

Is human fecundity declining – and does occupational exposures play a role in such a decline if it exists?

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OLSEN J. Is human fecundity declining — and does occupational exposures play a role in such a decline if it exists? *Scand J Work Environ Health* 1994;20 special issue:72—77. Demographers have analyzed fertility over time and between many populations for many decades. Much less is known about fecundity. Recent publications seem to indicate a decline in semen quality over time, but still no good data corroborate or refute this hypothesis. The very sparse data do not indicate any substantial changes in fecundity over the last 10—30 years in the United States, but none of the studies have a comparability which permit any firm conclusion. Several chemical and physical exposures interfere with human fecundity. Some are found at the worksite, sometimes in an intensity which does harm. The marked effect of dibromochloropropane on semen quality and fecundity was a clear warning to occupational health workers. Several other occupational exposures have shown an effect on gonads in men or women, and it is time to give more research priority to the topic. The rapidly rising cost of infertility treatment could be the stimulus to trigger the development of this research field.

KEY TERMS — epidemiology, fertility, occupational hazards, review, secular changes, semen quality.

Evidence for changes in fecundity over time

Once Cornfield was asked to give a lecture on the principles of research. His first thought was to rise, to say “Be careful,” and to sit down again (1). In like manner, this presentation could be short. The answers to the questions in the title are “don’t know,” “maybe,” and “thank you very much for the invitation.”

In strict terms fecundity refers to the ability to produce live offspring and fecundability to the ability to obtain conception within a menstrual cycle. In pragmatic research it is often more appropriate to focus upon the ability to produce a pregnancy which survives to clinical recognition, and the term fecundity is used in that meaning in the following discussion.

It is well known that the monthly probability of pregnancy (“fecundity”) among noncontracepting, sexually active couples varies. Therefore the waiting time to pregnancy differs among couples and also between populations. In a group of couples with normal fecundity of 25% (a 25% probability of conception within a menstrual cycle), 82% are expected to conceive within the first six months and 97% within the first year. If subfecundity is defined as a waiting time of more than six months, 18% of “normal couples” are expected to be misclassified as subfecund, and even for the classification of infertility (a

waiting time of 12 months or more) 3% of “normal couples” are expected to be classified as such. Subfecundity is a probability classification with an in-born error of misclassification at the individual level, but not necessarily at the population level.

It is possible to estimate fecundity at the population level, and there has been substantial advancement in developing methods within the field since the research activities gained speed about 10 years ago. The proportion of infertile couples in the Danish population is, for example, about 16% for the first pregnancy and 17% for subsequent pregnancies (2). There have been achievements in the development of statistical and measuring methods (3—8) and in the development of standardized and validated questionnaires (9, 10). European studies of infertility and subfecundity have, for example, developed questionnaires in several European languages. (Contact Wilfried Karmaus, NORDIG, Alte Kollaustrasse 32 A, D-22529 Hamburg, Germany, to obtain a copy in English, Spanish, Italian, French, German, Danish, Polish, or Greenlandic.)

More than 15% of all couples experience a delay in conception time of 12 months or more in their sexual cohabitation aimed at producing a child (2). About twice as many, however, have a similar period of sexual activity without the use of contraceptives but with or without wanting a pregnancy (7). Some couples know by experience that their fecundity is low and that they need no contraception. A waiting time to pregnancy is therefore a different measure than a time period of noncontracepting sexual activity. Waiting time to pregnancy and periods of unprotected sexual intercourse are the terms used in the European study to separate these two measures.

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The large difference between these measures illustrates the problems in comparing population figures over time. The use of contraceptive methods play a role in the awareness of fecundity, and the use of safe methods give little or no information. The use of unsafe methods will, on the other hand, gradually build up experience that can be used in pregnancy planning or in choosing contraceptive methods. Obviously the desire for a given family size also plays a role. Couples who want no children may be infertile without ever realizing it, whereas couples wanting a large family are more likely to identify a fertility problem if it exists. Different periods and cultures have different traditions for planning a pregnancy and different desires for a given family size. In many European populations more than 80% of all pregnancies are planned, whereas people in other countries leave plenty of room for chance for "family planning." These and other circumstances play a role in the comparability of fecundity measures, which otherwise may be easy to obtain even on a large scale. Comparability is only obtained if these and other circumstances are similar, which they typically will not be over longer periods.

The only data available that are comparable for longer periods, in the sense that they are based upon identical sampling principles and similar questionnaires, stem from the National Survey of Family Growth in the United States (US) (11–13). Their figures depend, however, upon the wish to become pregnant and past experience with reproduction. Impaired fecundity in the US study was defined as couples who said it was impossible to have a baby for some reason other than sterilization or that it was difficult or dangerous to conceive or deliver a baby or that married couples used no contraception without getting pregnant in 36 months or more. The prevalence of impaired fecundity measured in this way did not change between 1982 and 1988. For married couples in the United States, data also exist on infertility back to 1965. From 1965 to 1988 the prevalence of secondary infertility declined but was balanced with an increase in primary infertility (infertility among nulliparas).

In spite of the fact that the US surveys were carried out according to standardized principles of data collection and the use of representative sampling from the population, the comparisons over time could be biased. If, for example, habits of sexual cohabitation or the use of contraceptives changes over time, it could play a role in how many couples are able to estimate their fecundity status. It is to be expected that more couples with low fecundity would know this in societies of large families or those with stable sexual relationships who make limited use of safe contraceptive methods. In many industrialized societies the trend has been away from such a culture to more unstable relationships with smaller families. Even if the biological fecundity had remained unchanged over time, it could be expected that the fre-

quency of known cases of subfecundity would increase. An unchanged frequency of known subfecundity could perhaps be circumstantial evidence of a possible decline in biological subfecundity over time, but this is not known.

In fact what is left is circumstantial evidence because no hard data exist on the change of factual fecundity over time.

Litter size is sometimes taken to reflect fecundity in animal experiments, but it need not be the case for humans. Single pregnancies, or at least single deliveries, are the most common, and multiple pregnancies could indicate an anomaly just as well as being a sign of high fecundity. It is nevertheless striking that the proportion of dizygotic twins has declined substantially in many countries over a long period (14–16). It is one of the best documented changes in reproductive epidemiology for which there is no good explanation, but only hypotheses. Some of these hypotheses reflect an increasing load of exposure to reprotoxic factors. Apparently, the decline in twinning rates has stopped in some countries (17, 18), but the cessation could be due to an increasing use of hormones in the treatment of infertility.

Some of the problems related to the use of endpoint determinants of the ability to reproduce are related to the fact that nature has generously built in an overcapacity which will cope with even severe impairments. Even with very low fecundity most couples will be able to have the children they want. Many couples will go through life with impaired fecundity without noticing it, and, if the low fecundity is due to exposures which cause no other side effects, they need not bother. It is, however, not unlikely that such exposures cause other diseases as well (2), and some of the exposed couples do have problems getting the number of children they want. That is why proxy indicators of subfecundity are of great scientific interest. Semen quality and quantity is the most promising of these indicators for many reasons. Semen samples are available without invasive procedures and semen quantity and quality may be a very sensitive indicator of hazardous environmental exposures.

If there are representative surveys of semen samples over time, one would have a very valuable indicator of changes in environmental exposures with impact on male fecundity. Unfortunately, no data exist. Again, there is only circumstantial evidence which will not hold in court under close scrutiny.

Several reports in the last two decades have indicated a drop in semen quality over time (19–23). Basically two types of evidence are available, namely, semen samples from published studies in the literature and data from men seeking help at infertility clinics. Both types of data show a decline in sperm volume and concentrations over time. In a recent meta-analysis of 61 published studies of semen quantity from men expected to have normal semen (many

were reference groups in comparative studies), a decline of spermatozoa concentration from $113 \cdot 10^6 \cdot \text{ml}^{-1}$ in the 1940s to $66 \cdot 10^6 \cdot \text{ml}^{-1}$ in 1990 was reported. Volume had dropped from 3.40 ml to 2.75 ml in the same period (24). This finding is disturbing, regardless of the fact that none of the studies fulfilled even basic principles for being comparable. Bias due to information, selection, or confounding may distort results in every direction, also in the form of masking a more substantial declining trend.

The steady decline of sperm concentration, as illustrated in reference 24, is, however, only one of several possible ways of summarizing the findings. The justification for the declining trend does, in fact, depend upon the quality of merely a handful of studies from 1935 to 1955. The data may equally well fit two plateaus, one representing the time before 1965 and one after 1965. Since sperm volume and sperm concentration is closely related to time since last ejaculation, a difference in sexual activity could also explain the findings. It is possible that the "sexual liberation" in the 1960s, fewer workhours, and the better access to safe contraceptive methods have been followed by more sexual activity and thus a shorter time since last ejaculation in the later semen samples. The apparent decline in semen quantity could be due to an increase in sexual intercourse or different selection criteria for "normal" men to the samples.

Of greater concern are results from infertility clinics in which semen samples have been examined according to unchanged criteria by the same personnel. Such samples have also shown declined values (25), but they are surely not comparable due to selection bias. With these data it is, however, difficult to imagine selection bias exaggerating a decline. More infertile couples would be expected to seek help now than a decade ago, and the involvement of men in the examinations has, furthermore, changed. Previously, men were not examined unless no reason for subfecundity was found for the female partner. Now the diagnostic process often starts with a semen examination. It was thus more likely that men examined 10–20 years ago had low semen quality than what is expected today. One would expect older semen samples from the infertility units to oversample men with subfecundity compared with recent samples. The bias is expected to produce a positive trend in semen quality even if none existed — not to show a decline.

If the decline in semen quantity is real, there are no more than speculations to offer as to why. Relatively little research has been devoted to the studies of causes of infertility in comparison with the investments spent on research into treatment aspects. Environmental exposures which have increased over time, perhaps of the type that accumulates in food chains, could be a possibility. Polychloride biphenyl exposure plays, for example, a role in the fertility of

seals in the Baltic Sea. Life-style factors like smoking could also play a role, especially if such life-style factors show their effect in the next generation. Exposures in utero or early childhood could "program" the reproductive organs during critical phases of their development. Studies of this type will be an interesting area for research in the Nordic countries since their birth registers now cover several two-generation pairs.

It is more difficult to suggest occupational exposures which could be responsible for a decline in fecundity, if such a decline exists. Several occupational exposures are known which may impair fecundity, but most of these exposures have not increased over time. It is, however, true that an increasing number of women are participating in the work force, a phenomenon which perhaps could be important to a decline in couple fecundity for which no documentation exists. That would of course not explain a decline in semen quantity, for which there is some weak circumstantial evidence.

Occupational risk factors of subfecundity

The marked effect of the nematocide dibromochloropropane (DBCP) on male gonads was a clear warning to the medical world (26, 27). It had the message that male gonads can also be target organs for occupational exposures, and new chemicals must be monitored to avoid irreversible damage to human fecundity. Simple monitoring instruments based upon standardized fertility ratios were developed after the DBCP case (28), and they have been used in a few selected settings (29). The DBCP story initiated research into the occupational hazards of male fecundity, especially within the fields of pesticide and herbicide exposure (30). Many of the studies have, however, been rather small and with little information due to poor methodology and lack of statistical information.

A large case-referent study carried out more than 10 years ago identified several potential occupational risk indicators for subfecundity among men and women. Male exposures to heat and welding fumes were identified as such risk indicators, just as exposure to noise, textile dyes, lead, mercury, and cadmium for women (8). The association between welding exposure and the infertility couples was confirmed in other studies (31–33), and substantial work has been done in examining the association between welding exposure and sperm quality, as well as sex hormones (34). These studies have corroborated the hypothesis that welding exposure can reduce male fecundity. The studies do, however, detract from the hypothesis that this is a problem related specifically to welding on stainless steel, and the apparent effect may still be due to confounding by a parallel exposure to heat at the welding site.

Fecundity, as measured by waiting time to pregnancy during normal sexual cohabitation without the

use of contraceptives, has also been followed in the textile industry. Women exposed to dust in the textile industry had a prolonged waiting time to pregnancy, but the dust exposure was closely linked to jobs with a high level of job stress, which was not, however, measured (35, 36).

The range of occupational exposures with potential harmful effects on fecundity is very large, but substantial and convincing evidence is usually lacking. Intense exposure to heat, radiation, and lead may impair testicular function (37–40), but whether such exposures exist in sufficiently high concentrations in present well-organized industries is not known. There is some empirical support for a possible association between exposure to microwaves and fertility (41), but whether other types of exposure in the large range of nonionizing radiation play a role is under study, and there is hope for better data within the next decade.

Infertility and subfecundity have been reported among women occupationally exposed to anesthetic gases (8, 42, 43). Exposure to lead and mercury may also impair female fecundity (37). Females employed as pharmaceutical assistants and dental assistants have also shown impaired fecundity in some studies (44, 45).

The information on occupational causes of subfecundity is limited and scattered, and often out of date. Evidence from animal studies is usually not followed-up, and the research field has, in general, a rather low priority, which is not justified. Infertility is a large public health problem entailing huge costs in terms of suffering and expensive medical treatment. If the world is facing a decline in human fecundity which has roots in environmental exposures, research should be directed towards populations with the highest exposure, which are often specific occupational groups.

How to fill the gaps

First of all it should be realized that too little is known, partly because rather few research funds have been devoted to the field and cause-effect relationships are easier to study in occupational epidemiology and toxicology. Fecundity has been brought to the test only a few times in industrialized societies with low fertility. Fertility problems are often not diagnosed (46–48), partly because many couples with infertility problems do not seek medical advice. Fertility problems are sensitive matters which are difficult to accept and talk about for many, probably because they relate closely to fundamental biological issues of human life.

Research funding has often been denied, with reference to the global population growth, which undoubtedly is one of the main problems in the world today. Population control rests, however, on an entirely different mechanism that has little to do with

fecundity. Being able to get the desired number of children may in fact be one important element in reaching successful population control.

Impaired fecundity will often remain unrecognized, both for couples and for society. Only by using biological markers of subfecundity will it be possible to unmask hazardous exposures. The most promising marker is semen quality and quantity, for which technological development has improved the possibilities for mass screening and refined measures of a functional type are also available. One may hope that more relaxed attitudes towards normal body functions will make it possible to conduct studies on male fecundity with reliable participation rates. It could be worth trying in the northern European countries, and some studies are in progress.

Couple fecundity can be studied by measuring waiting time to pregnancy and infertility. In the "European Study of Infertility and Subfecundity" a very large data set has been collected throughout Europe. The study should permit an overview of the frequency of infertility and subfecundity in a large number of very different settings according to cohabitation norms, use of contraceptives, and occupational experience. The study should also permit infertility to be subdivided by different occupations, at least at a descriptive level. All in all, the study will provide information which may be used in setting priorities for further research tasks.

Clinical data suffer from the fact that they exist only for the couples who have surfaced to clinical diagnostics. Population surveys, on the other hand, usually only identify subfecundity without any clinical subdivisions in relevant subgroups. Since subfertility reflects a functional incapacity rather than an etiologic entity, one should try to combine the population approach with the clinical approach. A two-stage investigation using structured questionnaires to identify couples with subfecundity, followed by clinical evaluation and subdivision into different diagnostic entities, could be a rational approach for obtaining both validity and a reasonable detection level. Such a study would be rather expensive, but some investments into the research field is justified and the expertise is now available.

Better use of toxicologic data from animal experiments should also be made. The DBCP experience was not only illustrative in pointing out so clearly that occupational exposures can impair human reproduction, but also in illustrating that this effect had previously been shown in animal experiments (49).

Occupational exposures that are hazardous for human fecundity are probably rather specific, and they will likely remain undetected for a long time in the absence of any systematic surveillance. Standardized fertility ratios (28) for specific occupations could be a useful and important part of routine statistics, such as occupational cancer and mortality tables. Most of all, a research tradition needs to be established and maintained in a field that has to depend upon gen-

eral funding agencies and that lacks support from outspoken pressure groups. It is noted with pleasure that the World Health Organization advocates that higher priority be given to the field (50, 51).

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