

Combined First-Trimester Screening in Northern Finland: Experiences of the First Ten Years

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ABSTRACT

OBJECTIVE: To evaluate the efficacy of first trimester combined screening for Down's syndrome in Northern Finland during the first 10 years of practice.

METHODS: During 1 January 2002 to 31 December 2011, 47,896 women participated voluntarily in combined screening during first trimester. The risk cutoff was 1:250. The study period was divided into two time periods; 2002–2006 and 2007–2011.

RESULTS: During the first half of the study period, the detection rate (DR) was 77.3% with a 4.9% false-positive rate (FPR). During the latter half, the DR was 77.1% with a 2.8% FPR.

CONCLUSIONS: An important issue is the number of invasive procedures needed to detect one case of Down's syndrome. The screening performance improved markedly in the latter five years period since the FPR lowered from 4.9% to 2.8% and the number of invasive procedures needed to detect one case of Down's syndrome lowered from 15 to 11.

KEYWORDS: Down's syndrome, first trimester, nuchal translucency, combined screening, singleton pregnancy

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Introduction

Before the year 2002, pregnant women in Northern Finland were offered second-trimester serum screening with alfa-fetoprotein (AFP) and total human chorionic gonadotropin (hCG) since 1990. Voluntary combined first-trimester screening has been routinely offered in Northern Finland for every pregnant woman since 1 January 2002 by public health care centers, according to references of the Finnish Perinatal Committee. Ministry of Social Affairs and Health gave a new decree in 2006 (1339/2006) to standardize the screening process. Combined first-trimester screening consists of measurements of maternal serum pregnancy-associated plasma

protein-A (PAPPA) and free beta-hCG (fβ-hCG) and fetal nuchal translucency (NT) measurements by ultrasound. Most pregnant women sign themselves into the maternity clinics at health centers between their 6th and 11th weeks of pregnancy in Finland. Multiparas that were offered first-trimester screening for Down's syndrome were already aware of the screening test but information of screening process and voluntary participation was given for every woman by health care providers, mostly midwives. All women gave oral consent before participating in the screening program.

The risk of Down's syndrome increases with advancing maternal age.^{1–3} Screening works better in a population where



the incidence of Down's syndrome is high. Many studies have estimated the performance of first trimester combined screening. In large studies, the detection rates (DRs) have been 83%–92% for a false-positive rate (FPR) of 5%.^{4–6}

Screening for trisomy 21 (T21) is also beneficial, because it allows in some cases the early diagnosis of the other severe chromosomal abnormalities, trisomies 18 and 13 (T18, T13). During the first trimester, fetal NT is increased and maternal serum PAPP-A decreased as that in T21 pregnancies, but serum f β -hCG is decreased in trisomies 18 and 13.^{4,7–9} These two trisomies are lethal and about 80% of the cases lead to spontaneous abortion or fetal death between 12 and 40 weeks of gestation.

The main purpose of this study was to evaluate the clinical performance of first-trimester combined screening for T21 in Northern Finland during its first 10 years of practice. We divided the 10 screening years into two periods of 2002–2006 and 2007–2011 and compared the performance of the test DRs, FPRs, and the number of invasive procedures needed to detect one's case of Down's syndrome between those two time periods. The first five years period was perceived as a learning period.

Material and Methods

This study has been approved by the Ethical Committee of Oulu University Hospital (ref: 64/2007). Data handling followed the guidelines of the Ethical Committee in accordance with the Helsinki Declaration of 1975, as revised in 1996.

This study comprised voluntary women with singleton pregnancies who participated in Down's syndrome screening during the 9th–13th complete weeks of pregnancy within the public health care system in Northern Finland. The median gestation was 11 weeks (range 8/0–13/6). Screening was offered to all pregnant women and participating was voluntary. The study period was 1 January 2002 to 31 December 2011. Blood samples were drawn and NT was measured in primary care centers and in maternity clinics in Northern Finland. Biochemical results were corrected according to gestational age confirmed by ultrasound if a blood sample was taken prior to the ultrasound. Combined first-trimester screening for Down's syndrome was performed at the accredited laboratory of Oulu University Hospital, in accordance with the regulations of the Finnish Ministry of Social Affairs and Health. The study was carried out in the general population.

The serum samples were analyzed using the Perkin-Elmer AutoDELFIA[®] and Xpress[®] time-resolved fluoroimmunoassay kit (PerkinElmer Life and Analytical Sciences, Wallac Oy, Turku, Finland) for the measurement of PAPP-A and f β -hCG. The analytical sensitivities of PAPP-A and f β -hCG were 5 mU/L and 0.2 ng/mL, respectively. The within- and between-assay variations for PAPP-A were <2.4% and <4.0% in the detection range between 44 and 7300 mU/L and for S-f β -hCG both were <3.4% in the detection range of 4–157 ng/mL. External quality assurance was performed

under the supervision of an international quality assurance company (UK NEQAS, Edinburgh, United Kingdom). The results were calculated using Perkin-Elmer LifeCycle[™] software (PerkinElmer Life and Analytical Sciences) and were given as multiples of medians (MoMs).^{10–13} The software algorithm is based on parameters obtained from a meta-analysis based mostly on the results of white/Caucasian patients, and the others have been corrected for ethnicity according to the ethnicity-specific median result.¹¹ The screenees in North Finland are 98.5% Caucasians. The program took into consideration both maternal age and gestational age. The risk figures were corrected for maternal weight, diabetic status, and smoking. The risk cutoff figure 1:250 was used.

NT was measured in a university-, central-hospital, or health center. The NT measurements were performed using modern equipment available at the antenatal clinics or maternity units. The quality and the brand of the ultrasound machines were variable in different clinics and units. NT was measured by doctors and midwives who were trained on the job by experienced staff. The ultrasound services providers were not trained according to the Fetal Medicine Foundation or universally accepted guidelines. The screening software used NT MoM and centre-specific NT curves in the risk calculation. The NT providers did less than 50 to more than 200 NT measurements per year, although the recommendation in Finland is that the examiner should perform 200 scans on average per year. During the first 10 years that combined screening has been offered to pregnant women in Finland, there were no regulations concerning the quality control or audit of the NT measurements or training programs available to the examiners.

The data were analyzed using SPSS for Windows version 17.0 (SPSS Inc., Chicago, IL, USA) statistical software, OriginPro version 8.1 (OriginLab, Northampton, USA), and MedCalc software. Data for all Down's syndrome cases were obtained from the Genetics Laboratory of the Department of Clinical Genetics at Oulu University Hospital, which is responsible for chromosomal diagnostics in the Oulu area. Also data of infants born to women with negative Down's syndrome who participated in the screening were obtained. Data were also obtained from the National Research and Development Centre for Welfare and Health, which records the birth of all live and stillborn infants, and from the Finnish National Register of Congenital Malformations that receives information about all Down's syndrome cases diagnosed in Finland.

Results

During the study period of 1 January 2002 to 31 December 2011, altogether 47,896 women participated in combined first-trimester screening for Down's syndrome during pregnancy weeks 9 + 0 to 13 + 6.

During the first part, years 2002–2006, 16,749 women participated in combined first-trimester screening. Mean maternal age was 29.6 years and 17.4% of the women were \geq 35 years of age (Table 1). There were 53 cases of Down's syndrome, the

**Table 1.** Comparison of two screening periods in Northern Finland.

PERIOD	N	T21 N	PREVALENCE TOTAL BIRTH	MEAN AGE	PROPORTION ≥35 Y %	DR %	FPR %	INVASIVE PROCEDURES	NIPN*
2002–06	16.749	53	1:316 1:1396	29.6	17.4	77.3	4.9	795	15
2007–11	31.147	83	1:375 1:1639	29.4	15.3	77.1	2.8	913	11

Note: *Number of invasive procedures needed to detect one case of Down's syndrome.

prevalence being 1:316, and at birth 1:1396. The DR was 77.3% and FPR was 4.9%. The number of invasive procedures needed to detect one case of Down's syndrome was 15.

During the latter half, years 2007–2011, 31,147 women participated in combined first-trimester screening. The mean maternal age was 29.4 years and the proportion of women aged 35 years or older was 15.3%. There were 83 cases of Down's syndrome, the prevalence being 1:375, and at birth 1:1639. A total of 77.1% of the Down's cases were detected for an FPR of 2.8%. The number of invasive procedures needed to detect one case of Down's syndrome was 11. The participation rate in the screening in Finland did increase from 45% in the first part to 72% during the latter half.

Discussion

An important task of health care providers is to monitor the performance of routine screening programs. The performance of Down's screening is to balance on a good sensitivity and specificity, and in the other hand, to try avoid unnecessary fetal losses because of invasive procedures. To assess the screening performance, the literature often reveals DR and FPR, ignoring the issue of loss of healthy fetuses.

First five years period of our study, 2002–2006, was seen as a learning period since combined first-trimester screening had not been offered before 2002. The participation rate in the screening in Finland did increase from 45% to 72%. The DR remained nearly the same, 77.3% and 77.1%.

The DR depends on certain characteristics among screenees: complete ascertainment of all false-negative Down's cases, mean maternal age, the proportion of women ≥35 year

of age, so on the prevalence of Down's syndrome. The Down's prevalence increases with maternal age.¹⁴ DR is better if prevalence is high. Earlier, we have showed that the most problematic age group proved to be women of 25–29 years of age, who actually represented the most numerous group of those screened. In this group, the DR was only 63.6% with FPR of 2.7%.¹⁵ In Finland, all Down's syndrome cases have to be reported to Finnish Register of Congenital Malformation. In addition, all chromosomal analyses for fetuses and newborns in Northern Finland are made in the genetic laboratory of Oulu University Hospital. Therefore, we believe that in our study the ascertainment of Down's syndrome is likely complete.

The prevalence of Down's syndrome in first trimester should be around 1:300, because in general western population the prevalence should be the same.¹⁶ If the prevalence is high, then it is clear that DR is high, and if the prevalence is low in general population, then some cases might be missing and DR is probably overestimated. The DRs in our study were modest (limited) in comparison with those published in the literature. The reported DRs of the first-trimester combined screening range between 72.2% and 92.0%, with a fixed FPR of 5% (Table 2).^{3–13,17}

We have showed earlier that NT measurement was the most important factor leading to a false-negative result.¹⁸ During this study, there was no significant improvement of NT measurements; in the first part, median NT was 1.10 mm (0.95 MoM) for controls and 2.10 mm (1.7 MoM) for those with Down's syndrome; in the second-part, median NT was 1.20 mm (0.96 MoM) for controls and 2.15 mm (1.75 MoM) for those with Down's syndrome. NT measurement does not

Table 2. Screening performance of our study in 2007–2011 compared to three other studies.

	FASTER	SURUSS	DENMARK	FINLAND
N	36 120	39 983	54 830	31 147
Mean maternal age	27.1	NA	30.3	29.4
≥35 years %	13.2	NA	NA	15.3
Down's N	92	85	104	83
Down's prevalence	1:329	1:470	1:404	1:375
Detection rate %	77	83	82	77.1
False-positive rate %	5	5	3.5	2.8
Number of invasive procedures needed to detect one case of Down's syndrome	22	29	18.5	11

Abbreviation: NA, not available.



explain the decreased FPR in the second part of the study. However, the reason for a lower FPR might be the more accurate ultrasound measurement of fetal gestational age. At the time of the screening, there were no regulations in Finland with regard to the quality control or audit of the NT measurements or training programs available to the examiners. There might be an underestimation of the NT measurements, which might have an influence to a DR in this study. It may be reasonable to use resources to better educate health care providers to recognize additional ultrasound markers.

Although the DR did not improve in the latter screening five years period, what was important, the FPR lowered from 4.9% to 2.8%, which means 654 invasive procedures less, and saving probably five fetal lives, assuming a risk of 1%.¹⁹ The reason for lowered FPR might be the improved NT measurement. If the FPR during the years 2007–2011 was 4.9%, five more Down's syndrome cases would have been detected and the DR would have been increased to 83.1%. The number of invasive procedures needed to detect one case with Down's syndrome would have been higher, 17. We compared the latter half of our study with the FASTER, SURUSS and Danish studies (Table 2).^{5,6} In our study, there were lowest number of invasive procedures, 11.

In England and Wales, there was a 1% decrease in the affected live births between 1989/1990 ($n=752$) and 2007/2008 ($n=743$). The authors estimated that in the absence of terminations due to the antenatal diagnosis, the advancing maternal age would have resulted in a 48% increase in births with Down's syndrome.²⁰ Similar results have also been reported in other countries.²¹

In Denmark, combined screening has been recommended to be offered for all pregnant women since 2004. The number of live born Down's syndrome cases decreased from 55 to 65 per year in 2000–2004 to 32 in 2006. The proportion of cases that were diagnosed prenatally increased from 53 to 61% during the years 2000–2004 to 79% in 2006. In contrast to results in other countries, there was a 50% decrease in the number of live born Down's syndrome cases.¹⁷

According to the National Institute for Health and Welfare, the total prevalence of Down's syndrome (born and terminated) grew slowly and was approximately 1:388 during the years 1993–2010 and 1:325 during the years 2006–2009 in Finland. In 2010, the total prevalence decreased to 1:370. Increase in the total prevalence is probably because of the increase in maternal age and the changes in prenatal screening in Finland. The prevalence of Down's syndrome among born children was quite constant during the years 1993–2009 (1:787), but there was a slight decrease in 2010 (1:971). Altogether, there were on average 154 Down's syndrome cases each year (165 in 2010) and on average 75 cases were born yearly. Of all the Down's syndrome cases, 57.5% were among women aged 35 years or older. Differences in 2010 could be explained for example by changes in participating in the screening and/or further

examinations, occurrence associated with small case number, also, after 2004, the increase in maternal age evened.²² Therefore, also in Finland, the number of born Down's syndrome cases remained stable despite the increase in total prevalence of Down's syndrome.

The noninvasive prenatal diagnosis (NIPD) is one the hottest topics in prenatal medicine. Since 1997 many approaches have been made and today it is possible to determine fetal Rhesus D status, fetal sex and diagnose genetic disorders or carrier status for paternally inherited mutations.²³ It is anticipated that over the next few years also the NIPD of fetal aneuploidy will be possible. The maternal blood analysis of cell-free fetal nucleic acids (cffNA) is the most recent strategy for noninvasive prenatal gene profiling. Various methods for NIPD using cffNA in maternal circulation have been introduced. The reported DRs are between 79.1% and 100% and FPRs are between 1.1% and 0.3%.^{24,25} The literature indicates that highly accurate diagnosis of fetal chromosomal abnormalities by maternal blood sample is achievable during the first trimester of the pregnancy. However, the gestational window of NIPD is still unclear. Despite high sensitivities and specificities, approximately 1% FPRs have been reported. Therefore, invasive testing is still required after positive test result.²⁵ Large objective clinical trials are needed to evaluate the sensitivity and specificity of NIPD in low-risk general populations. The future costs of NIPD can be only estimated. Ultrasound scan during the early pregnancy will be necessary even if NIPD would become a routine screening method.

Abbreviations

DR, detection rate; f β -hCG, free beta-human chorionic gonadotropin; FMF, Fetal Medicine Foundation; FPR, false-positive rate; MoM, multiples of the median; NPV, negative predictive value; NT, nuchal translucency; PAPP-A, pregnancy-associated plasma protein-A; PPV, positive predictive value.

Author Contributions

Conceived and designed the experiments: AM, SP, MR, JM. Analyzed the data: TH, SP, HLK, PL, MR. Wrote the first draft of the manuscript: AM, SP. Contributed to the writing of the manuscript: AM, SP, TH, PL, HLK, MR, JM. Agree with manuscript results and conclusions: AM, SP, TH, PL, HLK, MR, JM. Jointly developed the structure and arguments for the paper: MR, JM. Made critical revisions and approved final version: TH, PL, HLK. All authors reviewed and approved the final manuscript.

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