ORIGINAL ARTICLE

Epidemiology of Congenital Anomalies in a Population-based Birth Registry in Taiwan, 2002

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Background/Purpose: Congenital anomalies are important medical and public health conditions. However, the occurrence rates of congenital anomalies and their risk factors are unknown in Taiwan. We used the medical-practitioner-reported birth registry in 2002 to determine the occurrence of individual congenital anomalies and their associated risk factors, such as maternal age, fetal sex, and plurality.

Methods: The birth registry was started in 2001 in Taiwan. We obtained the data for 2002 from the Department of Health, and translated the coding of congenital anomalies to International Classification of Diseases 9th revision–clinical modification (ICD-9-CM). The occurrence rates of individual congenital anomalies were calculated. The effects of maternal age, fetal sex, and plurality were calculated as odds ratios (ORs) by logistic regression analysis.

Results: A total of 1775 infants were diagnosed as having congenital anomalies among 242,140 live and deceased newborn infants delivered in Taiwan in 2002.The occurrence rates of congenital anomalies of the nervous system, eyes and face, cardiovascular, digestive, urogenital, musculoskeletal and respiratory systems, and chromosomes were 0.67‰, 1.86‰, 1.47‰, 0.62‰, 0.71‰, 2.05‰, 0.07‰ and 0.79‰, respectively. Sex chromosomal anomalies, Down syndrome, and trisomy 18 were associated with maternal age of ≥ 35 years (OR, 15.9, 4.6, and 2.3, respectively). Such elevation was even more prominent for maternal age ≥ 40 years (OR, 35.5, 22.2, and 11.62, respectively). A milder and borderline significant maternal age (≥ 40 years) effect was seen with cleft lip, with or without cleft palate (OR, 2.1). Female births had more cleft palates (OR, 1.6). There was no relationship between plurality and anomalies.

Conclusion: The occurrence rates for individual congenital anomalies in Taiwan were reported. Older maternal age was a risk factor for the occurrence of chromosomal and orofacial anomalies. More active prenatal screening and further investigation of causal factors of congenital anomalies are of major importance. [*J Formos Med Assoc* 2009;108(6):460–468]

Key Words: birth weight, congenital abnormalities, fetal gender, geographic area of residence, gestational age, maternal age, plurality

Congenital anomalies are defined as abnormalities of structure, function or body metabolism that are present at birth. The severity of birth defects ranges from minor and correctable, to mental and physical disability, and fatal anomalies.[1–3] In Taiwan, congenital anomalies are important causes of newborn mortality, as well as severe psychological suffering and financial burden.[4] It is important to identify risk factors for congenital anomalies in order to help prevent such conditions. However,

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studies on the occurrence rates and risk factors are lacking in Taiwan.

Known risk factors for congenital anomalies include fetal factors, such as plurality and sex,[5] and parental factors, such as ethnicity,[6,7] socioeconomic status,[8] lifestyle (including tobacco[9] and alcohol consumption,[10] drug use,[11] and medication during pregnancy[12]), age,[6,7,13–16] body weight,[17] congenital diseases,[18] and environmental exposure (including air[19] and drinking water pollutants,[20,21] organic solvents,[12] electromagnetic radiation,[22] and biological agents[23]). Other factors that affect pregnancy and delivery are also related to congenital anomalies.[24,25]

Information from physician-reported births is valuable for the study of fetal conditions including congenital anomalies. However, one limitation with such an approach is the amount of data available. Since obtaining information about some factors involves significant effort, only demographic data and information related to pregnancy and delivery might be available. We used the physician-reported birth data for Taiwan in 2002 to investigate risk factors that contribute to congenital anomalies.

Patients and Methods

This investigation included all confirmed live and deceased fetuses delivered in 2002, reported by physicians to the Bureau of Health Promotion, Department of Health, Taiwan. From 18 counties and seven cities, birth information was reported by medical practitioners or pediatricians in all hospitals and clinics. In addition to maternal age, birth date, fetal sex, plurality, birth weight, gestational age, location of parental residence, the practitioners were required to report information on congenital anomalies. These variables were collected for each child. Maternal age, birth weight, and gestational age were presented as continuous variables, plurality was categorized into singleton and multiple births, and residence area was categorized at county/city level. Subjects who lacked demographic information ($n = 9$) and with a gestational age < 20 weeks ($n = 509$) were excluded from the analysis. Those with a gestational age of < 20 weeks had a maternal age of 28 ± 6 years, birth weight of 572 ± 866 g, and fetal M/F sex ratio of 1.72.

The diagnoses of congenital anomalies were translated into the disease coding of the International Classification of Diseases 9th revision–clinical modification (ICD-9-CM).[26] Those whose diagnoses did not fit into ICD-9-CM ($n = 1319$) were excluded from the analysis. The occurrence rate of individual congenital anomalies was calculated. ArcGIS version 9.1 (ESRI, Redlands, CA, USA) was used to present the geographic distribution of the occurrence of specific congenital anomalies by resident county. To determine the relationship between individual congenital anomaly and demographic information, congenital anomalies with more obvious defective appearance were selected as outcome variables. These included cleft lip, with or without cleft palate, isolated cleft palate, autosomal anomalies, sex chromosomal anomalies, Down syndrome, and trisomy 18.

For statistical analysis, JMP statistical package version 5 (SAS, Cary, NC, USA) was used. The χ^2 or t test was used to determine the relationship between each demographic factor and individual congenital anomaly in 2002. In addition, the odds ratio (OR) of having an individual congenital anomaly and the 95% confidence interval (CI) for maternal age groups, fetal sex, and plurality were calculated by logistic regression analysis. Maternal age was classified as < 20, 20–29, 30–34, 35–39, and ≥ 40 years, and the 20–29 years group was used as a reference. We also drew a trend line for the occurrence rate of individual congenital anomalies according to maternal age.

Results

In the year 2002, a total of 1775 infants were diagnosed as having congenital anomalies among 242,140 live and deceased newborn infants delivered in Taiwan. The numbers and occurrence rates of individual congenital anomalies are shown in Table 1. Among all births, 161 (0.67‰) had

Table 1. Congenital anomalies in Taiwan, 2002, as compared with the rates reported in Georgia, USA, 1968–1995

Classification of congenital anomalies	ICD-9-CM	2002, Taiwan		1968–1995, Georgia, USA*	
		n	Rate† (‰)	*n*	Rate† (‰)
Total		1775	7.330	28,965	33.938
1 Congenital nervous system anomalies		148	0.665		
1.1 Anencephalus	740.0	26	0.107	357	0.418
1.2 Encephalocele	742.0	9	0.037		
1.3 Meningocele	741.9	12	0.050		
1.4 Spina bifida	741	14	0.058		
1.5 Congenital hydrocephalus	742.3	86	0.355		
1.6 Microcephalus	742.1	14	0.058	443	0.519
2 Congenital eye and face anomalies		434	1.863		
2.1 Congenital cataract anomalies	743.3	2	0.008		
2.2 Microphthalmos or anophthalmos	743.0–1	10	0.045		
2.3 Cleft lip with or without cleft palate	749.1–2	310	1.280		
2.4 Isolated cleft palate	749.0	113	0.467		
3 Congenital anomalies of cardiovascular system		283	1.474	7382	8.650
3.1 Ventricular septal defect	745.4	101	0.417		
3.2 Atrial septal defect	745.5	94	0.388	189	0.221
3.3 Patent ductus arteriosus	747.0	105	0.434		
3.4 Tetralogy of Fallot	745.2	20	0.083		
3.5 Endocardial cushion defects	745.6	6	0.025	31	0.036
3.6 Transposition of great vessels	745.1	10	0.041	414	0.485
3.8 Congenital anomalies of pulmonary artery	747.3	21	0.087		
4 Congenital anomalies of digestive system		149	0.624		
4.1 Congenital tracheoesophageal fistula, esophageal atresia and stenosis	750.3	16	0.066	124	0.145
4.2 Congenital megacolon	751.3	7	0.029	157	0.184
4.3 Anal atresia	751.2	76	0.314	209	0.245
4.4 Congenital atresia and stenosis of small intestine	751.1	9	0.037		
4.5 Congenital hypertrophic pyloric stenosis	750.5	4	0.017	1176	1.378
4.7 Congenital anomalies of abdominal wall	756.7	20	0.083		
4.8 Congenital anomalies of diaphragm	756.6	17	0.070	199	0.233
4.9 Biliary atresia	751.61	1	0.004		
4.10 Biliary dilatation or choledochal cyst	751.69	1	0.004		
5 Congenital anomalies of urogenital system		161	0.714		
5.1 Renal agenesis and dysgenesis	753.0	17	0.070	158	0.185
5.2 Obstructive defects of renal pelvis and ureter	753.2	38	0.157	874	1.024
5.3 Hypospadias	752.61	81	0.335		
5.4 Indeterminate sex	752.7	24	0.099	89	0.104
5.5 Congenital cystic kidney disease	753.1	13	0.054		
6 Congenital anomalies of musculoskeletal system		543	2.053		
6.1 Club foot	754.5–7	107	0.442		
6.2 Congenital dislocation of hip	754.3	14	0.058		

Continued

Table 1. *Continued*

Classification of congenital anomalies	ICD-9-CM	2002, Taiwan		1968–1995, Georgia, USA*	
		n	Rate† (‰)	*n*	Rate† (‰)
6.3 Polydactyly	755.0	293	0.797	1081	1.267
6.4 Syndactyly	755.1	105	0.434	653	0.765
6.5 Reduction deformities of limbs	755.2	78	0.322		
7 Congenital anomalies of respiratory system		17	0.071		
2.5 Choanal atresia	748.0	5	0.021		
7.2 Congenital agenesis, hypoplasia, and dysplasia of lung	748.5	12	0.050		
8 Chromosomal anomalies		190	0.793		
8.1 Down syndrome	758.0	76	0.314	867	1.016
8.2 Trisomy 13	758.1	8	0.033		
8.3 Trisomy 18	758.2	26	0.107		
8.5 XO syndrome	758.6	8	0.037		
8.6 XXY syndrome	758.7	10	0.041		
8.7 XXX syndrome	758.81	11	0.045		
8.4 Other chromosomal anomalies	758.89	52	0.215		

**Data from Reference 5; †occurrence rate of congenital anomalies: a fetus might have more than one anomaly, so the numbers of individual anomalies do not add up to the total number.*

nervous system anomalies, 452 (1.86‰) eye and face anomalies, 357 (1.47‰) cardiovascular system anomalies, 151 (0.62‰) digestive system anomalies, 173 (0.71‰) urogenital system anomalies, 497 (2.05‰) musculoskeletal system anomalies, 17 (0.07‰) respiratory system anomalies, and 192 (0.79‰) chromosomal anomalies.

The distribution of some demographic factors for congenital anomalies is presented in Table 2. The mean maternal age of all 242,140 births was 28 years. In congenital anomaly groups, maternal age of mothers of fetuses with chromosomal anomalies was about 4 years older than the average, whereas the maternal age for other anomalies was similar to the average.

The mean birth weight of the total population was 3088 g. Among all births, 18,703 (7.7%) were classified as having low birth weight (< 2500 g). In congenital anomaly groups, mean birth weight was 107–2272 g less than the mean birth weight of the total population (Table 2). Compared with the total population, a higher percentage of fetuses with anomalies had low birth weight, especially those with chromosomal anomalies.

The mean gestational age of the total population was 38 weeks, and 50,319 (20.8%) deliveries occurred before the 37th week of gestation. Compared with the total population, most fetuses with congenital anomalies had a lower gestational age and higher percentage of prematurity, especially those with chromosomal anomalies.

The fetal male:female sex ratio of the total population was 1.10. Most of the congenital anomaly groups had gender ratios similar to this. Plurality was similar between anomaly groups and the normal group.

Table 3 presents the OR and 95% CI for individual congenital anomalies according to maternal age, fetal sex, and plurality. The average maternal age of most mothers with fetuses with congenital anomalies was ≥ 30 years, especially in those fetuses with chromosomal anomalies.

Female newborn infants had a greater incidence of cleft palate (OR, 1.6). The risks for other congenital anomalies did not vary significantly

Table 2. Demographic characteristics of children, Taiwan, 2002

Variables		Total births (n = 242,140)	Cleft lip with or without cleft palate (n = 310)	Isolated cleft palate (n = 113)	Autosomal anomalies (n = 110)	Sex chromosomal anomalies (n = 28)	Down syndrome (n = 76)	Trisomy 18 (n = 26)
Maternal age (mean ± SD)		28 ± 5	28 ± 5	28 ± 5	32 ± 6*	35 ± 5*	32 ± 7*	30 ± 6
Fetal sex ratio (M/F)		1.10	1.14	0.63	1.18	0.75	1.42	0.85
Plurality								
Singleton	n (%)	235,833 (97.4)	302 (97.4)	112 (99.1)	110 (100.0)	27 (96.4)	76 (100.0)	26 (100.0)
Multiple birth	n (%)	6307 (2.6)	8 (2.6)	1 (0.9)	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)
Birth weight (mean ± SD)		3088 ± 499	2486 ± 1064*	2981 ± 521*	1172 ± 1037*	1529 ± 1353*	1241 ± 1117*	816 ± 661*
< 2500 g	n (%)	18,703 (7.7)	99 (31.9)*	16 (14.2)*	91 (82.7)*	18 (64.3)*	59 (77.6)*	26 (100.0)*
≥ 2500 g	n (%)	223,437 (92.3)	211 (68.1)*	97 (85.8)*	19 (17.3)*	10 (35.7)*	17 (22.4)*	0 (0.0)*
Gestational age (mean ± SD)		38 ± 2	35 ± 6*	38 ± 2	27 ± 7*	28 ± 8*	27 ± 7*	27 ± 7*
≤ 37 wk	n (%)	50,319 (20.8)	125 (40.3)*	26 (23.0)	90 (81.8)*	19 (67.9)*	64 (84.2)*	21 (80.8)*
> 37 wk	n (%)	191,821 (79.2)	185 (59.7)*	87 (77.0)	20 (18.2)*	9 (32.1)*	12 (15.8)*	5 (19.2)*

$p < 0.05$, χ^2 test or Student's t test was used to determine the relationship between each demographic factor and individual congenital anomaly (compared with total births group).

Table 3. Odds ratio and 95% confidence intervals for individual congenital anomalies according to maternal age, fetal sex, and plurality

	Cleft lip with or without cleft palate	Isolated cleft palate	Autosomal anomalies	Sex chromosomal anomalies	Down syndrome	Trisomy 18
Maternal age* (yr)						
< 20	1.33 (0.7–2.2)	1.38 (0.5–3.1)	1.36 (0.3–3.8)	–	1.42 (0.2–4.7)	1.61 (0.1–8.3)
20–29	reference	reference	reference	reference	reference	reference
30–34	0.75 (0.6–1.0)	1.16 (0.8–1.8)	1.50 (0.9–2.4)	0.67 (0.1–2.9)	1.45 (0.8–2.7)	1.28 (0.5–3.3)
35–39	1.02 (0.7–1.5)	1.59 (0.9–2.7)	3.76 (2.3–6.3)	15.90 (6.4–44.8)	4.59 (2.5–8.4)	2.32 (0.6–6.8)
≥ 40	2.05 (1.0–3.8)	1.33 (0.2–4.2)	17.48 (9.5–30.7)	35.50 (10.2–118.1)	22.20 (11.0–42.6)	11.62 (2.6–37.1)
Fetal sex*						
Male	1.04 (0.8–1.3)	0.62 (0.4–0.9)	1.02 (0.7–1.5)	–	1.25 (0.8–2.0)	0.67 (0.3–1.5)
Female	reference	reference	reference	reference	reference	reference
Plurality*						
Singleton	reference	reference	reference	reference	reference	reference
Multiple birth	0.99 (0.5–1.9)	0.32 (0.0–1.3)	–	0.39 (01–6.5)	–	–

**Maternal age, fetal sex, and plurality were used as individual risk factors for each congenital anomaly in the unadjusted logistic regression analysis.*

according to sex. There was no relationship between plurality and anomalies.

The occurrence rate of individual congenital anomalies according to residence is presented in Figure 1. The occurrence rate was highest in Yilan County (2.58‰) for cleft lip, with or without cleft palate, Hsinchu County (1.27‰) for isolated cleft palate, Tainan city (0.89‰) for autosomal anomalies and Down syndrome, Taipei city (0.41‰) for sex chromosomal anomalies, Tainan city (0.89‰), and Hsinchu city (0.47‰) for trisomy 18.

The occurrence rate of individual congenital anomalies according to maternal age is presented in Figures 2 and 3. Maternal age of ≥ 35 years was associated with increased risk of chromosomal anomalies (OR, 5.4; 95% CI, 3.8–7.7). Such elevation was even more prominent for maternal age of ≥ 40 years (OR, 15.1; 95% CI, 9.2–23.9). Among chromosomal anomalies, sex chromosomal anomalies appeared to have more prominent maternal age effects than trisomies do. A milder and borderline significant maternal age effect was seen with cleft lip, with or without cleft palate, among those newborn infants whose mother had a maternal age ≥ 40 years.

Discussion

This is the first report in Taiwan to examine the risk factors for congenital anomalies, based on

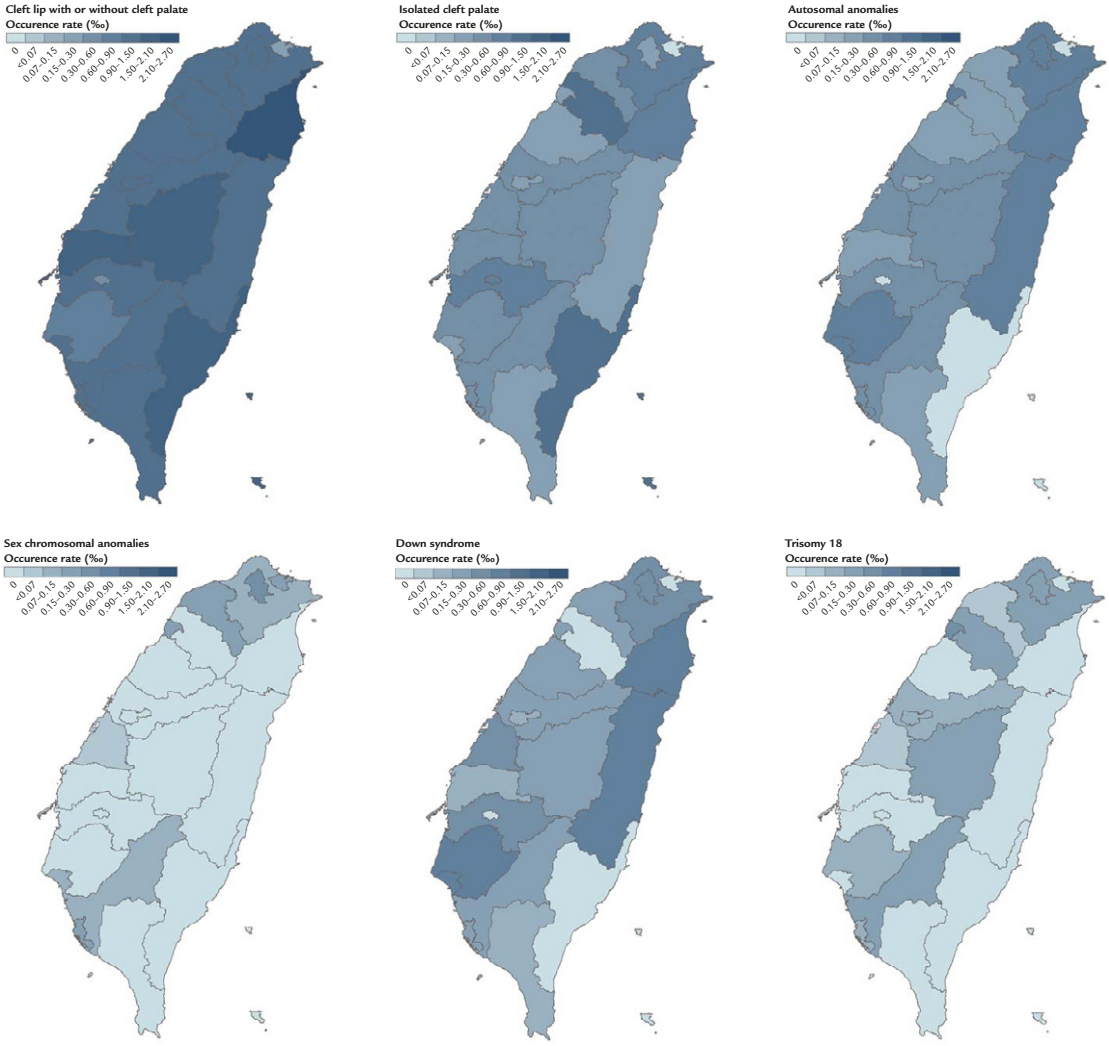

Figure 1. Geographic distribution of the occurrence of specific congenital anomalies in Taiwan by county, 2002.

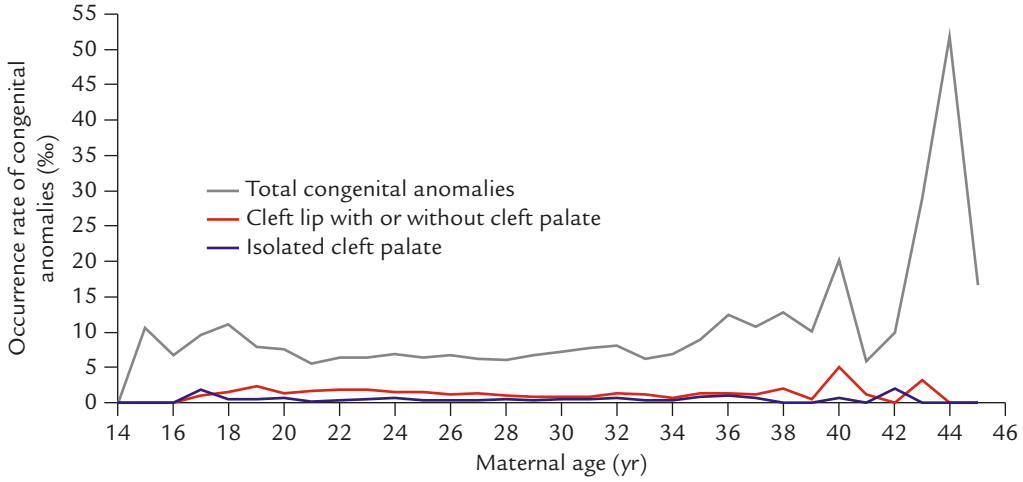

Figure 2. Occurrence rate of eye and facial congenital anomalies (by maternal age).

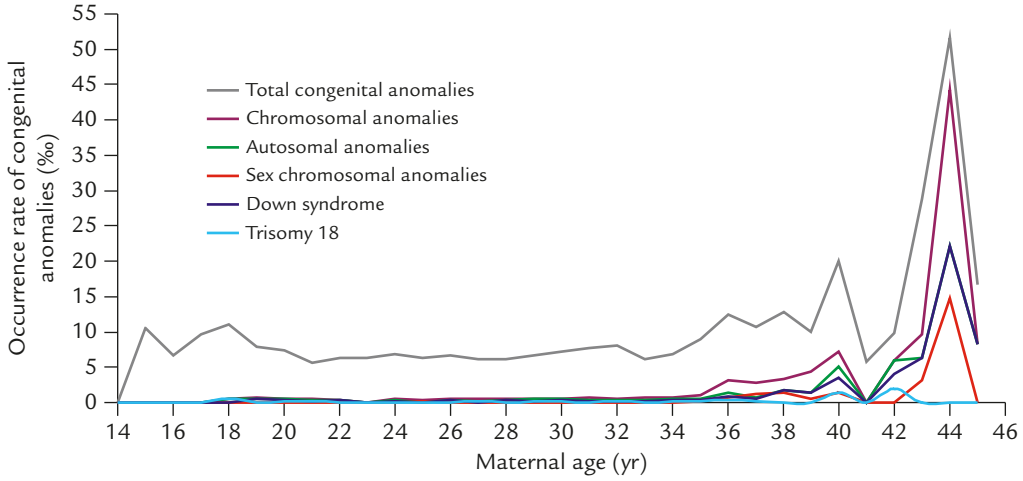

Figure 3. Occurrence rate of chromosomal congenital anomalies (by maternal age).

the 2002 birth registry. We found that maternal age affected development of chromosomal and orofacial anomalies.

The medical-practitioner-reported birth registry was officially started by the Department of Health of Taiwan in 1995 and later transferred to the Bureau of Health, Department of Health, Taiwan in 2001. The Bureau of Health Promotion requires reporting of births with a gestational age of ≥ 20 weeks, including live and deceased births. Therefore, we presumed that fetuses with gestational age ≥ 20 weeks were all reported regardless of their survival status. It is conceivable that some of the births with gestational ages < 20 weeks were reported to the Bureau. However, we are unaware of the proportion reported to the Bureau, therefore, we decided to exclude those with gestational age < 20 weeks from the analysis.

In comparison with the reliable household registry, which by law, requires registration of any live birth within 10 days of delivery,[27] the medical-practitioner-reported birth registry showed 7003 (2.8%) fewer live births. This was likely because the birth registry is not compulsory. However, the distribution of several demographic factors, such as maternal age and sex ratio, were consistent between these two different databases.

The occurrence rates of most congenital anomalies were lower than, but in the same ranges as the rates in the USA.[5] However, the rates for microcephalus (0.045‰), transposition of great vessels (0.041‰), hypertrophic pyloric stenosis

(0.017‰), obstructive defects of renal pelvis and ureter (0.157‰), and Down syndrome (0.314‰) were much lower than the occurrence rate in the USA, where the corresponding rates were 0.519, 0.485, 1.378, 1.024 and 1.02‰, respectively. Some of the anomalies are not obvious within a few days of birth, such as congenital cardiovascular diseases, hypertrophic pyloric stenosis, and renal pelvic or ureter obstruction. The lower rates of these anomalies might be caused by lower detection rates caused by the requirement of early reporting time (within a few days after birth) in Taiwan, compared with the US rates of anomalies, which were obtained at 1 year of age. Microcephalus was detectable readily by prenatal ultrasonic screening,[28] and Down syndrome was detectable by amniocentesis followed by chromosomal examination.[29] With rather frequent prenatal examination by ultrasound and amniocentesis in Taiwan, pregnancies with such anomalies might have been terminated. Therefore, the actual occurrence rates of these anomalies were likely higher than those presented here.

We found that chromosomal anomalies were associated with maternal age of ≥35 years. We also found that maternal age ≥40 years had a milder and borderline significant effect on orofacial anomalies. The relationship between chromosomal anomalies and maternal age has long been established,[30] but the effect of maternal age on orofacial anomalies is less conclusive. The most prevalent chromosomal anomalies are trisomies 13, 18 and 21, and Turner syndrome, which results from unequal meiotic division.[31] Older maternal age may induce this unequal meiosis, and the increase in maternal age may make the ova more likely to be exposed to teratogenic agents, and for a longer period of time.[16] On the other hand, our findings of the association between older maternal age and orofacial anomalies suggested that older maternal age had an adverse effect on the development of mesoderm and ectoderm.[31]

The finding of increased chromosomal anomalies in fetuses born to mothers aged ≥35 years, compared with those aged 20–29 years, indicated that screening for chromosomal anomalies by amniocentesis was not complete among mothers in age groups with increased risk. In Taiwan, amniocentesis has been encouraged for pregnant women aged ≥35 years. When chromosomal anomalies have been found, most pregnancies have been terminated.[32] In 2002, monetary incentives of US$67 towards the total cost were given to promote screening. However, the remaining charge of US$200 had to be paid by the mothers themselves. Here, it was apparent that many pregnant women aged ≥35 years did not undergo amniocentesis, even when they were known to be at higher risk. This resulted in many fetuses born with chromosomal anomalies to mothers in this age group in 2002. A more active program of screening is warranted to minimize the number of newborn infants with chromosomal anomalies.

One limitation of this study is the lack of information about some important risk factors, such as lifestyle, personal and family medical history, pregnancy history, ethnicity, socioeconomic status, tobacco and alcohol consumption, and prenatal care. This was because this investigation was secondary data analysis, and detailed personal information was lacking.

From the 2002 birth registry, congenital anomalies occurred in 0.7% of all births in Taiwan. Older maternal age was associated with the occurrence of chromosomal and orofacial anomalies. A more active screening program for chromosomal anomalies is important for pregnant women aged ≥35 years. Further investigation on more detailed risk factors is warranted to elucidate causal factors, and to prevent the occurrence of congenital anomalies.

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