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Evaluation of the introduction of the national Down syndrome screening program in the Netherlands: age-related uptake of prenatal screening and invasive diagnostic testing

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ABSTRACT

Objective: To study the effect of different government prenatal screening (PNS) policies on the uptake of PNS and prenatal diagnostic testing (PND) over the periods 2001–2003 (PNS on request), 2004–2006 (permission to offer the first-trimester combined test (FCT) to women of advanced maternal age (AMA), with women aged <36 years informed on explicit request) and 2007–2010 (introduction of population screening) and to evaluate whether trends in uptake are related to maternal age. The indication AMA for PND is still warranted, and the costs for FCT are only reimbursed for AMA women.

Study design: Analysis of data on the first- and second-trimester screening program ($n = 41{,}600$) for Down syndrome (DS) and on PND ($n = 10{,}795$) performed from 2001 to 2010 in the region North-Holland of the Netherlands. To evaluate the actual participation in PNS and PND in different maternal age groups, estimation of the age distribution of women who underwent a fetal anomaly scan in 2009 ($n = 14{,}481$) was used as a reference population (participation of 85.2%).

Results: The overall uptake of FCT was 35.2% in 2010. Over the years the number of FCT in all age groups increased significantly ($P < 0.001$). Overall the number of PND decreased significantly; the number of PND for AMA decreased and the number of PND for increased risk at FCT (in women <36 and ≥36 years) increased ($P < 0.05$). Since 2004 significantly more DS cases were detected with FCT in AMA women and fewer with PND for AMA, and since 2007 more DS cases were detected with FCT in women <36 years ($P < 0.001$).

Conclusion: The effect of the national screening program is limited. Significantly more women opt for PNS but the overall uptake remains low, especially in younger women. A significant number of AMA women still opt for PND for AMA. The choice for FCT and PND for AMA seems dependent on background risk. To accomplish a more effective screening policy, reimbursement of the cost of the test should apply to all women and the indication for PND for AMA should be abolished.

1. Introduction

In the Netherlands prenatal diagnostic testing (PND) for the detection of chromosomal abnormalities has been part of prenatal care for about four decades. The association of advanced maternal age (AMA) with an increased risk of DS led to the introduction of AMA (defined as ≥36 years of age at 18 weeks of gestation) as an indication for PND [1]. The uptake of PND for AMA in the Netherlands from 1991 to 2000 was quite constant over the years, at approximately 70% of the total number of PND performed [2].

Prenatal screening (PNS) for DS became available in 1988 with the introduction of the second-trimester serum screening (SST), combining maternal age, unconjugated oestriol, free β-human chorionic gonadotrophin and alpha-1-fetoprotein [3]. In the last decade the first-trimester combined test (FCT), combining maternal age, fetal nuchal translucency (NT) thickness and concentrations of maternal serum free β-human chorionic gonadotrophin (fβ-hCG) and pregnancy-associated plasma protein-A (PAPP-A), was introduced. Up until 2004 there was no nationwide policy for

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PNS in the Netherlands. Pregnant women were screened only on request by the SST, the FCT or by a risk assessment based on maternal age and NT (if implementation of serum sampling was not possible). Since 2004, all AMA women were informed of the possibility of PNS, but women aged <36 years only received information on their explicit request. Since January 2007 eight regional centers, covering the whole country, obtained a licence for implementation of prenatal screening in their region. All women, regardless of age, are informed about the first-trimester screening (FTS) options for DS [4]. Information on SST is only provided when gestational age is beyond 14 weeks. The indication AMA for PND is still warranted in the Netherlands, and the cost of FCT is only reimbursed for AMA women. The cost of PND for an increased risk at FCT is reimbursed for all women. Since May 2010 a licence under the Population Act was issued, allowing screening also for Patau and Edwards syndromes with FCT using a specific algorithm.

It has been demonstrated that with a higher uptake of FTS the number of PND for AMA will be reduced as women identified with a low risk of DS could avoid invasive testing and the possible procedure-related risk of miscarriage [5–7]. The reported uptake of FCT in the Netherlands is low, at about 25% [8,9]. Screening performance in our country has been reported with a detection rate up to 95% at a false positive rate of 6.6% [10].

We present data on PND and PNS from 2001 until 2010 in the region North-Holland in the Netherlands. The aim was to study the effect of the different government prenatal screening policies on the uptake of PNS and PND tests over the periods 2001–2003 (PNS on request), 2004–2006 (permission to offer FCT to AMA women, with women aged <36 years informed on explicit request) and 2007–2010 (introduction of population screening) and to evaluate whether trends in uptake are related to maternal age.

2. Materials and methods

In this population-based study, we studied data on the first-and second-trimester screening program for DS and on PND performed from January 01, 2001 until December 31, 2010, from a tertiary fetal medicine center (VU University Medical Center, Amsterdam, the Netherlands).

2.1. First-trimester combined test

In all singleton pregnancies serum was sampled at 9–14 weeks of gestation and analyzed at the endocrine laboratory of the VU University Medical Center (VUmc), using the Auto Delfia (Perkin Elmer Wallac Oy, Turku, Finland) from 2001 until 2003 and the Delfia Xpress from 2004 onwards (Perkin Elmer Wallac Oy, Turku, Finland). For twin pregnancies a fetus-specific risk was calculated for each one of the twins based on maternal age and NT. NT was performed according to the guidelines of the Fetal Medicine Foundation (FMF) with a fetal crown rump length (CRL) between 45 and 84 mm (FMF reference curve) [11] from 2001 through 2003, and with a CRL between 45 and 79 mm (VUmc reference curve) [12] from 2004 onwards. Gestational age (GA) was determined by CRL at time of NT. Information on earlier pregnancies with DS, smoking habits, and maternal weight were taken into account for risk assessment. From 2001 through 2003 the software program FTrisk1 and from 2004 until 2010 Elips/Lifecycle (Perkin Elmer Wallac Oy, Turku, Finland) was used. The cut-off value for increased risk was 1:200 (midterm).

2.2. Second-trimester serum test

Serum was sampled at 15–19 weeks of gestation and analyzed at the laboratory for infectious diseases and perinatal screening of the National Institute for Public Health and the Environment, Bilthoven, the Netherlands, using the Auto Delfia method (Perkin Elmer Wallac Oy, Turku, Finland). GA was determined on a dating scan and/or the first day of the last menstrual period. Until March 2003 the risk software program 'Alpha' (Logical Medical Systems, London, UK) was used and from March 2003 onwards Elipse/Lifecycle (Perkin Elmer Wallac Oy, Turku, Finland). The cut-off for increased risk was 1:250 (term).

2.3. Prenatal diagnostic testing

From the database of the cytogenetics laboratory of the VUmc, data of all cases that underwent PND were collected. Cases were classified to one of the following indications: AMA, woman's own wish (<36 years of age), increased risk at FCT, increased risk at NT, increased risk at SST, abnormalities on ultrasound scanning (US), or other.

2.4. Maternal age distribution

To evaluate the actual participation in PNS and PND in different maternal age groups, estimation of the maternal age distribution of the whole pregnant population is necessary. Due the lack of this information, maternal age distribution of women who performed the fetal anomaly scan in our region in 2009 (N = 14.481) was used as a reference population (participation of 85.2% [8]). First the percentages of women aged ≤25 years, 26–30 years, 31–35 years, 36–40 years and 41–45 years in this cohort were counted. The pregnant population in our region consisted of approximately (100/85.2 × 14,481 = 16,996) women in 2009. Then the expected number of pregnant women in the different age groups was calculated for a population of this size.

Statistical analyses were conducted using SPSS software (version 20). Chi-square tests for trend analysis were performed to test the differences in uptake of PNS and PND between the different periods and maternal age groups. Two-sided $P < 0.05$ was considered to reflect statistical significance. The study was approved by the Ethics Committee of the VUmc.

3. Results

3.1. Number of PNS and PND tests

Over the years 2001 to 2010, in total 41,600 screening tests were performed: 34,665 FCT, 6639 single NT measurements and 296 SST. The number of FCT increased significantly from 461 in 2001 to 5991 in 2010. The number of NT measurements in singleton pregnancies increased from 366 in 2001 to 1517 in 2005 and then decreased to 224 in 2010 and in twin pregnancies the number of NT increased from 35 in 2001 to 215 in 2010. The number of SST gradually decreased from 75 in 2001 to 5 in 2010. In the same period 10,795 prenatal diagnostic tests were performed. The mean number of PND over the years was 1078 (range 994–1171).

Table 1 shows the number of the different screening and diagnostic tests performed in the maternal age groups <36 and ≥36 years of age compared to the total number of screening and diagnostic tests performed in the separate maternal age groups over the periods 2001–2003, 2004–2006 and 2007–2010. The number of FCT increased and the number of PND decreased over the years in women both <36 and ≥36 years ($P < 0.001$).

Table 2 shows the number of prenatal diagnostic tests for the different indications in the maternal age groups <36 and ≥36 years of age over the periods 2001–2003, 2004–2006 and 2007–2010. There was a significant decrease in PND for AMA and an increase in PND for increased risk (in women <36 and ≥36 years) over the years ($P < 0.001$).