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?

Abstract

Objective To evaluate the performance of the first-trimester combined test (FCT) in different maternal age groups and to discuss whether adjustments in screening policies should be made.

Methods In this retrospective study data (n=26,274) from a fetal medicine center on FCT (maternal age, fetal NT, fβ-hCG, PAPP-A) were studied.

Results 70.6% of cases was <36 yrs and 43% of the Down syndrome (DS) cases were detected in this age group. For women <36 yrs and advanced maternal age (AMA) women (≥36 yrs) DR and FPR were 94.5% and 4.1%, 95.8% and 13.0% (cut-off 1:200). Lowering the cut-off showed an improved balance in DR and FPR. With increasing maternal age FPR and DR increased and OAPR decreased.

Discussion FCT is effective in women <36 and ≥36 yrs. The balance between FPR and DR is more favourable in women <36 yrs with comparable OAPR. Although FPR increases with increasing maternal age performance of FCT in AMA women is more effective than screening based on maternal age alone. Lowering the cut-off to 1:100 in AMA women is suggested to improve screening performance. Routinely offering diagnostic testing to AMA women as screening policy for the detection of DS seems not reasonable.
Introduction

In the Netherlands prenatal screening on Down syndrome (DS) with the first-trimester combined test (FCT), combining maternal age, fetal nuchal translucency (NT) thickness and concentrations of maternal serum free β-human chorionic gonadotrophin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A), is introduced in the last decade. Since 2004 health care professionals had permission to inform all pregnant women about the option of prenatal screening for Down syndrome. Since January 2007, a nationwide screening program is set by the Ministry of Health, Welfare and Sports for implementing FCT and the fetal anomaly scan at 18-22 weeks of gestation for all pregnant women. Eight regional centers, covering the whole country, obtained a licence for implementation of prenatal screening in their region with strict regulations allocated to the counsellors, the sonographers and the laboratories. In the Netherlands differences in screening performance between the regions are reported (Schielen et al., 2006; Wortelboer et al., 2009). Different reference curves are used for the NT measurements and maternal serum parameters. Adjustments on serum parameters are made for maternal weight and smoking; adjustments for monochorionic and dichorionic twin pregnancies and for pregnancies conceived with in vitro fertilization and intracytoplasmatic sperm injection are suggested to be applied in the near future (Linskens et al., 2009; Engels et al., 2010).

The cut-off level for increased risk is set at 1:200 at mid-term. Screening performance of FCT is reported up to 90 percent detection of the affected pregnancies for a false-positive rate of 5 percent (Spencer et al, 2003; Nicolaides et al., 2005; Wald et al. 2005; Go et al., 2005; Kaganet al. 2008). However, the detection rate (DR) and false positive rate (FPR) are strongly influenced by the age structure of the screening population. Both DR and FPR increase with increasing maternal age (Reynolds et al., 1993; Egan et al., 2000; Spencer, 2001, Wapner et al., 2003).

Dutch government policy is to offer women at advanced maternal age (AMA) of 36 years or older invasive diagnostic testing (chorion villus sampling and amniocentesis) for the detection of Down syndrome, even though half of aneuploid fetuses are born in younger women (Resta, 2005). Thus maternal age is in fact still used as a screening tool, whereas screening with FCT is proven to be more effective. In comparison with this policy prenatal screening for Down syndrome is part of secured care, only for AMA women. Diagnostic testing for increased risk at FCT on the other hand is covered in all cases. In our opinion these policies are not endorsed with solid arguments. Information on screening performance in different maternal age groups in the Netherlands can be valuable in the discussion to support or decline these policies.

We present the data on first-trimester prenatal screening with FCT from January 2004 until December 2009 in the province of North-Holland in the Netherlands. The aim of this study was to evaluate the performance of the FCT in different maternal age groups and to discuss whether adjustments in screening policies should be made.

Materials and methods
In this retrospective study data from a tertiary fetal medicine center (VU University Medical Center, Amsterdam, the Netherlands) of the first-trimester screening program for Down syndrome performed in the period from January 1st, 2004 until January 1st, 2010 in the province of North-Holland in the Netherlands were studied.

**First-trimester combined test**

The screening was performed at 9-14 weeks of gestation using maternal age, fetal NT thickness, and maternal serum concentrations of fβ-hCG and PAPP-A for risk calculation. In all cases serum was sampled at 9 – 14 weeks of gestation and the serum markers fβ-hCG and PAPP-A were analyzed at the endocrine laboratory of the VU University Medical Center (VUmc), using the Delfia Xpress (Perkin Elmer Turku Finland) as described before (Linskens et al., 2009). The NT measurements were performed according to the guidelines of the Fetal Medicine Foundation (Snijders et al., 1998) with a fetal crown rump length (CRL) between 45 and 79 mm (VUmc NT reference curve) (Go et al., 2005)

Gestational age was determined by fetal CRL at the time of NT measurement. Information on earlier pregnancy with Down syndrome, smoking habits, and maternal weight were taken into account for risk assessment on Down syndrome. All necessary data were transferred to the risk software program Elips / Lifecycle 2.2 (Perkin Elmer Turku Finland), and Down syndrome risk was calculated. The cut-off for increased risk was > 1:200 at mid-term.

Women with an increased risk were counselled concerning the risk on Down syndrome and the possibility of diagnostic testing with its procedure-related risk. Data on fetal karyotype were obtained from the database of the laboratory for cytogenetics of the VU medical center.

Twin pregnancies were excluded, because maternal serum markers were not taken into account for risk assessment, during the study period.

**Data collection**

Of all cases the following data were recorded: age at conception, gestational age at sample date, maternal weight, smoking habits, NT thickness (mm) and the corresponding CRL (mm), the absolute values of fβ-hCG (ng/ml) and PAPP-A (mU/l), the corrected MoM values of fβ-hCG, PAPP-A and NT, and the calculated risk on Down syndrome. Of all cases that underwent prenatal diagnostic testing for increased risk at first-trimester screening fetal karyotype was available.

**Follow-up**

Follow-up on cases involved in prenatal screening with FCT was collected with self-filled questionnaires and delivery room records and was 80%.
Results

Number of FCT

In the period from January 1st, 2004 until January 1st, 2010 in total 26,274 FCT were performed. In women ≤ 25 years of age 1,405 FCT (5.3%) were done, in women 26-30 years of age 5,161 FCT (19.7%), in women 31-35 years of age 11,980 FCT (45.6%), in women 36-40 years of age 7,117 FCT (27.1%) and in women 41-45 years of age 611 FCT (2.3%). In total 17,970 FCT were performed in women < 36 years of age (70.6%).

The overall median maternal age was 34.1 years. Median maternal age decreased from 35.4 years in 2004 to 33.3 years in 2009.

The overall median weight and smoking corrected MoM values (5th-95th percentile) of NT, fβ-hCG and PAPP-A between women < 36 years and ≥ 36 years of age were comparable (Table 1).

Table 1. The overall median weight and smoking corrected MoM values (5th-95th percentile) of NT, fβ-hCG and PAPP-A in women < 36 and ≥ 36 years of age.

<table>
<thead>
<tr>
<th>MoMvalues</th>
<th>5th percentile</th>
<th>median</th>
<th>95th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>fβ-hCG in women &lt; 36 yrs</td>
<td>0.389</td>
<td>1.030</td>
<td>2.939</td>
</tr>
<tr>
<td>fβ-hCG in women ≥ 36 yrs</td>
<td>0.399</td>
<td>1.052</td>
<td>2.986</td>
</tr>
<tr>
<td>fβ-hCG in all women</td>
<td>0.394</td>
<td>1.041</td>
<td>2.962</td>
</tr>
<tr>
<td>PAPP-A in women &lt; 36 yrs</td>
<td>0.332</td>
<td>0.982</td>
<td>2.592</td>
</tr>
<tr>
<td>PAPP-A in women ≥ 36 yrs</td>
<td>0.327</td>
<td>0.956</td>
<td>2.626</td>
</tr>
<tr>
<td>PAPP-A in all women</td>
<td>0.330</td>
<td>0.977</td>
<td>2.609</td>
</tr>
<tr>
<td>NT in women &lt; 36 yrs</td>
<td>0.672</td>
<td>1.014</td>
<td>1.605</td>
</tr>
<tr>
<td>NT in women ≥ 36 yrs</td>
<td>0.674</td>
<td>1.014</td>
<td>1.569</td>
</tr>
<tr>
<td>NT in all women</td>
<td>0.673</td>
<td>1.014</td>
<td>1.588</td>
</tr>
</tbody>
</table>

Increased risk results

In Table 2 the increased risk results (> 1:200) at FCT subdivided for the different age groups are shown over the years 2004-2009. The distribution of the increased risk results over the age groups was similar throughout the years. Compared to the total number of increased risk results each year the contribution of AMA women with an increased risk over the years was about 55% (with a minimum of 51.1% in 2004 and a maximum of 56.1% in 2005).
Table 2. The number of increased risk results (>1:200) of FCT in the different age groups over the years 2004-2009 (%).

<table>
<thead>
<tr>
<th>Number of increased risk results (%)</th>
<th>≤ 25 yrs</th>
<th>26-30 yrs</th>
<th>31-35 yrs</th>
<th>36-40 yrs</th>
<th>41-45 yrs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>8 (4.4)</td>
<td>17 (9.5)</td>
<td>52 (22.3)</td>
<td>80 (51.3)</td>
<td>22 (12.2)</td>
<td>179 (100.0)</td>
</tr>
<tr>
<td>2005</td>
<td>8 (2.8)</td>
<td>28 (9.9)</td>
<td>87 (29.0)</td>
<td>129 (47.5)</td>
<td>30 (10.6)</td>
<td>282 (100.0)</td>
</tr>
<tr>
<td>2006</td>
<td>2 (0.6)</td>
<td>27 (8.3)</td>
<td>113 (30.3)</td>
<td>152 (51.7)</td>
<td>29 (9.0)</td>
<td>323 (100.0)</td>
</tr>
<tr>
<td>2007</td>
<td>7 (2.0)</td>
<td>25 (7.1)</td>
<td>129 (31.5)</td>
<td>166 (52.3)</td>
<td>25 (7.1)</td>
<td>352 (100.0)</td>
</tr>
<tr>
<td>2008</td>
<td>8 (2.0)</td>
<td>40 (10.1)</td>
<td>141 (31.1)</td>
<td>181 (50.2)</td>
<td>26 (6.5)</td>
<td>396 (100.0)</td>
</tr>
<tr>
<td>2009</td>
<td>6 (1.4)</td>
<td>42 (9.8)</td>
<td>144 (28.8)</td>
<td>206 (52.5)</td>
<td>32 (7.4)</td>
<td>430 (100.0)</td>
</tr>
</tbody>
</table>

In Table 3 an overview is given of the increased risk results subdivided for different risk numbers over the years 2004-2009. The distribution of the risk results over the risk groups was quite similar throughout the years. Compared to the total number of increased risk results in 2004-2009, risk results > 1:50, risk results between 1:50 - 1:99, between 1:100 – 1:149 and between 1:150-1:199 contributed for 34.7%, 22.9%, 21.4% and 21.0% respectively.

Table 3. The number of increased risk results (>1:200) of FCT subdivided in risk results > 1:50, from 1:50 - 1:99, from 1:100 – 1:149 and from 1:150-1:199 over the years 2004-2009 (%).

<table>
<thead>
<tr>
<th>Number of increased risk results (%)</th>
<th>&gt; 1:50</th>
<th>1:50-1:99</th>
<th>1:100-1:149</th>
<th>1:150-1:199</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>66 (36.9)</td>
<td>31 (17.3)</td>
<td>28 (15.6)</td>
<td>54 (30.2)</td>
<td>179 (100.0)</td>
</tr>
<tr>
<td>2005</td>
<td>97 (34.4)</td>
<td>58 (20.6)</td>
<td>68 (24.1)</td>
<td>59 (20.9)</td>
<td>282 (100.0)</td>
</tr>
<tr>
<td>2006</td>
<td>114 (35.2)</td>
<td>73 (22.7)</td>
<td>67 (20.7)</td>
<td>69 (21.4)</td>
<td>323 (100.0)</td>
</tr>
<tr>
<td>2007</td>
<td>133 (37.8)</td>
<td>85 (24.2)</td>
<td>80 (22.7)</td>
<td>54 (15.3)</td>
<td>352 (100.0)</td>
</tr>
<tr>
<td>2008</td>
<td>133 (33.6)</td>
<td>87 (22.0)</td>
<td>86 (21.7)</td>
<td>90 (22.7)</td>
<td>396 (100.0)</td>
</tr>
<tr>
<td>2009</td>
<td>138 (32.1)</td>
<td>115 (26.8)</td>
<td>90 (20.9)</td>
<td>87 (20.2)</td>
<td>430 (100.0)</td>
</tr>
</tbody>
</table>

Test performance

In total 1,962 increased risk results were recorded; in 106 cases chromosomal abnormalities, other than Down syndrome were detected: 40 cases with Edwards syndrome, 17 cases with Patau syndrome, 19 cases with Turner syndrome and 7 cases with triploidy and 20 cases other chromosomal abnormalities like mozaicism, translocation, deletion, inversion and sex chromosomal abnormalities.

In Table 4 the test characteristics are presented of all FCT performed in 2004 until 2009 subdivided for different maternal age groups and at different cut-off values.

The FPR increased with increasing maternal age. Also more DS cases were detected with increasing maternal age. At a cut-off of 1:200 at mid-term the overall detection rate (DR) was 95.2% with a false-positive rate (FPR) of 6.6%. For women < 36 years the DR was 94.5% at a FPR of 4.1% and for AMA
Performance of first-trimester combined test for Down syndrome screening in different maternal age groups

women the DR was 95.8% at a FPR of 13.0%. The odds of being affected given a positive result (OAPR) was most favourable in women aged ≤ 25 years and women 41-45 years.

The OAPR calculated over the years for women < 36 years was 15.9 (52 DS cases versus 830 increased risk results) and for AMA women 14.9 (69 DS cases versus 1,026 increased risk results).

Lowering the cut-off level for increased risk demonstrated a decrease in DR and FPR. At a cut-off of 1:150 a DR was found of 94.2% at a FPR 5.2% and at a cut-off of 1:100 the DR was 92.6% with a FPR of 3.7%.

Subdivided for women < 36 and ≥ 36 years of age the DR and FPR were 94.3% and 3.4%, and 94.2% and 9.9% respectively at a cut-off of 1:150; 90.6% and 2.5%, and 94.2% and 6.7% respectively at a cut-off of 1:100.

Table 4. Test characteristics of all FCT performed in 2004-2009 subdivided for different maternal age groups at different cut-off levels for increased risk.

<table>
<thead>
<tr>
<th></th>
<th>≤ 25 yrs</th>
<th>26-30 yrs</th>
<th>31-35 yrs</th>
<th>36-40 yrs</th>
<th>41-45 yrs</th>
<th>&lt; 36 yrs</th>
<th>≥ 36 yrs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of FCT</td>
<td>1,443</td>
<td>5,254</td>
<td>12,244</td>
<td>6,709</td>
<td>625</td>
<td>18,941</td>
<td>7,334</td>
<td>26,274</td>
</tr>
<tr>
<td>Cut-off 1:200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPR</td>
<td>2.4</td>
<td>3.0</td>
<td>4.8</td>
<td>12.2</td>
<td>22.5</td>
<td>4.1</td>
<td>13.0</td>
<td>6.6</td>
</tr>
<tr>
<td>DR</td>
<td>100</td>
<td>90.0</td>
<td>95.1</td>
<td>94.9</td>
<td>100</td>
<td>94.5</td>
<td>95.8</td>
<td>95.2</td>
</tr>
<tr>
<td>OAPR</td>
<td>9.2</td>
<td>18.3</td>
<td>16.1</td>
<td>15.6</td>
<td>11.8</td>
<td>15.9</td>
<td>14.9</td>
<td>15.3</td>
</tr>
<tr>
<td>Cut-off 1:150</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPR</td>
<td>2.3</td>
<td>3.0</td>
<td>3.7</td>
<td>9.3</td>
<td>15.6</td>
<td>3.4</td>
<td>9.9</td>
<td>5.2</td>
</tr>
<tr>
<td>DR</td>
<td>100</td>
<td>90.0</td>
<td>94.8</td>
<td>92.8</td>
<td>100</td>
<td>94.3</td>
<td>94.2</td>
<td>94.2</td>
</tr>
<tr>
<td>OAPR</td>
<td>9.2</td>
<td>18.8</td>
<td>13.3</td>
<td>13.1</td>
<td>8.5</td>
<td>14.0</td>
<td>12.2</td>
<td>13.1</td>
</tr>
<tr>
<td>Cut-off 1:100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPR</td>
<td>1.9</td>
<td>2.4</td>
<td>2.6</td>
<td>6.0</td>
<td>15.5</td>
<td>2.5</td>
<td>6.7</td>
<td>3.7</td>
</tr>
<tr>
<td>DR</td>
<td>75</td>
<td>90.0</td>
<td>92.3</td>
<td>92.8</td>
<td>100</td>
<td>90.6</td>
<td>94.2</td>
<td>92.6</td>
</tr>
<tr>
<td>OAPR</td>
<td>10.0</td>
<td>14.7</td>
<td>10.0</td>
<td>8.8</td>
<td>7.5</td>
<td>10.9</td>
<td>8.6</td>
<td>9.6</td>
</tr>
</tbody>
</table>

*Down syndrome cases*

Of the 127 DS cases 121 were correctly detected with FCT, 52 (43%) in women < 36 years of age and 69 (57%) in AMA women. Of these DS cases 110 (90.9%) were detected at a risk > 1:50, 8 (6.6%) at a risk 1:50 – 1:99, 2 (1.7%) at a risk 1:100 – 1:149 and 1 (0.8%) at a risk 1:150 – 1:199. The 6 DS cases that were missed are listed by maternal age (risk result): 29 years (1:2800); 32 years (1:430), 35 years (1:710), 36 years (1:760), 37 years (1:290) and 38 years (1:580).
The median weight and smoking corrected MoM values (5th-95th percentile) of NT, fβ-hCG and PAPP-A in affected pregnancies were 2.78 (1.20 - 5.16), 1.72 (0.59 - 5.84) and 0.42 (0.17 - 1.10). Subdivided for women < 36 and ≥ 36 years of age these values for NT, fβ-hCG and PAPP-A were 2.84 (1.39 - 6.0), 1.41 (0.53 - 8.26), 0.41 (0.13 - 1.05) and 2.66 (1.20 - 5.16), 1.90 (0.59 - 5.60) and 0.46 (0.18 - 1.39) respectively.

Figure 1 outlines the distribution of nuchal translucency (NT) thickness in the DS cases subdivided for maternal age. Of the DS cases detected with FCT 95 of the 121 (78.5%) had a NT ≥ 95th percentile. According to the Dutch protocol for NT measurement, a NT ≥ 3.5 mm is defined as a sonographic abnormality. Of the DS cases detected 74 (61.2%) had a NT ≥ 3.5 mm.

Compared to all the DS cases detected in the different age groups, the contribution of DS cases with NT ≥ 3.5 mm in women aged ≤ 25 years, 26-30 years, 31-35 years, 36-40 years and 41-45 years was 75%, 71.4%, 60.9%, 55.3% and 68.2% respectively.

Figure 1. Distribution of nuchal translucency thickness in Down syndrome cases subdivided for different maternal age groups.

Discussion

Over the period 2004 – 2009 the majority of women (70.6%) involved in prenatal screening for Down syndrome were younger than 36 years of age. There was a shift notable over the years towards a larger participation in prenatal screening of women < 36 years of age. The range of distribution of increased risk results over the years between women aged < 36 years and ≥ AMA women was rather constant at 45% versus 55% (Fig 1). The fact that an increase in screen-positive results is not found in women < 36 years reflects a good performance of FCT in these women.
The detection rate (DR) of the first-trimester combined test (FCT) conducted in the region of North-Holland was 95.2% at a cut-off level of 1:200 at mid-term with a 6.6% false-positive rate (FPR) based on follow-up data of 80%. There were no reasons to assume that missing data on outcome lead to significant ascertainment bias. Compared to previous data from our center on the performance of FCT (Go et al., 2005), a shift in maternal age is seen from 51% participation of AMA women in the former study to 39.4% in this study. Taking into account this shift in maternal age, screening in our center has a constant performance, reflected in a comparable balance between DR and FPR over the years.

Lowering the cut-off level for increased risk demonstrated an excellent screening performance with good balance between DR and FPR at the cut-off levels of 1:150 (DR 94.2%, FPR 5.2%) and 1:100 (DR 92.6%, FPR 3.7%). These results support the idea that the choice of cut-off level should be based on the best test characteristics of the screening center instead of a nationwide used cut-off level.

The results of this study are in concordance with other previous reports (Spencer et al., 2003; Nicolaides et al., 2005; Wald et al. 2005; Go et al., 2005; Kaganet al. 2008). A recent study in a Dutch screening population (Wortelboer et al., 2009) reported an overall OAPR of 1:10 with a DR of 75.8% at a 3.3% screen-positive rate with a cut-off of 1:250 at term over the years 2004-2006. Differences in screening performance are probably explained by the use of different NT reference curves and cut-off levels. To compare screening performance DR should be calculated at a fixed FPR and at the same cut-off level. Our study shows a DR of 94.2% at a 5% FPR, with a cut-off of 1:150.

Comparing screening performance of FCT between women <36 of age and AMA women the balance between FPR and DR was definitely more favourable in women <36 years of age then in AMA women (4.4% FPR and 94.5% DR versus 13.7% FPR and 95.8% DR). The median weight and smoking corrected MoM values (5th-95th percentile) of NT, β-hCG and PAPP-A between women <36 years of age and AMA women with unaffected pregnancies were not significantly different. Also the median MoM values of NT, β-hCG and PAPP-A in DS cases were comparable in women aged <36 years and AMA women. The values of serum parameters in women with affected pregnancies are comparable to values reported previously (Spencer et al., 2007). The higher FPR in AMA women is presumably based on a higher background risk. Our study is in agreement with several studies (Reynolds et al., 1993; Snijders et al., 1994; Egan et al., 2000; Spencer, 2001, Wapner et al., 2003) who report that the background risk greatly increases the FPR in AMA women.

A good comparison of screening performance between the different maternal age groups is difficult. The OAPR is more favourable with increasing maternal age, however the FPR increases greatly with maternal age. Differences in FPR and OAPR between the maternal age groups are not communicated in daily practice.

In AMA women it appears that a risk assessment would be inappropriate in view of their high FPR. Although the background risk for Down syndrome increases with increasing age, cases with identical values of NT and serum parameters are not more often affected by Down syndrome in AMA women.
than in younger women. Eliminating the background risk by maternal age from the risk assessment would offer the opportunity to compare screening performance in the different age groups. Recently some studies have suggested to eliminate maternal age from the risk assessment and use the absolute risk screening approach defined as final risk at FCT/maternal age risk (Schmidt et al., 2008; Gebb and Dar. 2009; Hörmansdörfer et al., 2010). It would reduce the FPR in women aged 35 years or older and decrease the false-negative results in younger women. It would be of interest to validate this absolute risk screening method in a Dutch screening population.

Although the FPR in AMA women is higher, screening performance of FCT in this age group is effective (DR 95.8% at 13.0 FPR) and it is definitely more effective than screening based on maternal age alone. Lowering the cut-off to 1:100 in AMA women would improve screening performance. With the introduction of prenatal screening as population screening is to be expected that more DS cases are detected without an increase in invasive procedures and hence a stable number of iatrogenic miscarriages. If screening is used preferentially over maternal age in our region, about 85% of AMA women could avoid an invasive procedure. Thus routinely offering invasive diagnostic testing to AMA women as screening policy for the detection of Down syndrome seems not reasonable. Although knowledge about decision making on prenatal screening is available (Van den Berg et al., 2005a, 2005b, 2007 and 2008; Kleinveld et al., 2008), it is still important to find out more about the process. For instance: are AMA women more prone to chose invasive testing with a risk < 1:200 despite the fact that maternal age is incorporated in the risk assessment?

Screening for Down syndrome is part of population screening. In the Netherlands however the cost for FCT are only covered for AMA women, while the majority (70.6%) of the screening population is < 36 years of age. The cost for FCT might for some women < 36 years of age be a reason to refrain from prenatal screening.

This study reveals that screening with FCT is effective in both women < 36 years of age and AMA women. Moreover 43% of the DS cases were detected in women < 36 years. The emotional impact of the care or the loss of a child with DS is independent of maternal age (Cunningham and Sloper, 1977; Helm et al., 1998; Yildirim and Yildirim, 2010). Furthermore informed choice of the parents is considered as an important principle in prenatal screening (Van den Berg et al., 2006). The fact that women < 36 years of age in the Netherlands should pay for the test is in firm contrast with this principle. Maternal age should for all these reasons not be a limiting factor for covering costs.

**Conclusion**

This study shows an excellent screening performance of FCT in both women < 36 years of age and in AMA women. Lowering the cut-off level for increased risk improves the balance between DR and FPR. The balance between FPR and DR is even more favourable in women < 36 years of age with comparable OAPR. With increasing maternal age FPR increases distinctly, due to a higher a priori
risk, and the OAPR decreases. A good comparison of screening performance between different age
groups might be done by eliminating maternal age from the risk assessment. Differences in FPR and
OAPR between the different maternal age groups should be communicated in daily practice to meet
the requirements of informed choice. Although the FPR in AMA women is higher, screening
performance of FCT in this age group it is definitely more effective than screening based on maternal
age alone. Lowering the cut-off to 1:100 in AMA women may be an option to improve screening
performance. While invasive testing is reasonable in any well informed patient regardless of age or risk
result, arbitrary categorization based on maternal age is not appropriate. Maternal age should also not
be a limiting factor for covering costs of FCT.
References


