Original article

Comorbidities in Down syndrome livebirths and health care intervention: an initial experience from the birth defects registry in Southern Thailand

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Background: **Down syndrome (DS) is the most common chromosomal disorder causing mental retardation with a worldwide average prevalence of 1-2 cases per 1000 births. This study aimed to determine the comorbidities associated with DS and the coverage of health care services and developmental interventions for DS livebirths in Southern Thailand.**

Methods: **A total of 149 livebirth DS infants, recruited through the prospective birth defects registry system during 2009-2013 in 3 provinces in Southern Thailand, were regularly followed-up every 3-6 months. The data collection form included the infants' demographic data, associated congenital anomalies, and developmental interventions.**

Results: **The DS infants were born at an average gestational age of 38.5±2.3 weeks with average birth weight of 2760±478 g, length 48.5±2.2 cm, and head circumference 32.7±1.2 cm. Congenital heart diseases, gastrointestinal defects and congenital hypothyroidism were found in 43.0%, 6.7%, and 12.1% of the cases, respectively. The percentage of DS infants who received developmental interventions in this current study were significantly greater than in a previous study covering the years 1992-2002: early stimulation program 90.0% *vs.* 65.6% (*P*<0.01), and speech training program 74.8% *vs.* 38.9% (*P*<0.01), respectively, and the infants in our study began intervention programs significantly earlier, 0.58±0.39 years *vs.* 1.69±0.66 years, respectively.**

Conclusions: **Congenital heart disease was the most common comorbidity associated with DS. The coverage of health care services and developmental interventions for DS children has generally improved in Southern Thailand. One hundred percent coverage of health services and interventions for children with special needs is expected in the near future.**

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Key words: **developmental intervention; Down syndrome; trisomy 21**

Introduction

Down syndrome (DS) is the most common chromosomal disorder causing mental retardation and other congenital anomalies.[1-3] A retrospective study of the clinical characteristics and developmental interventions of 295 DS children in Southern Thailand attending or referred to our institute during 1992-2002 found that 38.6% of these DS infants had congenital heart disease, 16.9% had congenital gastrointestinal defects and 8.8% had congenital hypothyroidism.[4] Of the total 295 DS children, 39 died from severe bacterial sepsis or severe congenital heart disease at the average age of 2.5±2.0 years from bacterial pneumonia or severe congenital heart disease. Of the surviving 256 DS children, 65.6% received a developmental intervention and only 38.9% attended a speech training program.

During January 1, 2009 to December 31, 2013, a prospective birth defects registry of DS prevalence was conducted in 3 provinces (Songkhla, Phatthalung, Trang) in Southern Thailand[5] in which data were obtained from 1 university hospital, 3 medical education center hospitals, 1 provincial hospital, 34

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community hospitals, 421 health promoting hospitals, and 7 private hospitals. In brief, data entries in the birth defects registry included livebirths, stillbirths after 24 weeks gestational age, and terminations of pregnancy (ToPs) following a prenatal diagnosis of any congenital anomaly at any gestational age. The cases of mothers who were not resident in one of the three provinces or were non-Thai were excluded. Each neonate was examined by a pediatrician to screen for associated birth defects. During the 2009-2013 study period, 186 393 births were registered in the 3 provinces; including 198 pregnancies with fetal death in utero after 24 weeks gestation and 234 ToPs were included as the total births denominator. Two hundred and twenty-six DS cases (121 males and 105 females) were diagnosed with an average prevalence of 1.21/1000 births (95% confidence interval: 1.05-1.37). Of the total number of 226 DS infants, 77 (34%) were detected prenatally in mothers who were at or over 35 years and the pregnancies were later terminated. Advanced maternal age was found to be an important risk factor of DS with a prevalence of 1 in 220 in mothers aged 35 years and over compared with 1 in 1000 in mothers aged 30-<35 years and about 1 per 2000 pregnancies in mothers younger than 30 years.[5] The current situation is that the DS livebirths are mostly born to mothers younger than 35 years, a low-risk age group with an average prevalence of 1 per 1500-1800. Given the average number of livebirths in Thailand of 780 000-800 000 per year,[6] we would thus expect about 400-500 DS livebirths per year. It is of some importance to have an accurate estimation of the prevalence of DS livebirths in order to plan for health and other services for DS children beyond the neonatal period.[7]

The aim of this study was to determine the comorbidities associated with DS livebirths and the percentages of DS children receiving developmental interventions at the present time, and compare the current findings with the previous study to determine whether there has been an improvement in percentage of DS children receiving developmental intervention.

Methods

Patients

One hundred and forty-nine DS livebirth infants born between January 1, 2009 and December 31, 2013 were identified from the birth defects registry of 3 provinces (Songkhla, Phatthalung, Trang) in Southern Thailand. All DS infants were longitudinally followed-up every 3-6 months as a prospective cohort study. Gestational age was calculated by the last menstruation in women who had regular menses, or by ultrasonography, or by Ballard score. Each neonate was examined by a pediatrician to screen for associated birth defects. The data collection included gender, birth weight, length, head circumference, and associated congenital anomalies such as cardiovascular malformations or gastrointestinal defects. For comparison with general population of Thai newborns, body measurements (weight, height, head circumference) were transformed to standard deviation scores (SDSs) using standardized reference data of Thai children.[8] All infants had a blood test for thyroid stimulating hormone (TSH) level at around 3 days as part of routine nationwide neonatal TSH screening, and a chromosome study (G-banding) for each type of chromosomal abnormality. All DS infants were referred to a pediatric cardiologist for further evaluation by echocardiography.

Each DS infant was seen by a pediatrician every 3-6 months for evaluation of growth and development and appropriate developmental interventions were begun at 2-6 months or as soon as possible thereafter, and a speech training program begun at 9-18 months depending on the availability of a speech therapist at the local hospital. Developmental intervention and speech training programs were available in a university hospital, 3 medical education center hospitals, a provincial hospital, and only 10 community hospitals in the 3 provinces. The age the child began these interventions was also noted.

Statistical analysis

Data are expressed as median with interquartile range (IQR) or mean with standard deviation for continuous numbers, and percentage for categorical numbers. Chi-squared test was used to compare the differences in categorical data. Statistical differences were considered significant at a P value of <0.05.

This study was approved by the Institutional Review Board and the Ethics Committee of the Faculty of Medicine, Prince of Songkla University. Written informed consent was obtained from all participants.

Results

Clinical characteristics of the DS infants

There were 11 DS infants who were born preterm at gestational ages of 31-36 weeks with birthweights of 1260-2390 g. The 138 DS term infants were born at an average gestational age of 38.7±2.1 weeks (range: 37-42). The average birthweight, length, and head circumference of the DS term infants were lower than the comparable measurements of general Thai neonates without DS as shown by the SDS of weight, length, and head circumference lower than 0 (Table 1). The average TSH level was 9.33±10.2 mIU/L (IQR: 1.4-

92.0). Twenty-eight infants (12.1%) had a TSH level over 25 mIU/L, and repeated TSH levels at 1-2 months were over 10 mIU/L, consistent with a diagnosis of hypothyroidism. These infants were later treated with L-thyroxine supplementation and regularly followed-up with a thyroid function test every 3-6 months.

Congenital heart disease and gastrointestinal defect were found in 64 (43.0%) and 10 (6.7%) infants, respectively. The common congenital heart diseases were ventricular septal defect, patent ductus arteriosus, atrio-ventricular septal defect, and atrial septal defect. The common gastrointestinal defects were imperforate anus and duodenal atresia. The percentages of DS infants with a congenital heart disease and congenital hypothyroidism in this current study were greater than those in the previous study, but not to the level of statistical significance (P=0.44 and 0.14 for congenital heart disease and congenital hypothyroidism, respectively), while the percentage of infants with a congenital gastrointestinal defect was significantly lower than in the 1992-2002 study (P<0.01) (Table 2).

Chromosome studies

Chromosome studies were done in 131 cases (87.9%), with findings of trisomy 21 in 126 (96.2%), translocation 14/21 in 4 (3.0%), and translocation 21/21 in 1 (0.8%). Eighteen mothers (12.1%) aged over 40 years refused to have a chromosome study performed in their children, all saying they did not want to know the diagnosis as this was their child whatever the diagnosis was, and they intended to have no further children. The parents of the DS infants with 14/21 and 21/21 translocations had chromosomal studies done, of which all were normal, indicating that the etiology of these translocations was a *de novo* chromosomal defect.

Table 1. Clinical characteristics of 149 Down syndrome livebirth infants

Characteristic at birth (n=138, excluded 11 preterms), mean±SD	
Gestational age (wk)	38.7±2.1
Birth weight (g)	2760±478
Birth length (cm)	48.5±2.2
Head circumference (cm)	32.7±1.2
Birth weight SDS	-1.53±1.44
Birth length SDS	-0.90±1.25
Head circumference SDS	-1.48±1.31
Screening TSH level (mIU/L)	9.33±10.2
Associated congenital anomaly (n=149), n (%)	
Cardiovascular defect	64 (43.0)
Gastrointestinal defect	10 (6.7)
Transient myelodysplasia	4 (2.7)
Congenital hypothyroidism (screening TSH >25 mIU/L and repeated TSH >10 mIU/L)	18 (12.1)
Type of chromosomal abnormality (n=131), n (%)	
Trisomy 21	126 (96.1)
Robertsonian 14/21	4 (3.1)
Robertsonian 21/21	1 (0.8)

SD: standard deviation; SDS: standard deviation score; TSH: thyroid stimulating hormone; IU: international unit.

Developmental intervention and speech training programs

One hundred and forty DS infants (94.0%) had developmental assessment at the average age of 0.24±0.21 years (IQR: 0.1-0.6 years). One hundred thirty-five infants (90.6%) and 112 infants (75.2%) began developmental interventions and speech training programs at the average ages of 0.58±0.39 years (IQR: 0.2-1.0 years) and 1.69±0.66 years (IQR: 0.7-3.0 years), respectively (Table 3). These percentages were significantly greater than those from the 1992-2002 study (P<0.001). However, about 10% and 25% of the DS infants in this current study did not receive early developmental stimulation and speech training program, respectively. The reasons the parents gave for not enrolling their children in the early stimulation program were inconvenience and the expense of long distance travel between their home and the hospital,

Table 2. Comparison of congenital cardiovascular and gastrointestinal defects in Down syndrome livebirths between the current study (2009-2013) and previous study (1992-2002)

Associated congenital defects	2009-2013 (n=149)	1992-2002 (n=295)	P value
Cardiovascular defects, n (%)	64 (43.0)	114 (38.6)	0.440
Ventricular septal defect	16 (10.8)	35 (11.9)	
Patent ductal arteriosus	14 (9.4)	22 (7.4)	
Atrio-ventricular septal defect	13 (8.7)	26 (8.8)	
Atrial septal defect	13 (8.7)	15 (5.1)	
Tetralogy of Fallot	4 (2.7)	8 (2.7)	
Double outlet of right ventricle	4 (2.7)	0	
Others	0	8 (2.7)	
Gastrointestinal defects, n (%)	10 (6.7)	50 (16.9)	0.005
Imperforate anus	4 (2.7)	21 (7.1)	
Duodenal atresia	3 (2.0)	16 (5.4)	
Hirschsprung disease	1 (0.7)	8 (2.7)	
Tracheo-esophageal fistula	1 (0.7)	1 (0.3)	
Others	1 (0.7)	4 (1.4)	
Congenital hypothyroidism, n (%)	18 (12.1)	23 (8.8)	0.140

Table 3. Comparing percentages of Down syndrome children receiving stimulation and screening examination between the current study (2009-2013) and a previous study (1992-2002)

Varibles	2009-2013 (n=149)			1992-2002 (n=256), P value
	n (%)	Age (y) X±SD	Age (y) Median	n (%)
Evaluation of development	140 (94.0)	0.24±0.21	0.27	160 (62.5) <0.001
Early stimulation program	135 (90.6)	0.58±0.39	0.50	168 (65.6) <0.001
Speech training program	112 (75.2)	1.69±0.66	1.50	103 (38.9) <0.001
Reasons for not receiving early stimulation	14 (9.4)	-	-	ND -
Hospital is far from home	9 (6.0)	-	-	ND -
Expense	5 (3.4)	-	-	ND -
Reasons for not receiving speech training	37 (24.8)	-	-	ND -
Parents intended to train their child themselves	25 (16.8)	-	-	ND -
Hospital is far from home	12 (8.0)	-	-	ND -

X±SD: mean±standard deviation; ND: not determined.

and they said they themselves intended to provide their children with speech training.

At the time of this study, the DS cases were 1-5 years of age, and only gross motor development could be completely assessed with the other developmental areas still being followed-up. The average ages at the time of ability to roll over, sit unsupported and stand-up unsupported were 5.0±1.2, 9.2±2.8, and 16.6±4.5 months, all of which were at a slightly earlier age than those of the 1992-2002 study at 4.9±0.9, 10.3±3.3, and 19.3±5.3 months, respectively.

Discussion

It is known that DS children have multiple associated congenital anomalies such as congenital heart disease, gastrointestinal defects, congenital hypothyroidism. The prevalence of such associated congenital anomalies needs to be known in order to plan for adequate health care and other services for DS children living beyond the neonatal period. These prevalences in Thailand are still poorly known, as numbers vary depending on the source, with most previous studies based on data from tertiary medical centers, to which severe or complicated cases were referred for medical or surgical management. With such data, percentages of severe associated anomalies might be over-represented while percentages of minor anomalies or asymptomatic congenital defects which were not referred to medical centers might have their actual prevalence understated. Compared to our 1992-2002 study in which DS cases were collected from hospital-based data, this current study was based on population birth defects registry, and found increased percentages of congenital heart disease and congenital hypothyroidism and decreased percentages of congenital gastrointestinal defects. The increased percentages of congenital heart disease could be explained by echocardiography screening in DS livebirth infants, which is more widely performed now than in the earlier study, a process which can detect mild forms of the disease and also asymptomatic congenital heart diseases such as small atrial septal defect, small ventricular septal defect, or patent ductus arteriosus. The increased percentage of congenital hypothyroidism in this current study can be explained by the nationwide neonatal TSH screening program which was implemented in Thailand in 2000,[9] which has resulted in an overall higher detection rate of congenital hypothyroidism in all infants[9,10] and in infants with DS.[11,12] For congenital gastrointestinal obstruction, the percentage of DS infants in our current study was significantly lower than that in our previous study (6.7% *vs*. 16.9%, $P<0.001$). The lower percentages of congenital gastrointestinal obstruction in DS infants from our birth defects registry could be explained by noting that in the registry, the DS cases were recorded from all levels of hospitals (tertiary, secondary and primary care hospitals) in the study areas, while the greater percentages of associated gastrointestinal obstruction in the 1992-2002 study was biased, as the numbers were based on not only our own admissions, but included referred cases for surgical correction in our hospital, which is and was the only major tertiary medical center in Southern Thailand.

It is known that early stimulation programs can enhance brain development in children who are developmentally delayed through conditions such as Down syndrome or cerebral palsy or due to being preterm or low birth weight infants.[13] The American Academy of Pediatrics recommends that the appropriate ages for beginning developmental interventions and speech training programs are as early as possible, preferably beginning before 3 months and 1 year of age, respectively.[6] A study of DS cases in Thailand found that infants who were brought to attend an early stimulation program at younger than 3 months and a speech training program at younger than 18 months had significantly better developmental quotients than children who began the programs at later ages (67.52±11.58 *vs*. 61.43±10.52, $P=0.009$, and 70.89±9.60 *vs*. 67.52±11.58, $P<0.001$, respectively).[14] In our current study, we found that most DS infants received developmental evaluation (94.0%), and attended developmental interventions (90.6%) and speech training (75.2%), all in significantly greater percentages than those in the 1992-2002 study.[4] These findings indicate that health care services for children with special needs have generally improved, even at the level of primary care hospitals. However, in this study, we found that about 10% of DS infants were still not enrolled in an early stimulation program due to, as their parents said, the inconvenience and the expense of long distance travel between home and hospital, and about 25% were not attending a speech training program, with the parents saying they themselves could provide their child with adequate speech training.

Prenatal diagnosis was implemented in our institute in 1990 in pregnant women with a high risk of having a fetus with a chromosomal aberration, particularly those with advanced maternal age.[15] In recent years, approximately 1000-1200 amniocentesis procedures for fetal karyotyping have been performed in our hospital yearly with the very low rate of fetal loss within 14 days after performing the procedure of only 0.12% (10 losses in 8073 procedures), with a rate of DS detection of about 1% (72 cases).[15,16] A recent study in 714 pregnant Thai women, average age 29.9±6.4 years, found

generally positive attitudes towards amniocentesis screening for DS.[16] In our study of DS prevalences in the 3 provinces during 2009-2013, an increasing rate of termination of pregnancy after prenatal diagnosis of DS fetuses during the second trimester was found, mostly in mothers who were at or older than 35 years.[5] However, about two-thirds of DS fetuses were born from mothers under 35 years of age. At present, the American College of Obstetricians and Gynecologists recommends that all pregnant women, regardless of age, be offered the option of diagnostic testing for DS.[17,18] A study in 82 Thai obstetric residents training during 2006-2007 found that 80.4% had positive attitudes towards counseling all pregnant women to undergo DS screening.[19] The positive attitudes of both the obstetricians and the pregnant women could explain the increasing rate of DS screening and later termination of pregnancy following prenatal diagnosis of DS fetuses.

This current study had some strengths and limitations. The main strength was that this study was population-based and covered >95% of all DS cases from all levels of hospitals in the study area, thus eliminating selection bias. Second, because DS infants were clinically recognizable by pediatricians and the majority of patients (90%) had a chromosome study done to confirm the diagnosis, we feel that our ascertainment rate was quite high and that the diagnoses were accurate. The main limitation of our study was that about 10% of our DS children had not underwent chromosome study for confirming the diagnosis, however, the features of DS children born to mothers aged over 35 years have a typical clinical appearance (brachycephalic head shape, flat nasal bridge, upward-slanting palpebral fissures, small mouth, small ears, excessive skin at the nape of the neck, single transverse palmar crease, clinodactyly, wide spacing and deep plantar groove between the first and second toes, hypotonia and delayed development) and as the infants without a chromosome study in our study all had these characteristics, we are certain of the diagnosis. Second, the associated congenital malformations in the terminated DS fetuses were not recorded, which might have resulted in lower-than-actual percentages of congenital anomalies.

In conclusion, the common comorbidity associated with DS in our study from Southern Thailand was congenital heart disease. Congenital hypothyroidism and congenital gastrointestinal defects were found in 12.1% and 6.7% of DS cases, respectively. The coverage of health care services and developmental interventions for DS children has generally improved in Southern Thailand. One hundred percent coverage of health services and interventions for children with special needs is a goal in the near future.

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References

1 Rankin J, Pattenden S, Abramsky L, Boyd P, Jordan H, Stone D, et al. Prevalence of congenital anomalies in five British regions, 1991-99. Arch Dis Child Fetal Neonatal Ed 2005;90:F374-F379.
2 Boyd PA, Khoshnood B, Loane M, Garne E, Dolk H, EUROCAT working group. Survey of prenatal screening in Europe for structural malformations and chromosome anomalies, and their impact on detection and termination rates for neural tube defects and Down's syndrome. BJOG 2008;115:689-696.
3 Loane M, Morris JK, Addor M-C, Arriola L, Budd J, Doray B, et al. Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: impact of maternal age and prenatal screening. Eur J Human Genet 2012;21:27-33.
4 Jaruratanasirikul S, Soponthammarak S, Chanvitan P, Limprasert P, Sriplung H, Leelasamran W, et al. Clinical abnormalities, intervention program, and school attendance of Down syndrome children in Southern Thailand. J Med Assoc Thai 2004;87:1199-1204.
5 Jaruratanasirikul S, Kor-anantakul O, Chowvichian M, Limpitikul W, Dissaneevate P, Intharasangkanawin N, et al. A population-based study of prevalence of Down syndrome in Southern Thailand. World J Pediatr 2017;13:63-69.
6 Statistical Forecasting Bureau, National Statistical Office, Ministry of Information and Communication Technology, Thailand. Key Statistics of Thailand 2012. http://service.nso.go.th/nso/nsopublish/pubs/pubsfiles/Key55_T.pdf (accessed 14 February 2014).
7 Bull MJ, Committee on Genetics. Health supervision for children with Down syndrome. Pediatrics 2011;128:393-406.
8 Nutrition Division, Department of Health, Ministry of Public Health, Thailand. Reference for weight, height and nutritional indices in Thais aged 1 day to 19 years. Bangkok, Thailand. Department of Health, Ministry of Public Health: Bangkok; 2000.
9 Charoensiriwatana W, Janejai N, Boonwanich W, Krasao P, Chaisomchit S, Waiyasilp S. Neonatal screening program in Thailand. Southeast Asian J Trop Med Public Health 2003;34 Suppl 3:94-100.

10 Sutivijit Y, Banpavichit A, Wiwanitkit V. Prevalence of neonatal hypothyroidism and phenylketonuria in Southern Thailand: a 10-year report. Indian J Endocrinol Metab 2011;15: 115-117.
11 Jaruratanasirikul S, Patarakijavanich N, Patanapisarnsak C. The association of congenital hypothyroidism and congenital gastrointestinal anomalies in Down's syndrome infants. J Pediatr Endocrinol Metab 1998;11:241-246.
12 Unachak K, Tanpaiboon P, Pongprot Y, Sittivangkul R, Silvilairat S, Dejkhamron P, et al. Thyroid functions in children with Down's syndrome. J Med Assoc Thai 2008;91:56-61.
13 Bonnier C. Evaluation of early stimulation programs for enhancing brain development. Acta Paediatr 2008;97:853-858.
14 Wasant P, Boonyawat B, Tritilanunt S, Vatanavicharn N, Sathienkijakanchai A, Ratanarak P, et al. Factors influencing development of Down syndrome children in the first three years of life: Siriraj experience. J Med Assoc Thai 2008;91:1030-1037.
15 Hanprasertpong T, Kor-anantakul O, Prasartwanakit V, Leetanaporn R, Suntharasaj T, Suwanrath C. Outcome of second trimester amniocentesis in singleton pregnancy at Songklanagarind Hospital. J Med Assoc Thai 2011;94:1288-1292.
16 Pruksanusak N, Suwanrath C, Kor-anantakul O, Prasartwanakit V, Leetanaporn R, Suntharasaj T, et al. A survey of the knowledge and attitudes of pregnant Thai women towards Down syndrome screening. J Obstet Gynecol Res 2009;35:876-881.
17 ACOG Committee on Practice Bulletins. ACOG practice bulletin No. 77: screening for fetal chromosomal abnormalities. Obstet Gynecol 2007;109:217-227.
18 American College of Obstetricians and Gynecologists. ACOG practice bulletin No. 88, December 2007. Invasive prenatal testing for aneuploidy. Obstet Gynecol 2007;110:1459-1466.
19 Kor-anantakul O, Awapark P, Suwanrath C, Suntharasaj T, Hanprasertpong T. The knowledge and attitudes of Thai obstetrics and gynaecology residents towards Down syndrome screening. J Med Assoc Thai 2013;96:7-12.

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