(2)}$ = 1, if cohort, cohort2; 0 if cohort, not cohort 2
$X^{(3)}$ = 1, if cohort, cohort3; 0 if cohort, not cohort

3. Maximum-Likelihood-Estimation

In previous analysis the logistic models couldn't regard definitively the estimations of the probabilities of disease for the total study population. The Maximum-Likelihood-techniques don't consider the individual probabilities, but rather the total probability of disease for all probands.

Referring to the assumption of statistical independency between exposure and non-exposure we are formulating the following. To simplify the maximisation of function L habited by the parameters of the model we use the logarithm of the Log-Likelihood-Function.

$$\begin{aligned} l(a, b_1,..., b_m) = \ln\left[L(a, b_1,..., b_m)\right] &= \sum_{i=1}^{n} \ln\left[P(K_i = j \,|\, X_i^{(1)},..., X_i^{(m)})\right] \\ &= \sum_{\text{invalid}} \ln\left[1 + \exp\left\{- a - b_1 \cdot X^{(1)} .... - b_m \cdot X^{(m)}\right\}\right]^{-1} \\ &= \sum_{\text{healthy}} \ln(1 - \left[1 + \exp\left\{- a - b_1 \cdot X^{(1)} .... - b_m \cdot X^{(m)}\right\}\right]^{-1}). \end{aligned} \quad (5)$$

The Wald-Test is a convenient statistic for simultaneously tests for more than one parameter. This method gives information about the consistence and the real relationship of every regressor and dummy.

$$Z_j^2 = \frac{b_{estj}^2}{\text{Var}(b_{estj})},\ j = 1,..., m,$$
$$\text{with } Z^2 = (b_{est1},..., b_{estm'})^T \cdot K'^{-1} \cdot (b_{est1},..., b_{estm'}),$$
$$K' = \text{Cov}(b_{est1},..., b_{estm'})$$

Expected Results

With regard to the association between fertility status and lifetime mortality it is expected that differences in lifespan between fertile and infertile men are not the result of a direct causation of infertility on life time mortality in the sense of a biological mechanism. Currently there is no evidence that impaired spermatogenesis might have any direct influence on the lifespan.

Differences in mortality between infertile and fertile men can be attributed to differences in morbidity between the two groups, which are in turn the result of reproductive and partnership history. Thus there should be no differences in mortality between subfertile and fertile men under the same conditions.

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