Chapter 2

Unchanged prevalence of Down syndrome in the Netherlands: results from an eleven year nationwide birth cohort

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Journal

Prenatal Diagnosis 2012; 32:1035-1040

Abstract

Objective: This study aims to evaluate trends in prevalence of Down syndrome (DS) births in the Netherlands over an 11-year period, and how they have been affected by maternal age and introduction of prenatal screening.

Method: Nationwide data of an eleven year birth cohort (1997-2007) from the Netherlands Perinatal Registry were analyzed. First trimester combined screening was introduced in 2002, free of charge only for women 36 years of age or older and only on patients' request. Changes in maternal age, prevalence of DS births, and rates of births at <24 weeks (legal limit for termination of pregnancy in the Netherlands) during the study period were evaluated using logistic and linear regression analyses.

Results: In total 1,972,058 births were registered (91% of the births in 1997-2007). Mean prevalence of DS was 14.57 per 10,000 births (95% CI 14.43;14.73); 85% of DS were live births. No significant trend in overall prevalence of DS births was observed (p=0.385), in spite of a significant increase of mean maternal age during the same period (p<0.001). The increased prevalence of DS births at ≥24 weeks among women ≥36 years of age (p=0.011) was offset by a significant increase in the proportion of DS births at <24 weeks among women aged <36 years (p=0.013).

Conclusion: The proportion of DS births in the Netherlands has not changed during the period 1997-2007.

What's already known on this subject

— In the Netherlands, the live birth-prevalence of DS is an estimated 11-16 per 10,000.
— The overall prevalence of DS is positively correlated to increasing maternal age.
— A new screening policy for DS was introduced in 2002 in the Netherlands.

What does this study add

— Maternal age has increased progressively during the study period, with related increase in DS births.
— During 1997-2007 the prevalence of DS showed a stable trend.
— There was a significant increase in DS births at <24 weeks (including terminations of pregnancy) only among women younger than 36 years.

Introduction

Trisomy 21 is the most common chromosomal anomaly among newborns. In the Netherlands, the live birth-prevalence of Down syndrome (DS) is estimated to be 11-16 per 10.000.[1-3] This is similar to the prevalence in the United States (12 per 10,000 live births).[4] Children with DS have a well-recognized phenotype, including external characteristics, specific health problems and intellectual impairment with delayed cognitive and motor development.[5-7]

In the Netherlands before 2007, women aged 36 years or older and those with a family history of chromosomal abnormalities were offered chorion villous sampling or amniocentesis for the diagnosis of DS. However, in 2002 screening with the first-trimester combined test was introduced in the Netherlands, in a nonsystematic way and only at patients' request.[8-10] The test includes an assay of the serum concentrations of pregnancy-associated plasma protein A (PAPP-A) and the free ß subunit of human chorion gonadotrophin (fß-hCG) between 9-14 weeks of the pregnancy, and an ultrasound measurement of the nuchal translucency (NT) between 11-13^{+6} weeks of the pregnancy.[11] The risk for DS is calculated based on the results of these tests, maternal age and pregnancy duration, and fetal karyotyping is offered if the risk is ≥1 in 200. The first-trimester combined test is covered by health insurance for women with a family history of chromosomal abnormalities and for those ≥36 years of age, whereas younger women have to pay for the test (around 150 euros).

The effect of the introduction of the screen on the prevalence of live and stillbirths with DS in the Netherlands has not been studied previously. We analyzed the trends in prevalences of DS in the Netherlands based on an eleven year birth cohort. We hypothesized that the live birth-prevalence of DS in the Netherlands would decrease as a consequence of the increased prenatal detection and subsequent termination of DS pregnancies.

Methods

Dutch data on perinatal and neonatal care are registered anonymously on a voluntary basis. Three separate national professional registers operate: the National Perinatal Registry for Primary Care (LVR-1, midwife-assisted births); the National Perinatal Registry for Secondary Care (LVR-2, obstetrician-assisted births); and the National Neonatology Registry (LNR, neonatal hospital care). These three registries are managed by the Netherlands Perinatal Registry (PRN-foundation). The registries contain records for all infants born from 16 weeks (102 days) of gestation under care of a midwife at home or in a hospital, as well as born under care of an obstetrician in a hospital, or being admitted to a neonatology department within the first 28 days of life. Attainment has increased in the study period and varies between 88% and 99%.

The LVR-1 and LVR-2 register maternal demographic characteristics, details on pregnancy and delivery, and characteristics on the newborn including congenital anomalies detected

at birth or within the first week after birth. Both live and stillbirths are registered; at <24 weeks (the legal limit for terminations of pregnancy, TOP, in the Netherlands) there is no recorded distinction between spontaneous and induced abortions. The LNR contains brief perinatal information and detailed information about the physical condition of the newborns, including congenital anomalies diagnosed before or at birth or within the first month of life.

Since 1995, the LVR-1, LVR-2 and LNR have been linked annually by a deterministic record linkage procedure based on neonatal and maternal matching variables (date of birth, gender, plurality, birth weight in grams, gestational age in completed weeks and remaining days, the four digits of the postal code).[1] Prevalences of congenital anomalies – detected before or at birth or within the first month of life – are available from an eleven year birth cohort (1997 to 2007).[2] Infants with DS (Trisomy 21) are registered in the LVR as well as in the LNR with a specific code.

Statistical analysis

For all analyses data are weighted for the proportion of infants registered. Weighing factors were defined per place of birth (i.e. at home, in a general hospital or in a university hospital), and year of registration, because there are various proportions of registration in these groups. The participation of all clinics was registered annually, so the exact proportion of registration is known for every year of registration. In 1997 for example, 91% of the home births, 88% of the births in the general hospitals and 100% of the births in the university hospitals were registered; and in 2007 these percentages were 93%, 99% and 100% respectively. Besides this, a weighing factor is added for all births assisted by general practitioners, and not by a midwife or obstetrician (so not included in above-mentioned groups of births). This small group of births was not included in the registration (only the number of births assisted by general practitioners is registered and used in the weighing factors).

General characteristics of the total cohort were determined, separately for children with and without DS. The prevalence of DS per 10,000 births was calculated by dividing the number of newborns registered with DS, by the total number of newborns registered in the LVR/LNR. The proportion of DS cases born before vs. at or after 24 weeks of gestation was determined yearly. This cut-off was based on the legal limit of 24 weeks of gestation for TOP in the Netherlands. The trend in prevalence was tested by logistic regression analyses, for total DS births, and separately using a threshold of 24 weeks of gestation. Models were adjusted for maternal age (<36 years or ≥36 years). The 95% confidence interval was calculated using a *logit* transformation and finite population correction ((1-n)/N) was applied.

To evaluate the major factors that influenced the prevalence of DS, mean maternal age was determined yearly. Linear regression analyses were performed to assess the trend in maternal age. Time trends were further evaluated within the DS sample by assessing

the proportion of DS diagnosis born before 24 weeks of gestation adjusting for maternal age (<36 years or ≥36 years). The analyses were also separately performed for mothers younger than 36 years and mothers aged 36 or older, because of the differences in prenatal screening practice between these groups. In addition, to determine whether the effects for maternal age on the outcome variables were equal for both groups, the influence of interaction terms were assessed by adding cross-products (of the outcome variable and maternal age) to the regression equation. P-values less than 0.05 were considered to be statistically significant. All analyses were performed using SPSS version 17.0 for Windows (SPSS Inc, Chicago, IL, USA).

Results

Data of 1,972,058 registered newborns were available for analysis, which accounted for approximately 91% of the births in the Netherlands during this eleven year period. After weighing, the total sample amounted to 2,174,635 births, of which 3,169 were DS. The prevalence of DS was 14.57 per 10,000 births [95% CI 14.43;14.73], equivalent to 1 per 686 births. On average, each year 288 infants with DS were born, of which 245 were live born (85.0%). General characteristics of the study population are presented in Tables 2.1 and 2.2.

Table 2.1: *General characteristics of the Down syndrome population, stratified for gestational age (GA) at delivery (<24 weeks vs. ≥24 weeks).*

	GA <24w	**GA ≥24w**	
	n=405	**n=2,764**	
General characteristics	**%**	**%**	***p***
Male gender	57.2	53.1	0.127
Dutch origin	88.1	82.1	0.003
Twins	0.7	3.3	0.004
Live births	-	97.2	-
	Mean *(SD)*	**Mean *(SD)***	***p***
Maternal age (years)	37.2 *(4.1)*	33.5 *(5.1)*	<0.001
GA (weeks)	19.5 *(1.7)*	38.1 *(2.4)*	<0.001

Abbreviations: GA – gestational age , SD – standard deviation

Table 2.2: *General characteristics of the study population according to diagnosis of Down syndrome .*

General characteristics	Down syndrome n=3,169 %	Non-Down syndrome n=2,171,466 %
GA <24 weeks	12.8	0.7
GA ≥24 weeks	87.2	99.3
Live births (GA ≥24 weeks)	85.0	98.8
Male gender	53.6	51.3
Dutch origin	82.9	82.0
Twins	3.0	3.7
	Mean *(SD)*	**Mean *(SD)***
Maternal age (years)	34.0 *(5.1)*	30.8 *(4.8)*
GA (weeks)	35.7 *(6.6)*	39.4 *(2.6)*
GA live births (weeks)	38.2 *(2.2)*	39.6 *(2.0)*

Abbreviations: GA – gestational age , SD – standard deviation

Table 2.3 shows the prevalence per year; in total as well as stratified for gestational age at delivery (<24 vs. ≥24 weeks) and for maternal age (<36 vs. ≥36 years). Trends in prevalence of DS stratified for births <24 and ≥24 weeks of gestation are presented in Figure 2.1. The proportion of births with DS ≥24 weeks of gestation varied from 11.65 to 14.24 per 10,000; the proportion of births with DS <24 weeks of gestation from 1.12 to 2.58 per 10,000. Logistic regression analyses showed no significant trend in total births with DS over the years 1997-2007 (p=0.385), as well as in DS births ≥24 weeks (p=0.146). The trend in DS births <24 weeks showed a significant increase (p=0.006); however after correcting for maternal age (<36 or ≥36 years), the trend was no longer present (p=0.332). During the study period, mean maternal age in the total Dutch population increased from 30.4 years in 1997 to 31.1 in 2007 (p<0.001) (Figure 2.2).

Within the DS population, a total of 405 infants with DS were born <24 weeks in the study period (12.8% of all DS births). This proportion increased over the years from 9.9% in 1997 to 15.8% in 2007 (p=0.011) (Table 2.4). However, after correcting for maternal age (<36 years or ≥36 years) the trend was no longer significant (p=0.103). Indeed, analyses by maternal age groups showed that the proportion of births <24 weeks showed a significant increasing trend only among women under 36 years (p=0.013), whereas the trend remained stable over the years for women 36 years and older (p=0.759). Among women younger than 36 years, on average 5.1% of DS births occurred before 24 weeks, compared to 24.3% for women 36 years and older. In comparison, in infants without DS the proportions of births <24 weeks were 0.6% and 1.2%, respectively. A nearly significant interaction was observed between maternal age and year of registration (p=0.057).

Figure 2.1: *Trends in prevalence of Down syndrome per 10,000 births, with 95%-confidence intervals (n=3,169), stratified for gestational age (GA) at birth.*

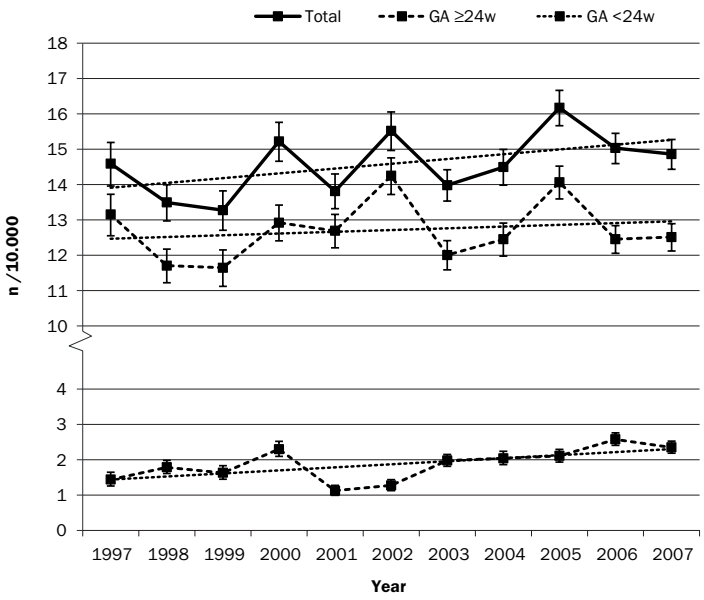
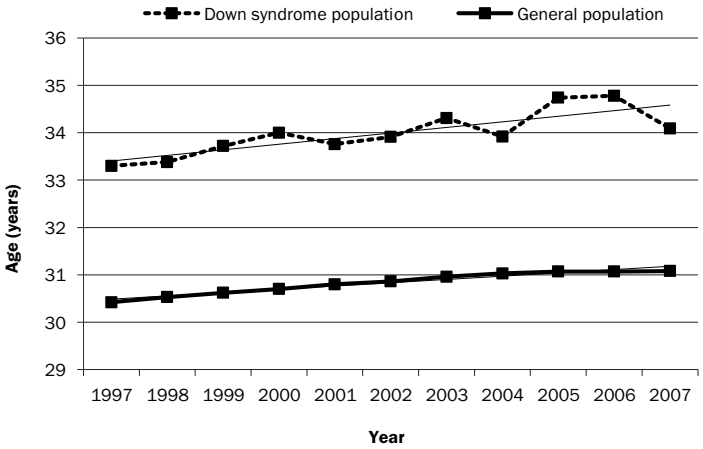


Table 2.3: *Prevalence of Down syndrome in the Netherlands during 1997-2007, born at or after 16 weeks of gestation; stratified for gestational age at delivery (<24 weeks vs. ≥24 weeks) and maternal age (<36 years vs. ≥36 years).*

	Number of births		DS prevalence per 10.000 [95% CI]	Number of DS births		Number of DS births	
Year	Total births	DS births		GA <24w	GA ≥24w	MA <36y	MA ≥36y
1997	194,663	284	14.59 [13.99;15.22]	28	256	92	192
1998	201,620	272	13.49 [12.99;14.01]	36	236	94	178
1999	202,649	269	13.27 [12.73;13.84]	33	236	99	170
2000	208,959	318	15.22 [14.68;15.78]	48	270	123	195
2001	204,880	283	13.81 [13.33;14.31]	23	260	112	171
2002	204,284	317	15.52 [14.98;16.07]	26	291	130	187
2003	202,429	283	13.98 [13.54;14.43]	40	243	113	170
2004	195,994	284	14.49 [13.99;15.00]	40	244	118	166
2005	189,837	307	16.17 [15.68;16.68]	40	267	138	169
2006	186,292	280	15.03 [14.61;15.47]	48	232	131	149
2007	183,028	272	14.86 [14.45;15.29]	43	229	107	165
Total	2,174,635	3,169	14.57 [14.43;14.73]	405	2,764	1,257	1,912

Abbreviations: GA – gestational age, MA - maternal age, DS - Down syndrome

Figure 2.2: *Mean maternal age in the Netherlands, stratified for total (n=2,174,635) and Down syndrome (n=3169) births.*



The distribution of gestational age in infants with DS, stratified for births before 24 weeks of gestation, and live and stillbirths at or after 24 weeks of gestation, is presented in Figure 2.3. Of all DS infants, 12.8% were born before 24 weeks of gestation (predominantly due to TOP, as suggested by the peak at 18-19 weeks of gestation). Mean gestational age in the total DS sample decreased from 36.2 weeks in 1997 to 35.1 in 2007 (Table 2.4).

Discussion

This nationwide eleven year birth cohort (1997-2007) shows that the prevalence of DS in the Netherlands remained stable at 14.57 per 10,000 births. Eighty-five percent of the infants were live born, resulting in on average 245 live born infants with DS annually.

Despite introduction of DS screening, there was no decrease in prevalence of DS. Prevalence of DS live births in the Netherlands was influenced by two factors. A postponement of childbearing to an older age led to an increase of DS pregnancies, also noted in other studies.[4,12,13] Such trend was offset by the effect of prenatal screening and diagnosis, which allows parents to choose whether to continue a DS pregnancy. However the counterbalancing effect of prenatal screening in the Netherlands was low. This is due to the fact that uptake of prenatal screening is rather low.[14] Towards the end of the study period only in a quarter of the pregnancies first trimester screening was carried out, resulting in a low total detection rate of DS pregnancies. Even after the official introduction of prenatal screening for all pregnant women, the uptake of first trimester screening with the combined test remained low, not surpassing 25%.[14] Factors that may influence uptake of prenatal screening may be the cost of the test (the test is free only for older women) and the attitude of parents towards DS.

Table 2.4: *Proportion of Down syndrome births according to gestational age (<24 weeks vs. ≥24 weeks).*

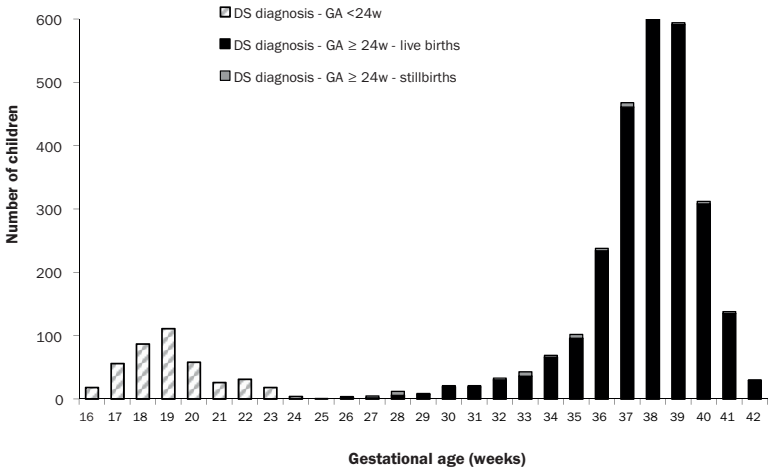
	Proportion within Down syndrome (%)					
	Total		Maternal age <36 years		Maternal age ≥36 years	
	gestational age		*gestational age*		*gestational age*	
Year	≥24w	<24w	≥24w	<24w	≥24w	<24w
1997	90.1	9.9	95.8	4.2	78.3	21.7
1998	86.8	13.2	95.5	4.5	71.3	28.7
1999	87.7	12.3	95.3	4.7	73.7	26.3
2000	84.9	15.1	95.4	4.6	68.9	31.1
2001	91.9	8.1	97.1	2.9	83.9	16.1
2002	91.8	8.2	97.9	2.1	82.9	17.1
2003	85.9	14.1	95.9	4.1	70.8	29.2
2004	85.9	14.1	91.5	8.5	78.0	22.0
2005	87.0	13.0	94.1	5.9	79.0	21.0
2006	82.9	17.1	92.6	7.4	71.8	28.2
2007	84.2	15.8	91.5	8.5	72.9	27.1
Trend		p=0.011		p=0.013		p=0.759

When interpreting the data, it should be taken into account that an underestimation of the total prevalence of DS is plausible, as a substantial number of terminations after first trimester screening will occur before 16 weeks of pregnancy, and these will therefore not be registered in the LNR/LVR. Another observation is that mean maternal age in DS births <24 weeks of gestation was much higher than in DS births ≥24 weeks (37.2 and 33.5 years, respectively). This implies that TOP was more prevalent among older women. This phenomenon could be the effect of the higher participation rate to prenatal screening in older women resulting in higher detection rates at older ages. Proportionally more older women undergo prenatal screening and diagnosis in the Netherlands, and consequently more terminations occur in this age group. The combination of the above mentioned factors resulted in a stable prevalence of DS (at or after 16 weeks of gestation) during 1997-2007. Also in other countries DS live births have not increased, despite an increasing maternal age.[15-17]

In our study TOP were not separately registered. The effect of TOP can be seen in the increase in proportion of DS births before 24 weeks of gestation. However, the increase is only significant among DS births to women younger than 36 years. This suggests that the (small) impact of first trimester screening is especially observable in younger women, while in older women participation in prenatal screening and diagnosis remained stable and low. The non-significant increase in DS births at or after 24 weeks of gestation in the study period confirms this trend indicating that the effect of increasing maternal age is not

counterbalanced by a higher participation of this age group in prenatal diagnosis.
We observed a peak in number of DS births at 18 to 19 weeks of gestation. This was most likely due to TOP. Indeed, after first trimester screening, fetal karyotyping can be performed by chorion villus sampling at 11-14 weeks with results available after 2 weeks, or by amniocentesis after 15 weeks of gestation, with results available after 3 weeks. With exclusion of early TOP, which would not be recorded in our database, the peak at 18-19 weeks account for the TOP after amniocentesis. A nationwide ultrasound screening is available in the Netherlands at 20 weeks; such screen could theoretically lead to late DS diagnoses and TOP up to the legal limit of 24 weeks, however such increase, if present, was negligible according to our analysis (see Figure 2.3). Of DS births from 16 to 23^{+6} weeks of gestation, TOP after 20 weeks accounted for a small proportion (19.3%).

Figure 2.3: *Distribution of gestational age (in weeks) in Down syndrome, presented by number of children born in 1997-2007 (n=3,169), stratified for gestational age (GA) at birth and (at ≥24 weeks) for live births or stillbirths.*



In the Netherlands, the number of invasive prenatal screening tests and TOP are registered by the Working Group on Prenatal Diagnosis and Therapy, a cooperation of the Dutch Society of Obstetrics and Gynecology and the Dutch Society for Clinical Genetics. They have reported an increase in the number of TOP from 1997-2009, before the legal term of 24 weeks of gestation.[18] This is in line with our observations. Unfortunately, no direct comparison can be made between these numbers and our data, because of insoluble registration differences.
The stable trend of prevalence in DS results in a continuous population of children with DS in the Netherlands. Prenatal screening for DS is introduced in the Netherlands for all pregnant women in order to allow pregnant women and their partners either to terminate the pregnancy if DS is diagnosed, or to prepare themselves for the birth of an affected

child.[8] Given the low uptake of prenatal screening in Dutch women and the observed stable trend in prevalence of DS, it seems that the first above-mentioned aim is not fully achieved. The reasons behind the low uptake of prenatal screening should be further explored. Maybe the practice and stable trend will change by offering the test free of costs to all pregnant women (at present it is free only for older women) or by replacing screening with non-invasive diagnosis on fetal DNA during pregnancy.[19,20] For now, a substantial number of children with DS are born alive in the Netherlands. For them, medical and social facilities are still needed to properly deal with their special needs.

Conclusions

National data of an eleven year birth cohort (1997-2007) from the Netherlands Perinatal Registry showed on average a prevalence of DS of 14.57 per 10,000 births. During this period, the prevalence of DS has not decreased: an estimated 245 children with DS were live born yearly. Apparently, the increase in maternal age and the low uptake of prenatal screening were observed to be stronger determinants of the prevalence of DS births than the effect of the introduction of first trimester screening. Among mothers younger than 36 years an effect of prenatal screening is observed (observed as an increasing trend in proportion of DS births before 24 weeks of gestation). So, the overall prevalence will remain stable, until the opportunities for performing prenatal screening will change (e.g. by offering the test costless or by replacing screening by non-invasive pregnant diagnosis on fetal DNA).

Acknowledgement

We thank the Netherlands Perinatal Registry (PRN-foundation) for giving us permission to use the data.

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