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Environmental semen studies — is infertility increased by a decline in sperm count?

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The objective of the studies was to evaluate infertility according to sperm count shifts. The distribution of the sperm count of 1024 Danish men (median 56 million/ml) served as reference. The data were transformed with multiplicative or additive models to create alternative distributions with median sperm count values changed by 25—100%. Sperm-count-specific fecundabilities were provided from a follow-up of first-pregnancy planners in a Danish population. The estimated average fecundability of the 1024 Danish men was 16.9% [95% confidence interval (95% CI) 16.7—17.2], and the proportion of cohabiting men with spouses pregnant within 1 year was 86.0% (95% CI 84.1—87.8). Simulations of alternative sperm count distributions indicated that the relationship between sperm count shift and fertility strongly depends on the median level of the sperm count at onset and the type of shift, a dramatic decline from a high level in a multiplicative model indicating a marginal change and a minor decline from a low level in an additive model representing a strong decrease in fertility. In some cases sperm count, therefore, may be an early warning of changes in fertility.

Key terms fertility, male reproduction, secular trends, semen quality.

For several decades semen quality has been used as a marker of male reproductive function in various occupational settings (1, 2), but it is still largely unknown how shifts in sperm count and other measures of semen quality influence the fertility of worker populations (3). Because of the large reserve capacity of sperm production, which is well known in several rodent species, it might in fact be questioned whether even a large shift in sperm count translates into an increased occurrence of infertility. Unique data enabling a closer look at this question was recently established in a population-based study describing the relation between sperm count and the probability to conceive in one menstrual cycle among sexually active, noncontracepting, first-pregnancy planners (4). The objective of this paper was to examine how changes in the population distributions of sperm count would influence fecundability (a couple's probability to achieve a pregnancy in a menstrual cycle) and fertility (a couple's probability to conceive within 1 year). Throughout this paper sperm count denotes the concentration of sperm cells in the ejaculate.

Populations and methods

Population data on sperm count. The distribution of sperm count in large random samples of men in the fertile age range has never been determined in any population (3). To define a base-line distribution of sperm count, we used the data from 10 separate Danish occupational semen studies conducted from 1986 through 1995 at 2 centers (5—14) (table 1).

Most of the studies were designed to examine male reproductive toxicity of workplace exposures, for example, pesticides (studies 1 and 5), psychological distress (study 2), metal welding (studies 3, 4 and 10), styrene (study 6), high-frequency electromagnetic radiation (study 8), and organic solvents (study 9), while one of the studies was undertaken to create a reference population of organic farmers (study 7). Eligible men were invited by written brochures to participate, and, if feasible, the men received information at workplace meetings. The eligibility criteria differed only slightly between the studies (age from 18—20 to 45—60 years; no

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Table 1. Characteristics of 10 occupational study populations.

Reference	Population	Sampling year	N	Participation rate (%)	Age at sampling		Days of sexual continence	
					Median	Range	Median	Range
Larsen et al, 1997 (5)	Farmers	1995—1996	250	32	37.8	26—56	3.0	0.3—20
Bonde et al, 1998 (6)	Husbands to clerks and nurses	1994—1995	209	10—20	28.0	21—37	3.0	0.3—19
Hjollund et al, 1998 (7)	Metal workers	1994—1995	201	10—20	28.0	21—37	3.0	0.3—30
Bonde, 1990 (8)	Black smiths	1987	131	37	31.0	20—50	3.0	1.0—42
Abell et al, 1997 (9)	Green house workers	1994	121	64	27.0	20—43	2.0	0.3—40
Kolstad et al, 1999 (10)	Reinforced plastics workers	1994—1995	31	32	27.0	20—46	3.0	0.3—60
Abell et al, 1994 (11)	Members of the organic farmers' organization	1994	30	70	35.5	28—44	1.3	0.3—14
Hjollund & Bonde, in press (12)	Radar workers	1995	30	42	29.0	25—42	3.0	0.5—30
Bonde et al, 1987 (13)	Flexo printers	1984	19	90	33.0	23—45	4.0	2.0— 9
Bonde, 1992 (14)	Tube welders	1989	16	85	33.0	23—49	4.0	3.0—14
All studies		1984—1996	1024	33	30	20—50	3.0	0—60

vasectomy) with the exception of studies 2 and 3, which only included cohabiting men in the age range of 20—35 years who did not have earlier reproductive experience and who had stopped birth control to get a child. The lowest rate of participation was 10—20% and the highest was 90% (table 1). In most of the studies the men provided several semen samples, but only the first samples were used for the purposes of this study. With the exception of investigations on high-frequency electromagnetic radiation and radiant heat, none of the studies indicated workplace effects on sperm count, but minor associations between occupational exposure and other measures of semen quality were revealed in a few of the studies (eg, in reference 8 for greenhouse workers). In all the studies the men were asked to collect semen by masturbation, and the samples were examined within 2 hours. The number of sperm cells was counted in either a Makler or Neubauer chamber (Aarhus) or a Bürger-Türk chamber (Aalborg) using a phase-contrast technique at a magnification of 200. All the analyses were carried out by trained laboratory technicians.

The distribution of the sperm count across all the studies is outlined in figure 1. The median sperm count was 56 (range 0—504) million/ml, and the median period of sexual abstinence was 3.0 (range 0—60) days.

Sperm-fertility relation. The correlation between sperm count in an ejaculate and the probability to conceive in a menstrual cycle was recently described in a population-based prospective follow-up study of 430 Danish first-pregnancy planners who had never brought their fecundity to a test when they stopped contraception to be enrolled in the study (4). The fecundability increased from 0% to 20% with increasing sperm count up to a level of about 40 million/ml, but above this concentration the sperm count was not associated with higher fecundability (table 2 and figure 1).

Simulation of alternative sperm count distributions. Using the data from the 10 occupational cohorts, we computed the sperm count distributions in fictive populations in which the sperm count of each man was either 50% or

Table 2. Sperm-specific fecundabilities observed in a Danish prospective follow-up study of 430 first-pregnancy planners (4).

Range of sperm count	Fecundability (%)
0 million/ml	0.0
0-< 5 million/ml	2.5
5 -<10 million/ml	7.5
10-<20 million/ml	10.0
20-<30 million/ml	15.0
30-<40 million/ml	17.5
≥40 million/ml	20.0

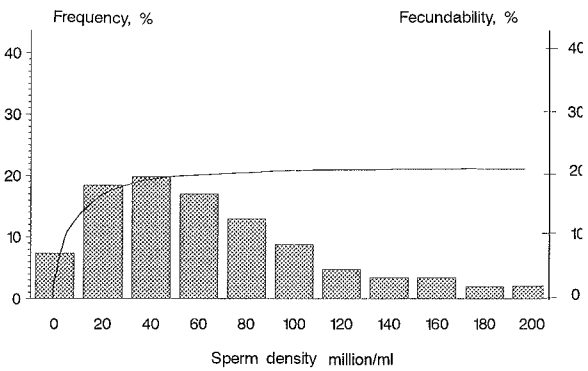

Figure 1. Frequency distribution of sperm count for 1024 men from 10 occupational cohorts, left axis, and the relation between sperm count and fecundability in a study of first-pregnancy planners (solid line), right axis (4).

100% higher or lower than the observed value (multiplicative models) (figure 2). These models assumed that the shift in sperm count was proportional. In order to test the effect of a shift based on a constant increase or decrease in sperm count independent of the level of the starting value, we also computed distributions based on the addition or substraction of fixed values — namely 25% and 50% of the observed median value of 56 million/ml (additive models) (figure 2).

Computing of fecundability and infertility. Each man in the simulated populations was assigned a fecundability value given by the observed sperm-count-specific fecundabilities (table 2). The population fecundability was computed as the average of the individual fecundabilities. The proportion of couples becoming pregnant within 1 year was computed by the expression

$$\Sigma P_i [1 - (1 - F_i)^{12}],$$

where P_i and F_i denotes the proportion and the fecundability, respectively, of men with a sperm count within interval I and n is the number of sperm count ranges. The confidence intervals were computed by standard methods (15).

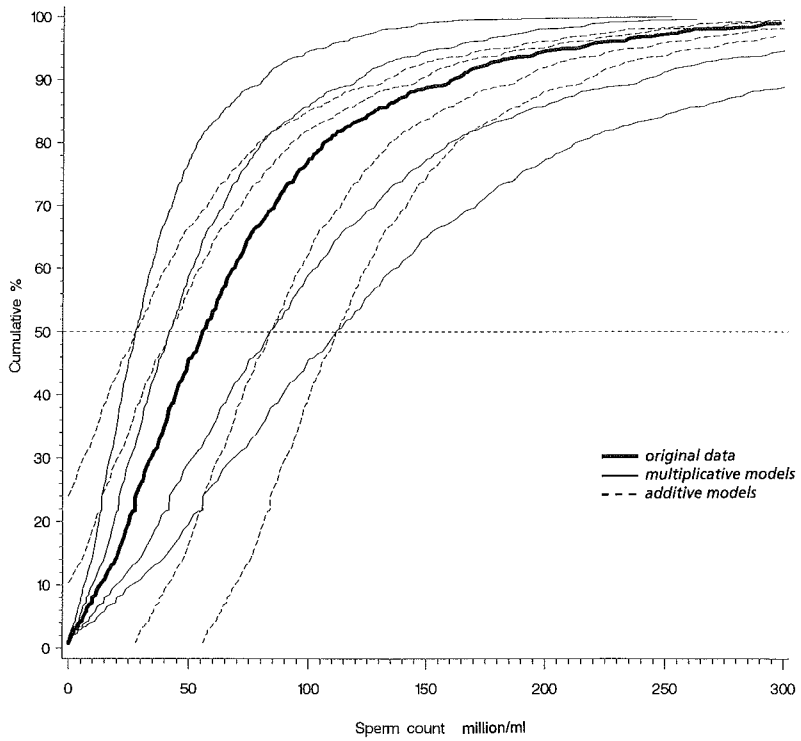

Figure 2. Observed (bold line) and simulated cumulative percentage distributions of sperm count according to multiplicative (solid lines) and additive (dotted lines) models, which shift the median by 25% and 50% to the left and right, respectively.

Table 3. Average fecundability and fertility (proportion of couples becoming pregnant within 1 year) in a Danish occupational cohort and in simulated distributions of sperm count according to multiplicative and additive models. (95% CI = 95% confidence interval)

	Median sperm count (million/ml)	Model	Fecundability (%)	95% CI of fecundability	Fertility (%)	95% CI of fertility
Occupational data	56	Observed	16.9	16.7—17.2	86	84—88
Simulated sperm count distributions						
+100%	112	Multiplicative	18.4	18.2—18.7	89	87—91
		Additive	19.7	19.4—20.0	93	91—95
+50%	84	Multiplicative	18.0	17.7—18.2	88	86—90
		Additive	19.2	18.9—19.5	92	90—94
-25%	42	Multiplicative	16.0	15.7—16.2	84	82—86
		Additive	14.6	14.3—14.8	76	74—78
-50%	28	Multiplicative	14.1	13.9—14.4	79	77—81
		Additive	11.9	11.7—12.1	63	61—64

Results

The average fecundability and fertility rates of the simulated sperm count distributions are given in table 3. A 100% higher median sperm count following a multiplicative model would result in a rather small increment in the fecundability and fertility rates by 8.8% and 3.7%, respectively. On the other hand, a 50% lower sperm count following an additive model would decrease fecundability by 30% and fertility by 27%. The fertility value corresponds to an almost 3-fold increase in infertility, from 14% to 37%. The impact of the other simulations are in between (table 3).

Discussion

Our findings indicate that even a substantial decline in the median sperm count would not necessarily be associated with a severe reduction in the average probability to conceive or with a sharp increase in the rate of infertility. The consequences as to fertility are strongly dependent on the absolute level of sperm count at the onset and on how the causal factors change the underlying sperm count distribution. A multiplicative effect would have minor implications, whereas an additive effect may have detrimental effects on fertility. In workers exposed to the nematocide 1,2-dibromo-3-chloropropane (DBCP) the median sperm count was 46 million/ml as opposed to 79 million/ml in a reference group (16). The cumulative percentage distributions for the sperm counts of exposed and never exposed workers seems to indicate that DBCP causes shifts in sperm count according to an additive rather than a multiplicative model (16). Consistent with the findings reported in our paper, the fertility of the DBCP-exposed workers was strongly reduced (17). On the other hand, effects of season and the duration of sexual abstinence seems to be of a multiplicative nature, and therefore the effect on fertility may be marginal (data not shown). Unfortunately, reports on the spermatotoxic effects of occupational exposures seldom indicate how the distribution of sperm count is changed.

The sperm count is related to such other seminal characteristics as sperm morphology and motility, and these measures of semen quality are independent predictors of fecundability (4). The sperm count per se may not be causally related to fecundability but, instead may simply be a marker of one or more unknown true causal factors. By extrapolating the sperm-count-specific fecundabilities to the simulated distributions, it can be assumed that the stratum-specific correlations between sperm count and causal factors of known and unknown nature are equivalent in the observed and simulated populations. It is obvious that this need not be true. It has been hypothesized that the declining sperm count in some populations — if true — is caused by the depletion of Sertoli cells in the fetal testis (18). This phenomenon may selectively reduce the sperm count in adult life without affecting the quality of semen. In such a situation our extrapolation would exaggerate the effect of a shift of sperm counts. However, the opposite could also be true. An environmental exposure may have a stronger effect on other determinants of fecundability than on sperm count, and then the extrapolation would underestimate the effect on fertility.

Concluding remarks

The impact on fertility resulting from a shift of the median sperm count is strongly dependent on the absolute level of sperm count at the onset and on the underlying causes of the shift. A strong decline from a high level following a multiplicative model would only be associated with a marginal change in fertility, whereas a minor decline from a low level according to an additive model would be related to a rather strong decrease in fertility. In some risk scenarios sperm count, therefore, may provide an early warning, before any detectable change in fertility has taken place.

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