

# **Birth Defects Monitoring in Japan**

## **- Possible Effects of Environmental Endocrine Disrupters -**

**Fumiki Hirahara**

Yokohama City University School of Medicine

Thank you, Paul. It is my great pleasure to be here and talk about our monitoring systems and some data. Today, I would like to talk about the three major points shown here.

This is our institution. First of all, I would like to talk about our Japan Birth Defects Monitoring system and the International monitoring system. Secondly, I would like to talk about hypospadias and some other birth defects in Japan. Thirdly, I would like to talk a little bit about our ongoing prospective study. We are looking at bisphenol A in early pregnant women under informed consent.

I would like to talk about our birth defect monitoring center. This is the headquarters of the Japan Birth Defects registry and also Birth Defects Surveillance Systems. Our center is participating with the ICBDMS, International Clearinghouse for Birth Defects Monitoring Systems. I would like to talk about the next slide about ICBDMS.

The program director Prof. Sumiyoshi and the head of the Center is myself. ICBDMS is the International Clearinghouse for Birth Defects Monitoring Systems. This is a worldwide surveillance system for congenital abnormalities. This is a WHO related non-governmental organization, and participants include more than 25 countries such as the United States, England, Australia, France, Netherlands, Japan, China, and so on.

Next, I would like to talk about the history of birth defects monitoring. Human beings experienced the thalidomide tragedy at the end of the 1950s and the beginning of the 1960s. This tragedy gave an impact to establish birth defect monitoring. In Japan in 1972, our registry started as a nationwide birth defects monitoring system, and WHO organized the international clearinghouse since 1974. In the early 1970s, the Tokyo area and some other areas developed localized programs of birth defects monitoring.

Our birth defect registry is called the JAOG program: Japan Association of Obstetricians and Gynecologists. This is a nationwide hospital-based monitoring started in 1972 and covering about 10% of whole births in Japan. It has been joined to ICBDMS since 1988, and we are registering after 22 weeks of gestation until 7 days postpartum. More than 150 marker abnormalities are registered in our monitoring system. It is supported by Japanese government funds including the Ministry of the Environment and the JAOG Foundation.

Here is the JAOG district map. We collect data from nine separate areas in the whole country. Our center is located in Yokohama, just next to Tokyo. Tsukuba is right here.

We are surrounded by many kinds of teratogenic factors such as infectious agents, maternal diseases, drugs, chemicals, foods, radiation and electromagnetic fields, and some kinds of mechanical environmental factors are teratogenic.

Here you can see the incidence of congenital abnormalities in our country. You can see the percentage from 1972 to 1999 about 1% of the births are recognized as a congenital abnormalities. But in 1997, it goes up. Why does this go up?

After 1997, JAOG program started to register cardiovascular abnormalities. So this shows the period between 1972-1991, and a 20-year ranking of the congenital abnormalities. This is the rate per 10,000 births. In our country, the most frequent abnormality is the cleft lip and palate, second is anencephaly, and abnormalities of the extremities are frequent abnormalities in our country. Here is Down

Syndrome. You can see that hypospadias is 2.1/10,000. Also you can see the omphalocele and gastroschisis, an abdominal wall defect.

But in the last three years, there has been a change in the congenital malformation in our country. This is the cardiovascular abnormalities: ventricular septal defects are the first most frequent abnormality. The cleft lip and palate is also frequent, but PDA and ASD also are ranked as frequent abnormalities.

Here you can see one of the stable abnormalities in our country: total cleft lip. You can see that rate per 10,000 births from 1972 until 1998 was about 15. You can see the stable incidence.

Another abnormality, anencephaly, is decreasing yearly. Why? Why is it going down? Because right here we have the technological development of the ultrasound examinations.

We have ultrasound, just directly, and transvaginal ultrasound examination is developed here, so the anencephaly incidences are going down, but presumably the rest of the anencephaly cases have been aborted. Here you can see the digest of the technological development of ultrasound examination. In 1980, real-time scanning was developed, and after that in 1988 transvaginal scanning was developed. I will show you another example in the next slide.

Here you can see the incidence of hydrocephaly. Hydrocephaly is easy to recognize with ultrasound scanning. One point is right here: the real-time ultrasound examination is developed. Another point is right here: the transvaginal ultrasound examination is developed. So the incidence is totally going up in our country.

Here you can see the incidence of hypospadias. Hypospadias is not so easy to be recognized by ultrasound examination, but is still increasingly recognized. In 1974, we recognized 1.4/10,000 births. But in 1985, 2.5, and in 1998, it goes up to 3.5. So we recognize the increasing trend in hypospadias in our country.

When we look at the incidence of hypospadias, let us separate the age groups: here is the maternal age — under 19, 20-24, and here is rate per 10,000 births. So a higher incidence in the under 19-group and also the 35-39 age group, and the lowest incidence is seen in the 30-34 age group. If you look at the primipara and the multipara, the primipara have a much higher incidence as compared to multipara. These kinds of trends are reported elsewhere.

Hypospadias is quite often associated with other major congenital abnormalities. Look at 1993-1998, there is no obvious trend in each group, but the associated hypospadias is relatively high.

Here you can see the gestational weeks: 22 gestational weeks and 42 gestational weeks. Here is the birth weight: 2,000 g and 3,000 g. This line is the mean birth weight. The black dot represents a solitary hypospadias case, and the red dot represents an associated case. Many cases are below the mean birth weight curve. So hypospadias risk factors are light birth weight infant, prematurity, and primipara, and toximia of pregnancy. Also toximia of pregnancies are reported in the literature.

According to ICBDMs reports, an increasing trend is recognized in the United States, France, Czech, Finland, and Japan, and no changes in Canada, England, and South America.

I would like to show you another abnormality. Here you can see the gastroschisis trend, also the rate per 10,000 births. It looks like an increasing trend in the incidence. Omphalocele is also one of the abdominal wall defects, is also an increasing trend in our country. Here we have 10/10,000 births.

We move on to the next topic. This slide shows you just preliminary data, but here you can see the blood and urine level of bisphenol A in pregnant women. Under informed consent, we collected from early pregnant women and also at delivery. There is no previous report like this prospective epidemiological study.

To our surprise, most of the pregnant women, almost 93% of 339 samples, were detected with bisphenol A; the average is 0.5 ng/ml. In addition, we also looked at 100 babies using umbilical cord blood. To our surprise, 100% of the samples showed bisphenol A, and a higher concentration of bisphenol

A as compared to their mother's level. This study is still going on and more than 1,000 pregnant women are cooperating to this prospective project.

A risk assessment should be established or evaluated from various kinds of standpoints. From our standpoint, epidemiological and human monitoring is helping to do risk assessment.

In conclusion, in Japan there is an increasing trend in hypospadias and abdominal wall defects. The reason for this trend is not clear at the moment. Prenatal ultrasound in diagnostic screening has influenced the prevalence rate in birth defects. For toxicological risk assessment, epidemiological approaches including birth defects monitoring and prospective studies are playing an important role.

This study is accredited to the more than 300 JAOG participating hospitals and the executive committee of JAOG members, and colleagues and center members. Also I would like to thank Prof. Mori, Chiba, Graduate School of Medicine, and the Ministry of Environment. Thank you for your attention. Thank you very much.

## Q&A

Lancaster: Thank you very much, Prof. Hirahara. Do we have some questions, please?

Q: Thank you for your excellent talk. I was wondering whether you have an explanation for the relatively low rates in Japan compared with, for example, the rate for the United States, which is about ten times higher than what you report.

Hirahara: It is quite difficult to answer. Many arguments are there. Maybe you are talking about the data. There are many kinds of problems in collecting the data. We can explain one of the reasons: some kinds of technological development will help the...

Q: You aren't thinking they are genetic factors, are you? Another thing that I saw in one of the graphs was that about 50% of hypospadias is associated with another abnormality.

Hirahara: You mean the associative?

Q: Yes, I understood that there was another congenital abnormality as well in 50% of the hypospadias.

Hirahara: You mean the associated hypospadias?

Q: Yes, that is quite odd. Is there data for all the registries?

Hirahara: We have no special program for the hypospadias collecting. We are collecting all of the birth defects, more than 100 markers. So maybe you are suggesting using some kind of specialist to interpret these data. But now we can collect the data just only so far as it is recognized by an obstetrician, and then they collect the data.

Q: But you do not know for other countries whether there is also so much associative hypospadias? Do you know?

Hirahara : Sorry?

Q: Is it very frequent — the associative hypospadias in the other registries of the International Clearinghouse?

Hirahara: I did not understand what you mean.

Q: The other countries in the International Clearinghouse of Birth Defects — do they also see associated hypospadias?

Hirahara: I do not think there are any plans. Maybe there are small groups doing so, but I do not know.

Lancaster: Any other questions? Yes.

Q: I have a question in Japanese. Do you know what stage of pregnancy determines whether or not hypospadias will occur?

Hirahara: It is determined at an extremely early stage, during the stage when the organs are formed. From 7 to 10 weeks, or from 12 to 13 weeks or so.

Q: My name is Tsunegi. I really appreciate your sharing such comprehensive statistics with us. There was a lot of stuff I wanted to know but just couldn't seem to find out.

Have you analyzed regional distribution in Japan – whether the rate of incidence is high or low, or what the characteristics are?

Hirahara: I do not know much about regional distribution. As I previously stated, we conducted our study by dividing Japan into nine segments, such as cities and so on. Is that what you mean?

Q: Were there any distinguishing characteristics among the nine segments?

Hirahara: There were some characteristic differences, but there are few such examples.

Although there was significant movement among those few examples, we only observed this for a short period of time so we are not sure if there was a fixed tendency in all cases.

Q: Thank you very much.

Q: Can I ask two brief questions? One is about following on the question about the low incidence of hypospadias in Japan compared to many other countries in the world. As you well know, there is variable ascertainment of that particular birth defect by examiners once the babies are born.

Do you have any hospital studies that have been done in Japan that might show a different incidence rate for hypospadias compared to what the population data show, and secondly, if those studies have not been done, are you aware of what the hypospadias rates are in other populations close to Japan? What their levels are?

Hirahara: If we wanted to know the precise and collective incidence of hypospadias, I think it is very difficult to know. I guess you can estimate about 60% or 70% of all hypospadias cases from our registry. But we need a pediatric urologist to support our registry data. Anyway, I cannot explain the answer to your question.

Lancaster: OK, well time is up, so thank you very much, Prof. Hirahara.