Trends in Male Reproductive Health

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Thanks very much Prof. Hirahara, and I would like to add my thanks to the Ministry of the Environment and especially to Prof. Hirahara for inviting me to what has been a real eye-opener of a symposium. I think for those of us who came as guests from outside Japan, it has been incredibly stimulating to have the opportunity to also make the tour last week of the National Institute for Environmental Studies; it was a very special half-day for us, I think.

Until effective treatment of male infertility became widely available in the past decade, I think that male reproductive health was really largely neglected.

This topic was really of interest mainly to clinical andrologists, the clinical specialists who treat male infertility, some of the reproductive medicine specialists who treat infertile couples, and of course, to the infertile couples themselves — the men and women who were trying to have children and were unsuccessful in doing so. Until a successful treatment came along they had to rely on adoption or artificial insemination to overcome their infertility.

But that has all changed very substantially in the past decade because now scientists only need to find a single sperm and it really does not have to be a very healthy one at that, and that can be used to achieve fertilization and hopefully a baby by injecting a single sperm into an oocyte and then transferring the resulting embryos to the woman's uterus. I think because of those clinical advances, we now see that male reproductive health is gaining much wider attention than it did in the past.

In this presentation, I would like to briefly review the possible relationship between male reproductive health and exposure to environmental chemicals and endocrine disrupters in particular, and then briefly comment about the treatment of male infertility.

If we look at the world literature in this field in recent years, it covers five main areas; two of them have been covered in some detail by the previous speakers, so I will be very quick in discussing the overlap of my presentation with those previous ones.

There has been an interest in sperm counts, seminal fluid volume, the sex ratio at birth, and also the changing trends in testicular cancer.

If we look at what was a rather seminal article in the attention, it gained in the "British Medical Journal" by Carlsen and this group of Danish researchers in the early 1990s, from that overview we come to conclude that there had been an apparent decline in the sperm count worldwide. Those authors did a meta-analysis and aggregated data from 50 or 60 studies over a period of several decades, and they purported to show a decline from about 115 million sperm/mL to a figure a bit more than half of that.

There was also an increase in the proportion of men with a low sperm count of less than 20 million sperm/mL.

These studies extended over a period of decades, from the 1930s up to the 1990s, and suggested a decline in sperm count of about 1 million/mL/year. The studies were not all in agreement one with the others, and this is why this has become a very controversial area because there were variable findings depending on which study you were looking at.

Why is the sperm count important? When I said that you only need one sperm these days to fertilize, and even from natural efforts at conception, it is only one sperm in the end that gets through. But there is all these other ones, and you can see that the probability of a woman becoming pregnant during a normal menstrual cycle in relation to the sperm concentration, the chances of conceiving expressed as a percent here does not really fall off until the sperm count gets below 20 million/mL.

This is again from Carlsen's article, and you can see that trends in the sperm counts these are dated over time from the United States, from European countries, and then there were a few studies from other countries not included in the previous groups that showed a different pattern or different trend over time.

What are some of the possible reasons for these variations in results in different populations around the world? Well, not surprisingly, sperm counts vary with the age of the male, whether or not the sperm were collected from men with proven fertility, or often the studies were done in infertile hospital-based studies and there was not a representative sampling of the populations at risk.

The sperm count increases with the increasing period of abstinence, so that is clearly a factor. In some of the studies, there was variable inclusion or exclusion of men with genital abnormalities as well as sub-fertility.

The method of sperm collection becomes important. One wonders sometimes how these collections are done: it also affects the sperm count whether it is done during sexual intercourse or whether the sperm are collected by masturbation.

In looking at the trends over time, it depends on whether it was a collection year or the publication year for the study. There may often be a gap between the collection time and the publication time, and quite a few studies did not make that clear. The way the sperm count is actually presented, whether it is presented as a mean sperm count or a median sperm density.

We see a lot of media reporting about reproductive health generally and in recent times male reproductive health. There was a suggestion at one stage when they sent other species — non-humans — into space, that the sperm were swimming faster and that fertilization could be achieved more readily in space, but you will be pleased to hear that you do not have to take a space flight if you are a bit sub-fertile because when they sent sea urchins into space they had another explanation.

So what are some of the possible causes of this decline in sperm counts? These authors again, the Danish group — this time in the "Lancet" — suggested that there may be increased organochlorines in seminal fluid. We know from exposure of women to diethylstilbestrol in the 1940s and 1950s, that as well as causing vaginal adenocarcinoma in the daughters of those women so exposed, that some of their sons had reduced sperm counts and genital abnormalities. Of course, another possible source of exposure to environmental disrupters is various estrogens *in utero*.

As I indicated earlier, that study in 1992 by the Danish group attracted a lot of attention. Then, the critical reviews came in and the points were made that many of the men were attending infertility clinics, and so were unsuitable to look at trends over time. Often the sample size was quite small and might account for much of the variation that was noted in those small studies. There were various criticisms of the statistical methods that had been used in analyzing the findings, and so this group reanalyzed the data using a different type of statistical analysis.

What we are then left with is that while there has seemingly been a huge amount of publicity about a declining sperm count, when you take the various risk factors account, and whether or not they had been adjusted for in interpretation of changes in sperm counts over time, I really do not think we have got a clear answer that there has been a decline in the human sperm count over a period of decades.

As our chairman indicated, as an epidemiologist, I go to many world congresses on *in vitro* fertilization and infertility. I have heard this topic debated I guess four or five times now and there are people strongly in the declining sperm count camp, but equally there are many people who believe there has not been a change over time. I will leave you to perhaps look at some of the references and draw your own conclusions.

Another possible indicator that has been suggested as a sentinel health event that can be used to monitor trends in exposure of human populations to environmental endocrine disrupters is information that is readily available, the sex ratio at birth. This is just the ratio of males to females, sometimes

expressed as a male proportion: usually, it is about 106 males to every 100 females, or if you express it as a proportion it comes out at 0.516, as you see there.

Again, there are conflicting studies on sex ratios in different populations around the world. In Denmark and the Netherlands, there has been a decline in the proportion of males born since the 1950s, similar to the decline in a group of other countries. In various studies, whether it is these population based studies of sex ratio or much smaller studies based on small samples of births where occupational exposure has been looked at, many of the authors of those studies have suggested that there may be a decreased sex ratio because of pesticides and occupational exposure and so on.

A group in the United States, as I say, have suggested that this should be a sentinel health event. So let's just look briefly at some of the data.

Even though the data are in annual numbers, take note of the scale: it runs from 0.508 to just 0.518; this is a very tight scale. But you get quite a lot of random variation one year to the next even in population data based on 50,000 or 100,000 births. But in both Denmark and in the Netherlands, the sex ratio declined in that period of about 50 years from the 1950s up to the mid 1990s. If we look at the data for Canada on the top line and for the United States, it is something similar.

We were then stimulated by that to look at the Australian data, and it is a slightly different scale but roughly of the same magnitude as we saw in the previous couple of slides. In fact, the sex ratio has either increased slightly or shown very little change over a period of 30 years. This is a period of 70 years going back to the early part of the 20th century. Again, as with the data on sperm count, we see specific patterns in some countries, but a different emerging pattern in other countries. Because, of cause, environmental chemicals are ubiquitous, we have got to have an adequate explanation for that.

Hypospadias, and I will be very brief about this, this is the definition used by the International Clearinghouse that Prof. Hirahara mentioned, and certainly as both of those people showed, there is variable ascertainment in reporting at birth.

As we will see in a moment, there are variable figures; we do not really need to concentrate on this because Dr. Pierik showed that there are all sorts of degrees. The normal opening is in the center of the glans penis, but of course, the opening may occur anywhere along the shaft of the penis down into the penoscrotal region, and we saw the proportions of those different abnormalities in the Rotterdam births.

If we look at the International Clearinghouse data — and this is presenting it in a different way to what my colleagues presented earlier — these are the data for Japan, and it has already been commented how the reported rates in Japan are much less than in other countries. These are three French monitoring programs and it does not matter which region we are talking about, but two of them are pretty flatline and one seems to have an increase over time. These are different countries and some of them even have a downward trend, but many are horizontal.

Again, clearly there is international variation in the incidence of hypospadias in those different populations. If we look at the Australian data, there is a relatively high rate of 20:10,000 compared to other countries; we have got a slight upward trend. But I would be careful to attribute causation to that for the reasons of variations in ascertainment.

Cryptorchidism: we do not need to dwell on this because it has already been discussed in some detail by Dr. Pierik. But as he indicated, the prevalence is often said to be about 1%. These are the wide ranges in published studies depending again on the sources of males that were being examined, some at birth and then some in adult life. Again, there is a problem of differing criteria for diagnosis. Preterm babies born at less than 37 weeks gestation are certainly more likely to have cryptorchidism, and there has been a suggestion of a doubling in the United Kingdom.

Again, I will not dwell on possible mechanisms here and I am really not competent to do so, but these references are included in the abstract. But there is certainly sound biological plausibility about why

endocrine disrupters might cause an increase in either hypospadias or cryptorchidism. That is the second article.

Let us now come to testicular cancer. In many countries these days, it has become the most common malignant disease of young men. It has increased in incidence in many countries over a period of decades since the Second World War. There are marked variations by country and ethnic group. There are abnormalities of spermatogenesis in men with testicular cancer, and cryptorchidism perhaps accounts for about 10% of cases in many studies.

These are the trends taken from a whole lot of countries in Europe and countries nearby. You can see, as we saw with hypospadias, that these are the rates for Denmark: about a threefold increase over a period of 40 or 50 years, but lesser increases in nearby countries like Finland and Sweden.

There has to be explanations apart from ascertainment to account for those changes. I think in contrast to the trends for hypospadias and cryptorchidism, this is more likely to be a genuine increase, although again there are ascertainment problems in cancer registries just like in birth defects registries.

The peak incidence of testicular cancer is for men in their 20s and early 30s. This suggests that factors operating perhaps during fetal life or certainly in early childhood may be important in the causation in testicular cancer.

We looked at the Australian data for a shorter period of time. The incidence has gone up largely from about 4-5 per 100,000 population, so it is not as big a jump as some of the European countries with much larger increases in that time period, although the time periods as well differed from one study to another.

This Danish group — and many of you will be familiar with this hypothesis – they are suggesting that there may be common causal pathways that account for the changes in testicular cancer, cryptorchidism and hypospadias which all arise during fetal development and also that some of those causing exposures may account for what they perceive as a real reduction in sperm counts.

They suggest that overexposure to the estrogens and estrogenic chemicals accounts for those abnormalities of the male reproductive tract. Some might think men and wildlife are more or less equal; in fact, as we have heard from presenters earlier today, there is some emerging evidence from wildlife studies. If there are environmental chemicals that are responsible, these are preventable causes.

What have been the implications of these changes? As we have indicated, there has been possibly an increase in male infertility although there are very few national studies of the prevalence of male infertility and that gap needs to be closed.

The infertile males are more likely to need assisted reproductive technologies like IVF. Constantly, there is a problem of good measurements of exposure and that has really proved difficult except in a very crude sense, and as I indicated earlier, there is a good series of plausible biological mechanisms to account for these male abnormalities.

These just show some Australia/New Zealand data in the last decade. The single sperm injection only started in the early 1990s, but now accounts for about 40% of all pregnancies that result from those procedures in our two countries.

Sorry, that this is a fairly messy slide. If you can follow the squares, for the causes of infertility amongst assisted conception pregnancies, the male causes have gone up from about 10-30% over a period of two decades. The multiple causes are also relatively high; where there are multiple causes it is often both the male and the female partner. Together, the male only and the male/female mixed causes account for about 50% of all of the treated cases.

Very briefly again, it is in this article in the “Lancet” that are listed what are some of the possible sources of increased exposure. It can be in the diet, there are differences in people with different levels of body fat, they may come from oral contraceptive use, perhaps anabolic estrogens used to feed livestock,

from plants, of course, like soybean, from other dietary sources that affect dairy produce, and then the environmental chemicals that we have heard so much about during this symposium.

Future studies: there are some under way, looking at collaborative studies, using more representative samples of men to look at sperm counts. I think that many people agree that we ought to look at populations beyond the developed countries in Europe and North America and Japan. Well, maybe the studies have not been done yet in Japan? We need to standardize the methods of sperm counts and we need better measures of exposure to the chemicals.

This very briefly outlines the hypothesis that increased exposure to endocrine disrupters during fetal or early post-natal life may effect the male reproductive tract development and has these adverse effects that we have just been summarizing.

Finally, as an epidemiologist it seems to me that there is a huge gap between our knowledge of the emerging significance of ubiquitous exposure to environmental endocrine disrupters, which we have heard about during the course of this meeting, and now what we are presenting in terms of studies in humans that are aiming to find evidence of possible adverse effects on population health.

Some of you may be familiar with the so called Barker Hypothesis, which suggests that many common adult diseases — or a sizable proportion of those adult diseases such as coronary heart disease, hypertension, renal infections — may be attributable to nutritional and other problems that arise during fetal development.

That Barker Hypothesis has spawned a huge industry research effort around the world to test that hypothesis. I think, as I have listened to all of the presentations at this meeting and read a little bit on the subject in recent times, I think we really are at a similar stage — a much earlier stage compared to the Barker Hypothesis — in looking for the possible health effects in humans of environmental endocrine disrupters. You have already heard from the speakers so far about the problems with existing databases — the sex ratio at birth that is pretty sound information — but the others have variable ascertainments, sometimes.

I really think that we can start to try and use existing national and regional databases to look at variations in the counts and just see how much variation there is, and start thinking about making some crude correlations with exposures to known environmental chemicals.

We were involved in a study back in my home state of New South Wales in Australia in the mid 80s. It is extraordinarily difficult to get any reliable information on environmental chemicals. Even the sales numbers are often not available because of company confidentiality.

We need more intensive study of specific occupational groups to test hypotheses about endocrine disrupters, and we have mentioned about the sperm counts. Finally, just to see what is happening to male populations around the world, as well as the sperm counts, there need to be regular national surveys of the prevalence of infertility in our populations. Thank you very much.

Q&A

Hirahara: Thank you very much, Dr. Lancaster. We have a few minutes for discussion. Are there any questions or discussion?

Q: My name is Kitami. It has been at least reported in book that the birth rate of males in Australia has gone up. In numerical terms, it has risen…

Lancaster: Yes, it has gone up over a period of 70 or 80 years, but in the last 30 or 40 years, it is closer to a plateau.

Q: The exact figure I believe was 0.513. The fact is that this is below the actual average of 0.516. Even though there has been a tendency to rise, the sex ratio for males is going down. I believe you might consider this a statistical normality, whereby although there may seem to be more males now, what we actually have is a slight rise in the birth rate of males on top of a drop in male birth rate. What do you think?

Lancaster: Yes, for this presentation I am expressing it as male proportion. Actually, I am much more used to dealing in terms of the sex ratio expressed as 106 males to 100 females.

But you may be right. There may be marginal differences between the baseline rate in Australia and some of those other countries. But as you have rightly pointed out, the trends are different. We have not looked to compare the absolute rates in the different countries; rather, the emphasis was in looking at the trends over time.

It raises the possibility of going out and trying to look at regional variations within countries that have a decreasing rate of the sex ratio, or decreasing male proportion, and comparing that with countries where there is either a plateau or an increasing sex ratio.

Hirahara: Thank you very much, Dr. Lancaster.