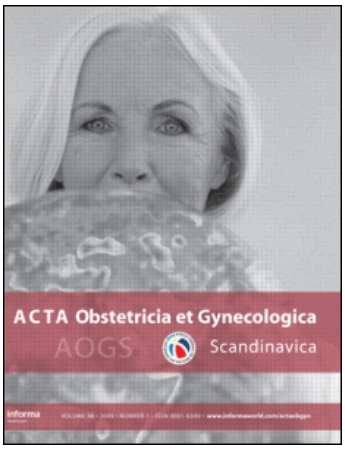

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SHORT REPORT

Invasive prenatal diagnostic practice in Denmark 1996 to 2006

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Abstract
The Danish National Board of Health recommended in 2004 routine ultrasound scanning in week 12 with nuchal translucency measurement, combined with the double test to all pregnant women. Those who were found to have a risk of trisomy 21 higher than 1:300 were offered amniocentesis or chorionic villus sampling (CVS). The total number of pregnancies in Denmark with an invasive prenatal procedure decreased from 6,929 in 1996 to 3,103 in 2006, the percentage of CVS increased from 45 to 69%, and the percentage of women below 35 years among those undergoing invasive procedures increased from 38 to 52%. The mean gestational age at which the procedures were done increased – for CVS from week 11 to 13, and for amniocentesis from week 16 to 17. We thus achieved to more than double the offer of prenatal screening and at the same time reduce the number of invasive procedures by 55%.

Key words: *Amniocentesis, chorionic villus sample, prenatal diagnosis, Denmark*

Introduction

Invasive prenatal diagnosis is done to detect fetuses with chromosomal abnormalities, primarily Down's syndrome. Analyzing fetal cells from amniotic fluid or chorionic villus tissue has been and still is the only way to make a definite prenatal diagnosis. However, invasive prenatal tests induce a risk of pregnancy loss of 0.5–1% (1). Therefore, attempts have been done to select by screening those women at an increased risk of fetal chromosomal abnormalities, and then offer invasive diagnostics to only women with a risk over a certain limit.

Advanced maternal age is the most important risk factor for fetal chromosomal abnormalities (2). In Denmark before 2004, primarily women over 35 years of age or women at risk of hereditary diseases were offered amniocentesis (AC) or chorionic villus sampling (CVS). However, this strategy detected only about half of Down's syndrome cases prenatally. At the same time, many women had an invasive procedure for each chromosomal abnormality detected (3). Screening with a combination of maternal age, fetal nuchal translucency thickness, maternal serum free β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) was calculated to be able to identify 92% of cases with trisomy 21 for a 5% false-positive rate (4).

By the end of 2004, the Danish National Board of Health revised their guidelines for prenatal diagnosis and recommended all pregnant women to be offered prenatal screening consisting of nuchal translucency measurement between the 12th and 14th week of gestation, and the double test (β-hCG and PAPP-A) between the ninth and 14th week of pregnancy. The 15 counties implemented first trimester combined screening between 1 October 2004 and 1 June 2006. Initially, the cut-off used for referral to invasive diagnostic testing was 1:250 in some centers, but gradually, all centers have agreed upon 1:300 as the national cut-off level (3). The aim of this study was to quantify changes in the invasive prenatal diagnostic practice in Denmark from 1996 through 2006.

Material and methods

In Denmark, all women referred to hospital have since 1977 been recorded in the National Registry of

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Patients with discharge diagnoses according to the International Classification of Diseases, from 1994 the10th revision (ICD-10), and surgical codes including specific codes for AC and CVS procedures. In addition, a unique personal identification number is given to all Danish citizens at birth or at immigration. The personal identification number enables follow-up on individuals and linking information from different registries.

Included in this study were all singleton pregnancies with an AC or CVS procedure done during the period January 1996 through December 2006 at public or private hospitals or in private clinics. To ensure the validity of the data, only pregnancies with recorded information on type and date of the prenatal procedure, involved hospital, gestational age at which the procedure was done, and a relevant outcome of the pregnancy within 34 weeks after the procedure, were included. The included surgical codes and discharge diagnoses to identify invasive procedures and pregnancy outcome are listed in a detailed description of the establishment of the study population on www.dachre.dk.

In addition to the National Registry of Patients, we retrieved data from the Danish Central Cytogenetic Registry, which collects information about persons who since 1960 have undergone pre- or postnatal chromosomal analysis. This was done in order to secure completeness in number of prenatal invasive procedures, especially before 2003 where the National Registry of Patients was not complete.

After linking the two databases, pregnancies with prenatal diagnosis were constructed through a number of medically founded premises and criteria, the details of which are accessible on www.dachre.dk. Thereby a cohort of 64,237 pregnancies with an invasive procedure and a pregnancy outcome was established. Thirty pregnancies had both an AC and a CVS procedure during the first contact – they were counted as CVS procedures. Information on the number of live births in Denmark in the study period was extracted at Sundhedsdata.sst.dk, the website of the Danish National Board of Health.

Results

The target group of pregnant women increased 4.8 times by also including routinely women below 35 years. Despite the increased size of the target group we actually experienced a halving of invasive tests. Before 2003, the concordance between the two registries was about 40–76% as many of the procedures were not recorded in the National Registry of Patients. From 2003, the majority of invasive procedures were recorded in both registries.

The number of pregnancies with prenatal invasive procedure decreased from 6,929 in 1996 to 3,103 in 2006 or by 55% (Figure 1). At the same time the percentage of these pregnancies of all singleton births decreased from 11 to 5%. The percentage of CVS out of all invasive procedures increased through the study period from 45% in 1996 to 69% in 2006.

In 2002, 75% of the pregnancies with an invasive procedure were among women over 35 years old (Figure 1). From 2002, the number of procedures in women below 35 years increased, and in 2006, 52% of the pregnancies with an invasive test were among women younger than 35 years.

The mean gestational week in which the procedures were done increased over the period – more for

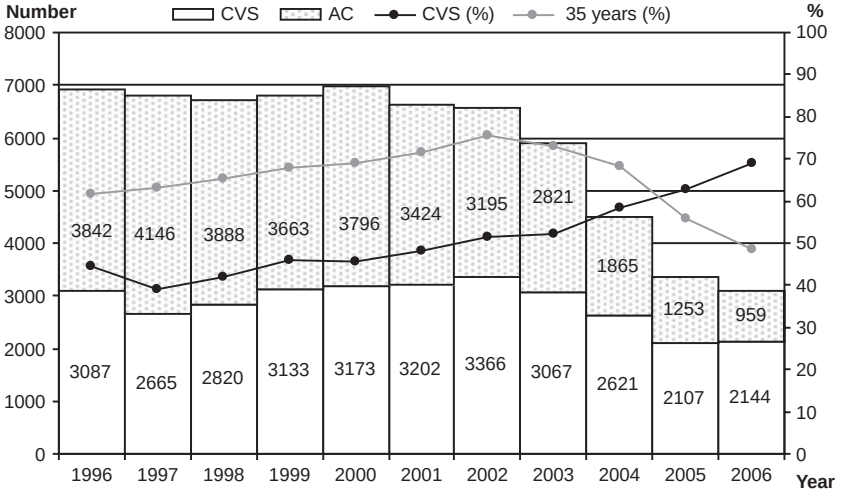

Figure 1. Number of pregnancies with amniocenteses (AC), chorionic villus samples (CVS) (Y1), through the period 1996–2006, percentage of pregnancies with CVS procedures out of all pregnancies with invasive procedures (Y2), and percentage of pregnancies with invasive procedure performed in women 35 years or older (Y2).

CVS than for AC (Figure 2). Previously, most CVS procedures were done in week 11, from 1998 to 2004 in week 12, and since 2005 in week 13. From 1996 to 2004, the mean gestational age for AC procedures was week 16, and from 2005 week 17.

Discussion

In principle, the National Registry of Patients covers all hospitals. The recording of the procedure codes for AC and CVS was, however, not complete throughout the study period. The Danish Central Cytogenetic Registry has received information from all prenatal diagnostic centers except from one out of 15 counties. Therefore, both registries were necessary to achieve a complete coverage through the 11-year study period.

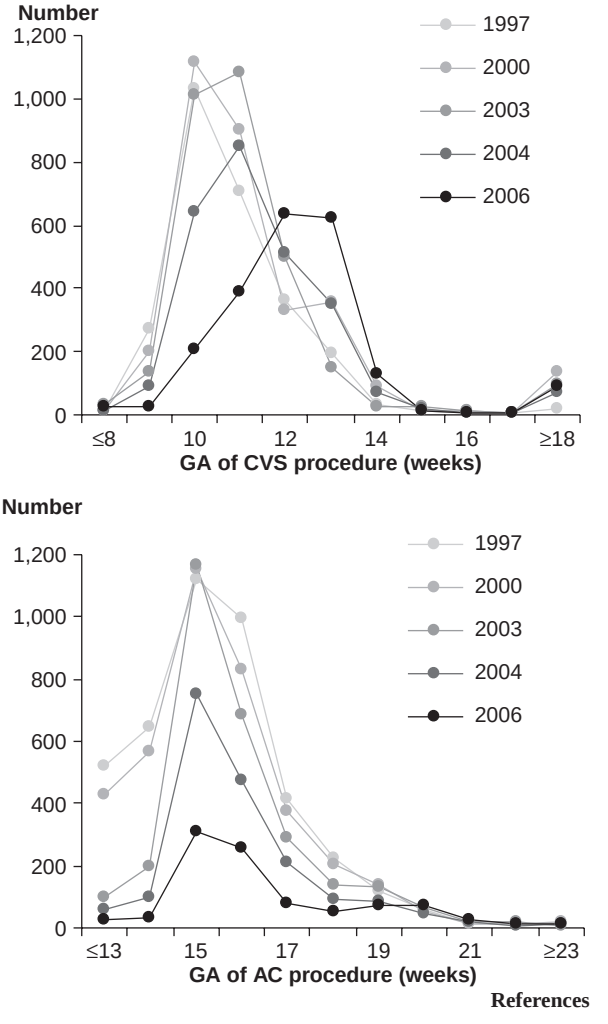

Figure 2. Distribution of pregnancies with chorionic villus samples (part A) and amniocenteses (part B) according to gestational age (GA) and year.

Generally, the prenatal diagnostic practice was unchanged in Denmark until 2003. From this year, remarkable changes were observed. Through a four-year period we succeeded in expanding prenatal screening to all pregnant women, focusing the invasive procedures to women at an increased risk of trisomy 21, and thereby halving the number of invasive procedures. At the same time CVS gradually increased its share of invasive procedures to 70% in 2006. As CVS is done three to four weeks before AC, this change provided earlier intervention in case of abnormal findings. On the other hand, the measurement of nuchal translucency and combining this measurement with biochemical assessment of β-hCG and PAPP-A has gradually delayed the CVS procedures on average from week 11 to week 12. The later gestational age at which AC is performed is a consequence of abnormal findings at the time of the ultrasound scan for fetal malformations in week 18–20, as also recommended by the national guidelines (3).

The increase over time in the percentage of women over 35 years old undergoing invasive tests is primarily a consequence of the on average general two years' increase of age at delivery through the study period. The proportion reached its maximum in 2002. Since then invasive procedures were gradually offered to more young pregnant women, despite the new guidelines from the National Board of Health not being published until 2004. The working group recommending this change in practice published their report in 2003 (5), but similar recommendations had been given already in 2001 (6) and 2002 (7). These reports concluded that expanding screening to also young pregnant women and at the same time focusing the invasive tests to those at an increased risk, could reduce rather than increase the number of invasive tests, and at the same time increase the prenatal detection rate of chromosomal abnormalities substantially. CVS is today considered to be as safe as AC (1,8). Combining CVS with primarily Polymerase Chain Reaction (PCR)-analysis provides a result within 2–3 days thereby making induced abortion possible several weeks before the results from an AC would be available. Besides a higher detection rate, this shift in practice has improved the quality of prenatal diagnosis, as an induced abortion in week 13–14 is less stressful for the mother than pregnancy termination 4–5 weeks later.

Conclusion

From 2002 to 2006, first trimester combined ultrasound and biochemical screening to all pregnant

References

women was implemented. Invasive procedures were through the same years gradually only offered women at a high risk of trisomy 21, with a halving in the number of invasive procedures as consequence. These changes have increased the quality and efficacy of the prenatal screening practice substantially.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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