

Concluding panel on direction for future research on male reproductive capability

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Jørn Olsen

First, I think that we should stress the need for changing the focus of the period of exposure. I think we now have sufficient indication that we should look at prenatal life. We heard Sharpe mention that the number of Sertoli cells at birth determine the sperm concentration in adult life, and it has also been indicated that estrogen exposure in fetal life affects the number of Sertoli cells. Therefore, from an epidemiologic point of view, we should try a whole new series of studies since good data are lacking so far, at least in two generation types of studies, to look at markers of estrogen exposure in fetal life. We do have good markers, perhaps not for external estrogen exposure, but for internal estrogen exposures. Age of the mother, parity, twinning, hypertension, eclampsia, and nausea are all markers of different levels of internal estrogen exposure in fetal life, and we could try to see if these data correlate with the findings on sperm concentrations in adult males. There is an existing model, for example, breast cancer and cancer of the testes, and we have seen that some of these hormone-sensitive cancers correlate with some of the prenatal markers of estrogen exposure. Therefore an entire new field would open up that would be of interest for study.

I think that we should also put more focus on an issue that has received little attention in this conference. In the field of reproductive health we now see a series of publications addressing the theories of programming, the interference with organ growth in prenatal life, permanently changing the function of these organs, and there is really no reason to believe that this phenomenon only exists for the pancreas and for the liver, etc. It might also exist for the reproductive organs. Therefore, expanding the programming theorem — which is now being heavily examined in respect to cardiovascular and pulmonary diseases and cognitive functioning — to reproductive functioning would definitely be of interest. Even though our experiments with this programming theory mainly address the issue of nutrition in experimental animal studies, we really do not know whether other external exposures or environmental exposures or other exposures that interfere with fetal growth may have these effects, and this question could also be a new area for research. All this information points toward a need to start collecting

data on exposures by studying birth cohorts or, preferably, conception cohorts.

I think that another aspect of high relevance is to obtain sperm data and data on fecundability from other populations. Today we mainly have data from countries of the European Union and the United States. We need data from other populations with different genetic and environmental backgrounds.

I think that it would also be of interest to look at diet and fecundity in fetal life, as just described, but also later on. And I think that diet could certainly be looked upon as a vehicle of environmental pollution, especially in Denmark, where we have 2 areas of high interest for that particular type of study, namely, the Faroe Islands and Greenland, where they have an extremely high intake of marine food, which is, for example, heavily polluted with pesticides and heavy metals. But it might also be of interest to look at other aspects of diet that are focused on in other areas than reproduction, especially the ratio of n-6 to n-3 fatty acids.

I think that for some of the life-style factors we have talked about, we do have information of sufficient quality to try these proposals and see if they work in randomized controlled trials. It could be of real interest for smoking, and, of course, the randomized controlled trial for smoking would be, for ethical reasons, a smoking cessation trial using couples planning a pregnancy, and I think that this design could provide perhaps necessary additional evidence, and it could also be of interest to see if it is possible to improve fecundability.

Stress is an issue that I think we would like to study. In many of the studies what we have discussed so far, we have lacked the clear distinction between studies of qualitative nature, whether it causes harm in extreme situations and in situations more likely to be seen in daily life or in worklife. For stress exposure I think that there would be opportunities for collaboration within the countries of the European Union to look at some of the extreme exposures to stress, to look at people who have been exposed to extreme stress in war situations or refugees or people who have experienced earth quakes or perhaps couples who have experienced severe life events — to try to identify some exposure groups in the extreme scale.

We also need to set up population surveys to monitor time to pregnancy and semen quality that could be repeated over time, even though there are limitations, which have already been discussed. We need to develop the methodologies for the time-to-pregnancy studies. I think that we are in a situation in which we could actually come up with standardized validated questionnaires and would have to have 2 sets of questionnaires, one type could be specifically related to studies that seriously address the issue of time to pregnancy, and I think that we have sufficient information now to say that this questionnaire needs to contain several issues. Then we could have a few questions that could be added to most of the questionnaires we have used in other studies of reproductive health.

Donna Baird

Some years ago this field was at its very beginning, but it has clearly progressed a lot, and a lot of work has been done. I think that we still have many methodological issues that we need to concentrate on, and I think that one way of doing that is by involving specific methodological questions in every serious study that is done and including side issues within any given study that is proposed. I think this is not only a very efficient way of doing research, but of also developing methodology. For example, looking at how much change occurs over time in exposures for women from the time they start to conceive to the time they actually get pregnant. These kinds of questions could be asked in many types of studies in a subset of women to look at the specific issue for any given kind of study.

One methodological issue that has not come up very much is the problem of assessing time to pregnancy and collecting good data, but there is a whole field of qualitative research which tries to address the issue of how people think about these things and how they respond to different questions, what kinds of words they use, and I think that, if we can develop a standardized questionnaire, the qualitative research methodology would be very useful in contraception, in order to get questions which are relevant to how they think about these issues. One of the issues that has come up is these huge variations among countries, and part of that probably is the way that people responded to the given questions that were asked in the time-to-pregnancy studies. I think that this is an area where methodology is available already.

I think that there is also an area in some of the detailed assessments of female outcome related to hormone levels that is actually very exiting and relates to some prenatal exposure. We know very little about what metabolism does and how important it is. There are some recent works that suggest that both estrogen metabolism and progesterone metabolism may be very important because of the types of metabolites that are formed. An-

other look at the biology in relation to diet and in relation to exposures could be very important. I think there are innumerable kinds of opportunities in a given study to ask specific questions that could be very informative both methodologically and biologically for future studies.

Steven Schrader

One of the things that I think we need to do is to come up with a screening method or a decision model of what needs to be studied, what are the hot issues, where do we go, how do we decide what needs to be done. Is there some way we can take these 300 000 compounds in the workplace and determine which ones really need to be studied. These investigations are very expensive and very time consuming. Is animal experiments the direction that leads us to these studies?

The second point is exposure assessment — I believe very strongly in biomarkers and would recommend that if you are going to go out and look at public health measures, if you are doing something like sperm count or other assessment, make sure that you really have an exposure. I have made such errors in studies, and I know many others who have been very frustrated when they finally got down to discovering that there was actually really no exposure. Just because the chemical is in the area does not mean that it is inside the persons. Some biological markers can be used to determine the body burden of the exposed.

The 3rd point is statistical power, and I would love to see papers start with describing the power to detect an effect, especially in negative studies. We need to look at statistical power in many of these measures. Certainly, looking at the semen characteristics, the data are there, and so is the variation. We should do these power calculations before we plan the study and in the end "did I have a chance of finding anything?"

The last thing is how do we exchange the data. I almost feel like 10—15 years ago. The United States was taking the lead in a lot of this type of research, but in the last 10 years, several very well done studies have been conducted in Europe, and your communication among yourself is very good. With the use of electronic networking, the internet, and e-mail, we can come up with a method for communicating better what each of us is doing and the results. I am not so concerned that someone is going to steal an idea or a report. When we publish things, we can use e-mail or put it on some home page somewhere, at least the abstract, so we all know what the other is doing. Maybe when you are doing your study designs, cast it among the persons who are interested and say "Here is what I want to do, it is going to cost lots of money, give some idea if my approach is right". Maybe even someone would like to administer a home page where we could keep everybody up to date on that

information. If nobody else wants to do it "please e-mail me the abstract".

Richard Levine

I would like to emphasize the studies dealing with normal fertility, normal variations in fertility. We really need to know a lot more about what happens normally in order to be able to understand when things are abnormal. I think that the seasonal variation in semen quality is something that may be real and may be important. And this is a topic that can be best approached internationally because we need to know if different birth patterns in the different locations are related perhaps to different patterns of changes in the fecundity of people, and we need the help of all of you. Many of you already have the data collected, many of you have excellent data on the numbers and quality of semen analysis done over many years. Many of you have good time-to-pregnancy studies, and I would be very interested for you to explore your own data to see what you find about the possibility of seasonal variation. The better studies will be prospective studies of semen quality within the same persons. And I think that the best months to look at might be August and February. You could get species from these 2 months from the same person and look for differences. I would be especially interested in the results of artificial inseminations. I do not think that it has yet been measured, but we could separate the male effect and the female effect by season if we use frozen semen and look at the month of semen collection versus the month of insemination to separate the male and female differences. In addition we know nothing about the seasonal variation of female fecundity. We would expect that such variation may occur, and it is up to researchers to look at ovulation patterns, variation of cycle lengths, and so forth. In addition I think that it might be of interest to look at seasonality of birth. To look at the changes in birth pattern with the change in time. Of course it would also be instructive to know about the seasonality of reproductive hormones and semen quality. If it is light, the reproductive hormones should peak or go up high before the semen parameters also increase, or likewise they should drop before the semen parameters dropped. On the other hand,

if it is heat, you might expect, by feedback mechanisms, that the reproductive hormones might go up after the semen quality has dropped. So you might be able to see different things there. And finally, I think that a very interesting population to look at would be the people that are totally blind. We believe that some of these seasonal patterns might be inherited by a biological rhythm, but people who are totally blind have difficulties with their circumdiurnal rhythms, they probably also have differences in their seasonal rhythm. So I hope that I hear from studies that you have all done on this topic, and I look forward to your contributions.

Jens Peter Bonde

One thing to state is that we have made real progress during the past 10—20 years in this field. Much has been learned on the available methods. We know about their strengths, and we also certainly know about their limitations. Therefore we are much better off now when we try to set up new studies than we were earlier.

I have the belief that collaboration between people with their roots in biology and people with their roots in epidemiology is a key which may unlock many things in the future. And I think that we can see that studies combining epidemiology with biology really are providing the most informational results. So I would say that this is one very important thing that is generally to go for in the future.

I also think, besides methods, that our understanding of couple fecundability has improved a lot. But nevertheless — when all comes to all, is not what we have achieved rather limited from a forensic point of view? I mean we have only identified, in my view, a few definite risk factors for fertility. I think that it is relevant, even at this conference and at this time, to put forward the following question: "Why is that?" So many questions arise: "Are we looking at the wrong exposures?" "Are we looking at the wrong exposure time window?" "Are we too crude in our exposure assessments?" "Is it the wrong outcome?" — All questions, I think, are in fact open. But also I think we have heard so many good suggestions on how to proceed that no one can be in doubt that there is a lot of work to do.