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Effects on Health

Birth Defects Monitoring in Japan -Possible Effects of Environmental Endocrine Disruptors-

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Introduction:

Birth defects monitoring is important to detect the unusual changes in the incidence which suggesting environmental exposures or other influencing factors. In recent years, there has been increased concern for environmental endocrine disruptors as teratogenic agents for human beings as well as wild animals. In particular, there is some evidence that hypospadias and undescended testes have increased. Possible hypotheses has been raised for these trend which implicating in environmental endocrine disruptors.

This study is aimed to investigate the recent trend of the prevalence rate of birth defects including male reproductive organs by analyzing Japan Birth Defects surveillance database (JAOG database).

Materials and Methods:

JAOG Birth Defects Registry program is covering nation-wide area of Japan with 330 participating hospitals and routinely detect about 10% of whole births in Japan. This hospital-based birth defects monitoring includes congenital malformations identified after 22 gestational weeks to 7 days postpartum (1972-1981, after 28 weeks; 1982-1991, after 24 weeks). In our Birth Defects registry, program case report including checkboxes for more than 100 marker abnormalities was collected at the JAOG program office (International Clearinghouse for Birth defect Monitoring Systems (ICBDMS), Japan Center, located at Yokohama City University Hospital, Yokohama, Japan), and case ascertainment was carried out based on the multiple sources, including medical records from the participated hospital and referred pediatric or pathologic records when /available/they have attached with program case report.

JAOG Programme committee including teratologists confirmed these case reports and the whole data were /examined/analyses by using computer-generated analyzing program.

Results:

From the results of analysis for 25 years, covering 3,180,254 births, about 10% of whole births in Japan, main frequent types of birth defects was cleft lip/palate, Polydactyly, Anencephaly, Hydrocephaly, syndactily. Down syndrome and others (overall prevalence of abnormalities are 0.91%). In the past few years, along with recent technological progress, including ultrasound scanning, decline trend in anencephaly and increasing trend in cardiovascular abnormalities are recognized. On the other hand, the prevalence rate of hypospadias has increased (1.4/10000births in 1975, 2.8/10000births in 1985, 3.5/10000births in 1998). Enrolled 178 cases (1993-1997) were employed for further investigations. Among the cases, 59 (33.1%) cases were associated with other major malformations. Higher incidence of hypospadias was observed in primipara cases. In the preterm delivered cases, most of the the affected infants showed as light for date infants. In addition, our database showed some possible increase in total abdominal defects (gastroschisis).

Conclusion:

Our database has indicated increased trend of hypospadias in Japan. Hypospadias is thought to be an abnormality which would be influenced by endocrine disruptors. The surveillance for abnormalities in male reproductive organs such as hypospadias and undescended testes is important from the vew point of evaluating environmental teratogens.

Cryptorchidism and Hypospadias in The Netherlands: Are Endocrine Disrupters Involved?

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The endocrine disrupter hypothesis

In various countries adverse trends in reproductive health have been reported in recent times. These include increased hypospadias and cryptorchidism rates in newborn boys, declining sperm quality, and increased incidence of testicular cancer in adult men. It has been suggested that these disorders all arise during foetal development and, hence, have a common aetiology affected by exposure to endocrine disrupters (ED).¹ The endocrine disrupter debate has been extended to include a series of adverse effects, including breast cancer, endometriosis, neurodevelopmental, immune system effects, and thyroid effects.² The hypothesis can be partly corroborated by findings in wildlife and experimental animal studies, and some human studies have shown the involvement of various hormonal systems in these effects.

In the debate on the role of ED in increasing trends in hypospadias and cryptorchidism 2 critical issues have emerged: (1) are the observed increased trends a mere result of changes in case ascertainment and diagnostic procedures?, (2) is it possible to link the occurrence of health effects to specific levels of exposure to particular EDs? These issues need to be addressed to facilitate and strengthen future research efforts in this area.

1. The accuracy of health surveillance systems.

Reports on rising trends in birth rates of cryptorchidism and hypospadias are almost exclusively derived from registry systems. It has been suggested that these registries may be inaccurate as not all cases are assessed and reported, and as the denominator has to be approximated. Dolk (1998) recently described the possibility that the rise in hypospadias might be explained by a trend to increasingly report cases of minor severity.³

In a recent study, we accurately assessed the occurrence of cryptorchidism and hypospadias subtypes by prospective examination of all newborns in Rotterdam over a 2-year period. In the Netherlands, all parents of new registries in the birth register are invited by Child Health Care centres to participate in the national preventive child healthcare programme (e.g. vaccination). After training in a standardised examination, child health care physicians (n=30) examined the external genitalia of boys born in Rotterdam in the period October 1998 to October 2000. Of the 7,652 boys registered in the birth register, 7,292 boys (95%) were examined before the age of 6 months. Cases of cryptorchidism and hypospadias were referred to 2 experienced paediatric urologists at the University Hospital for verification and classification. The verification rate was 73 and 88% for cryptorchidism and hypospadias, respectively. The rates of cryptorchidism and hypospadias among newborn boys were 1.1% (79/7292) and 0.7% (53/7292). The prevalence of cryptorchidism is in accordance with comparable studies. However, the hypospadias rate in Rotterdam was 4 times the rate of 16 European regions and the rate of The Netherlands given by the European Registration of Congenital Anomalies (EUROCAT). If we exclude cases of minor severity (as EUROCAT does), the rate is still 3-fold higher ($p < 0.0001$; χ^2 -test), suggesting underreporting in EUROCAT as explanation for the striking difference with our rate. No historical data is available to assess hypospadias trends over time in our study area due to registry incompleteness. We conclude that accurate monitoring of cryptorchidism and hypospadias trends requires a complete case ascertainment and a standardised diagnosis with grading of subtypes. The reported increasing trends may be the result of changes in case ascertainment and diagnostic procedures, but this has yet to be clarified.

2. Establishing the role of exposure to EDs in the occurrence of hypospadias and cryptorchidism.

Another critical issue in the debate is the relationship between actual human exposure to exogenous endocrine active substances, particularly in utero exposure, and adverse health effects caused via endocrine modulation. The impact of environmental oestrogenic and anti-androgenic compounds on human health has yet to be substantiated, partly due to the lack of appropriate strategies to quantify patterns of exposure to EDs. 1 Most human populations are exposed to a complex mixture of chemicals from several compartments (e.g. occupation, nutrition, general environment, and consumer products) and via different routes (e.g. inhalation, ingestion, dermal absorption). Integrated exposure assessment strategies are complicated and should take into account several aspects.

First, assessment of prenatal exposure is crucial and, thus, exposure of the parents has to be investigated with regard to reproductive effects in male newborn infants. Most likely, the critical time window is shortly before and after conception. Second, different exposure sources have to be considered, e.g. in many food products phyto-oestrogens are a natural component and the consumption of plant-derived oestrogens in diet may result in a much higher daily intake than is possible by exposure to environmental endocrine-disrupting chemicals. It is perhaps the biggest challenge in this area to address simultaneously potential exposures in the workplace, the environment, consumer products, and diet, in order to facilitate an integrated assessment of total exposure to endocrine disrupters. With regard to the large variety of potential EDs, development of selection procedures for the most potent EDs is inevitable and in epidemiologic research grouping of specific EDs into large classes is an essential prerequisite for any measurement strategy. Environmental monitoring should be validated with analysis of the internal dose of EDs in biological material (e.g. blood). There is a clear need for development and validation of markers as to their capacity to assess internal dose and their ability to differentiate among groups with different exposure profiles shortly before conception and during early pregnancy.

In our current hypospadias and cryptorchidism case-control study, the exposure assessment strategy starts with a thorough interview of parents of cases and controls on different sources and exposure pathways. First, a detailed occupational history is taken which will be linked to external information on magnitude of ED exposure in distinguished jobs. Second, the dietary pattern is established. A specific dietary questionnaire has been developed which estimates the average intake of products rich on iso-flavonoids and lignans, the most potent phyto-oestrogens. Food products have been selected in 3 steps: 1) the product contains pseudo-oestrogens, 2) the product is known to be used with relevant frequency, and 3) the concentrations of pseudo-oestrogens in the product have been measured in food surveys. Third, environmental sources of ED exposures are retrieved from existing monitoring systems for air and water quality in the area. Other important information on exposure and confounders relates to personal lifestyle, ED uptake through medication, living conditions, and health aspects.

This information on ED exposures from different compartments and via different routes will be applied in an integral exposure assessment strategy. This strategy will be validated by comparing the exposure assessment with the internal dose of substances with oestrogenic properties as measured in the blood of mothers and newborns (marker of exposure). Results of this study will become available next year.

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Trends in Male Reproductive Health

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In recent decades, questions have increasingly been raised about the relationship between exposure to environmental chemicals and trends in male reproductive health. Also, the major advances in treating male infertility by intracytoplasmic sperm injection (ICSI) since the early 1990s have drawn more attention to what was previously a somewhat neglected field of study. The outcomes of male reproductive health that have attracted particular interest include sperm counts and semen quality, testicular cancer, the sex ratio at birth, hypospadias, and undescended testes. It has been hypothesised that increased exposure to environmental endocrine disrupters during fetal or early postnatal life may affect the development of the male reproductive tract through oestrogenic or anti-androgenic mechanisms.^{1,2,3}

Evidence of possible changes in male reproductive health has been derived from studies of sperm counts and semen quality among selected groups of men, and from population-based data systems for cancer, sex ratio at birth, and birth defects.

Numerous studies have claimed to show declining sperm concentrations over recent decades and deterioration of other parameters of semen quality such as semen volume and sperm morphology.^{4,5} Other researchers have failed to detect any decline in sperm counts, often criticising the laboratory and statistical methods of studies purporting to show a decline, and the interpretation of these studies.⁶ Major international prospective studies have been initiated to address the many issues that influence these often conflicting findings. Because population-based surveys of the prevalence of infertility are infrequent, it is difficult to assess whether any decline in sperm counts may be affecting fertility trends.

In contrast to the debate on trends in sperm counts, there is strong evidence that testicular cancer has increased in many countries, including Australia, in recent decades.^{7,8} Because the peak incidence of testicular cancer occurs among younger men in their third decade, and because of the higher risk associated with cryptorchidism (undescended testes), it has been postulated that the rising rate of testicular cancer is due to a birth cohort effect and that some common exposure accounts for the increase.

Hypospadias is a relatively common congenital malformation of the penis. The reported incidence of hypospadias has increased in some national and regional birth defects monitoring programs.^{9,10} As there may be variable reporting of minor degrees of hypospadias, interpretation of apparently rising trends should be made cautiously.

Various studies in the northern hemisphere have shown a decline in the ratio of male to female births over the past three to five decades.¹¹ Among possible causal factors, it has been suggested that environmental chemicals and pollutants may be responsible for these trends. We analysed Australian data between the 1920s and early 1990s and showed a slight increase in the sex ratio, in contrast to the findings in Europe and North America.¹² Some studies of changes in the sex ratio among the offspring of men exposed to chemicals at work have lent support to the hypothesis that environmental chemicals alter the sex ratio, but these studies have often been based on small numbers of births.

In considering these indicators of male reproductive health and in assessing the plausibility of hypotheses linking them to environmental endocrine disrupters, the differing trends in various countries and among specific

population groups need to be considered and explained. As it is difficult to obtain precise information about the level of exposure of human populations to environmental chemicals, particular attention should be given to indicators of male reproductive health among men exposed at work to potential endocrine disrupters. This research should be analysed in conjunction with the findings from animal studies.

There is much scope for improving international collaboration by using existing databases to test specific hypotheses concerning male reproductive health and environmental exposures. High-quality epidemiological data on key indicators such as testicular cancer, hypospadias and the sex ratio at birth are available in many countries, enabling studies of national and regional variations in relation to measurable environmental exposures. Further systematic studies of sperm counts in unselected populations and the prevalence of male infertility are also needed.

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1,1-Dichloro-2,2-Bis(P-Chlorophenyl) Ethylene and Polychlorinated Biphenyls and Breast Cancer: Combined Analysis of Five US Studies

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BACKGROUND: Environmental exposure to organochlorines has been examined as a potential risk factor for breast cancer. In 1993, five large US studies of women located mainly in the northeastern United States were funded to evaluate the association of levels of 1,1-dichloro-2,2-bis (p-chlorophenyl) ethylene (DDE) and polychlorinated biphenyls (PCBs) in blood plasma or serum with breast cancer risk. We present a combined analysis of these results to increase precision and to maximize statistical power to detect effect modification by other breast cancer risk factors.

METHODS: We reanalyzed the data from these five studies, consisting of 1400 case patients with breast cancer and 1642 control subjects, by use of a standardized approach to control for confounding and assess effect modification. We calculated pooled odds ratios (ORs) and 95% confidence intervals (CIs) by use of random-effects model. All statistical tests were two-sided.

RESULTS: When we compared women in the fifth quintile of lipid-adjusted values with those in the first quintile, the multivariate pooled OR for breast cancer associated with PCBs was 0.94 (95% CI = 0.73 to 1.21), and that associated with DDE was 0.99 (95% CI = 0.77 to 1.27). Although in the original studies there were suggestions of elevated breast cancer risk associated with PCBs in certain groups of women stratified by parity and lactation, these observations were not evident in the pooled analysis. No statistically significant associations were observed in any other stratified analyses, except for an increased risk with higher levels of PCBs among women in the middle tertile of body mass index (25-29.9 kg/m²); however, the risk was statistically nonsignificantly decreased among heavier women.

CONCLUSIONS: Combined evidence does not support an association of breast cancer risk with plasma/serum concentrations of PCBs or DDE. Exposure to these compounds, as measured in adult women, is unlikely to explain the high rates of breast cancer experienced in the northeastern United States.