A population-based study of prevalence of Down syndrome in Southern Thailand

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Background: **Down syndrome (DS) is the most common chromosomal disorder that causes mental retardation. In 2009, a population-based birth defects study was implemented in three provinces in southern Thailand. This study aimed to determine the prevalence of DS in the studied regions, and the proportion of DS fetuses detected by prenatal screening.**

Methods: **Data were obtained from a population-based surveillance study undertaken during 2009-2013. Entries in the birth defects registry included live births, stillbirths after 24 weeks gestational age, and terminations of pregnancy following prenatal diagnosis. Infants with clinical characteristics of DS had a chromosomal study to make a definite diagnosis.**

Results: **Of the total 186 393 births recorded during the study period, 226 DS cases were listed, giving a prevalence of 1.21 per 1000 births [95% confidence interval (CI) 1.05-1.37]. The median maternal age was 36.5 years with a percentage of maternal age ≥35 years of 60.6%. Seventy-seven cases (34.1% of all cases) were diagnosed prenatally and these pregnancies were terminated. The prevalence of DS per 1000 births was significantly higher in older women, from 0.47 (95% CI 0.28-0.67) in mothers aged <30 years to 0.88 (95% CI 0.59-1.17) in mothers 30-<35 years (*P*<0.01), and to 4.74 (95% CI 3.95-5.53) in mothers ≥35 years (*P*<0.001).**

Conclusions: **The prevalence of DS significantly increased with maternal age. About 35% of DS cases were detected prenatally and later terminated. Hence, examining only registry live births will result in an inaccurate prevalence rate of DS.**

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Key words: **birth defect registry; Down syndrome; prenatal screening; termination of pregnancy; trisomy 21**

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Introduction

Down syndrome (DS) is the most common chromosomal disorder that causes mental retardation.[1,2] The prevalence of DS is 1-2 cases per 1000 births in Caucasian[2-6] and Asian countries,[7-10] and depends on the maternal age distribution, notably the proportion of mothers at or older than 35 years of age. Over the past 20 years, there have been major advances in the field of prenatal screening for detecting congenital anomalies including DS fetuses, and also the increased availability of termination of pregnancy (ToP) for fetal anomalies, which have resulted in a decreasing prevalence of live births with congenital birth defects and an increasing prevalence of pregnancy termination due to fetal anomalies.[2,4,7]

In Thailand, there have been two earlier studies regarding the prevalence of DS, the first based on data from 1969-1978[11] and the second from 1988-1999,[12] each based on data from only one university hospital, and finding DS prevalences of 0.89 and 1.07 per 1000 live births, respectively. In 1998, prenatal diagnosis by amniocentesis for chromosomal abnormalities was implemented in Songklanagarind Hospital, the only university hospital and major tertiary care center in southern Thailand, particularly in women aged over 35 years.[13] A survey in pregnant Thai women attending antenatal care at our hospital in 2007 found that most

pregnant women had a positive attitude towards DS screening.[14] In 2009, a population-based birth defects study was implemented in three provinces in southern Thailand as a preliminary program to establishing a birth defects registry. The primary outcome of this present study was to determine the prevalence of DS during 2009-2013 using the new population-based birth defects registry of southern Thailand. The secondary outcome was to determine the proportion of DS fetuses detected by prenatal screening.

Methods

Data collection

A population-based study of DS prevalence was conducted from January 1, 2009 to December 31, 2013 in three provinces (Songkhla, Phatthalung, Trang) in southern Thailand. Data were obtained from one university hospital, three medical education center hospitals, one provincial hospital, 34 community hospitals, 421 health promoting hospitals, and seven private hospitals. Data entries in the birth defects registry included live births, stillbirths after 24 weeks gestational age, and terminations of pregnancy following a prenatal diagnosis of any congenital anomaly at any gestational age. Gestational age was calculated by the last menstruation in women who had regular menses or by a newborn Ballard score. Each neonate was examined by a pediatrician to screen for associated birth defects. The fetuses of abnormalities detected by prenatal diagnosis and terminated before 24 weeks of gestation were examined after termination by an obstetrician, and the findings recorded in the registry system. The maternal data collection included age at delivery, mode of delivery, birth order, history of abortion and previous pregnancies, congenital anomalies in previous children, current illness and medication use during pregnancy, exposure to smoking, alcohol, infections, etc. The infant's data included date of birth, sex, birth weight, length, head circumference, and congenital anomalies such as cardiovascular malformation, gastrointestinal defects, congenital hypothyroidism, etc. All infants were followed-up at a well-child clinic for scheduled vaccinations at 2, 4, 6, 9, 12, 18 and 24 months of age. At each visit, the infants were re-evaluated for associated birth defects, and at this time, infants with clinical features suggestive of DS were referred to a medical center for chromosomal analysis and, if found to have any such defects, were then registered in the birth defects registry system.

The term "birth prevalence" was used as an indicator of incidence, as it is not practically possible to determine an exact incidence rate because the population at risk at any given time changes during gestation.[15] We calculated the total DS prevalence rate by combining live births, stillbirths, and pregnancy terminations in both the numerator and denominator. Both the numerator and denominator were based on data obtained from all public and private hospitals in the studied provinces. All the recorded cases and data were checked for duplicate cases and verified for accuracy (e.g. impossible or inconsistent data entries were queried) and completeness of the data by the project's manager (JS). A chromosomal study (G-banding) was performed in infants who had clinical characteristics of DS to confirm a definite diagnosis.

Statistical analysis

The number of live birth DS cases and terminations of pregnancy prevalence of DS fetuses by specific province were calculated. Cases were grouped by the live births or termination data. The age-specific risk rates associated with mothers based on 5-year age group categories were compared. The prevalence rates of DS calculated per 1000 total births by calendar year (January 1 to December 31) were calculated with 95% confidence intervals (CIs). The Pearson's Chi-squared test was used to compare the prevalences of DS among different maternal age groups.

This study was approved by the Institutional Review Board of the Faculty of Medicine, Prince of Songkla University.

Results

During 2009-2013, 186 393 births were registered in the three provinces: Songkhla 116 075 with an average of 23 215/year, Phatthalung 27 283, averaging 5457/year, and Trang 43 035, averaging 8607/year. Of the total births, 198 pregnancies with dead fetus *in utero* after 24 weeks of gestation and 234 ToPs were included in the denominator. Of the total ToP cases, fetal chromosomal abnormalities were indicated in 94 cases (40.2%), of whom 77 (81.9%) were trisomy 21, 7 (7.4%) trisomy 18, 6 (6.4%) trisomy 13, and 4 (4.3%) were other chromosomal abnormalities.

Prevalence of Down syndrome

Two hundred twenty-six DS cases (121 male and 105 female) were diagnosed, with an average prevalence of 1.21/1000 births (95% CI 1.05-1.37). The prevalence rates of DS with 95% CIs in each province in each year of the study ranged from 0.86-1.99 per 1000 births (Table 1). There were no significant differences of prevalence rates yearly among the 3 provinces. The majority of the mothers of DS children or fetuses reported no use of alcohol, tobacco, or any medications, and had no illnesses during their pregnancy (Table 2).

Only five mothers (2.2%) with DS offspring had an underlying disease, two with diabetes mellitus, and three with hypertension.

Chromosome studies

Chromosome studies were done in 208 cases (92.0%), finding trisomy 21 in 202 (97.1%), translocation 14/21 in five (2.4%), and translocation 21/21 in one (0.5%). Of the total cases of DS, 80 (35.4%) were diagnosed prenatally and later underwent terminations of pregnancy; most (77 out of 80, or 96.3%) were mothers aged at or over 35 years. Eighteen DS mothers (8.0%) were over 40 years of age and refused to have a chromosome study performed since they intended to have no further pregnancies and later underwent permanent sterilization. The diagnosis of DS in these 18 neonates was based on typical DS characteristic features.

Table 1. Prevalence of Down syndrome in the three provinces

Provinces	Total births	Down syndrome		Prevalence per 1000 births	95% CIs
		Live births	ToPs		
Songkhla					
2009	22 585	21	4	1.11	0.67-1.54
2010	22 364	24	6	1.34	0.86-1.82
2011	23 114	13	11	1.04	0.62-1.45
2012	24 797	23	10	1.33	0.88-1.78
2013	23 215	14	12	1.12	0.69-1.55
Total	116 075	95	43	1.19	0.99-1.39
Phatthalung					
2009	5512	5	6	1.99	0.82-3.17
2010	5645	4	5	1.59	0.55-2.64
2011	5439	1	6	1.29	0.33-2.24
2012	5046	2	5	1.39	0.36-2.41
2013	5641	1	10	1.95	0.80-3.10
Total	27 283	13	32	1.65	1.17-2.13
Trang					
2009	7718	8	0	1.04	0.32-1.75
2010	8452	9	0	1.06	0.37-1.76
2011	8741	9	0	1.03	0.36-1.70
2012	9346	8	0	0.86	0.26-1.45
2013	8778	7	2	1.03	0.36-1.69
Total	43 035	41	2	1.00	0.70-1.30
Total three provinces					
2009-2013	186 393	149	77	1.21	1.05-1.37

CIs: confidence intervals; ToPs: terminations of pregnancy.

Table 2. Characteristics of pregnant mothers with Down syndrome (*n*=226)

Characteristics	
Maternal age at time of pregnancy (y)	
Mean±standard deviation	34.7±7.0
Median	36.5
Range	17-48
Maternal age distribution, *n* (%)	
≥35 y	137 (60.6)
≥30-<35 y	35 (15.5)
<30 y	54 (23.9)
Maternal disease before pregnancy, *n* (%)	5 (2.2)
Maternal drug use during pregnancy, *n* (%)	2 (0.9)
Mothers receiving prenatal diagnosis, *n* (%)	80 (35.4)
Mothers aged ≥35 years receiving prenatal diagnosis, *n* (%)	79/137 (57.7)
Parity, *n* (%)	
First pregnancy	54 (23.9)
Second pregnancy	69 (30.5)
Third pregnancy	55 (24.4)
Fourth pregnancy	31 (13.7)
>Fourth pregnancy	17 (7.5)
Mothers with history of abortion in previous pregnancy, *n* (%)	31 (13.7)

Maternal age

The most common maternal age group at the time of pregnancy was between 25-30 years (26%-30%) (Fig. 3). In this study, the percentage of all delivering mothers at and over 35 years of age increased from 14.7% in 2009 to 15.5% in 2013, and the national data also showed a similar trend of increasing percentage of delivering mothers at and over 35 years of age from 12.3% in 2006 to 12.8% in 2011;[16] however, no significant differences were found on the overlapping percentage of the 95% CIs. For the DS mothers in our study, the mean and median maternal ages were 34.8 and 36.5 years, respectively, range 17-48 years, with the percentage of maternal ages over 35 years of 60.6%. There were no statistical differences in the mean maternal ages among the 3 provinces: Songkhla 34.7±6.9 years, Phatthalung 35.1±6.9 years, and Trang 33.7±5.9 years (P=0.40). Of the 137 mothers of Down infants aged at and over 35 years, 79 (57.7%) had undergone prenatal diagnosis and the fetuses were found to be affected with trisomy 21. The average gestational age at the time of prenatal diagnosis was 17.2±3.1 weeks (range 14-22 weeks) and the average gestational age of ToP was 20.5±4.5 weeks (range 16-28 weeks)

Live births and terminations of pregnancy

The average prevalence of DS, including live births and ToPs, was only a little different between the three provinces and years of study, ranging from 0.83-1.99/1000/year without significant statistical

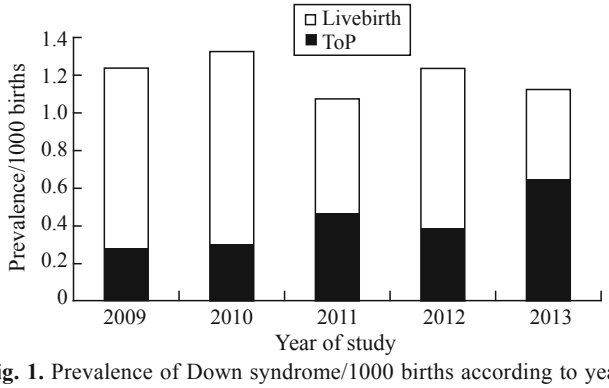

Fig. 1. Prevalence of Down syndrome/1000 births according to year of study. ToP: termination of pregnancy.

differences. We also found an increasing proportion of prenatal detection of DS and ToP in mothers who were over 35 years at the time of pregnancy from 0.23 in 2009 to 0.53 in 2013 (Fig. 1). It is of note that all mothers who had their pregnancies terminated for severe congenital anomalies had attended routine antenatal care at the university hospital or a provincial hospital where prenatal diagnosis was available.

Prevalence of Down syndrome according to maternal age

Maternal age at the time of pregnancy was divided into 5-year intervals: <20, 20-<25, 25-<30, 30-<35 and ≥35 years. Prevalence of DS per 1000 births significantly increased from 0.45 (95% CI 0.31-0.62) or 1 in 2200 in mothers younger than 30 years to 0.88 (95% CI 0.61-1.16) or 1 in 1100 in mothers aged 30-<35 years (P<0.01), and to 4.74 (95% CI 3.76-5.54) or 1 in 220 in mothers aged ≥35 years (P<0.001) (Table 3 and Fig. 2). The prevalence of DS live births was relatively the same over time at 0.44-0.47 per 1000 births from mothers under 30 years of age.

Table 3. Prevalence of Down syndrome according to maternal age from our current study

Maternal age (y)	Total births	DS	Prevalence/1000 births (95% CI)	P value
<25	69 338	31	0.45 (0.29-0.60)	<0.001
25-<30	48 462	23	0.47 (0.28-0.67)	
30-<35	39 702	35	0.88 (0.59-1.17)	
≥ 35	28 891	137	4.74 (3.95-5.53)	

CI: confidence interval; DS: Down syndrome.

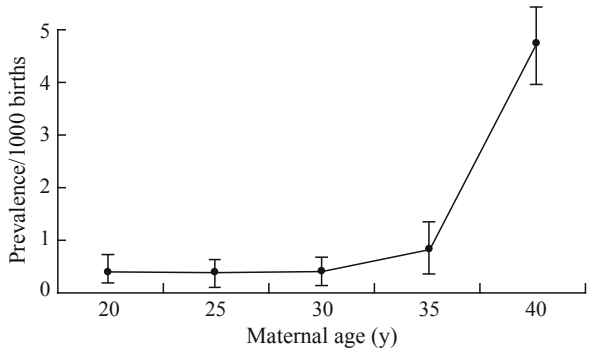

Fig. 2. Prevalence of Down syndrome/1000 births according to maternal age at pregnancy

Discussion

At present, the birth defects registry in Thailand is still in an ongoing process of being established and is expected to be fully implemented at the national level within a few years. Our current study firstly studied DS prevalence in Thailand on a population-base. The prevalence was higher in Phatthalung than Trang and Songkhla but with no significance due to the variations in each year of the study period and the overlapping 95% CIs. The overall prevalence of DS in the five years was 1.21 per 1000 births, which was greater than the prevalence of 0.89 per 1000 live births during 1969-1978[11] and 1.07 per 1000 live births during 1988-1999.[12] This increasing prevalence of DS in our study was postulated to be related to the increasing percentages of advanced maternal age pregnancies, as 60% of the DS cases were delivered by mothers who were over 35 years old. Moreover, increased percentages of advanced maternal age at the time of giving birth were found in all 3 study provinces and are consistent with the findings of the Thai national report of the increasing percentage of maternal age at and over 35 years of age from 12.3% in 2006 to 12.8% in 2010.[16] The prevalence of DS has been demonstrated to be related to increased maternal age in many studies. In Japan, the live birth prevalence of DS has been increasing in Japan since 1970,[10] and the increasing frequency of DS from 1.34 per 1000 live births in 1980-1989 to 1.74 per 1000 live births in 1990-1999 was attributed to an increased average maternal age from 31.0 in 1980-1989 to 32.4 years in 1990-1999.[10,17] In Europe, the average age of women giving birth has steadily increased since the

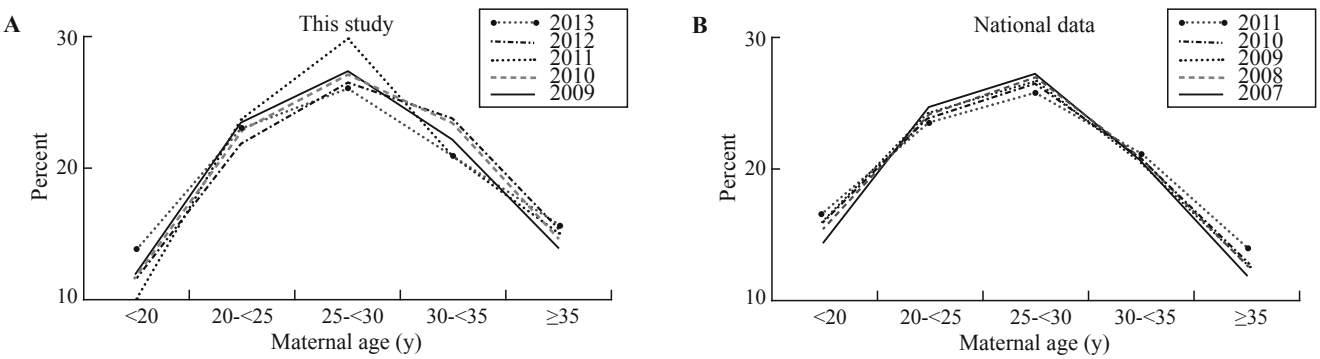

Fig. 3. Distribution of maternal age groups in our study during 2009-2013 (**A**) compared with the national data during 2007-2011 (**B**).

late 1970s.[18] In the USA, the percentage of advanced maternal age births has increased, along with an increase in the prevalence of DS at birth from 9.0 to 11.8 per 10 000 live births in 10 USA regions during the 25-year period 1979-2003.[19,20] Studies of DS in various parts of the world have shown increasing trends in affected pregnancies attributed to increasing percentages of maternal age at and over 35 years (Table 4).[2-12]

It is known that the risk of having a child with DS increases with maternal age from 1 in 800 to 1 in 50, in mothers from 25 to 40 years old. However, a study in the USA in 1970 found that more than 60% of infants with DS were born to mothers under 35 years of age.[21] In our study, the overall prevalence of DS in our studied areas was 1.21 per 1000 births or 1 in 770 births. Dividing the mothers into 5-year age groups, the risk of having a child with DS in mothers younger than 30 years was 1 in 2200 births, which increased to 1 in 1100 births in mothers aged 30-35 years, and 1 in 220 in mothers at and older than 35 years. The obvious increased risk in mothers over 35 years can probably be explained by the increased detection by prenatal screening as a medical policy for this age group in the university hospital, medical education center hospitals, and provincial hospitals. However, nearly 40% of mothers aged at and over 35 years in this study had not performed prenatal diagnosis due to the limitation of this procedure at the community hospitals. The risk of having a child with DS in mothers younger than 30 years was low, at 1 in 2200 and only one mother, aged 27 years, underwent prenatal diagnosis in a university hospital as a study project for congenital anomaly screening in pregnant women. One possible explanation for the low prevalence of DS in pregnant women aged under 30 years in the study was that abortions or miscarriages before 24 weeks gestation were not included in our study. Previous studies have shown that 10%-15% of all recognized pregnancies result in spontaneous abortions, mostly in the first trimester, and 50%-60% of these abortions are found to have chromosome abnormalities, of which about 10% are trisomy 21.[22,23] Estimating the prevalence of DS in young maternal age groups based on these data might increase from 1 in 2200 to 1 in 1800. However, abortions in early pregnancy would not be much of concern since fetuses with major anomalies rarely survive to term.

A national policy concerning prenatal screening in Thailand has still not been established. In our institute as a university hospital, over the past 20 years there have been advances in the field of prenatal screening for DS and fetal anomalies. A study of the outcomes of second-trimester amniocentesis in singleton pregnancies in our institute during 1998-2006 in over 8000 mothers found that the indication was advanced maternal age in 96% of cases and that fetal loss within 14 days after the procedure was 0.12%.[13] The low prevalence of DS in mothers aged under 30 years of 0.45-0.47 per 1000 births or 1 in 2200 supports our policy that amniocentesis is not necessary in mothers under 30 years of age without some specific indication. In our study, the DS live births were mostly born to mothers

Table 4. Prevalence of Down syndrome in various countries

Study	Countries and regions	Year of study	Total births	Maternal age ≥35 y (%)	Prevalence per 1000 births
Europe					
Loane et al[2]	EUROCAT (21 countries)	1990-2009	6 117 757	18.2 (2000-2009)	2.20 (LB 1.12, ToP 1.08)
Wellesley et al[6]	EUROCAT (21 countries)	2000-2006	2 354 668	-	2.30
UK+Australia					
Savva et al[3]	UK+Australia (BINOCAR)	1989-2004	4.5 million	-	1.53 (1989-1996) 1.94 (1997-2004)
North America					
Cocchi et al[4]	ICBDSR (USA+Canada+Europe +Australia)	1993-2004	1.5 million/y	14.5 (1993) 22.7 (2004)	1.31 (LB 0.93, ToP 0.48) 1.82 (LB 0.83, ToP 0.99)
Parker et al[5]	NBDPN, USA	2004-2006	3 120 605	-	1.45
Asia					
Jou et al[7]	Taiwan of China	1993-2001	1 331 616	4.8 (1993) 8.3 (2001)	0.49-0.89 (LB 0.14-0.63)
Wang et al[8]	China (Fudan, Futuo)	2001-2004	15 120	-	1.60
Takeuchi et al[10]	Japan	1980-1989 1990-1999	60 592 47 574	-	1.34 1.74
Thailand					
Siripoonya et al[11]	Ramathibodi Hospital, Bangkok	1969-1978	46 276	-	0.89
Dissaneevate et al[12]	Songklanagarind Hospital, Songkhla	1988-1999	27 061	-	1.07
The present study	Southern Thailand (Songkhla, Phatthalung, Trang)	2009-2013	186 393	57.7	1.21 (LB 0.80, ToP 0.41)

BINOCAR: British Isles Network of Congenital Anomaly Registers; EUROCAT: European Surveillance of Congenital Anomalies; ICBDSR: International Clearinghouse for Birth Defects Surveillance and Research; NBDPN: The National Birth Defects Prevention Network; LB: live births; ToP: termination of pregnancy; UK: United Kingdom; USA: The United States of America.

aged under 35 years whereas most DS fetuses detected by prenatal screening in mothers aged at and over 35 years were subsequently terminated. The percentage of prenatal diagnosis of DS and ToP varied in each province depending on the availability of amniocentesis. In Phatthalung, amniocentesis for prenatal diagnosis was implemented before 2009 and in 2013 this procedure was successfully performed in over 90% of pregnant women aged at and over 35 years, whereas in Trang province prenatal diagnosis was only introduced in 2013. The increased availability of prenatal DS screening and subsequent terminations of pregnancy during the past few years resulted in a lower DS live birth prevalence than the actual prevalence. In our study, the live birth prevalence of DS decreased from 0.95 to 0.58 per 1000 births during the years 2009 to 2013. In Singapore, the live birth prevalence of DS decreased from 1.17 to 0.89 per 1000 births from 1993 to 1998 due to antenatal diagnosis and elective abortion.[24] Failure to include these cases and count only registered live births and stillbirths in any birth defects surveillance system will result in inaccurately low DS prevalence rates since the frequency of ToP following prenatal diagnosis of congenital anomalies has been increasing. Accurate estimations of the prevalence of DS in each maternal age group, particularly mothers in the younger age groups, are needed for calculating risks and benefits for prenatal screening programs, and for predicting the impact of changes in the maternal age distribution on the prevalence of DS. However, new technologies to detect fetal chromosome abnormalities are available such as prenatal chromosome microarray and noninvasive prenatal testing which have higher detection rates, high accuracy and specificity than the cytogenetic testing which can increase the availability of ToP and reduce the overall prevalence of DS births in any maternal age group. However, the cost-effectiveness of these methods has to be further evaluated.[25-27]

This current study had some notable strengths and limitations. The strength was that our calculation of the birth prevalence of DS was probably a close estimate of the true incidence in the study areas, for the following reasons. First, the surveillance system was population-based and covered >95% of pregnant women in all public and private hospitals, thus eliminating any possible selection bias. Moreover, the data of the prospective survey were rechecked by the retrospective study from both hospital levels by medical personnel. Second, we had access to data for all pregnancy outcomes, including termination following prenatal diagnosis of a birth defect, as well as live births and stillbirths. The limitations of our study were first that about 10% of our DS children did not have a chromosome study done to confirm the diagnosis; however, the typical facial appearance and delayed development of DS children from mothers at and over 35 years of age are characteristic for clinical diagnosis of DS, and the possible misdiagnosis rate of such cases would be very low, if any at all. Second, some data might not complete, even though this was a prospective population-based study, as the total numbers of stillbirths may not have been recorded in some smaller hospitals, which could have resulted in an incomplete number of total pregnancies in the denominators of the affected calculations. However, such numbers, if any, would have been so small that they would not make any important difference to the prevalence rate. Third, chromosome studies were not performed in stillbirths cases in which chromosome abnormalities might have been detected, which might then have resulted in lower prevalence rates of DS in our study.

In summary, our study using birth defects registry system in southern Thailand shows the prevalence of DS 1.21 per 1000 births and the prevalence significantly increases with maternal age. A birth defects registry should be implemented nationwide as a national policy to allow researchers to study the prevalence and the risk factors of the major congenital birth defects.

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