Improved prenatal detection of chromosomal anomalies

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ABSTRACT

INTRODUCTION: Prenatal screening for karyotype anomalies takes place in most European countries. In Denmark, the screening method was changed in 2005. The aim of this study was to study the trends in prevalence and prenatal detection rates of chromosome anomalies and Down syndrome (DS) over a 22-year period.

MATERIAL AND METHODS: The study was based on data collected from the EUROCAT registry of congenital anomalies for Funen County. The registry includes information about live births, foetal deaths with a gestational age > 20 weeks and terminations of pregnancy after prenatal diagnosis of foetal anomaly (TOPFA). The study includes all foetuses/infants diagnosed with a chromosome anomaly born between 1986 and 2007 of a mother residing in Funen County.

RESULTS: A total of 431 foetuses/infants had a chromosome anomaly corresponding to an overall prevalence of 35.6 chromosome anomalies per 10,000 births. This figure remained constant during the study period. Two hundred and three cases were live births (47% of total), 26 foetal deaths (6%) and 202 TOPFAs (47%). The prenatal detection rate for chromosome anomalies increased from 27% in the 1980s to 71% in the new millennium ($p < 0.001$). There were 235 cases with DS (55% of total cases), which yields an overall prevalence of 19 DS cases per 10,000 births.

CONCLUSION: The prevalence of all chromosomal anomalies and DS did not change over time. The prenatal DS detection rate more than doubled from 1986-1989 to 2000-2007. The number of TOPFAs increased, which is consistent with a decrease in the number of live births with DS as well as in all chromosomal anomalies.

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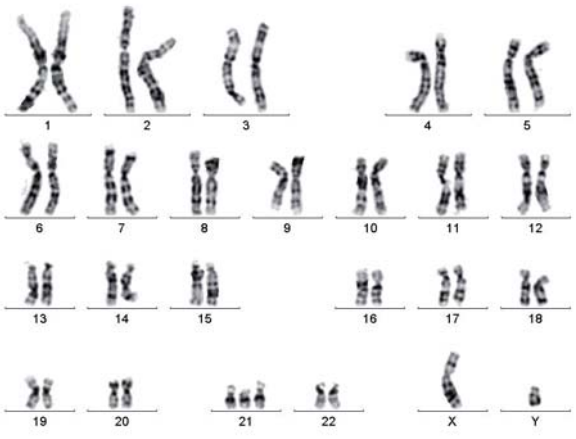
Prenatal screening for Down syndrome (DS) is performed in most European countries [1]. Structural malformations or chromosomal anomalies are present in 2-3% of all foetuses or newborns [2]. Congenital anomalies were previously the main cause of death in infancy, but today preterm birth is the main cause [3]. During the past decades, prenatal diagnosis of congenital anomalies has improved owing to the improved quality of ultrasonography [4-6].

In Denmark as in most other developed countries, DS screening has been based on the offer of an invasive test to women aged 35 years or above. However, this test is associated with a 1% risk of miscarriage and only 50% of Danish pregnant women aged 35 or more accepted the offer of invasive testing [7]. In 2004 the Danish National Board of Health changed its DS screening recommendations. As from 2005, all pregnant women have been offered a first trimester DS screening in the form of a combined test of maternal pregnancy-associated plasma protein A and human chorionic gonadotropin (β-hCG) plasma values and nuchal translucency. An increased risk of carrying a foetus with DS was defined as 1:300 or more.

A study from all 19 Danish screening centres found that the national prenatal DS detection rate increased to 86% in 2005 and 93% in 2006 in the population offered the first trimester screening with a false positive rate of 5% [8]. Further, the study found that the number of live-born infants with DS decreased significantly in the 2000-2007 period [8].

The present study presents data on the prevalence and the prenatal diagnosis of DS and all other chromosome anomalies for Funen County covering the 1986-2007 period and compares the total DS prevalences and live birth prevalences over time.



Karyotype 47XY+21, Down syndrome.

ORIGINAL ARTICLE

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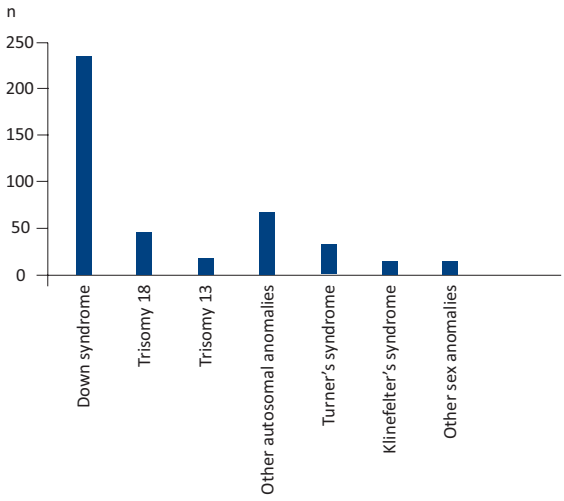
FIGURE 1

Distribution of types of chromosomal anomalies, Funen County, 1986-2007.



MATERIAL AND METHODS

The study was based on routinely collected data from the EUROCAT registry of Funen County [2]. The EUROCAT registries are population-based and use standardised methods of case ascertainment.

The registries are based on multiple sources of information including hospital records, birth and death certificates, annual reports from the cytogenetic laboratory and post-mortem examinations, information about live births (LB), foetal deaths (FD) with a gestational age (GA) of 20 weeks or more and termination of pregnancy (TOPFA) at any GA after prenatal diagnosis of foetal anomaly. All structural malformations, syndromes and chromosome anomalies are included in the database except for minor and poorly specified malformations found on an exclusion list.

The present study included all cases diagnosed with a chromosome anomaly with the following International Classification of Diseases (ICD) 10 codes: Q900-Q999, independent of other malformations. Chromosome anomalies that cannot be diagnosed with conventional analysis were excluded, e.g. micro deletions and positive comparative genomic hybridisation (CGH) arrays. Cases diagnosed with a mosaic or partial trisomy 21, 18 or 13 included in the group of cases with DS, trisomy 18 or 13, respectively.

Our study population includes all foetuses/children born in 1986-2007 where the pregnant woman resided in Funen County at the time of birth or abortion. The dataset includes the following variables: type of birth (LB, FD, TOPFA), birth weight, GA at diagnosis and maternal age.

Maternal age data for the study population were found at statistikbanken.dk. However, this population-based registry includes only live birth data.

As from 2005, all pregnant women have been offered an ultrasound examination to identify any foetal anomalies. Newborns have been examined by midwifes and if anomalies were suspected a pediatrician undertook any further examination.

The total number of births (live- and stillbirths) in Funen County during the study period was 121,066.

Statistics: The ratio of F distribution and the binomial distribution were used to calculate the 95% confidence interval (CI) for our population proportions. The chi-square test was used to calculate p values when appropriate.

Trial registration: not relevant.

RESULTS

The total number of foetuses/infants with a chromosome anomaly was 431. The overall prevalence of chromosomal anomalies was 35.6 per 10,000 births. The distribution of types of chromosomal anomalies is presented in **Figure 1**.

There were 203 live births (47% of total), 26 foetal deaths (6%) and 202 TOPFAs (47%). There was no change in the total prevalence of chromosome anomalies during the study period (**Table 1**), but the proportion of live births decreased and the proportion of TOPFAs increased significantly ($p < 0.0001$). The preva-

TABLE 1

Type of birth, prevalence and time of diagnosis for all chromosome anomalies. Funen County 1986-2007.

	Total births, Funen County, n	LB with karyotype anomalies, n (%)	FD with karyotype anomalies, n (%)	TOPFA with karyotype anomalies, n (%)	Total cases, n	Prevalence, n per 10,000 (95% CI)	Prenatal diagnosis, n	Postnatal diagnosis, n	Prenatal diagnosis, %, mean (range)
1986-1989	20,038	53 (73)	5 (7)	15 (20)	73	36.4 (28-46)	20	53	27 (18-39)
1990-1999	58,253	95 (49)	13 (7)	87 (45)	195	33.5 (28-41)	102	93	52 (45-60
2000-2007	42,775	55 (34)	8 (5)	100 (61)	163	38.1 (32-46)	116	47	71 (63-78)
Total	121,066	203 (47)	26 (6)	202 (47)	431	35.6	238	193	55

CI = confidence interval; FD = foetal death; LB = live births; TOPFA = termination of pregnancy after prenatal diagnosis of foetal anomaly.

lence of foetal deaths remained constant during the 22-year study period.

The prenatal detection rate for chromosome anomalies increased significantly throughout the study period. The detection rate increased nearly threefold from 27% in the 1980s to 71% in the last decade of the study period ($p < 0.001$). The increase was statistically significant from one decade to the next throughout the study period (Table 1).

Down syndrome

During the 22-year study period, the maternal age distribution among all births changed from 7% of all mothers ≥ 35 years to 17% of all mothers ≥ 35 years at the time of giving birth (**Figure 2**). This trend was also observed for foetuses/infants diagnosed with DS. The percentages of mothers ≥ 35 years among all Down syndrome cases increased from 27% to 57% (Figure 2).

There were 235 cases with DS (55% of all cases). The prevalence of DS did not change significantly throughout the study period, although the last three years (2005-2007) saw a higher prevalence than previous years (**Table 2**).

Table 2 also shows the increasing prenatal DS detection rate throughout the entire study period. The increase was statistically significant when 1980s were compared with 2005 ($p < 0.0001$) and the 1990s with 2006-2007 ($p < 0.005$). However, we found no statistically significant change in the prenatal detection rate from 2000-2004 (screening by maternal age) to 2006-2007 (first trimester screening by the combined test offered to all).

The total prevalence of DS over time and the live birth prevalence over time are presented in **Figure 3**. We have added a trend line to illustrate that the prevalence of live births over time was decreasing.

Evaluating the prenatal DS detection rate, we also need to consider the women who declined the offer of prenatal screening. In 2006-2007, 35 cases with DS were diagnosed. Thirty one of these were screened prenatally. Exclusion of women who did not accept the offer of prenatal screening yielded a detection rate in 2006-2007 of 74% (23/31), 95% CI (55-88).

Associated structural malformations were diagnosed in 76 of 128 liveborn infants with DS (59%). This percentage did not change over time. Fifty-eight infants had congenital heart defects (CHD), eight infants had CHD and another major congenital malformation, eight infants had isolated gastro-intestinal malformation and two had limb malformations (club foot, syndactyly). The most frequent types of CHD were atrial septal defect, ventricular septal defect and common atrioventricular canal.

The distribution by type of birth showed the same pattern as total chromosome anomalies, including a de-

FIGURE 2

Percentages of Down syndrome cases and percentages of all births with maternal age ≥ 35 years by year of study.

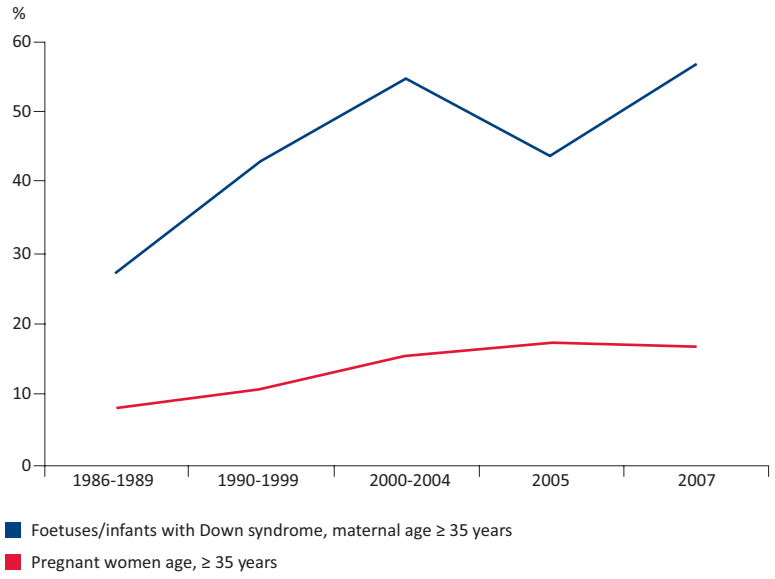


TABLE 2

Type of birth, prevalence and prenatal detection rate for Down syndrome. Funen County 1986-2007.

	Live births with Down syndrome, n (%; 95% CI)	Foetal deaths with Down syndrome, n (%)	TOPFA with Down syndrome, n (%; 95% CI)	Total Down syndrome cases, n	Prevalence, n per 10,000 births (95% CI)	Prenatal diagnosis, n	Postnatal diagnosis, n	Prenatally diagnosed, %, (95% CI)	GA at TOPFA, weeks, median (range)
1986-1989	34 (77; 62-89)	2 (5)	8 (18; 8-33)	44	22 (16-29)	8	36	18 (8-33)	Not known
1990-1999	57 (60; 49-69)	8 (8)	31 (32; 23-43)	96	16 (13-20)	33	63	34 (25-45)	16 (10-23)
2000-2004	20 (46; 30-61)	1 (2)	23 (52; 36-68)	44	16 (12-22)	26	18	59 (43-74)	13 (11-21)
2005	4 (25; 7-52)	0	12 (75; 48-93)	16	30 (17-51)	12	4	75 (48-93)	13 (11-19)
2006-2007	13 (37; 22-55)	1 (3)	21 (60; 42-76)	35	32 (23-45)	22	13	63 (45-78)	14 (10-21)
Total	128 (55)	12 (5)	95 (40)	235	19	101	134	43	

CI = confidence interval; GA = gestational age; TOPFA = termination of pregnancy after prenatal diagnosis of foetal anomaly.

creasing proportion of live births ($p < 0.001$) and an approximate threefold increase of TOPFAs ($p < 0.0001$). The number of foetal deaths was low and did not change over time.

The median GA at TOPFA for DS decreased from 16 weeks to 14 weeks throughout the study period (Table 2). This decrease was not statistically significant.

DISCUSSION

We evaluated the prevalence of all chromosome anomalies during the 22-year study period and found no statistically significant change over time.

When evaluating the overall prenatal detection rate, we found a statistically significant increase during all three decades. This increase was expected owing to the improvement in ultrasound technology and health care professionals' skills during the study period. The increase in detection rate also explains the increase in TOPFA which was highly significant and the decrease in the number of live born infants with chromosome anomalies.

The prevalence of DS did change, but not significantly during the study period, although the number of mothers aged 35 or more rose (Figure 2). It is also well-known that early diagnosis of DS (first trimester) identifies some cases that would have otherwise been aborted spontaneously without knowledge of the chromosomal anomaly. The prevalence of DS is therefore expected to be higher in areas with first-trimester screening than in areas with no prenatal screening.

However, we observed an increase in the prevalence of DS in 2007. This increase may represent a cluster of DS in this year. The same phenomenon was found in 1988 with a very low number of DS cases the following years (Figure 3). We still need to assess the number of DSs in 2008-2009 to establish whether the expected decrease has occurred. The increase in DS in 2007 in our area will also be followed by the EUROCAT surveillance system.

We found no statistically significant change in the detection rate when comparing the early years of the new millennium with 2006-2007. This may have several causes. In 2005 the screening had not yet been fully implemented. The prenatal DS detection rate for 2006-2007 was 74% (55-88) among the women screened in the first trimester. In a nationwide Danish study performed in the years 2005 and 2006, the prenatal detection rates were 86% and 93%, respectively [8]. Compared with the detection rates in our study, the differences are not statistically significant. A study based on data from EUROCAT found a prenatal DS detection rate of 90% in France and 96% of the pregnancies with DS diagnosed prenatally were terminated [1]. The prenatal DS detection rate in the European countries in which TOPFA is allowed ranged from 32% to 95% in 2002-2004 [1].

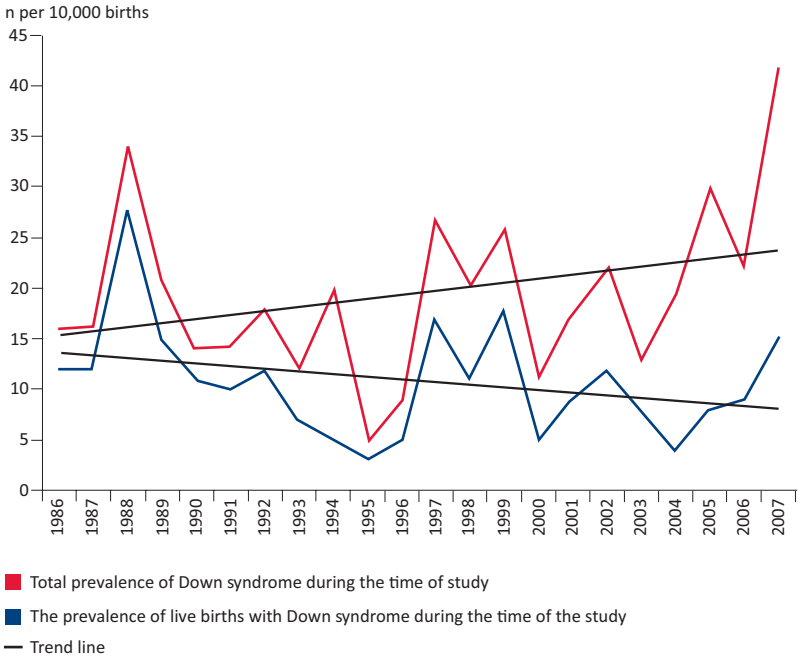
In a comparison of the old and the new screening procedures, it is important to discuss the number of invasive procedures. It is well-known that chorion villus sampling (CVS)/amniocentesis carries a risk of miscarriage of approx. 1%. The number of invasive procedures in Denmark decreased by 50% to approx. 3.5% from 2000 to 2006. The decrease was mainly caused by the implementation of a new screening program in 2005 [8].

We assessed whether the number of DS infants with associated structural malformations changed during the study period. We consistently found that 59% of all live born infants with DS had one or more associated malformations, but our study covers only a short part of the period during which the new screening procedure was performed. It would be of major interest to assess whether the implementation of the first-trimester DS screening will decrease the number of live born infants with DS and associated major congenital malformations.

When implementing a screening program, it is well-known that the screening is not universally accepted by the persons who are offered the test. One study found that 84.4% accepted the offer of a first-trimester DS screening [8]. In the present study, 35 infants were diagnosed with DS in 2006-2007. In 31 of these cases, the mother had attended the screening program. The detection rate among the screened women was 74% and we

FIGURE 3

Prevalence of Down syndrome versus live births with Down syndrome during the study period.



still need to see whether the detection rate in our area will reach the level generally achieved in Denmark.

The prevalence of all chromosomal anomalies and DS did not change significantly over time during the study period. The prenatal DS detection rate more than doubled from 1986-1989 to 2000-2007. The number and proportion of TOPFAs increased which is consistent with a decrease in the number of LBs with DS as well as the overall decrease in chromosomal anomalies. The new screening program from 2005 offered to all pregnant women has further increased the prenatal detection rate. Additionally, the median GA at TOPFA has decreased from 16 to 14 weeks. However, a 100% prenatal detection rate is unrealistic as the first trimester screening does not detect all foetuses with chromosomal anomalies, some women do not accept the test and some pregnancies are detected too late for a first trimester screening. The health care system can offer a screening test, but it is the pregnant woman who decides if she wants the screening procedure performed.

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CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedbul.dk.

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