

## A Multi-center Study for Birth Defect Monitoring Systems in Korea

The aim of this study was to establish a multi-center birth defects monitoring system to evaluate the prevalence and the serial occurrence of birth defects in Korea. Ten medical centers participated in this program. A trained nurse collected relevant records from delivery units and pediatric clinics in participating hospitals on a monthly basis. We observed 1,537 cases of birth defects among 86,622 deliveries, which included live births and stillbirths. The prevalence of birth defects was 1.8%, and the sex distribution of the birth defect cases was 55.2% male and 41.6% female. The highest proportion of birth defects was in the cardiovascular system (17.5%), followed by birth defects involving in the genitourinary system (15.6%). Chromosomal anomalies were detected 30.0 per 10,000 births. Of these chromosomal anomalies, Down syndrome was most frequently observed. This study led to an establishment of a multi-center active monitoring system for birth defects. To better understand the serial occurrence of birth defects in Korea, it is necessary to increase the number of participating hospitals and to launch on a nation-wide multi-center study.

**Key Words :** Birth Defects; Abnormalities; Congenital abnormality; Multicenter Studies

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## INTRODUCTION

Birth defects are an important contributor to infant mortality among all racial/ethnic groups. Major congenital anomalies are defined as those that threaten life, require major surgery, or lead to a significant disability. Between 2% and 3% of all infants have a major congenital anomaly identified at birth and approximately 6% to 10% of such infants die within the first year of life (1). In more than 60% of such cases, the etiology of the congenital birth defect is unknown and primary prevention is impossible. In approximately 20% of congenital cases, the causes are monogeneous defects, 50% are caused by chromosome aberrations and 20% by virus infections, such as rubella, cytomegalovirus, and herpes virus (2, 3). Many environmental factors have been suspected to play an etiologic role in the formation of congenital anomalies. Chemical pollutants, dietary imbalances, ionizing radiation, pharmaceutical substances, and infections provide examples of known

or suspected agents (4). Unlike animal studies, molecular and biochemical studies in pregnant women are impossible. Therefore, epidemiological data about congenital malformations is of vital importance to scientific research on pathomorphogenesis, aimed at prevention and public health education (3).

Currently, no nationwide birth defect monitoring system exists in Korea. Only a small number of reports on birth defect monitoring are available from general hospitals (5-7). Thus, our aim is to establish a multi-center birth defects monitoring system for the evaluation of the prevalence and serial occurrence of birth defects in Korea.

## MATERIALS AND METHODS

### Study materials

The study materials were all recorded deliveries at 10 med-

ical centers in Korea, between May 1999 and October 2002. The ten medical center were: the Samsung Cheil Hospital, Samsung Medical Center, Asan Medical Center, Cheil Women's Clinic, Ilsan Cheil Hospital, Bombit Women's Hospital, Ewha Women's University Mokdong Hospital, Kangnam St. Mary's Hospital, Sanggye Baik Hospital, and Seoul National University Hospital.

### Active data collection

Records were obtained monthly, from delivery units and pediatric clinics by a visiting nurse. Trained staff from each center provided the medical records that included delivery files, stillborn files and newborn files. The entire medical record of each case was reviewed for followings: hospital stay, prenatal diagnostic test results, birth certificate work sheet, labor and delivery records, progress notes, pathology/autopsy findings, physical examination findings, and a discharge summary. The collected database was checked by trained medical doctor monthly.

### Definition and coding of diagnoses

All live births, stillbirths, and spontaneous abortions after the 16th week of gestation were included. All neonates born

**Table 1.** General characteristics of study populations

Study period	Total delivery	Total birth defect case (%)	Maternal age (years)	Percent of primipara
May-Dec. 1999	16,350	250 (1.5)	29.6±4.3	56.4%
Jan.-Dec. 2000	25,906	414 (1.6)	30±4.0	52.2%
Jan.-Nov. 2001	23,307	479 (2.1)	29.9±4.1	59.1%
Dec.-2001 -Sep. 2002	21,059	394 (1.9)	30.5±4.2	55.1%
Total	86,622	1,537 (1.8)	29.9±4.1	55.1%

**Table 2.** General characteristics of infants with birth defects (n=1,537) analysed by year

	1999 n=250	2000 n=414	2001 n=479	2002 n=394	Total n=1,537
Cesarean section	65 (26%)	104 (25.1%)	144 (30.1%)	121 (30.7%)	438 (28.5%)
Termination	80 (32%)	136 (32.9%)	159 (33.2%)	110 (27.9%)	484 (31.5%)
Fetal sex					
male	138 (55.2%)	209 (50.5%)	278 (58%)	219 (55.6%)	848 (55.2%)
female	103 (41.2%)	186 (44.9%)	187 (39%)	164 (41.6%)	639 (41.6%)
ambiguous	1 (0.4%)	1 (0.2%)	2 (0.4%)	1 (0.3%)	5 (0.3%)
unknown	13 (5.2%)	13 (3.1%)	12 (2.5%)	7 (1.8%)	45 (2.9%)
Twin pregnancy	7 (2.8%)	17 (4.1%)	21 (4.4%)	24 (6.1%)	69 (4.5%)

at one of the 10 centers were examined by a pediatrician within the first week of life. In addition to the clinical examination, information from the prenatal and postnatal ultrasound examinations of the heart, brain and other organs were recorded. Chromosome analysis was available for a number of birth defects that were coded according to the EUROCAT (European Registration of Congenital Anomalies and Twins, an European Union Registry) (4) and the International Clearinghouse for Birth Defects Monitoring System (ICBDMS) (8).

The nineteen groups of malformations as described by the ICBDMS (8) were 1) anencephaly, 2) spina bifida, 3) encephalocele, 4) hydrocephaly, 5) microtia, 6) cleft palate, 7) total cleft lip, 8) esophageal atresia or stenosis, 9) anorectal atresia or stenosis, 10) hypospadias, 11) renal agenesis/dysgenesis, 12) limb reduction defects, 13) omphalocele, 14) gastroschisis, 15) abdominal wall defects, 16) diaphragmatic hernia, 17) transposition of the great vessels, 18) hypoplastic left heart syndrome, and 19) Down syndrome.

## RESULTS

During the 4-yr period (May 1999-October 2002), we observed 1,537 cases of birth defects among 86,622 births, including live births and stillbirths, the prevalence rate being

**Table 3.** Incidence comparison of 19 congenital anomalies by ICBDMS (1998) with other reports

Congenital anomalies	Korea	Japan	China	USA: Atlanta
	Observed /10,000	Observed /10,000	Observed /10,000	Observed /10,000
Anencephaly	3.3	1.9	5.4	1.8
Spina bifida	0.2	3.2	8.0	3.8
Encephalocele	1.6	0.9	2.5	1.1
Hydrocephalus	3.6	7.5	6.5	7.1
Microtia	2.7	1.6	-	0.9
Cleft palate, only	1.4	4.8	2.4	6.0
Cleft lip, and/or cleft palate	10.3	15.9	13.6	9.9
Esophageal atresia or stenosis	2.4	3.3	0.5	0.9
Anorectal atresia or stenosis	3.5	4.0	3.0	4.0
Hypospadias	1.2	3.5	3.1	7.7
Renal agenesis/dysgenesis	7.6	4.3	0.9	5.3
Limb reduction defect	1.3	3.8	5.3	4.9
Omphalocele	3.0	4.6	1.6	2.0
Gastroschisis	1.6	2.3	2.7	2.0
Abdominal wall defects	1.4	7.1	4.3	4.0
Diaphragmatic hernia	4.8	4.9	0.5	1.6
Transposition of great vessels	2.1	2.1	-	4.2
Hypoplastic left heart syndrome	1.3	1.9	-	2.9
Down syndrome	9.2	10.4	1.7	11.3

Table 4. Frequency estimates of chromosomal abnormalities

	1999		2000		2001		2002		Total		
	No.	Per 100 Anomalies	No.	Per 100 Anomalies	Per 10,000 Births						
Autosomal trisomy	21	8.4	45	10.9	38	7.9	98	24.9	202	13.1	23.3
Trisomy 21	15	6	21	5.1	21	4.4	80	20.3	137	5.0	15.8
Trisomy 18	6	2.4	21	5.1	14	3.4	16	4.1	57	3.6	6.5
Trisomy 13	0	0	3	0.7	3	0.6	2	0.5	8	0.5	0.9
Sex chromosomal	2	0.8	6	1.4	8	1.7	4	1.0	20	1.4	2.3
Turner syndrome	2	0.8	4	1.0	3	0.6	4	1.0	13	0.8	1.5
Klinefelter syndrome	0	0	2	0.5	2	0.4	0	0	4	0.3	0.5
Others	0	0	0	0	3	0.6	0	0	3	0.3	0.3
Structural abnormality	6	2.4	10	2.4	9	1.9	3	0.8	28	2.2	3.2
Others	3	1.2	1	0.2	5	1.0	1	0.3	10	0.8	1.2
Total	32	12.8	62	15.0	60	12.5	106	26.9	260	13.5	30.0

Table 5. Birth defects according to the involved organs

Organs	No.	Per 100 anomalies
Genitourinary tract	240	15.6
Cardiovascular	269	17.5
Central nervous system	186	12.1
Face	152	9.9
Extremities	108	7.0
Gastrointestinal tract	124	8.1
Thoracic	79	5.1
Hydrops fetalis	56	3.6
Tumors	61	4.0
Abdominal wall defects	42	2.7
Skeletal	29	1.9
Others	191	12.4
Total	1,537	100.0

1.8%. The mean maternal age was 29.9 ( $\pm 4.1$ , 95% CI) yr, with a range 19–45 yr. Nineteen percent (291 cases) of the birth defects were associated with an elderly mother ( $\geq 35$  yr). Primipara birth and multipara birth accounted for 55.1% and 44.9%, respectively. Table 1 shows the changes in the prevalence of birth defects over time.

The general characteristics of the birth defects are summarized in Table 2. The mean gestational age at delivery was  $32.5 \pm 8.6$  weeks, ranging from 11 weeks to 43 weeks. The mean birth weight was  $2,198 \pm 1,319.5$  g, with a range from 5 g to 5,060 g. Non-living births (termination or intra-uterine fetal death) accounted for 31.5% of deliveries, and 438 babies (28.5%) were born via Cesarean section. The sex distribution of the birth defect cases was 55.2% male and 41.6% female. Five cases had (0.3%) ambiguous genitalia, and in 45 cases (2.9%), the gender of the fetus could not be determined. Twin pregnancies accounted for 4.5% of cases.

Table 3 shows the comparison of incidences of 19 congenital anomalies in Korea as defined by ICBDMs (5) with those in Japan and China and with Atlanta, U.S.A. as determined by the Metropolitan Atlanta Congenital Defects Program

(MACDP) (9).

Among 1,537 birth defect cases, 260 cases (16.9%) had chromosomal abnormalities (Table 4). Among these, Down syndrome was most common (137 cases), followed by Edwards syndrome (57 cases).

Table 5 shows the birth defects according to the involved organs. The highest proportion of birth defects (17.5%) involved the cardiovascular system, followed by the genitourinary system (15.6%). Multiple anomalies accounted for 16% of all birth defect cases.

Thirty-four cases had polydactyly of the hand (4.0 per 10,000 fetuses) and 20 cases had polydactyly of the foot (2.4 per 10,000 fetuses). Syndactyly of the hand and foot occurred in 9 cases (1.2 per 10,000 fetuses) and 7 cases (0.8 per 10,000 fetuses), respectively.

## DISCUSSION

The concept of congenital malformation is not strictly defined, and includes functional and metabolic disorders that, although present, may not necessarily be recognizable at birth (10, 11). Different classifications of congenital anomalies are used in different countries. The two most commonly used classification systems are: (1) the International Classification of Diseases system (12, 13), and (2) the International Clearing-house for Birth Defects Monitoring System (ICBDMS) (14). In our study, the classification of birth defects was performed according to the European Registration of Congenital Anomalies and Twins (EUROCAT) and the ICBDMs (1994) system.

The EUROCAT program was initiated in 1979. This surveillance system details 900,000 births per annum in 17 countries. The International Clearing-house for Birth Defects Monitoring System (ICBDMS) is a WHO-related non-governmental organization, and more than 25 countries including the United States, England, France, Australia, Japan, and China participate in the program. These monitoring systems are

based on registration. The Japanese Association of Obstetricians and Gynecologists (JAOG) program started in 1972. This system is a nationwide hospital-based monitoring system that covers about 10% of all births in Japan. In our study, the 10 medical centers (six tertiary centers, one secondary center, and three large local obstetric clinics) covered only about 3% of births in Korea.

During the 4-yr study period, the overall incidence of birth defects from the 10 medical centers in Korea was 1.8%. This is lower than the incidence of 2.4% provided by the EURO-CAT registration system, which tends to produce lower figures than other passive registries (15). Moreover, it has been reported that active monitoring systems detect 50% more congenital malformations than passive monitoring systems (16). Therefore, the prevalence of birth defects in this study would be lower than the actual incidence.

The incidence of total chromosomal abnormalities was 0.3% and the incidence of the trisomy 21 was 9.2 per 10,000 births, which is slightly lower than the incidence in Glasgow (12.4 per 10,000 births) (17), in Atlanta, U.S.A. (11.3 per 10,000 births), and in Japan (10.4 per 10,000 births) (15).

In the present study, the most frequent abnormality was a cleft lip with or without a cleft palate with a prevalence of 10.3 per 10,000 births, which is higher than in the Atlanta (U.S.A.) study (9.9 per 10,000 births), but lower than in Japan (15.9 per 10,000 births) or China (13.6 per 10,000 births) (15). The incidence of cleft palate without cleft lip in Korea was found to be 1.4 per 10,000 births, which is lower than in other countries; Japan: 4.8 per 10,000 births, China: 2.4 per 10,000 births, and U.S.A.: 6.0 per 10,000 births. And the incidence of renal agenesis/dysgenesis in Korea was 7.6 per 10,000 births, which is higher than in Japan (4.3 per 10,000 births) and in the U.S.A. (5.3 per 10,000 births). The incidence of anencephaly and microtia in Korea (3.3 per 10,000 births and 2.7 per 10,000 births) were also higher than in Japan (1.9 per 10,000 births and 1.6 per 10,000 births) and in the U.S.A. (1.8 per 10,000 births and 0.9 per 10,000 births). The incidence of hypospadias (1.2 per 10,000 births) and spina bifida (0.2 per 10,000) in Korea were lower than in Japan (3.5/3.2 per 10,000 births) and in the U.S.A. (7.7/3.8 per 10,000 births). The incidences of hydrocephalus (3.6 per 10,000 births) and limb reduction defect (1.3 per 10,000 births) in Korea were lower than in Japan (7.5/3.8 per 10,000 births) and in the U.S.A. (7.1/4.9 per 10,000 births). Also, the incidence of gastroschisis (1.6 per 10,000 births) and abdominal wall defect (1.4 per 10,000 births) were lower than in Japan (2.3/7.1 per 10,000 births) and in the U.S.A. (2.0/4.0 per 10,000 births). The incidence of omphalocele (3.0 per 10,000 births) was lower than in Japan (4.6 per 10,000 births) but higher than in the U.S.A. (2.0 per 10,000 births).

The frequency of birth defects varies markedly between countries and depends on the observation time after birth, the types of malformations included, and on differences in the reporting and statistical procedures used (18). On the other

hand, this difference in the frequency of birth defects within countries would be affected by ethnicity, eating habits, and environmental factors, or combined. More studies are needed to elucidate the underlying causes for the different incidences.

The highest proportion of birth defects involved the cardiovascular system (17.5%) followed by the genitourinary system (15.6%). Recently, it was proposed that poor semen quality, cryptorchidism, hypospadias and testicular cancer are symptoms of one underlying entity, testicular dysgenesis syndrome (TDS) (19). TDS may be caused by genetic or environmental factors, or both. Even though the clinical symptoms appear postnatally, TDS can cause an irreversible testicular dysgenesis during early fetal development. In addition, there are many recent reports that environmental factors, especially endocrine disrupting chemicals (EDCs), can be the cause of congenital malformation (20). These EDCs may cause a variety of defects in the endocrine and reproductive systems (21, 22). However, little is known about the underlying biochemical and molecular mechanisms, or the determinants of teratologic susceptibility, particularly in humans (20).

Possible explanations for the lower incidence of birth defects in the present study than in the EUROCAT program are: (1) we included neonates only within the first week of life, so that the defects recognizable thereafter might have been lost; (2) in stillbirth cases, autopsy is carried out less frequently than in the EUROCAT program. The lower frequency of autopsy in our study might have resulted in a lower detection rate of defects in the internal organs.

Our aim is to establish a multi-center birth defects monitoring system to evaluate the prevalence and serial occurrence of birth defects in Korea. Birth defect registries that acquire data through active rather than passive reporting can provide additional important data on birth defects (21). Such a multi-center birth defects monitoring system can provide high-quality information on birth defects in Korea. To check the serial occurrence of birth defects, it is necessary to increase the number of participating hospitals and to launch a nation-wide multi-center study.

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