CHAPTER 2

Prenatal diagnosis in the Netherlands, 1991-2000: Number of invasive procedures, indications, abnormal results, and terminations of pregnancy

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Abstract

Objective  To provide an overview of invasive prenatal diagnosis in the Netherlands and to analyse trends.

Methods  Annual results from all centers for invasive prenatal diagnosis in the Netherlands over the period 1991-2000 were combined and described, with particular emphasis on indications, abnormal results, type of invasive procedures, and terminations of pregnancy.

Results  The percentage of invasive prenatal diagnosis increased from 5% of births in 1991 to 6% in 1996 and subsequently remained level. During the study period, the number of pregnant women aged 36 and older increased by 70%, but the number of procedures performed because of maternal age remained stable. The detection rate for abnormal results was 2 to 3% for maternal age and rose from 9 to 13% for other indications. Other trends during the studied time period included the relative decrease of cordocentesis (-82%) and chorionic villi biopsy (-18%) in favour of amniocentesis (+48%), and a strong decrease in the number of amniocentesis procedures for increased risk of neural tube defect. In 71% of cases with abnormal results, the pregnancy was terminated.

Conclusion  There was a significant decrease in the percentage of pregnant women aged 36 or older who underwent invasive prenatal diagnosis without previous screening.
Introduction

In the Netherlands, Section 2 of the Special Medical Procedures Act limits the number of centers granted a permit to perform invasive prenatal diagnostic procedures. Only 13 centers are licensed to perform invasive prenatal diagnosis: the university centers Amsterdam (two centres), Groningen, Leiden, Maastricht, Nijmegen, Rotterdam, and Utrecht, as well as 5 non-university so-called satellite clinics (Arnhem, Dordrecht, Eindhoven, Enschede and Zwolle). The Special Medical Procedures Act covers amniocentesis, chorionic villi biopsy (transabdominal and transcervical), and cordocentesis. These procedures are performed for chromosomal or DNA-analysis, for α-foetoprotein (AFP) measurement, or for metabolic testing. Indications for invasive prenatal diagnosis are listed in Table 1. The act also requires that each center provide an annual report following a standardized format.

Table 1. Indications for chromosomal and or DNA-analysis in the Netherlands  
(Special Medical Procedures Act).

- pregnant women who have reached the age of 36 years in the 18th week of gestation
- increased risk for neural tube defect
- one of the future parents is carrier of a chromosomal abnormality
- ultrasound suspicion of fetal abnormalities
- pregnant women who have delivered a fetus or child with a chromosomal abnormality after a gestational age of 16 weeks
- pregnant women who had a chromosomal abnormal fetus confirmed by prenatal genotyping in a previous pregnancy
- pregnant women with an increased risk on a autosomal dominant, autosomal recessive or X-chromosomal inherited disease
- pregnant women with an inherited mitochondrial abnormality
- after abnormal result of maternal serum screening
- pregnancy after Intracytoplasmic Sperm Injection (ICSI) procedure

The Dutch Working Party on Prenatal Diagnosis has collected data relating to invasive prenatal testing in the Netherlands since 1989. This paper summarises the results from the annual reports from 1991 to 2000.

Methods

The 13 licensed centers in the Netherlands annually report the numbers of
performed procedures, indications, detected abnormalities, and the number of pregnancy terminations to the Working Party on Prenatal Diagnosis, using a standard form. The annual report committee of the Working Party checks the numbers for plausibility and consistency. By referring to the Central Bureau of Statistics for data on the total annual birth rate in the Netherlands, and the age of mothers at the time of birth, the committee is able to calculate the number of women aged 36 and older in the 18th week of pregnancy quite accurately. These annual reports do not mention amniocentesis and cordocentesis performed for non-genetic diagnostic procedures in cases of fetal alloimmune anemia, uncertainty about fetal lung maturity or infectious diseases, or for therapeutic reasons (amniodrainage, intra-uterine transfusion). Non-invasive screenings, such as maternal serum testing (triple test) and nuchal translucency measurement, are also not recorded. At the time of the study period, maternal serum screening and nuchal translucency measurement for Down syndrome risk assessment were not authorized in the Netherlands. The annual reports mention the numbers of cordocenteses, but not the indications and abnormal results.

After 1995, the reports provide more detail regarding the detected abnormalities, and also whether the pregnancy was terminated or not. In cases where a pregnancy was not terminated after an abnormal test result, the mother either chose to continue with the pregnancy or was not allowed to terminate the pregnancy because of advanced gestational age at the time of diagnosis. The number of pregnancy losses after an invasive procedure is not mentioned in the annual reports. In 1997, the term "other chromosomal abnormality" was defined more precisely in order to exclude some common variants, that may have been reported by some centers and not by others in the previous years. At the same time, the fetus was adopted as the base measure rather than the pregnant woman.

Chi-square linear-by-linear association (SPSS inc., Chicago, Illinois, USA) was used for trend analysis between the years 1991-2000.

**Results**

The mean annual number of invasive procedures was 11,839, with a minimum of 10,126 in 1991 and a maximum of 12,574 in 1997. This means that around 6% of the approximately 200,000 children born each year in the Netherlands during the study period underwent invasive prenatal diagnosis. **Figure 1** shows the annual number of amniocenteses, chorionic villi biopsies (transcervical and transabdominal), and cordocenteses. The number of amniocenteses increased from 6,059 in 1991 to 8,977 in 1998 (+48%), the number of chorionic villi biopsies decreased from 3,985
in 1992 to 3257 in 2000 (-18%) and the number of cordocenteses decreased from 186 in 1991 to 33 in 2000 (-82%). The decrease in both chorionic villi biopsies and cordocentesis is statistically significant (p<0.001).

**Figure 1.** Overview of prenatal diagnostic procedures 1991-2000.

Maternal age was the indication for 72% of the amniocenteses and chorionic villi biopsies. The other indications for prenatal invasive testing are listed in Table 2. The total number of women aged 36 and older who underwent invasive prenatal testing increased during the study period from 7058 to 8878 (Table 2), an increase of 25.8%. However, the number of pregnant women aged 36 and older (at the 18th week of gestation) increased far more during the study period, from 15,140 to 25,730 (Figure 2), an increase of 69.9%.

**Figure 2.** Overview of prenatal diagnostic procedures 1991-2000.
Table 2. Amniocentesis and Chorionic villi biopsy 1991-2000. Shown is the number (%) of women

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<tbody>
<tr>
<td>Maternal age</td>
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<td>Increased risk for neural tube defect</td>
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<td>Parent carrier of a chromosomal abnormality</td>
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<td>Ultrasound abnormality</td>
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<tr>
<td>&lt;24 weeks</td>
<td>1066 (10.7)</td>
<td>912 (8.7)</td>
<td>920 (8.0)</td>
<td>819 (7.2)</td>
<td>738 (6.1)</td>
<td>537 (4.3)</td>
<td>374 (3.0)</td>
<td>363 (2.9)</td>
<td>304 (2.5)</td>
<td>261 (2.2)</td>
<td>6134 (5.4)</td>
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<tr>
<td>&gt;24 weeks</td>
<td>344 (2.9)</td>
<td>378 (3.1)</td>
<td>270 (2.2)</td>
<td>302 (2.4)</td>
<td>307 (2.5)</td>
<td>354 (2.9)</td>
<td>407 (3.3)</td>
<td>381 (3.1)</td>
<td>3757 (3.2)</td>
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<tr>
<td>Previous child/fetus with a chromosomal abnormality</td>
<td>315 (3.2)</td>
<td>362 (3.4)</td>
<td>388 (3.4)</td>
<td>375 (3.2)</td>
<td>416 (3.4)</td>
<td>394 (3.2)</td>
<td>354 (2.8)</td>
<td>365 (2.9)</td>
<td>407 (3.3)</td>
<td>381 (3.1)</td>
<td>3757 (3.2)</td>
<td></td>
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<tr>
<td>DNA examination</td>
<td>160 (1.6)</td>
<td>132 (1.2)</td>
<td>185 (1.6)</td>
<td>210 (1.8)</td>
<td>191 (1.6)</td>
<td>243 (2.0)</td>
<td>248 (2.0)</td>
<td>255 (2.0)</td>
<td>270 (2.2)</td>
<td>267 (2.2)</td>
<td>2161 (1.8)</td>
<td></td>
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<tr>
<td>Metabolic examination</td>
<td>62 (0.6)</td>
<td>55 (0.5)</td>
<td>32 (0.3)</td>
<td>17 (0.1)</td>
<td>36 (0.3)</td>
<td>32 (0.3)</td>
<td>48 (0.4)</td>
<td>48 (0.4)</td>
<td>28 (0.2)</td>
<td>27 (0.2)</td>
<td>385 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Serum screening</td>
<td>187 (1.9)</td>
<td>202 (1.9)</td>
<td>282 (2.5)</td>
<td>383 (3.3)</td>
<td>740 (6.1)</td>
<td>796 (6.4)</td>
<td>606 (4.9)</td>
<td>619 (5.0)</td>
<td>574 (4.7)</td>
<td>537 (4.4)</td>
<td>4926 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>519 (5.2)</td>
<td>656 (6.1)</td>
<td>720 (6.3)</td>
<td>619 (5.3)</td>
<td>604 (5.0)</td>
<td>537 (4.3)</td>
<td>671 (5.4)</td>
<td>647 (5.2)</td>
<td>556 (4.6)</td>
<td>531 (4.4)</td>
<td>6060 (5.2)</td>
<td></td>
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<tr>
<td>Total</td>
<td>9940</td>
<td>10677</td>
<td>11445</td>
<td>11676</td>
<td>12043</td>
<td>12355</td>
<td>12490</td>
<td>12479</td>
<td>12210</td>
<td>12115</td>
<td>117830</td>
<td></td>
</tr>
</tbody>
</table>

Average percentage of multiple pregnancies in pregnant women who underwent prenatal testing is 3%.

*From 1991 to 1994 ultrasound abnormalities were not categorized in gestational age.
The percentage of pregnant women aged 36 and older who underwent an invasive prenatal test because of maternal age significantly (p<0.001) decreased from 46 to 34%. The percentage of procedures performed because of ‘increased risk of neural tube defect’ significantly (p<0.001) decreased during the study period from 10.7 to 2.2% (Table 2). The percentage of procedures with the indication ‘abnormal result at serum screening’ rose from 1.9% in 1991 to 6.4% in 1996 and dropped to 4.4% in 2000. For the indication ‘abnormalities on fetal ultrasound,’ the percentage rose from 4.4 to 8.8%.

The average percentage of abnormal test results was 4.7%, increasing from 3.6% in 1991 to 5.4% in 2000. The total number of abnormalities detected as a result of invasive prenatal diagnostic procedures increased from 362 in 1991 to 638 in 2000. The number of abnormal test results and terminations of pregnancy during the 6 year period from 1995 to 2000 are listed in Table 3, according to the main indication for invasive prenatal testing. An average of 70.8% of the pregnancies with abnormal results was terminated (Table 3).

Table 3. Abnormal results and termination of pregnancy at invasive prenatal testing, 1995-2000.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Procedure</th>
<th>Abnormal result</th>
<th>Termination of pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>53 196 (72.2)</td>
<td>1259 (2.4)</td>
<td>923 (73.3)</td>
</tr>
<tr>
<td>Increased risk of neural tube defect</td>
<td>2577 (3.5)</td>
<td>37 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Parent carrier of a chromosomal abnormality</td>
<td>978 (1.3)</td>
<td>160 (16.4)</td>
<td></td>
</tr>
<tr>
<td>Ultrasound abnormality &lt;24 weeks</td>
<td>3558 (4.8)</td>
<td>990 (27.8)</td>
<td></td>
</tr>
<tr>
<td>Ultrasound abnormality &gt;24 weeks</td>
<td>1955 (2.7)</td>
<td>335 (17.1)</td>
<td></td>
</tr>
<tr>
<td>Previous child/fetus with a chromosomal abnormality</td>
<td>2317 (3.1)</td>
<td>45 (1.9)</td>
<td>1522 (69.3)</td>
</tr>
<tr>
<td>DNA-examination</td>
<td>1474 (2.0)</td>
<td>379 (25.7)</td>
<td></td>
</tr>
<tr>
<td>Metabolic examination</td>
<td>219 (0.3)</td>
<td>37 (16.9)</td>
<td></td>
</tr>
<tr>
<td>Serum screening abnormal</td>
<td>3872 (5.3)</td>
<td>130 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3546 (4.8)</td>
<td>82 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>73692</td>
<td>3454 (4.7)</td>
<td>2445 (70.8)</td>
</tr>
</tbody>
</table>

The percentage of abnormal test results was 4.7%, increasing from 3.6% in 1991 to 5.4% in 2000. The total number of abnormalities detected as a result of invasive prenatal diagnostic procedures increased from 362 in 1991 to 638 in 2000. The number of abnormal test results and terminations of pregnancy during the 6 year period from 1995 to 2000 are listed in Table 3, according to the main indication for invasive prenatal testing. An average of 70.8% of the pregnancies with abnormal results was terminated (Table 3).
The percentages of abnormalities found as a result of invasive testing varied significantly according to indication, from 1.4% for ‘increased risk of neural tube defect’ and 2.4% for ‘maternal age’, to 25.7% for ‘increased risk of DNA abnormalities’ and 27.8% for ‘ultrasound abnormalities <24 weeks.’ While the percentage of abnormal test results for the indication ‘maternal age’ remained fairly constant throughout the study period, it rose considerably for the other indications after 1998 (Figure 3). The number of terminations of pregnancies because of fetal abnormality increased during the study period, but the percentage remained constant (Figure 3).

Figure 3. Percentage abnormal test results at invasive prenatal testing 1995-2000, shown per indication

The number of different DNA abnormalities for which prenatal diagnostic procedures were performed increased from 41 in 1995 to 100 in 2000. The total number of DNA abnormalities that were detected also increased, from 55 in 1995 to 72 in 1999 (Table 4). The most frequent DNA abnormalities were cystic fibrosis, fragile-X, myotonic dystrophy (Steinert), Huntington’s disease, Duchenne muscular dystrophy, spinal muscular atrophy type 1 (Werdnig-Hoffmann) and adrenogenital syndrome. The most frequently diagnosed chromosomal abnormalities were trisomy 21, trisomy 18, triploidy, Turner’s syndrome (45,X), and Klinefelter’s syndrome (47,XXY) (Table 4).
Table 4. Detected abnormalities and termination of pregnancy after invasive prenatal testing 1995-2000.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of diagnosis; number of terminations of pregnancy (%) in the year</th>
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<tbody>
<tr>
<td>trisomy 18</td>
<td>72:53 (74)</td>
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<tr>
<td>trisomy 13</td>
<td>18:13 (72)</td>
</tr>
<tr>
<td>45,X</td>
<td>37:22 (59)</td>
</tr>
<tr>
<td>47,XXX</td>
<td>5:1 (20)</td>
</tr>
<tr>
<td>47,XXY</td>
<td>6:5 (83)</td>
</tr>
<tr>
<td>47,XYY</td>
<td>4:0 (0)</td>
</tr>
<tr>
<td>Triploidy</td>
<td>11:4 (36)</td>
</tr>
<tr>
<td>DNA-abnormalities</td>
<td>55:49 (83)</td>
</tr>
<tr>
<td>Neural tube defect</td>
<td>58:44 (76)</td>
</tr>
<tr>
<td>Metabolic abnormality</td>
<td>29:6 (21)</td>
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<tr>
<td>Total</td>
<td>574:377 (66)</td>
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</table>
Discussion

Thanks to the centralisation of procedures, and the annual reports of the Working Party on Prenatal Diagnosis, the precise number of invasive prenatal diagnostic procedures performed in the Netherlands is known; in addition, the indications, the number of abnormal test results, and the number of terminations of pregnancy because of fetal abnormality are also known. There was a slight rise in the total number of pregnant women who underwent invasive prenatal diagnosis during the study period: from 5% of births in 1991 to 6% in 1996. After that, the percentage remained at the same level. Almost three-quarters of the procedures were performed because of ‘maternal age,’ and this number remained fairly stable during the study period. An interesting finding was that the number of pregnant women aged 36 and older increased by 70% in the study period, whereas the number of women who underwent invasive testing increased by only 26%.

The percentage of abnormal test results was highly dependent on the indication for the procedure. The percentage varied from 1.4% for ‘increased risk of neural tube defect’ and 2.4% for ‘maternal age,’ to 25.7% for ‘increased risk for DNA abnormalities’ and 27.8% for ‘abnormalities on fetal ultrasound’.

In 1999, the number of terminations of pregnancy because of fetal abnormality was 1.8% of the total number of registered terminations of pregnancy in the Netherlands (www.stisan.nl). It is estimated that around 150 children with spina bifida, encephalocele or anencephaly, and 210 children with Down syndrome (trisomy 21) were born in the Netherlands in 1998, after 24 weeks’ gestation.

Many numbers remained remarkably constant between 1991 and 2000. Nevertheless, on closer consideration, several interesting trends can be observed. The first trend is an 82% decrease in the number of cordocenteses and an 18% decrease in chorionic villi biopsies. The most plausible explanation for this is that women choose amniocentesis more often because they consider it a safer procedure. The relative decrease in the use of chorionic villi biopsy compared to the use of amniocentesis is probably because of the slightly higher risk of miscarriage, and probably also because of reports in the literature of a possible relation between chorionic villi biopsy and transversal limb defects if the test is performed early in pregnancy (<10 weeks). It is currently assumed that there is no relation between limb defects and chorionic villi biopsy performed after 10 weeks of pregnancy.

In addition, some centers changed their policy in favour of amniocentesis during the study period, because 1-2% of pregnant women receive an indistinct result from chorionic villi biopsy and then have to undergo a second procedure (generally amniocentesis). Therefore, several centers advise performing amniocentesis instead of chorionic villi biopsy, when there is a low probability of an abnormal result. In recent years, amniocentesis interphase fluorescence in situ hybridisation (FISH) for the most frequent trisomies has also been increasingly preferred in
cases with a high a priori risk (e.g., abnormality fetal ultrasound) because it gives a quick result for certain trisomies." As interphase FISH is performed on non-dividing cells in amniotic fluid, a time-consuming cell culture is not necessary. Before interphase FISH became available, a quick result could only be obtained by examination of metaphases in fetal blood or chorionvilli in uncultured material. The decrease in cordocentesis is obviously explained by the introduction of fast results from the interphase FISH.

The second trend is the decrease in the number of amniocenteses performed for detecting neural tube defects. While around 11% of all procedures in 1991 were performed because of high risk of neural tube defect, by 2000 the percentage was close to 2%. The explanation for this spectacular decrease is obvious: when there was an increased risk of neural tube defect, a detailed ultrasound was performed, frequently combined with serum testing, which provides equal sensitivity without the risk of a miscarriage."

The third trend is the decrease from 46 to 34%, of pregnant women who underwent an invasive procedure because of ‘maternal age.’ This trend can be explained by the rise of (non-invasive) prenatal screening at 15-17 weeks gestation by means of the triple test, and screening by means of nuchal translucency measurement at 11-14 weeks gestation, though the Population Screening Act does not authorize either of these tests. From the annual reports of the National Institute of Public Health and Environment (RIVM) and the University Hospital Groningen, which together process >90% of all triple tests in the Netherlands, we know that the percentage of pregnant women who underwent a triple test rose from 1.6% in 1991 to 2.8% in 1999. The RIVM data show that half of these pregnant women were older than 36 years. In the last 6 years of the study period, more prenatal diagnostic procedures were performed because of abnormal serum screening test results. In 1991, 1.9% of all procedures were performed because of ‘abnormal test result after serum screening’, whereas in 1996 this percentage was 6.4% and in 2000 it was 4.4%. The number of pregnant women who underwent a nuchal translucency measurement was not registered in the Netherlands, but members of the Dutch Working Party on Prenatal Diagnosis estimate that the percentage went from <1% in 1996 to between 8% and 10% in 2002. An increasing number of pregnant women 36 years and older resort to invasive procedures only when prenatal screening indicates a higher risk. This double screening (maternal age and nuchal translucency or serum screening) is more effective than screening for maternal age only. This explains why the increased number of pregnant women 36 years and older did not lead to an increase of invasive testing, but still led to a higher number of detected abnormalities. Prenatal screening in the first trimester by means of nuchal translucency measurement, combined with first trimester maternal serum screening and other ultrasound observations, is an inevitable evolution. The literature indicates that the percentage
of detected Down syndrome cases is 85% when prenatal screening is performed after combined first trimester screening compared to 30% when screening is only done for maternal age only, assuming that the 5% of pregnant women with the highest risk undergo an invasive procedure. Even if only the 1% of pregnant women considered at the highest risk by first semester screening undergo an invasive procedure, it is anticipated that 72% of fetuses with Down syndrome would still be detected. As soon as prenatal screening is authorized in the Netherlands (and this is expected to take place in 2007), a nationwide registration system will start, providing an integrated report on the effects of maternal serum testing, first- and second trimester detailed ultrasound, invasive prenatal diagnosis, and pregnancy outcome.

**Conclusion**

Invasive prenatal testing is well organized in the Netherlands. Annual reports on invasive testing are consistent, and the total number of procedures in the study period was stable. There was a clear decrease in the number of pregnant women 36 years and older who chose invasive testing without prior prenatal screening. There was also a clear increase in the number of detected fetal abnormalities. We expect this trend to continue: the number of non-invasive testing will increase, the number of invasive procedures will decrease, and the number of detected fetal abnormalities will increase.

**Acknowledgements**

We thank the co-workers of the clinical genetic centers and the members of the Working Party on Prenatal Diagnosis who prepared the annual reports.
References

