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National screening guidelines and developments in prenatal diagnoses and live births of Down syndrome in 1973–2016 in Denmark

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Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Abstract

Introduction. Denmark was the first country in the world to implement a national, free-for-all offer of prenatal screening for Down syndrome to all pregnant women. It has a high uptake (>90%) compared to other countries. Thus, Denmark offers an interesting case for investigating the consequences of implementing comprehensive, national prenatal screening guidelines. The aim of this study was to describe the historical developments in invasive procedures, pre-/postnatal diagnoses of Down syndrome and Down syndrome live births in the period 1973–2016 in Denmark. *Material and methods.* Data on invasive procedures, pre- and postnatal Down syndrome diagnoses were retrieved from the Danish Cytogenetic Central Registry. *Results.* From 1973 to 1993, screening based on maternal age and high-risk indications resulted in a constant increase in invasive procedures. After the introduction of the triple test in 1994, invasive procedures decreased for the first time in 20 years. Following the introduction of an offer of combined screening to all pregnant women in 2004, the number of invasive procedures decreased markedly, while there was a concurrent increase in prenatal diagnoses of Down syndrome. Additionally, the number of Down syndrome live births decreased suddenly and significantly, but subsequently stabilized at 23–35 annual live births. Of these, the majority were diagnosed postnatally. *Conclusion.* Though prenatal screening technologies constantly improve, it was the introduction of and adherence to national guidelines that resulted in marked shifts in screening procedures and outcome in Denmark.

Abbreviations: cFTS, combined first trimester screening; DCCR, Danish Cytogenetic Central Registry; DFMS, Danish Fetal Medicine Society; DS, Down syndrome; LB, live birth; NIPT, non-invasive prenatal testing; TOP, termination of pregnancy.

Introduction

Over the last decades, numerous prenatal screening programs have been successively introduced in many countries. Prenatal screening for Down syndrome (DS), for example, has developed significantly over the years with regard to screening tools and diagnostic options (1–5). The consequences of implementing and offering such screening programs with regard to number of

prenatal DS diagnoses, termination of pregnancy (TOP) and live births (LB) have been estimated in different contexts (6–9). Such estimates are essential for monitoring and future planning of prenatal offers.

Since 1968, all Danish data on prenatal and postnatal chromosome analyses have been systematically reported by all cytogenetic laboratories in Denmark to the Danish Cytogenetic Central Registry (DCCR) (10). The DCCR thus has virtually complete coverage of constitutional chromosomal abnormalities diagnosed in the country. Consequently, in Denmark, we have a unique opportunity to retrieve and present the historical development in actual numbers of invasive diagnostic procedures as well as numbers of DS prenatal diagnoses, TOPs, and LB for the past 40 years.

Developments in screening for and diagnosis of DS are not only determined by technological developments. The changing demographics of the target population as well as the impact of policy and guideline changes must also be taken into account to understand the impact and outcome of offering prenatal screening for DS. Denmark was the first country in the world to implement a national, free-for-all offer of combined first trimester screening (cFTS) as well as a second trimester ultrasound examination for fetal malformations to all pregnant women (11,12). Additionally, Denmark has a high uptake (>90%) in the prenatal screening program (13) compared to other North European countries (14–16). Thus, Denmark offers an interesting case for investigating the consequences of implementing comprehensive, national prenatal screening guidelines.

The aim of the study was to describe the historical developments in Denmark concerning DS prenatal screening and testing for the period 1973–2016 with regard to the number of invasive procedures, pre-/postnatal DS diagnoses and DS LBs.

Material and methods

All results from pre- and postnatal chromosome analyses are registered in the DCCR. We retrieved information about invasive procedures as well as pre- and postnatal DS diagnoses regardless of diagnostic method. The prenatal DS diagnoses are distributed according to the due date (not day of invasive procedure or TOP) in order to make data comparable with postnatal DS diagnoses, which are recorded after LB. Information about annual birth rate and distribution of maternal age at delivery was retrieved from the Danish Health Data Authority.

Ethical approval

The present study is based on anonymous registry data. According to Danish laws, research not involving human material or sensitive personal data does not require ethical approval (17) or data protection approval (18).

Results

Denmark has a population of 5.7 million. The annual number of pregnancies and the number of pregnancies in women aged ≥35 years at delivery are presented in Figure 1.

Developments in screening policy

Table 1 presents developments in the Danish national guidelines for DS prenatal screening and diagnostics. However, it must be noted that before 2004 there were some regional and local differences in the organization and offer of prenatal screening with some hospitals using expanded screening criteria or offering additional examinations/testing to some groups, not included in the guidelines. The 2004 guidelines represented the most prominent change as the offer of screening was expanded to *all* pregnant women. Simultaneously, the screening technology was significantly improved by the nationwide and mandatory introduction of an offer of the cFTS in addition to a first and a second trimester ultrasound examination. Thus, the previous regional differences were thoroughly eliminated.

Developments in invasive procedures

Figure 2 presents the number of annual invasive diagnostic procedures in Denmark. It includes all indications and all trimesters. The figure illustrates that following the initial introduction of DS screening based on age and pregnancy history in 1973, there was a constant and substantial increase in invasive procedures until 1993, when the number peaked at 8592 annual procedures. During this period, some obstetric departments had introduced screening based on biochemical markers; however, this offer was unevenly distributed. In 1994, the triple test was added to the national screening program

Key Message

The outcomes of prenatal screening in Denmark depend on national uniform guidelines. Following a national implementation of combined first trimester screening in 2004, Down syndrome detection rates increased and invasive procedures decreased. Since 2004, the number of Down syndrome live births has been halved.

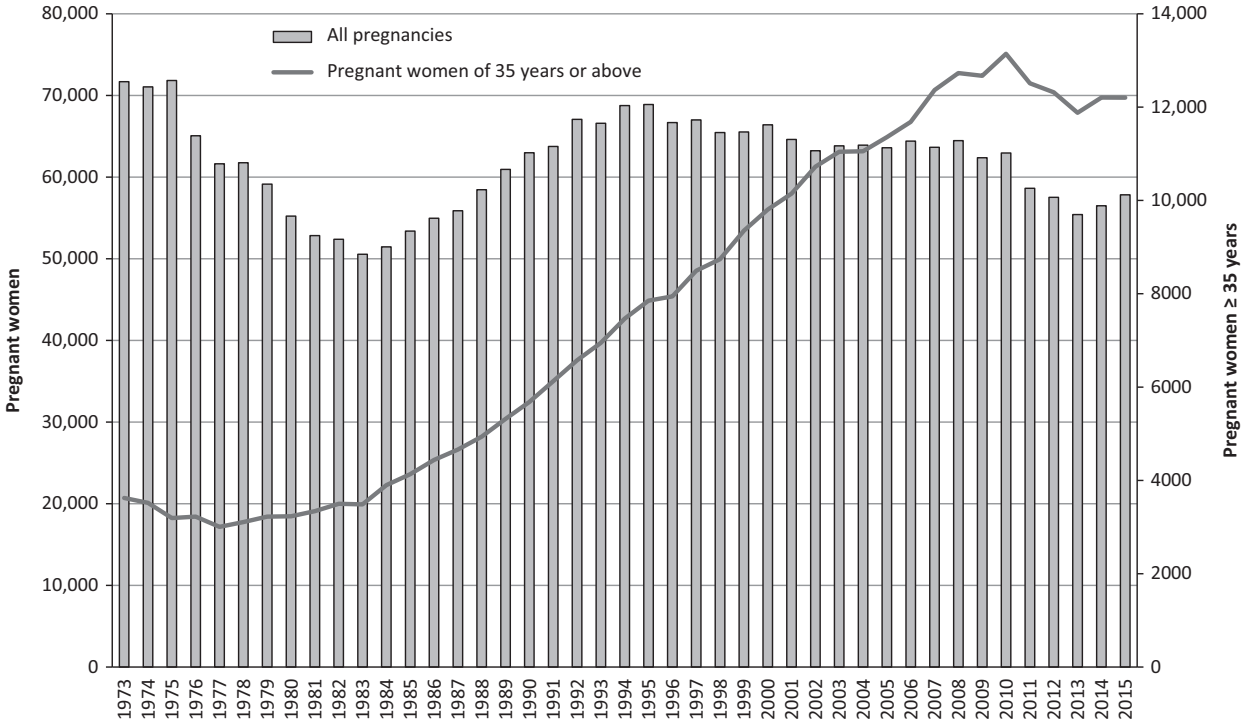

Figure 1. Total number of pregnant women and number of pregnant women ≥35 years giving birth in Denmark 1973-2015 (numbers for 2016 not available).

guidelines (19), which allowed a more targeted identification of the risk population (previous criteria was maintained, see Table 1). Subsequently, the number of invasive procedures dropped and stabilized at an average of 7211 annual procedures (1993–2003), until the cFTS was introduced in the 2004 guidelines. Despite screening now being offered to all and accepted by most pregnant women, the number of invasive procedures decreased markedly. Interestingly, despite the increase in maternal age (and consequently increased risk of DS), the number of invasive procedures has stabilized at approximately 3300–4000 annual procedures between 2005 and 2016. The 2016 increase in invasive procedures consists of a decrease in the number of chorionic villus sampling but a concurrent increase in amniocentesis.

Developments in prenatal diagnoses and live births

Figure 3 presents the annual distribution of pre- and postnatal DS diagnoses; that is, the actual cases of DS prenatal diagnoses and the actual cases of DS LB. It should be noted that the vast majority of prenatal diagnoses of DS result in TOP, and the majority of DS LB are not diagnosed until after birth (see Figure 4). Figure 3 shows that the number of prenatal DS diagnoses steadily increased from 1973 to 2003. The figure suggests a small increase in diagnoses following the 1994 introduction of the triple test. From 1993 to 2003, the number of DS prenatal diagnoses increased from 47 to 85 and the number of invasive procedures decreased from 8595 to 6352 per year. This suggested increase is supported when dividing the number of prenatal DS diagnoses with the total number of invasive procedures on all indications (hereafter referred to as the aggregate positive predictive value) (Figure 2). Up to 1994, the aggregate positive predictive value of the overall prenatal screening program was approximately 0.5% which increased to 1% following the introduction of the triple test.

The introduction of cFTS in 2004 resulted in a marked decrease in invasive procedures and a concurrent increase in DS diagnoses to 97–137 cases annually (Figure 3). Following the introduction of cFTS screening (2005–2016), the aggregate positive predictive value of the overall national screening program increased to 3.8% annually (range 3.4–4.3%) (Figure 2).

Developments in Down syndrome live births

Figure 4 shows the distribution of pre- and postnatal diagnoses in the group of DS LB. During 1973–2003, there were 36–81 DS LB annually. Following the 2004 guidelines, the number of DS LB decreased suddenly and significantly, but subsequently stabilized at 23–35 DS LB

Table 1. Danish national guidelines on prenatal screening.

Year	Stated purpose	Screening indication	Screening technology	High-risk group	Diagnostic test
1978	To prevent birth of children with severe, lifelong disability	Maternal age ≥35 years or paternal age ≥50 or pregnancy history	None	Maternal age ≥35 years or paternal age ≥50 or pregnancy history	Invasive
1981	To prevent birth of children with severe, lifelong disability	Maternal age ≥35 years or pregnancy history	None	Maternal age ≥35 years or pregnancy history	Invasive
1994	To offer women a choice of prenatal diagnosis if at increased risk	Maternal age ≥35 years or pregnancy history	Triple test (age AND AFP AND estriol AND hCG) or straight to invasive diagnostic test	Maternal age ≥35 years or Triple Test result >1:400 for DS	Invasive
2004	To offer information and a choice of prenatal screening	All	cFTS (age AND (PAPP-A AND b-hCG) AND nuchal translucency) AND 2nd trimester malformation scan	cFTS risk for DS >1:300 or risk for Edward or Patau syndrome >1:150 or pregnancy history or malformation	Invasive
2017	To offer information and a choice of prenatal screening	All	cFTS (age AND (PAPP-A AND b-hCG) AND nuchal translucency) AND 2nd trimester malformation scan	cFTS risk for DS >1:300 or risk for Edward or Patau syndrome >1:150 or pregnancy history or maternal age >45 or outliers for PAPP-A or b-hCG or Nuchal translucency >3.5 mm or malformation	Invasive or NIPT^{+} invasive if positive

AFP, alpha-fetoprotein; hCG, human chorionic gonadotropin; cFTS, combined first trimester screening; DS, Down syndrome; NIPT, non-invasive prenatal testing, PAPP-A, pregnancy associated plasma protein-A.

annually. There has been no change in the TOP legislation in Denmark between 1973 and 2016. Interestingly, of the annual DS newborns, only one to nine children were diagnosed prenatally, meaning that only very few parents choose to continue the pregnancy when DS is diagnosed during pregnancy. Thus, the majority of DS LB was either not detected by screening or parents declined prenatal screening or diagnostic procedures.

Between 2004 and 2016, the number of prenatal DS diagnoses steadily increased despite a relatively constant number of invasive procedures and LB. Since 1988, there has been a small subpopulation who chooses to continue the pregnancy and where the pregnancy results in an LB. The highest numbers of prenatally diagnosed DS LB occurred in 2013 and 2016. In 2016, nine of 27 DS LB had been diagnosed prenatally. This corresponds to 33% of the DS LB that year, but only 7% of the total number of DS prenatal diagnoses in 2016. In comparison, the numbers in 2014 were 12% and 3%, respectively.

Discussion

The results demonstrate the effect of implementing national guidelines for DS screening in 1973–2016 in Denmark. The increase in detection rate and decrease in invasive procedures after 2004 was a clear result of a joint implementation of and adherence to the national guidelines across all regions and hospitals.

The impact of the guidelines are even more notable when taking into account the preceding regional and local differences, which meant that first and/or second trimester ultrasound were offered at some hospitals (20–22). For example, ultrasound screening examinations were not included in the national guidelines until 2004; nevertheless, in 2000, 55% of the pregnant population had at least one offer of an ultrasound screening examination during pregnancy (22). This figure, however, covers great regional variation. A study shows that in 2000, cFTS was routinely offered in one hospital (1.1% of the pregnant population) and offered as a pilot study in three hospitals (21). However, the significant and additional (non-guideline) screening activities in Danish obstetric departments prior to the 2004 guidelines occurred without significant changes in the number of invasive procedures or prenatal diagnoses, which underscores the effect of a collective commitment to a joint prenatal screening program.

Our study shows that between 2004 and 2016 the number of prenatal diagnoses of DS increased but the number of invasive procedures and LBs remained constant. This may be explained by increasing maternal age (more cases to detect) combined with refinements in the screening technology (for example, the inclusion of pregnancy-

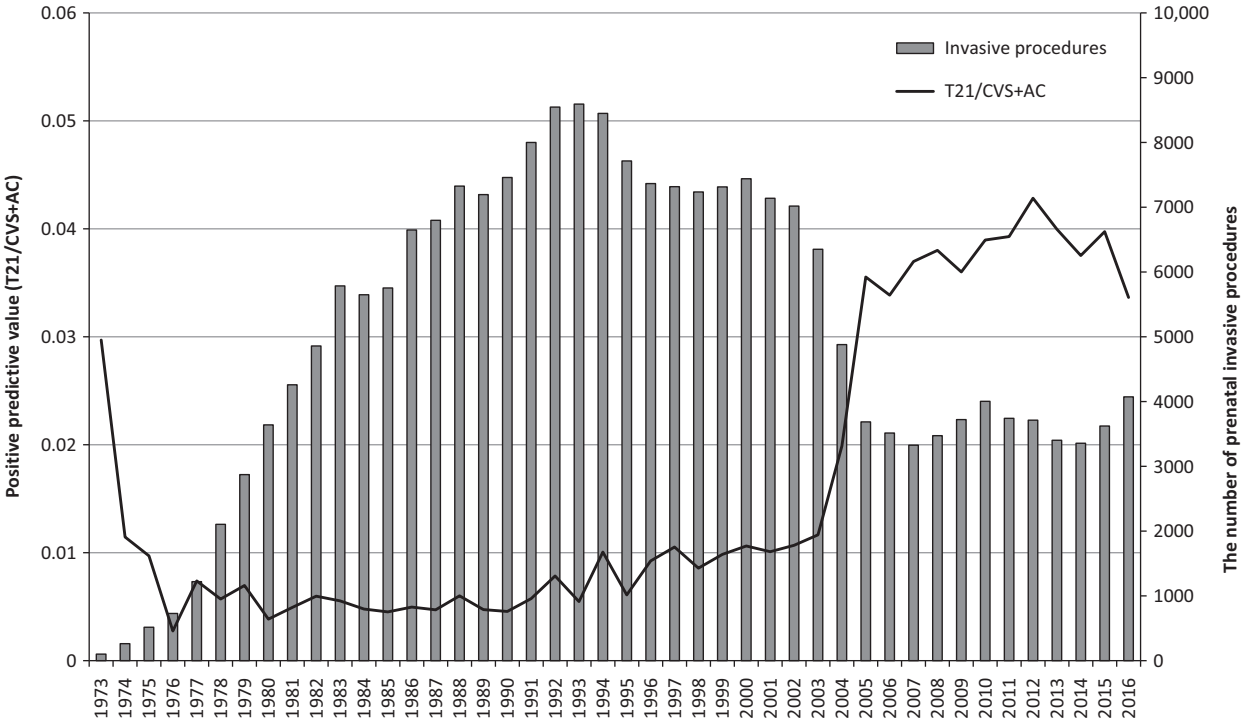

Figure 2. Number of invasive procedures and the aggregate positive predictive value defined as trisomy 21/chorionic villus sampling + amniocentesis (T21/CVS + AC) (all indications) in Denmark 1973–2016.

associated plasma protein-A (PAPP-A) <0.2 multiples of the median in the risk algorithm), which allow more precise detection of high risk for DS (5). The most recent change in the national guidelines is an expansion of the high-risk category to include maternal age ≥45 years, nuchal translucency measurement ≥3.5 mm and outlier biochemical results (23). However, it is not only the developments in the risk algorithm or the increased understanding of additional risk factors that have increased the prenatal detection of DS. Over the past 10 years, there has been a significant development and improvement in ultrasound technology. This development may explain the increase in amniocentesis procedures seen in 2016, as it may reflect improvements in second and third trimester detection of malformations by ultrasound.

The 2017 guidelines include an offer of non-invasive prenatal testing (NIPT) as an alternative to invasive testing for high-risk pregnant women. One could expect the offer of NIPT to reduce significantly the number of invasive procedures for the group of high-risk women in Denmark. Such decrease has been the result of offering NIPT in other contexts (24). However, unpublished results from the Central Denmark Region show that only 20% of women in the high-risk group chose NIPT as an alternative to invasive diagnostics. A possible explanation could be that the Danish Fetal Medicine Society (DFMS) generally agrees that invasive diagnostics and chromosomal micro-array (CMA) are valuable diagnostic techniques in identifying a significant number of genomic aberrations in high-risk pregnancies. These aberrations are not detected by NIPT. This common understanding is based on recent Danish studies (5,25). Thus, clinicians are alert to the importance of pre-test counseling and informing high-risk women of the advantages and disadvantages of NIPT and CMA, respectively. As the implementation of NIPT is still relatively new, it is not possible to draw final conclusions, but the preliminary data suggest that Danish women at high risk often choose CMA over NIPT. This finding resonates with Dutch studies indicating that a majority of pregnant women at high risk for aneuploidies (26) or with an abnormal ultrasound finding (27) want maximum information about the fetus.

However, NIPT has other potentials to influence prenatal screening in Denmark. For example, prior to the 2017 guidelines, approximately 15% of the high-risk population declined the offer of invasive procedures (5). For women who decline invasive procedures due to fear of procedure-related risk of miscarriage, NIPT is a genuine alternative that allows women to make a choice based on their desire for knowledge rather than their fear of miscarriage (28). For this group, the offer of NIPT is expected to increase the number of prenatal diagnoses.

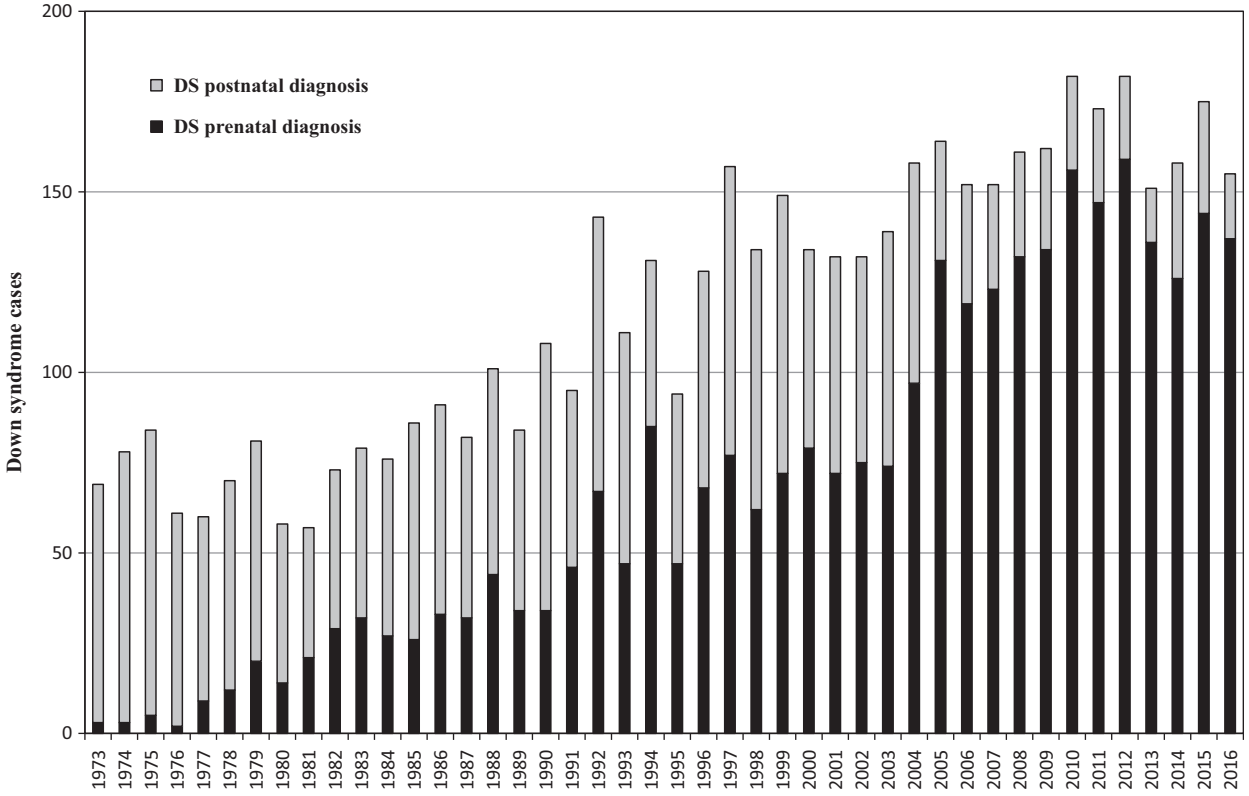

Figure 3. Number of Down syndrome (DS) cases according to pre- or postnatal diagnosis in Denmark 1973–2016.

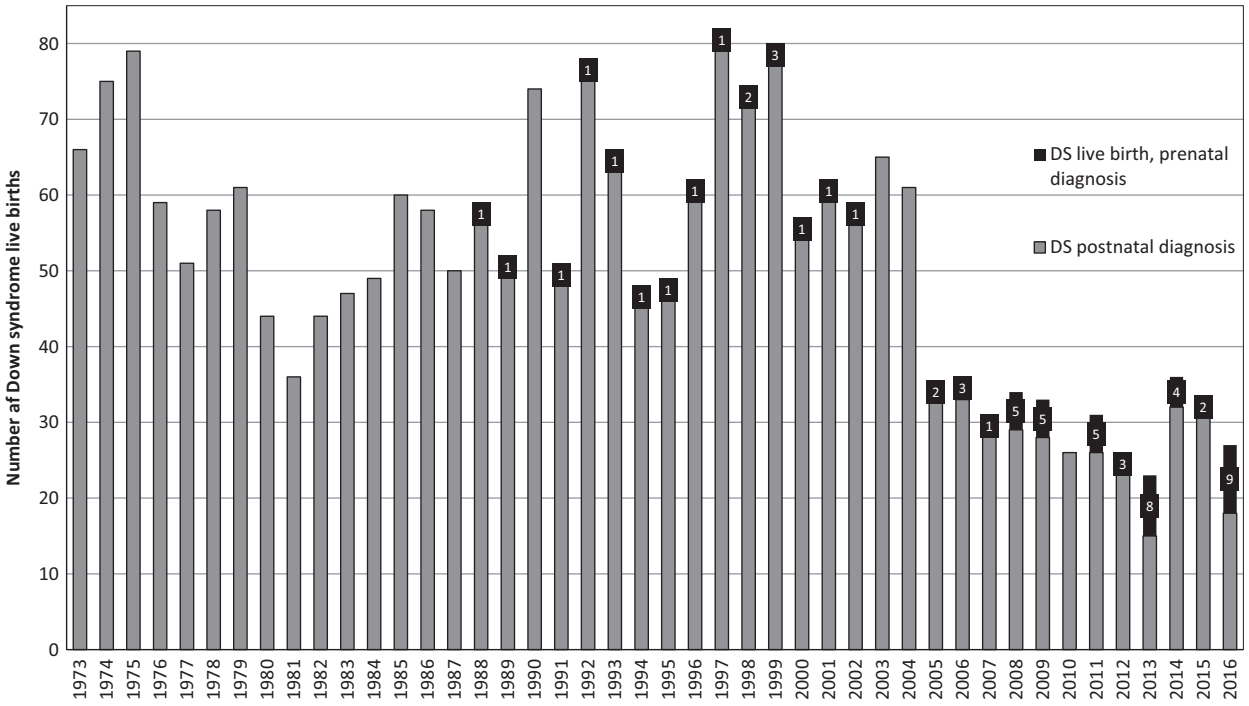

Figure 4. Down syndrome (DS) live births and time of diagnosis in Denmark 1973–2016.

As long as the screening program detection rate is less than 100% for DS, undiagnosed DS LB will occur among women who have been screened. The number of DS LB remains relatively constant in Denmark. This study shows that DS LB are primarily a result of lack of prenatal detection rather than active choice. However, we have little knowledge about the screening status of mothers of newborns with a postnatal diagnosis of DS. It would be valuable to know how many of those had declined screening, had declined diagnostic procedures or simply had a low-risk cFTS result.

A recent systematic review found that parents who choose to continue the pregnancy following a severe diagnosis – such as DS – requested timely and adequate information, and continued and empathic interactions with clinicians (29). In Denmark, the number of women and couples who choose to continue the pregnancy is very low, and it is very important that the needs of this subpopulation are not overlooked and that the decision to continue is positively supported and legitimized by clinicians.

Looking back, the 2004 guidelines impacted more than invasive procedures and detection rates. It also influenced the professional and clinical context into which it was implemented in several other ways. First, based on preceding dialogue with clinicians, the National Health Authorities initiated the 2004 guidelines to counteract emerging local discrepancies in prenatal screening and care. With the exception of a few university hospitals, the offer of cFTS to all women was new to most hospitals. Thus, the guidelines represented a considerable, collective challenge for all departments with regard to increased requirements for equipment, staff and education. However, these collective challenges served as a common platform, for example for developing educational standards and for procurement of equipment, which further advanced collaboration within clinical genetics, fetal medicine and across obstetric ultrasound units. Secondly, the clinical collaborations following the 2004 guidelines gave the medical speciality a joint understanding of the importance of a high-quality, uniform clinical practice to ensure a consistent and equal offer of prenatal screening, testing and care to all pregnant women in Denmark. This understanding was, and is supported by, the work of the DFMS that initiates and produces clinical guidelines that are continuously discussed, revised and collectively approved at annual meetings. The DFMS guidelines specify and explicate the national guidelines in line with current clinical developments, interests and concerns. Thirdly, another result of the standardization of prenatal screening practices has been the establishment of the Danish Fetal Medicine Database (30). The database enables close and consistent monitoring of a wide range of quality parameters to assess performance (for example false-positive rates), allow benchmarking between hospitals, and support continuous quality improvement. Fourthly, a joint decision was made that the cFTS is carried out in all departments by nurses and midwives, who must be certified in sonography by the Fetal Medicine Foundation, including annual audits and re-certification. And finally, from the consistent and high uptake, we have learned that Danish pregnant women are very positive towards a free-for-all, comprehensive prenatal screening program.

Strengths and limitations

A key methodological strength in this study is the validity of data. Today, Denmark has a nationally homogeneous prenatal screening program with a very high uptake of more than 90% of the pregnant population. Until very recently, no private clinics offered NIPT or invasive testing, and thus very little data was lost. One registry, the DCCR, has continuously collected the data over the entire period and has an extremely high follow-up rate due to the Danish personal identifier, the CPR (personal registration number) (10). A limitation is that the DCCR has some results on miscarriage and these have been included. However, data on miscarriages are known to be of a lesser quality, and some under-reporting of miscarriages caused by DS is likely.

It should also be noted that we have calculated the aggregate positive predictive value based on all invasive procedures. Thus, our results reflect the positive predictive value of the overall screening program, including invasive procedures for all indications (not only DS) and including diagnoses of DS in both the second and third trimesters. Moreover, approximately 15% of women at high risk choose to forego invasive diagnostics. Identifying women in this group who either had spontaneous abortion of a DS fetus or DS LB would provide a more accurate positive predictive value of the screening program.

Conclusion

Many factors influence the outcome of a prenatal screening program: demographics, technical advances, attitudes and not least the implementation of national guidelines. In Denmark this has resulted in stable numbers of DS LB until 2004, when the cFTS was implemented. As a consequence the number of DS LB has since been halved.

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References

1. Alfirevic Z, Sundberg K, Brighem S. Amniocentesis and chorionic villus sampling for prenatal diagnosis. Cochrane Database Syst Rev. 2003;3:CD003252.
2. Tabor A, Alfirevic Z. Update on procedure-related risks for prenatal diagnosis techniques. Fetal Diagn Ther. 2010;27:1–7.
3. Nicolaides KH, Spencer K, Avgidou K, Faiola S, Falcon O. Multicenter study of first-trimester screening for trisomy 21 in 75 821 pregnancies: results and estimation of the potential impact of individual risk-orientated two-stage first-trimester screening. Ultrasound Obstet Gynecol. 2005;25:221–6.
4. Chitty LS, Kagen KO, Molina FS, Waters JJ, Nicolaides KH. Fetal nuchal translucency scan and early prenatal diagnosis of chromosomal abnormalities by rapid aneuploidy screening: observational study. BMJ. 2006;332:452–4.
5. Petersen OB, Vogel I, Ekelund C, Hyett J, Tabor A; Danish Fetal Medicine Study Group; Danish Clinical Genetics Study Group. Potential diagnostic consequences of applying non-invasive prenatal testing: population-based study from a country with existing first-trimester screening. Ultrasound Obstet Gynecol. 2014;43:265–71.
6. Graaf G, Engelen JJM, Gijsbers ACJ, Hochstenbach R, Hoffer MJV, Kooper AJA, et al. Estimates of live birth prevalence of children with Down syndrome in the period 1991–2015 in the Netherlands. J Intellect Disabil Res. 2017;61:461–70.
7. de Graaf G, Buckley F, Skotko BG. Estimates of the live births, natural losses, and elective terminations with Down syndrome in the United States. Am J Med Genet A. 2015;167:756–67.
8. Morris JK, Alberman E. Trends in Down's syndrome live births and antenatal diagnoses in England and Wales from 1989 to 2008: analysis of data from the National Down Syndrome Cytogenetic Register. BMJ. 2009;339:b3794.
9. Rudolf G, Tul N, Verdenik I, Volk M, Brezigar A, Vokač NK, et al. Impact of prenatal screening on the prevalence of Down syndrome in Slovenia. PLoS ONE. 2017;12: e0180348.
10. Nguyen-Nielsen M, Svensson E, Vogel I, Ehrenstein V, Sunde L. Existing data sources for clinical epidemiology: Danish registries for studies of medical genetic diseases. Clin Epidemiol. 2013;5:249–62.
11. Ekelund CK, Jørgensen FS, Petersen OB, Sundberg K, Tabor A. Impact of a new national screening policy for Down's syndrome in Denmark: population based cohort study. BMJ. 2008;337:a2547.
12. Danish National Board of Health. Retningslinjer for prænatal diagnostik. [Guidelines for prenatal diagnosis]. (In Danish, no abstract available). Copenhagen: Danish National Board of Health, 2004.
13. Regionernes kliniske kvalitetsudviklingsprogram. Dansk Føtalmedicinsk database. National årsrapport 2014. [Danish fetal medicine database. Annual report]. (In Danish. No abstract available). Copenhagen: Regionernes kliniske kvalitetsudviklingsprogram, 2014. http://www.dfms.dk/images/foetodatabase/Arsrapport_FOTO_2014_final_anonymiseret.pdf (accessed 3 August 2017).
14. Crombag NMTH, Vellinga YE, Kluijfhout SA, Bryant LD, Ward PA, Iedema-Kuiper R, et al. Explaining variation in Down's syndrome screening uptake: comparing the Netherlands with England and Denmark using documentary analysis and expert stakeholder interviews. BMC Health Serv Res. 2014;14:437.
15. Bakker M, Birnie E, Pajkrt E, Bilardo CM, Snijders RJM. Low uptake of the combined test in the Netherlands – which factors contribute? Prenat Diagn. 2012;32:1305–12.
16. Alderdice F, McNeill J, Rowe R, Martin D, Dornan J. Inequalities in the reported offer and uptake of antenatal screening. Public Health. 2008;122:42–52.
17. The Danish Health Research Committees. Available online at: http://www.nvk.dk/english/the-system-of-health-research-ethics-committees (accessed 4 September 2017).
18. The Danish Data Protection Agency. Available online at: https://www.datatilsynet.dk/english/health-research-and-statistics-projects/private-research-and-statistics-projects/ (accessed 4 September 2017).
19. Danish National Board of Health. Vejledning og redegørelse: Prænatal genetisk information, rådgivning og undersøgelse. [Guideline and report on prenatal genetic information, counseling and examination]. Copenhagen: Danish National Board of Health, 1994.
20. Jørgensen FS. Epidemiological studies of obstetric ultrasound examinations in Denmark 1989–1990 versus 1994–1995. Acta Obstet Gynecol Scand. 1999;78:305–9.
21. Jørgensen FS. Ultralydundersøgelse af gravide kvinder i Danmark 1999–2000 – med beskrivelse af udviklingen siden 1989–90. [Ultrasound examinations of pregnant women in Denmark 1999–2000 – with description of the development since 1989–1990] (In Danish, abstract available). Ugeskr Laeger. 2003;165:4409–15.
22. Jørgensen FS. Organisation af obstetrisk ultralyd i Danmark 2000 – med beskrivelse af udviklingen siden 1990. [Organisation of obstetric ultrasound in Denmark

2000 – with description of the development since 1990]. (In Danish, abstract available). Ugeskr Laeger. 2003;165:4404–9.
23. Danish National Board of Health. Retningslinjer for fosterdiagnostik (Guidelines for prenatal diagnosis) (In Danish. No abstract available). Copenhagen: Danish National Board of Health, 2017.
24. Khalifeh A, Weiner S, Berghella V, Donnenfeld A. Trends in invasive prenatal diagnosis: effect of sequential screening and noninvasive prenatal testing. Fetal Diagn Ther. 2016;39:292–6.
25. Vogel I, Petersen OB, Christensen R, Hyett J, Lou S, Vestergaard EM. Chromosomal microarray as a primary diagnostic genomic tool for pregnancies defined as being at increased risk within a population based combined first-trimester screening program. Ultrasound Obstet Gynecol. 2017; https://doi.org/10.1002/uog.17548.
26. van der Steen SL, Diderich KEM, Riedijk SR, Verhagen-Visser J, Govaerts LCP, Joosten M, et al. Pregnant couples at increased risk for common aneuploidies choose maximal information from invasive genetic testing. Clin Genet. 2015;88:25–31.
27. Srebniak M, Boter M, Oudesluijs G, Joosten M, Govaerts L, Opstal D, et al. Application of SNP array for rapid prenatal diagnosis: implementation, genetic counselling and diagnostic flow. Eur J Hum Genet. 2011;19:1230–7.
28. Bjerregaard L, Stenbakken AB, Andersen CS, Kristensen L, Jensen CV, Skovbo P, et al. The rate of invasive testing for trisomy 21 is reduced after implementation of NIPT. Dan Med J. 2017;64:A5359.
29. Lou S, Jensen LG, Petersen OB, Vogel I, Hvidman L, Møller A, et al. Parental response to severe or lethal prenatal diagnosis: a systematic review of qualitative studies. Prenat Diagn. 2017;37:731–43.
30. Ekelund CK, Petersen OB, Jørgensen FS, Kjaergaard S, Larsen T, Olesen AW, et al. The Danish Fetal Medicine Database: establishment, organization and quality assessment of the first trimester screening program for trisomy 21 in Denmark 2008–2012. Acta Obstet Gynecol Scand. 2015;96:577–83.