Session 5 Children's Health

Regional Differences and Temporal Trends in Semen Quality

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Recent retrospective studies on secular trends in male reproductive health have provided conflicting evidence, with some investigations suggesting that sperm counts have declined significantly, whereas others have found no evidence of any change. However, a striking feature of much of the data is the appearance of regional difference in semen quality, which are at least as great as the possible secular trend. The possibility that these regional differences in sperm counts may be biologically meaningful has been suggested.

The controversies of much of the published data are in part due to fact that previous clinical studies on semen quality have dealt with selected groups of men. In many studies, historical data collected for other purposes have been used without close attention to confounding factors which would be relevant to an analysis of secular or geographical trends. Although much of the present literature may suggest temporal and regional differences in male reproductive health, it has also been pointed out that definitive evidence will only be provided by prospective studies.

Cross-sectional studies in Europe has been undertaken focusing on the possible geographical differences in semen quality, by studying male partners of pregnant women from Denmark, France, Scotland and Finland and young men from the general populations in Denmark, Norway, Finland, Estonia and Lithuania. Altogether, 1,082 fertile men and 1,834 young men from the general population have been examined and results published so far. The men were included to the projects and investigated according to standardised criteria and quality control procedures were included to control the used methods. Apparently, an East-West gradient in the European area, in parallel to the incidences of testicular cancer, exists regarding semen parameters: Significantly better semen quality and lower incidence of testicular cancer in Finland, Estonia and Lithuania. It remains to be investigated whether the findings are due to genetic differences, a different environment or perhaps a combination of both factors. In addition to semen samples, the men also had blood samples drawn for hormonal assessments, had a physical examination performed and answered a comprehensive questionnaire. The analysis of these results may be able to indicate causative factors.

According to a recently proposed hypothesis testicular cancer does not occur at random but in men with testicular dysgensis syndrome (TDS). Depending on severity TDS may include one or more disorders, such as impaired spermatogenesis, testicular cancer, hypospadias and undescended testes. This hypothesis implies that populations with high risk of testicular cancer also have an increased frequency of men with poor semen quality and vice versa.

The studies of young men in the Nordic-Baltic area of Europe will continue in the coming years in order to describe a possible time trend in male reproductive health.

Current Status of Semen Quality in Japan

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During the past decade, the possible declining trend in human semen quality has been one of the major topics not only among scientists but also in the public. According to a recent hypothesis, degradation of semen quality does not seem to be an independent phenomenon showing deteriorated trend but rather one of various symptoms such as testicular cancer, cryptorchidism and hypospadias, which derived from one common entity named the testicular dysgenesis syndrome (1). The reasons for these secular trends are unknown, but the rapid pace of the change points to environmental causes including the impact of endocrine disruptors (2-3). It remains controversial whether semen quality has globally declined during the past several decades, however, it is plausible that the geographical variations of the level of semen quality and its secular trends exist in various regions of the world (4-5). A comparison of the epidemiological data from geographically different male populations with different genetic and environmental backgrounds is necessary to identify the factors affectable to male reproductive function.

Many of the studies on this domain have been carried out in highly developed countries such as the United States and Europe. Only a small number of the studies have been conducted in Asia and other non-Western countries. In Japan there has been no longitudinal epidemiological study on male reproductive function so far. We have nothing but very limited information in semen quality, and a little or no declining trend has been suggested as far as we know from a few Japanese studies in cross-sectional approaches (6-7). Japan is supposed to have a basically similar environmental condition to other developed countries considering the use of synthetic chemicals, but to be substantially different from these countries as to genetic background and lifestyle. Reliable data on male reproductive function in Japanese men must provide the useful information for comparative studies of this field as well as for understanding current situation of this problem in Japan.

Recently we have participated in the multinational collaborative study on male reproductive function, which was proposed by Niels E Skakkebaek's group in Denmark (8). The study items include semen analysis, blood sampling for determination of reproductive hormone levels, andrological examination and questionnaire. Study subjects are two different Japanese male populations, fertile men (partners of pregnant women) living in Kawasaki/Yokohama and young men with unknown fertility attending universities in Kawasaki. Both studies have been performed based on the common protocols of the collaborative study under the quality control of semen analysis (8). In addition to that, the study on fertile Japanese men has expanded into the multicenter study adding four new centers in Sapporo, Kanazawa, Osaka, and Fukuoka to our Kawasaki center in order to investigate regional difference of reproductive function on a nationwide scale. This project is the first large-scale epidemiological study on Japanese male reproductive function available for comparing the data on a worldwide scale.

This presentation will introduce a preliminary data from our Japanese studies and discuss the current status of Japanese male reproductive health. Mean variables $\pm$ SD (median) of semen parameters of 352 fertile Japanese men (mean age 31.7, range 20-44) from the Kawasaki/Yokohama area were as follows: abstinence time 213.4 $\pm$ 256.9 (133) hours; semen volume 3.3 $\pm$ 1.5 (3.1) ml; sperm concentrations 121.5 $\pm$104.7 (93.5) million/ml; motile spermatozoa 55.7 $\pm$ 14.7 (57) %. On the other hand, those of 335 Japanese young men (mean age: 20.4, range 18-22) from the Kawasaki area were as follows: abstinence time 74.6 $\pm$ 32.3 (63) hours; semen volume 2.8 $\pm$1.3 (2.6) ml; sperm concentration 71.7 $\pm$ 62.0 (53.3) million/ml; motile spermatozoa 58.4 $\pm$ 14.6 (59) %. We observed seasonal variation in sperm concentration on the specimens from a part of the young men (72 out of 335) collected 4 times a year at different seasons. The mean sperm concentration in spring (87.3 million/ml) was significantly higher than those in each of other three seasons (81.0/summer, 82.7/autumn and 72.9/winter). Forty-six (33 out of 72) percent of the young men showed the highest sperm concentration in spring when the sperm concentrations were compared within each individual. We are investigating the reproducibility on this seasonal trend by repeating the same study at present. We would like to also discuss about geographical differences in semen quality among five cities in Japan and attempt to compare our Kawasaki data with those from four European cities already reported (8).

Regional and Temporal Trends in the Prevalence of Cryptorchidism and Hypospadias

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Increasing trends of hypospadias have been reported in several European countries on the basis of the data collected by the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS). According to recent publications, increased rate of hypospadias in the USA has continued from the 1970s to the 1990s. The ICBDMS has also reported data on cryptorchidism, but these data are not reliable because of apparent discrepancies with the data from cohort studies. According to two comparable English studies, the incidence of cryptorchidism in full-term boys approximately doubled between the 1950s and the 1980s. Our new data on the prevalence of cryptorchidism and hypospadias in Finland and Denmark show a marked geographical difference that is of similar magnitude as the difference between the incidence of testicular cancer in these countries. Testicular cancer, cryptorchidism and hypospadias share risk factors, such as intrauterine growth retardation. Prevalence of all these disorders are lower in Finland than in Denmark. Regional and temporal trends may help to identify environmental and genetic factors that might be associated with these disorders.

Persistent Organic Pollutants (POPs) in Human Breast Milk Collected from Asian Developing Countries: Risk Assessment for Infants

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Persistent Organic Pollutants (POPs) such as polychlorinated dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs), biphenyls (PCBs) and organochlorine insecticides are lipophilic stable contaminants, and have been of great concern regarding their toxic effects on humans and wildlife. In developed countries, it is suggested that residue levels of these contaminants in various environmental media and biota have generally decreased in recent decades. In Asian developing countries, however, few studies have reported regarding exposure to these contaminants, especially dioxins and related compounds, for humans. In dumping sites of municipal wastes in Asian developing countries, secondary formation of dioxins and related compounds is anticipated, because a lot of various wastes has been dumped daily and continuously burned under low temperature by spontaneous combustion or intentional incineration. In addition, it is doubtful that organochlorine insecticides have been used there for public health purposes. These are suspected that many residents around these dumping sites are exposed to these contaminants. The present study attempted to elucidate the contamination status of PCDDs, PCDFs, PCBs and organochlorine insecticides in human breast milk collected from dumping sites of municipal wastes and reference sites in Asian developing countries, such as India, Cambodia, Vietnam and Philippines during 1999-2000, and to assess the risk of exposure in their infants.

PCDDs, PCDFs, PCBs and organochlorine insecticides were detected in all the samples of human breast milk analyzed in this study, indicating that the residents around dumping sites of municipal wastes and reference sites in India, Cambodia, Vietnam and Philippines have been exposed to these contaminants. Concentrations of dioxins and related compounds in human breast milk from dumping sites in India were significantly higher than those from reference sites and other Asian developing countries and the levels of TEQs were comparable to those in general public of developed countries. This indicates that significant pollution sources of dioxins and related compounds present in dumping sites in India and residents around there have been exposed to relatively high levels of these contaminants. On the other hands, TEQs in human breast milk from Cambodia, Vietnam and Philippines were relatively low and not significantly different between dumping sites and reference sites. The dominant organochlorine insecticides in human breast milk from India, Cambodia, Vietnam and Philippines were HCHs, DDTs, DDTs and DDTs, respectively, and not significantly different between dumping sites and reference sites. As examined the relationship between concentrations of TEQs and organochlorines in human breast milk and the number of delivery times, levels of these contaminants tended to decrease with increase of the number of delivery times. Furthermore, estimated daily intakes (EDIs) of TEQs exceeded 4 pg TEQs/kg/day of TDI (WHO, 1998) for all the Asian developing countries, and EDIs of HCHs and DDTs exceeded 0.3 μg /kg/day of TDI (Health Canada, 1996) for all the Indian and 20 μg /kg/day of TDI (WHO, 1982) for a few of Vietnamese and Cambodian, respectively. These results suggest that first infants have been exposed to higher levels of dioxins and related compounds and organochlorine insecticides from breast milk and might be at higher risk for these contaminants.

New Ways to Investigate Contamination and Human Health

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Human research tends to center on specific exposures, although we are exposed to numerous unknown chemicals during our life time. Investigative techniques, centering on communities-at-risk, rather than the individual, demonstrates the multiple impacts of exposures. Changes in the level of health, including childhood growth and development, take precedence over disease incidence.

A longitudinal study of children living in towns surrounded by agriculture demonstrated assorted neurological and physiological deficits. Research techniques, representative of body function, were based on activities that children of various ages enjoy. Examples include running games for measuring stamina and walking on a narrow board as a test of balance. Mental abilities for memory, problem solving and abstract thinking were measured by adapting portions of intelligence tests. All activities could be adjusted for ages four through eighteen. Physical measurements extended beyond to usual, such as measuring actual mammary gland growth in pre-pubescent girls. The variations among exposed individuals were large, but when placed on a community level the decreases in the level of health, with the identification of previously unknown cognitive and developmental deficits, became significant in comparison to the reference site.

Fetal Exposure to Endocrine Disruptors during Human Pregnancy in Japan

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Introduction

Environmental disruptors have been shown to affect organogenesis in various kinds of wild and experimental animals. However, little is known concerning to teratogenic potentials of these endocrine disrupting substances in human beings. Bisphenol A (BPA), one of the environmental estrogens, is widely used in the manufacture of polycarbonate plastics and consisting of essential component for lining of metal foods cans. The aim of the present study was to evaluate the condition of fetal exposure to BPA in Japanese pregnant women.

Methods

Blood samples were obtained from pregnant women during the first and third trimester under their informed consent and the approval of IRB in Yokohama City University School of Medicine. Umbilical cord blood samples were drawn during their deliveries. Immunoreactive BPA was measured by ELISA assay (Kodaira T *et al*., Biomedical Research, 21: 117, 2000, Otsuka Assay Laboratories, Otsuka Pharmaceutical Co. Ltd.). Newborn infants were carefully screened for the presence of congenital abnormalities. Obstetric complications were ascertained from their record throughout pregnancy.

Results

Among 1690 maternal blood samples, 1665 samples(98.5%) were shown detectable levels of BPA. On the other hand, all umbilical cord blood samples (398) were shown detectable levels of BPA.

Maternal blood BPA levels showed 0.407±0.007 (M±SE, n=1665) ng/ml, while, 398 samples obtained from their umbical cord showed 1.366±0.115(M±SE, n=398) ng/ml.

Conclusions

Higher levels of BPA in the umbilical cord blood in comparison with maternal blood levels were demonstrated. Few cases of congenital abnormalities, however, showed higher levels of maternal BPA during their pregnancy. Based on our data, it has not been shown completely whether or not environmental disruptors has play a possible role in developing human male reproductive abnormalities such as hypospadias. Further studies are required for elucidation of the mechanisms and significance of the differences in BPA levels between mother and fetus.