Engels MAJ, Bhola SL, Twisk JWR, BlankensteinMA, van Vugt JMG.

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

Accepted in Eur J Obs Gyn. 2013.

Abstract

Objective

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

Study design

Analysis of data on the first-and second-trimester screening (N = 41.600) program for Down syndrome (DS) and on PND (N = 10.795) performed from 2001 to 2010 in the region North-Holland in the Netherlands. To evaluate the actual participation in PNS and PND in different maternal age groups, estimation of maternal age distribution of women who performed the fetal anomaly scan in 2009 (N = 14.481) was used as a reference population (participation of 85.2%).

Results

The overall uptake of the 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 as well as the number of PND for AMA ($P< 0.001$) and the number of PND for increased risk at FCT (in women < 36 and ≥ 36 years) increased ($P< 0.001$). Since 2004 significantly more DS cases were detected in AMA women with FCT and less 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. Still a significant number of AMA women 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.

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 test (SST), combining maternal age, unconjugated oestriol, free β-human chorionic gonadotrophin (fβ-hCG) 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 fβ-hCG and pregnancy-associated plasma protein-A (PAPP-A), was introduced. Up until 2004 there was no nationwide policy for 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 (in case 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 8 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 the SST is only provided in case gestational age (GA) is beyond 14 weeks. The indication AMA for PND is still warranted in the Netherlands. The cost for FCT are only reimbursed for AMA women. The cost for PND for an increased risk at FCT are reimbursed for all women. Since May 2010 a license under the Population Act was issued, allowing screening also for Patau and Edwards syndrome with the 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 the FCT in the Netherlands is low at about 25%[8,9]. Screening performance in our country has been reported up to 95% DR at a 6.6% FPR[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 governmental policies on prenatal screening on the uptake of PNS and PND tests over the periods from 2001 – 2003 (PNS on request), 2004 – 2006 (permission to offer FCT to AMA women; women aged < 36 years informed on explicit request) and from 2007 – 2010 (introduction population screening) and to evaluate whether the trends in uptake are related to maternal age.

Materials and methods

In this population-based study 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 (VUMC), Amsterdam, the Netherlands) were studied.

First-trimester combined test

In all singleton pregnanciesserum was sampled at 9 – 14 weeks of gestation and analyzed at the endocrine laboratory of the VUMC, using the Auto Delfia (PerkinElmer, WallacOy, Turku, Finland) from 2001 until 2003 and the Delfia Xpress from 2004 onwards (PerkinElmer, WallacOy, 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. 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 *(*PerkinElmer,WallacOy, Turku, Finland) was used. The cut-off value for increased risk was 1:200 (midterm).

Second- trimester serum screening 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 (PerkinElmer, WallacOy, Turku, Finland). GA was determined on a dating scan and / or on 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 (PerkinElmer, WallacOy, Turku, Finland). The cut-off for increased risk was 1:250 (term).

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 or other.

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 to 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 x 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.

Results

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 5.991 in 2010. The number of NT measurements in singleton pregnancies increased from 366 in 2001 to 1.517 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 in2010. In the same period 10.795 prenatal diagnostic tests were performed. The mean number of PND over the years was 1.078 (range 994 - 1.171).
In Table 1 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 are shown. The number of FCT increased and the number of PND decreased over the years in both women < 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 at FCT (in women < 36 and ≥ 36 years) over the years (*P*< 0.001).
Of women with a screen-positive result at the FCT, 92.3% of women < 36 years and 89.2% of AMA women decided to perform PND.
Figure 1 shows the distribution of number of PND for AMA subdivided for different maternal ages (36 - ≥ 44 years) over the years 2001-2010.

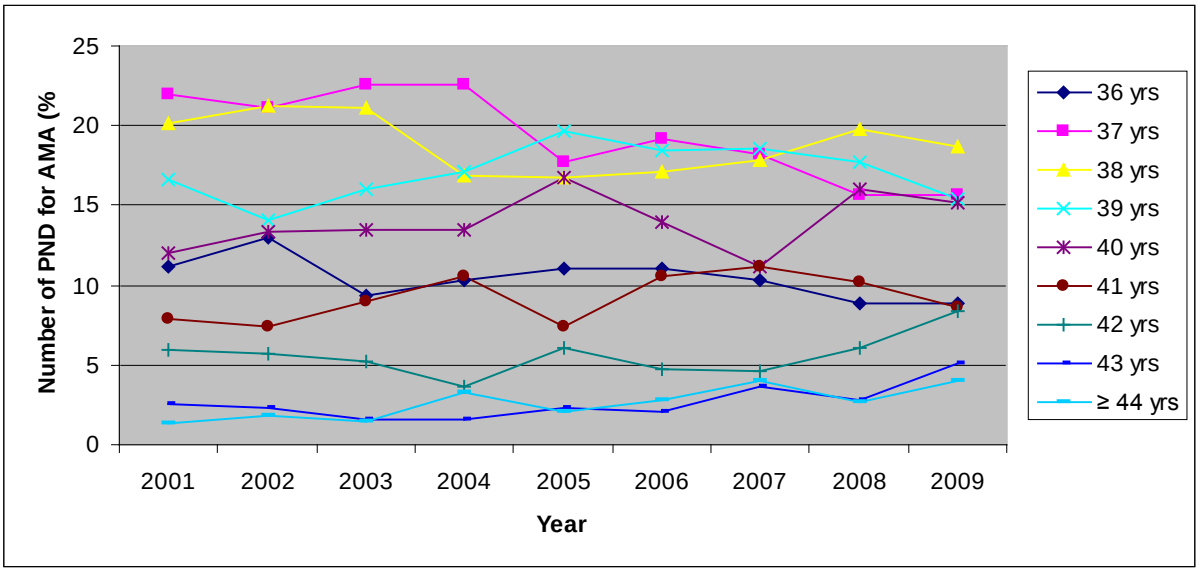
Table 1. The number of the different screening tests and diagnostic tests performed in the maternal age groups < 36 years and ≥ 36 years of age compared to the total number of screening and diagnostic tests performed in the separate maternal age groups over the periods 2001-2003, 2004-2006 and 2007-2010 (%).

Number of tests < 36 years (%)					
Period	**FCT**	**NT**	**SST**	**PND**	**Total PNS and PND**
2001-2003	1.023 (53.6)	256 (13.3)	101 (5.3)	531 (27.8)	1.911 (100)
2004-2006	6.686 (67.3)	2.466 (24.8)	60 (0.6)	723 (7.3)	9.935 (100)
2007-2010	15.665 (87.9)	887 (5.0)	20 (0.1)	1.242 (7.0)	17.814 (100)
Number of tests ≥ 36 years (%)					
Period	**FCT**	**NT**	**SST**	**PND**	**Total PNS and PND**
2001-2003	1.375 (29.2)	527 (11.1)	78 (1.7)	2.731 (58.0)	4.711 (100)
2004-2006	3.563 (45.2)	1.853 (23.5)	28 (0.4)	2.431 (30.9)	7.875 (100)
2007-2010	6.349 (62.6)	650 (6.4)	9 (0.1)	3.317 (30.9)	10.145 (100)

Table 2. The number of prenatal diagnostic tests for different indications in the maternal age groups < 36 and ≥ 36 years of age over the years 2001-2003, 2004-2006 and 2007-2010 (%).

Number of tests per PND indication (%)	**2001-2003**	**2004-2006**	**2007-2010**
Woman'sownrequest< 36 yr	86 (2.7)	80 (2.6)	95 (2.2)
AMA	2334 (72.3)	1844 (58.7)	2117 (48.3)
Increased risk at FCT < 36 yr	56 (1.7)	173 (5.5)	518 (11.8)
Increased risk at FCT ≥ 36 yr	117 (3.6)	310 (9.9)	727 (16.6)
Increased risk at NT < 36 yr	43 (1.3)	90 (2.9)	70 (1.6)
Increased risk at NT ≥ 36 yr	22 (0.7)	76 (2.4)	58 (1.3)
Increased risk at SST < 36 yr	27 (0.8)	16 (0.5)	0 (0.0)
Increased risk at SST ≥ 36 yr	26 (0.8)	19 (0.6)	5 (0.1)
US abnormalities	234 (7.3)	228 (7.2)	410 (9.4)
Other	284 (8.8)	305 (9.7)	379 (8.7)
Total (100%)	3229 (100)	3141 (100)	4379 (100)

Figure 1. Number of PND for AMA subdivided for the different maternal ages over the years 2001-2010 (%).



Uptake of FCT and PND in the different maternal age groups

Based on maternal age distribution of the reference population the expected numbers of pregnant women for a population of 17.000 women were calculated: 2.805, 5.270, 6.154, 2.533, 238 women aged ≤ 25 yrs, 26-30 yrs, 31-35 yrs, 36-40 yrs and 41-45 yrs respectively. For each year (2001 – 2010) these expected numbers were used as reference. In Table 3 the uptake of the FCT, of PND for increased risk at FCT and of PND for AMA in the different maternal age groups over the periods 2001-2003, 2004-2006 and 2007-2010 is shown compared to the expected number of pregnant women in these age groups. The increase in uptake of the FCT from 2001 - 2003 to 2007 - 2010 was significant in all age groups ($P< 0.001$). The number of PND for increased risk at FCT increased significantly for women aged 26-30 years, 31-35 years, 36-40 years and 41-45 years ($P< 0.001$). Compared to a pregnant population of approximately 17.000 women, the overall uptake of FCT was 35.2% in 2010.

Table 3. The number of FCT, the number of PND for increased risk at FCT and the number of PND for AMA in the different maternal age groups over the periods 2001-2003, 2004-2006 and 2007-2010 compared to the expected number of pregnant women in the same age groups and over the same periods (%).
P <0.05 is considered significant.

	2001 – 2003	2004 – 2006	2007 – 2010	*P*-value
FCT				
≤ 25 yrs	67 (0.8)	527 (6.3)	1.185 (10.6)	< 0.001
26-30 yrs	274 (1.7)	1.546 (9.8)	4.971 (23.6)	< 0.001
31-35 yrs	1.099 (5.9)	4.807 (26.0)	9.891 (40.2)	< 0.001
36-40 yrs	851 (11.2)	3.057 (40.2)	5.552 (54.8)	< 0.001
41-45 yrs	108 (15.1)	314 (43.9)	416 (43.7)	< 0.001
PND for increased risk at FCT				
≤ 25 yrs	0 (0)	13 (0.2)	18 (0.2)	0.07
26-30 yrs	8 (0.1)	61 (0.4)	143 (0.7)	0.001
31-35 yrs	25 (0.1)	227 (1.2)	436 (1.8)	< 0.001
36-40 yrs	118 (1.6)	324 (4.3)	669 (6.6)	< 0.001
41-45 yrs	11 (1.5)	62 (8.7)	127 (13.3)	< 0.001
PND for AMA				
36-40 yrs	1.925 (25.3)	1.489 (19.6)	1.642 (16.2)	0.016
41-45 yrs	409 (57.3)	355 (49.7)	475 (49.9)	0.027

Detection of Down syndrome cases

From the 267 DS cases detected over the years, 160 cases were detected with the FCT, 44 with PND for AMA, none at woman's own request, 30 with increased risk at single NT, 1 with the SST, 16 at US abnormalities and 6 at other indications. The number of DS cases that was to be expected according to maternal age and gestational age distribution[13] in this cohort was 66 for women < 36 years and 203 for AMA women.

In Table 4 the number of DS cases detected with the FCT and PND for AMA in the periods 2001 – 2003, 2004 – 2006 and 2007 – 2010 are shown. The number of DS cases detected with the FCT in women < 36 and ≥ 36 years was significantly higher and with PND for AMA significantly lower (*P*< 0.001).

Table 4. The number of Down syndrome (DS) cases detected at the indications increased risk at FCT in women < 36 and ≥ 36 years of age and at PND for AMA over the periods 2001-2003, 2004-2006 and 2007-2010.

Number of DS cases (%)	2001-2003	2004-2006	2007-2010
PND for increased risk at FCT in women < 36 yrs	13 (25)	14 (28)	39 (34.8)
PND for increased risk at FCT in women ≥ 36 yrs	16 (30.7)	25 (50)	53 (47.3)
PND for AMA	23 (44.3)	11 (22)	20 (17.9)
Total	**52 (100)**	**50 (100)**	**112 (100)**

Comments

Our studyshows that the introduction of the FCT as population screening has had only a limited effect on the participation of both women aged < 36 and ≥ 36 years, resulting in an overall uptake of 35% with a small decrease in uptake of PND for AMA (< 10%), but with significantly more DS cases detected. Earlier reports on uptake of PNS and PND in the Netherlands showed similar results[8,9].

Since 2004 (permission to offer the FCT to AMA women) the increase in uptake of the FCT was more pronounced in AMA women than in women aged < 36 years, and with the introduction of population screening in 2007 the increase in uptake was approximately comparable in both age groups. In the period 2004 - 2006 the number of single NT measurements increased in both age groups, because serum sampling was not always possible, but decreased from 2007 – 2010 when serum sampling was standard implemented. Probably the provided information on a better screening performance with the FCT than with a single NT measurement, has influenced this trend as well. The number of SST decreased to almost nil. An important goal of the national screening program is that every woman is informed timely about first-trimester screening options (informed choice). The reduction in SST, supports the basic assumption that information provision on first-trimester screening in our country is accurate.The decrease in PND for AMA was comparable to the increase in PND for increased risk (in women < 36 and ≥ 36 years), resulting in a stable number of PND over the years and with the number of procedure related miscarriages and cost of PND to be constant as well.

The participation of the FCT is maternal age related with an increase over the years of approximately 10%, 20%, 35%, 45% and 30% in women aged ≤ 25 years, 26-30 years, 31-35 years, 36-40 years and 41-45 years. Remarkably PND for AMA remained the main indication for diagnostic testing. Especially women aged ≥ 39 years opt for PND for AMA; a decline in uptake is seen only in women aged 36 - 38 years. The most important reason for the rather small decline in PND for AMA is presumably the low uptake of the FCT.

The effect of changing maternal age of the pregnant population over the years needs to be considered when interpreting our results. It is to be expected that mean maternal age increased over the years. In this study information of maternal age distribution over the years was lacking. Furthermore only a part of the pregnant population was tested with significantly more younger women included. Thus the effect of changing maternal age on the uptake of PNS and PND cannot be determined.

It has been demonstrated that the total number of invasive tests will decline only if significant numbers of women, especially AMA women, will perform the FCT[6-8,14], and then decide, based on the risk result, to perform diagnostic testing. In England the number of PND decreased with 72% over a 9-year period when offering the FCT as the primary screening method. Moreover women are not offered PND on the basis of age alone[15]. The introduction of a combined risk assessment in Denmark resulted in an uptake of 85%, in a sharp decline in the number of PND and halved the number of infants born with DS[16].

The fact that only few women in our country opt for PNS will have multiple causes. With the introduction of population screening, informed choice of the pregnant women was the basic assumption. However, it might be that women do not fully understand the principle of screening.It is known that informed decision-making on prenatal screening is a complicated process[17-20] and this makes the counselling even more difficult. Differences in ethnic backgrounds[21], socio-economic status, education level and religion may affect the uptake in FCT as well as the fact that the cost forthe FCT for women < 36 years of age are not reimbursed. Also the misunderstanding that screening performance of the FCT in younger women would be less, may influence the counselling[10,22].On the other hand, it has been shown, that neither uptake rates, nor attitude towards prenatal screening of pregnant women were significantly predicted by counsellors' attitudes towards prenatal screening[23]. We suggest that the choice of FCT or PND for AMA is dependent of the woman's background risk. Wasden*at al*. showed that women aged ≥ 35 years are more likely to undergo diagnostic testing, despite the fact that maternal age is already included in the risk assessment[24].It might be that only AMA women with a background risk near to the cut-off value are more prone to opt for the FCT, possibly because the background risk is not experienced as very high and therefore no reason to perform PND for AMA. Women < 30 years of age might experience their background risk as very low and thus refrain from prenatal testing. In the counselling it should be emphasized that the calculated risk is more reliable in the prediction of chromosomal abnormalities than the background risk. Birth prevalence of children with DS in the Netherlands has increased[25], more reason for realizing a high uptake of prenatal screening in AMA women interested in performing a prenatal test.

Further effort should be made to gain more insight into the different age related variables that contribute to the low uptake of the FCT in our country.

To establish a higher uptake of the FCT, barriers to screening should be removed. So reimbursement of cost should apply to all women and information should be related to educational level and possibly given in a preconception consultation. Furthermore it should be promoted that decision-making should be based on the best possible information. PND for AMA is an inappropriate screening tool for the detection of chromosomal abnormalities. The FCT should be the first step in prenatal testing because it provides a good risk assessment for women of all ages[10]. A change of screening policy should be that PND for AMA is abolished.

References

1. Leschot NJ, Kloosterman MD. Prenatal diagnosis in the Netherlands, Dutch Working Party of Prenatal Diagnosis. *Eur J Hum Genet* 1997;5:51-56.

2. Nagel HTC, Knegt AC, Kloosterman MD, Wildschut HIJ, Leschot NJ, Vandenbussche FPHA.Invasive prenatal diagnosis in the Netherlands, 1991-2000: number of procedures, indications and abnormal results detected. *NedTijdschrGeneeskd* 2004;148:1538-1543.

3. Beekhuis JR, Mantingh A, de Wolf BT, van Lith JM, Breed AS.Serum screening of pregnant women for fetal neural tube defects and Down syndrome; initial experiences in the Netherlands. *Ned TijdschrGeneesk* 1993;137:1303-1307 (in Dutch).

4. Health Council of the Netherlands. Prenatal Screening (2); Down's syndrome, neural tube defects. The Hague: Health Council of the Netherlands, 2004; publication no. 2004/06 (in Dutch).

5. Wray AM, Ghidini A, Alvis C, Hodor J, Landy HJ, Poggi SH. The impact of first-trimester screening on AMA uptake of invasive testing. *PrenatDiagn* 2005;25:350-353.

6. Muller PR, Cocciolone R, Haan EA. Trends in state/population-based Down syndrome screening and invasive prenatal testing with the introduction of first-trimester combined Down syndrome screening. South Australia, 1995-2005. *Am J ObstetGynecol* 2007;196:315.e1-315.e7.

7. Nakata N, Wang Y, Bhatt S. Trends in prenatal screening and diagnostic testing among women referred for advanced maternal age. *PrenatDiagn* 2010;30:198-206.

8. Fracheboud J, Van Agt HME, De Koning HJ. 2011. [Monitoring 2009 screeningsprogramma Downsyndroom / Structureel Echoscopisch Onderzoek]. www.rivm.nl.

9. Lichtenbelt KD, Alizadeh BZ, Scheffer PG, Stoutenbeek p, Schielen PCJI, Page-Christiaens LCML *et al.*Trends in the utilization of invasive prenatal diagnosis in the Netherlands during 2000-2009. *PrenatDiagn* 2011;31:765-772.

10. Engels MAJ, Heijboer AC, Blankenstein MA, Van Vugt JMG. Performance of first-trimester combined test for Down syndrome in different maternal age groups: reason for adjustments in screening policy? *PrenatDiagn* 2011;31:1241-1245.

11. Snijders RJ, Noble P, Sebire N Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal translucency thickness at 10-14 weeks of gestation. Fetal Medicine Foundation First Trimester Screening Group. *Lancet* 1998;352:343-346.

12. Go AT, Hupkes HW, Lomecky M, Twisk J, Blankenstein JM, van Vugt JM. [Evaluation of a programme for the prenatal screening for Down's syndrome by ultrasonographic nuchal translucency measurement and serum determinations in the first trimester of pregnancy]. *NedTijdschrGeneeskd* 2005;149:2795-2799.

13. Snijders RJ, Holzgreve W, Cuckle H, Nicolaides KH.Maternal age- and gestation-specificrisk for trisomy 21. *Ultrasound ObstetGynecol*1999;13:167-170.

14. Lo TK, Lai FK, Lueng WC, Lau WL, Tang LC, Chin RK. A new policy for prenatal screening and diagnosis of Down's syndrome for pregnant women with advanced maternal age in a public hospital. *J MaternFetal Neonatal Med* 2010;23:914-919.

15. Morgan S, Delbarre A, Ward P. Impact of introducing a national policy for prenatal Down syndrome screening on the diagnostic invasive procedure rate in England. *Ultrasound ObstetGynecol* 2013;41:526-529.

16. Ekelund CK, Jorgensen FS, Petersen OB, Sundberg K, Tabor A. Impact of a new national screening policy for Down's syndrome in Denmark: population based chort study. *BMJ* 2008;337:a2547.

17. Van den Berg M, Timmermans DRM, Kleinveld A, Garcia E, van Vugt JMG, van der Wal G. Accepting or declining the offer of prenatal screening for congenital defects: test uptake and women's reasons. *PrenatDiagn* 2005a;25:84-90.

18. Van den Berg M, Timmermans DRM, ten Kate LP, van Vugt JMG, van der Wal G. Are pregnant women making informed choices about prenatal screening?
Genetics Med 2005b;7:332-338.

19 Van den Berg M, Timmermans DRM, Knol DL, van Eijk JThM, Knol DL, de Smit DJ *et al*. Understanding pregnant women's decision making concerning prenatal screening. *Health Psych* 2008;27:430-7.

20 Kleinveld JH, Timmermans DRM, van de Berg M, van EijkJThM, van Vugt JMG, van der Wal G. Does offering prenatal screening influence pregnant women's attitudes regarding prenatal testing? *Comm Genet* 2008;11:368-74.

21. Fransen MH, Schoonen HMHJD, MackenbachJP¸Steegers JP, De Koning EA, Laudy HJ *et al.*Ethnic differences in participation in prenatal screening for Down syndrome: a register-based study. *PrenatDiagn* 2010;10:988-994.

22. Spencer K. Age related detection and false positive rates when screening for Down syndrome in the first trimester using fetal nuchal translucency and maternal serum free beta hCG and PAPP-A. *Br J ObstetGynecol* 2001;108:1043-1046.

23. Van den Berg M, Timmermans DRM, Kleinveld A, van Eijk JThM, Knol DL, van der Wal G *et al.*Are counselors attitudes influencing pregnant women's attitudes and decisions about prenatal screening? *PrenatDiagn* 2007;27:518–524.

24. Wasden SW, Adams BN, Chasen ST. Are agecutoffs still used to identify candidates for invasive testing for chromosomal abnormalities? *J ReprodMed*2011;56:113-6.

25. De Graaf G, Haverman M, Hochstenbach R, Engelen J, Gerssen-Schoorl K, Poddighe P *et al.*Changes in yearly birth prevalence rates of children with Down syndrome in the period 1986-1997 in the Netherlands*. J Intellect DisabilRes* 2011;55:462-473.