PRENATAL DIAGNOSIS IN WOMEN OF ADVANCED MATERNAL AGE

ISBN 90–9005585–1

Met dank aan Schering Nederland b.v.

Cover:
A group of women at Baartmansfontein in the Southern Cape. From "Africa's vanishing art. The Rock Paintings of Tanzania" by Mary Leaky. Published by Hamish Hamilton/Rainbird 1983.

Prenatal diagnosis in women of advanced maternal age

Prenatale diagnostiek op leeftijdsindicatie

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
AAN DE ERASMUS UNIVERSITEIT ROTTERDAM
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF. DR. C.J. RIJNVOS
EN VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN.
DE OPENBARE VERDEDIGING ZAL PLAATSVINDEN OP
WOENSDAG 11 NOVEMBER 1992 OM 15.45 UUR

DOOR

HELEN BRANDENBURG

GEBOREN TE AMSTERDAM

1992
Pasmans Offsetdrukkerij b.v., 's-Gravenhage

Promotiecommissie:

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Human power is very limited and infinitely surpassed by the power of external causes.

Spinoza, Ethica, c.1665.

Aan mijn ouders.

Contents

Chapter 1

Definition of study objectives and general introduction to pregnancy and prenatal diagnosis in women of advanced maternal age.

1.1 Objectives of the study.

Since the availability of prenatal diagnosis to women of advanced maternal age in the late sixties, certain changes have taken place world-wide, in the Netherlands and in our department.

Firstly, the number of elderly gravidas increased during the last ten years in the Netherlands as in other western countries (Hansen, 1986; Utian and Kiwi, 1988; Fonteyn and Isada, 1988; Tas, 1990). Secondly, chorionic villus sampling (CVS) was introduced in our department in 1984.

Another change occurred in 1984 when in the Netherlands the age limit for women who were entitled to have prenatal diagnosis was lowered from 38 to 36 years of age.

Finally, from 1987 onwards in our department all CVS procedures for advanced maternal age were performed transabdominally as opposed to the transcervical approach between 1984-1987.

The purpose of the present study was to determine the impact of these changes on prenatal diagnosis in women of advanced maternal age during the period 1984-1990. The following aspects were studied:

1. The uptake (utilization) of prenatal diagnosis in women of advanced maternal age in the Southwest region of the Netherlands.
2. The effect of the introduction of CVS on the utilization of prenatal diagnosis; which sampling approach should be adopted and the acceptability of CVS by the patient and the referring physician.
3. The effect of CVS on pregnancy termination and spontaneous fetal loss and subsequent reproductive behaviour.
4. The difference in prenatal diagnostic approach between singleton and twin pregnancies.

1.2 General introduction to pregnancy and prenatal diagnosis in elderly women. Effect of maternal age on complications of pregnancy.

Introductory remarks.

During the last ten years an increasing number of women has been postponing childbearing until their midthirties (Hansen, 1986; Utian and Kiwi, 1988; Fonteyn and Isada, 1988).

Not only has the absolute number in the age group of 35-45 years grown because of the post second world war baby boom, but also a higher percentage of these women has become pregnant (Davidson and Fukushima, 1985; Utian and Kiwi, 1988). One reason for the increased tendency to delay pregnancy is that more women complete their training and establish a career before starting a family of their own (Daniels and Weingarten, 1979; Kessler et al., 1980). Another reason for delayed parenthood is a history of infertility (Kessler et al., 1980). Further, as a result of present medical care pregnancy at advanced maternal age is no longer subject to considerable risks (Kirz et al., 1985). However, pregnancy outcome and maternal mortality are still less favourable in women over 35 years compared with younger women (Hansen, 1986; Högberg, 1986; Utian and Kiwi, 1988).

A brief review concerning pregnancy and fetal outcome in women of advanced maternal age will be presented in this introductory chapter in order to define the position of prenatal diagnosis. Fetal loss after prenatal diagnosis and genetic termination of pregnancy can only be judged when compared with the natural course of pregnancy in the elderly gravida.

1.2.1 *Conception.*

Despite a regular menstrual period and no obvious explanations for reduced fertility, women beyond the age of 38 may have an infertility rate as high as 50% (Stein, 1985; Hansen, 1986).

Likewise, in a series of women between 35 and 40 years of age receiving donor insemination, the conception rate was as low as 50% (Ceros et al., 1982; van Noord-Zaadstra et al., 1990).

The following explanations for the reduced fertility in elderly women have been put forward: 1) uterine and ovarian dysfunction (luteal insufficiency) caused by an impaired circulation resulting in early, unnoticed abortions (Stein, 1985); 2) an increased number of pre-implantation abortions as a result of a higher incidence of chromosomal abnormalities (Simpson, 1990); 3) It has recently been demonstrated that poor oöcyte quality plays an important role in age-related reduction in fertility (Navot et al., 1991).

1.2.2 *Abortion risk.*

Both the difficulty in conceiving and the risk of early abortion constitutes a problem for the elderly woman. After the age of 35 there is a steep increase in the percentage of spontaneous early abortions (McFadyen, 1985; Fonteyn and Isada, 1988), from approximately 10-15% at the age of 35 to 25% at the age of 40 years (Stein, 1983; Hassold and Chiu, 1985). Similar data were found in our department (Cohen-Overbeek et al., 1990).

The increased abortion risk for elderly gravidas reflects the impaired function of the uterus and ovaries as well as the increased rate of trisomic conceptions (see 1.2.3).

1.2.3 *Cytogenetic studies.*

Aneuploidy of chromosomes, monosomy or trisomy, is caused by non-disjunction during meiosis or by anaphase lag, when a chromosome is lost during early mitosis of the zygote. The risk of aneuploid conceptions increases with advancing maternal age (Ferguson Smith and Yates, 1984; Hook et al., 1988; Morton et al., 1988). Down's syndrome with trisomy 21 in pregnancies of older mothers is usually caused by non-disjunction in maternal meiosis I (Stewart et al., 1988). The recurrence risk of trisomy 21 is 1-2%, irrespective of maternal age and should be added to a possible age factor.

The role of paternal age in trisomy has long been subject to debate. Initially, the age of 55 served as the paternal age limit, beyond which prenatal diagnosis should be offered (Stene et al., 1977). However, many later studies showed that the paternal age appeared to be of little, if any, influence (Hook and Cross, 1982; Ferguson Smith and Yates, 1984; Morton et al., 1988).

The recurrence of trisomy 21 in a subsequent pregnancy should always be an indication for karyotyping both parents, preferably in more than one cell type, to detect mosaicism. There is a possibility of gonadal mosaicism as was found in the ovaries of a woman whose first child displayed Down's syndrome, followed by three subsequent pregnancies with trisomy 21 (Sachs et al., 1990b).

Down's syndrome can also be caused by an unbalanced Robertsonian translocation of chromosome 21, mostly to chromosome 14. Approximately one third of these are caused by a parental carrier, with 45 chromosomes, however, 95% of the Down's syndromes are caused by non-disjunction (Pulliam and Huether, 1986).

The unexpected finding of a balanced reciprocal translocation after prenatal diagnosis occurred in 0.23% in our centre. In nearly 70% one of the parents appeared to be carrier (personal communication E.S.Sachs). A translocation (whether balanced or unbalanced) in the (fetal) index patient should always be followed by chromosome studies in the family, starting with the parents, to detect familial translocations and by counselling of carriers on their risk for an unbalanced translocation, causing Down's syndrome.

In general, the incidence of chromosomal aneuploidy depends on both gestational and maternal age. (Fig 1, table 1,2 and 3). The percentage of abnormal fetal karyotypes increases with advancing maternal age but decreases as pregnancy advances because of spontaneous abortion of fetuses with aneuploidy (Hassold and Chiu, 1985; Hook, 1988 and 1989) (Fig 1).

Early spontaneous abortions showed an abnormal fetal karyotype in 60-70% (Boué et al., 1975; Stein, 1985; Hassold and Chiu, 1985). A survey of nearly 3000 spontaneous abortions by Jacobs et al. (1987) showed autosomal trisomy in 53% of abnormal karyotypes and both monosomy X and polyploidy in about 20%. Because of this natural selection of chromosomally abnormal fetuses, only few pregnancies with an abnormal karyotype will result in the birth of a live infant. Recurrent abortions may be caused by a parental carrier of a mosaic or a structurally balanced anomaly. For this reason couples should be karyotyped when they have had two or more spontaneous abortions, to detect these carriers and counsel them about their risks. In a study by Sachs et al. (1985) a carrier was detected in about 5% of couples.

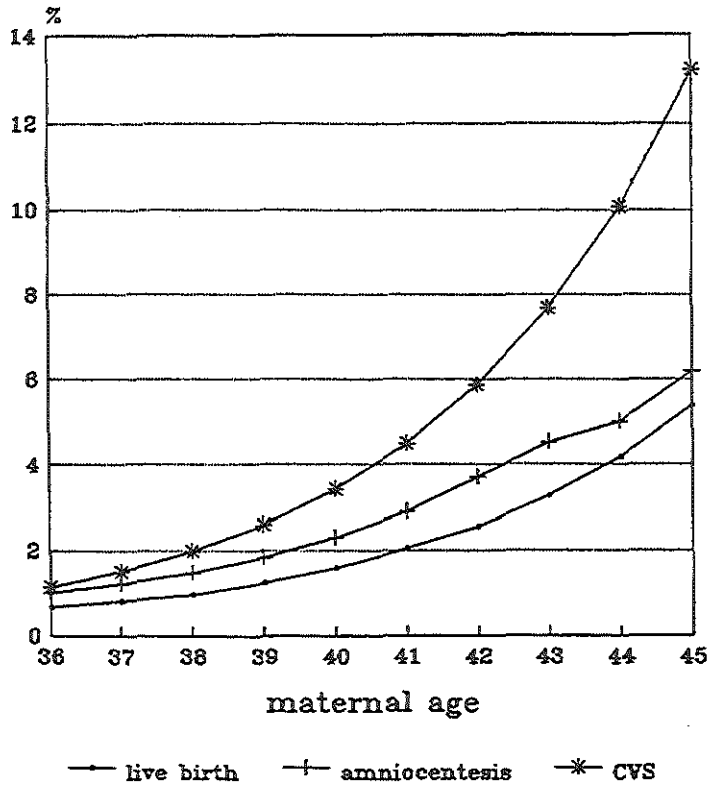

Fig. 1. Percentage of abnormal fetal karyotype at CVS, amniocentesis and at live birth relative to maternal age.

Table 1. Incidence of chromosomal abnormalities per year of age in CVS at 10 weeks.

Maternal age (years)	Down's syndrome %	All chromosomal abnormalities %
36	0.6	1.1
37	0.7	1.5
38	1.0	2.0
39	1.3	2.6
40	1.8	3.4
41	2.4	4.5
42	3.2	5.9
43	4.2	7.7
44	5.6	10.1
45	7.5	13.2

Based on Hook et al. 1988; Hook and Cross, 1989.

Table 2. Incidence of chromosomal abnormalities per year of age at amniocentesis.

Maternal age (years)	Down's syndrome %	All chromosomal abnormalities %
36	0.5	1.0
37	0.6	1.2
38	0.8	1.5
39	1.0	1.8
40	1.3	2.3
41	1.7	2.9
42	2.2	3.7
43	2.7	4.5
44	3.5	5.0
45	4.4	6.2

Based on Ferguson Smith, 1983.

Table 3. Incidence of chromosomal abnormalities per year of age in live births.

Maternal age (years)	%
36	0.7
37	0.8
38	0.9
39	1.2
40	1.6
41	2.0
42	2.5
43	3.3
44	4.2
45	5.4

Based on Hook, 1981.

Abnormal karyotypes with trisomy which are compatible with life after birth are trisomy 21 (Down's syndrome), trisomy 13 (Patau syndrome) and trisomy 18 (Edwards' syndrome). Autosomal trisomies are associated with congenital malformations and severe mental retardation. About half of all Down's syndrome infants display a congenital heart anomaly, which will shorten their life expectancy. The other two trisomies are usually assiociated with more serious malformations resulting in perinatal death, whilst only 10% of these children survive their first year. The anomalies caused by aneuploidy of X-chromosomes are less evident. Turner's syndrome (45,X) can be diagnosed at birth by short length and lymphedema of the hands and feet, whilst Klinefelter's syndrome (47,XXY) in most cases will only manifest itself at puberty or later by small testes and sterility. Cognitive development in Klinefelter boys is slightly impaired compared to the average range. Their IQ is on average 10 points lower compared to a control group. Speech and language skills are reduced. Most boys need special attention for learning difficulties (Robbertson et al.,1991).

In the triple X syndrome (47,XXX) cognitive skills are depressed with a significant lower IQ than controls. Furthermore, speech, language and educational progress are delayed (Robbertson et al.,1991).

If a sex chromosome aneuploidy is diagnosed after prenatal testing counselling of the parents must include information about the expected phenotype, fertility and psychosocial abilities and behaviour (Verp et al., 1988).

In case of unexpected cytogenetic results in prenatal karyotyping it is often necessary to karyotype the parents to detect familial anomalies. Additional ultrasound examinations may support the diagnosis of an abnormal fetal karyotype.

1.2.4 *Congenital abnormalities.*

Congenital abnormalities, unrelated to chromosomal disorders were only found slightly more often in children born to mothers over the age of 40 (Hay and Barbano, 1971; Stein, 1985). Heart defects show a relationship with maternal age for all parities. Clefts, syndactyly and reduction deformities show a relationship with elderly primiparas only. All other catagories of malformations demonstrate a slightly raised incidence with advancing maternal age especially after the age of 40 (Hay and Barbano, 1972).

Czeizel (1988) established a positive correlation between maternal age and the incidence of neural tube defects, cleft lip whether or not associated with cleft palate and congenital inguinal hernia after birth. Other malformations (hypertrophic pyloric stenosis, ventricular septal defect and orthopedic malformations) showed no statistically significant relation with maternal age.

In 1982, Gillberg et al. reported that fine motor-problems and visuo-perceptual dysfunction were significantly more common in children born to older women (mean age 39.4 years) than in children born to younger mothers (mean age 27.9 years).

However, a large population-based analysis in Canada could not demonstrate any association between the indicence of birth defects of unknown etiology and advancing maternal age (Baird et al.,1991).

1.2.5 *Obstetric complications.*

It seems that in the majority of serious threats to the fetus in elderly mothers (prematurity, stillbirth and low birth weight), hypertensive disorders must be held responsible (Grimes, 1981; Kirz et al., 1985; Hansen et al., 1986; Fonteyn and Isada, 1988). The incidence of hypertensive disorders increases with age. Pregnancy increases the incidence of hypertensive disorders in elderly women 2-4 times (Utian and Kiwi, 1988). In the study of Stein (1983) in which all elderly gravidas with pre-existing hypertension, diabetes, obesity and thrombophlebitis were excluded, no increased perinatal mortality could be established compared with younger gravidas. Also,

the increased maternal mortality rate in women over the age of 35 finds its origin in a higher incidence of pre-eclampsia and eclampsia (Högberg, 1986).

Complications of labour associated with advanced maternal age include abruptio placentae, placenta praevia and a raised caesarean section rate (Naeye, 1983; Hansen, 1986; Martel et al., 1987; Berkowitz et al., 1990).

1.3 **Closing remarks.**

Women of advanced maternal age without hypertensive disorders or other conditions that may effect the vascular system, are not at increased risk for pregnancy complications when compared with younger women.

However, the elderly woman is less fertile, runs a higher risk of spontaneous early abortion and has an increased risk for chromosomally abnormal offspring. Since the number of women who postpone childbearing until their mid-thirties is growing, the medical profession must be prepared for more requests for assisted fertility, a rise in spontaneous abortion rate, more requests for prenatal diagnosis and a rise in chromosomally abnormal infants.

Prenatal diagnosis offers the elderly pregnant woman the possibility of avoiding the delivery of a chromosomally abnormal infant.

Chapter 2

Aspects of prenatal cytogenetic diagnosis in women of advanced maternal age.

Introductory remarks.

The earliest medical literature on a specific type of congenital mental retardation, now known as trisomy 21, dates from 1846 (Séguin). In 1866 John Langdon Down wrote his important book 'Observations on an ethnic classification of idiots'. Because of the frequently observed round facies and the typical eyefold, these patients had features in common with the Mongolian people. Down therefore called these mentally retarded people Mongols. Fraser and Mitchell noticed in 1876 that a great number of these patients were born as the youngest of many brothers and sisters. They held exhaustion of the uterus responsible for Down's syndrome. In 1909 Shuttleworth noted that in large families maternal age was advanced and could be the cause of Down's syndrome. It was not until 1933 that Penrose actually proved the relationship between maternal age and the frequency of Down's syndrome, independent of parity.

Two years after Tjio and Levan showed that the human cell has 46 chromosomes (1957), Lejeune et al. (1959) demonstrated an extra chromosome in cells of Down's syndrome patients, later identified as chromosome 21. In 1966 Steele and Breg were the first to analyze chromosomes of cultured amniotic fluid cells. One year later Jacobson and Barter (1967) reported on amniocentesis for prenatal detection of chromosomal abnormalities. The first publication on prenatal diagnosis of Down's syndrome originates from Valenti et al. (1969).

In the early seventies amniocentesis for prenatal diagnosis starts to play a role of clinical importance, the majority of procedures being done for advanced maternal age. For almost fifteen years amniocentesis was the procedure of choice for prenatal karyotyping. In 1983 chorionic villus sampling (CVS) and karyotyping of uncultured chorionic villi appeared to be an alternative to amniocentesis (Simoni et al., 1983). The advantages were obvious; the procedure is carried-out early in pregnancy (4-8 weeks earlier compared with amniocentesis) and the results are rapidly available, providing a diagnosis at 10-11 weeks compared with 18-19 weeks after amniocentesis. This time difference has major consequences in terms of early termination of pregnancy and reduced maternal anxiety. Since the mid-eighties CVS has become an important method in prenatal diagnosis for women with high genetic risks but also for women of advanced maternal age.

In this chapter attention is given to clinical aspects of prenatal diagnosis in women of advanced maternal age. First we will deal with the technical aspects and risks of the two procedures, amniocentesis and chorionic villus sampling (2.1).

The uptake rate of prenatal diagnosis in women of advanced maternal age in our

region is presented in 2.2. Factors that influence the utilization of the facilities for prenatal diagnosis are discussed.

Sub-chapter 2.3 focuses on chorionic villus sampling. Sampling approach (transcervical or transabdominal), utilization and acceptability of CVS are discussed.

2.1 **Procedures; technical aspects and risks.**

Amniocentesis.

Today, notwithstanding the widespread use of chorionic villus sampling (CVS), amniocentesis remains an important tool in obtaining cells for fetal karyotyping.

During the early years of prenatal diagnosis most gynaecologists used a static B-mode ultrasound scanner to identify the most suitable place for tapping amniotic fluid (Gerbie and Shkolmik, 1975; Hill et al., 1982; Librach et al., 1984). With the arrival of the real-time ultrasound technique it became possible to perform amniocentesis under continuous ultrasound guidance (Benacerraf and Frigoletto, 1983; Jeanty et al., 1983). A 20 or 22 gauge needle with stylet is widely used. Between 10-20 ml of amniotic fluid is aspirated to obtain sufficient amniotic fluid cells for karyotyping. Aspiration of 20 ml amniotic fluid represents 7-12.5% of the total volume at 16 weeks (Finegan, 1984). In our centre amniocentesis is performed as an outpatient procedure. No local anaesthesia is used. The results are known within 12-16 days, depending on the quality and growth rate of the cultured fibroblasts.

The risks of amniocentesis to the fetus have been well studied during the past twenty years. Fetal loss rates after the procedure differ between the various centres. A procedure related fetal loss rate of 1.5% is reported in early studies (Working Party on Amniocentesis, 1978; Hill et al., 1982). Later studies show lower abortion rates of approximately 0.5-1% (Sachs et al., 1982; O'Brien, 1984; Leschot et al., 1985; Tabor et al., 1986). In 1991 the fetal loss rate in our centre was 0.3% (1268 amniocenteses) before 28 weeks of pregnancy.

Other complications associated with amniocentesis include loss of amniotic fluid, post partum respiratory problems and mild orthopedic abnormalities (Working Party on Amniocentesis, 1978) Amniotic fluid leakage after amniocentesis varies between 0.2% and 1.7% (Hanson et al., 1985; Tabor et al., 1986).

The incidence of unexpected respiratory difficulties at birth was 1.15% in the amniocentesis group and 0.42% in a control group ($p=0.006$) (Working Party on Amniocentesis, 1978). This finding was explained by the possibility of mild oligohydramnios appearing after amniocentesis which could cause hypoplasia of the fetal lungs.

Mild orthopedic abnormalities were found in the same study in 2.2% of the amniocentesis group compared with to 1.1% in a control group. Other studies could not confirm the increased risk for respiratory and orthopedic problems (NICHD Amniocentesis Registry, 1976; Simpson et al., 1976; Crandall et al., 1980).

Fetal injury during amniocentesis is extremely rare. It was seen only once in a group of 1745 women who underwent amniocentesis (Hanson et al., 1985), none

were seen in the study of Tabor et al. (1986), who evaluated 4606 children after amniocentesis. The Working Party on Amniocentesis reports a similar incidence of needle-like scars in the study group and in a control group. An early report from our centre reported no fetal punctures (Niermeijer et al., 1976). Until now no serious needle injuries were reported in our centre other than a few questionable skin scars in a series of more than 17000 amniocenteses.

The risk of Rhesus sensitization after amniocentesis in Rhesus negative mothers can be reduced, or even eliminated by the administration of a low dose of anti-D gamma-globulin (Brandenburg et al., 1989).

Chorionic villus sampling.

Chorionic villus sampling (CVS) was introduced in our centre in 1983. Since then the number of procedures has increased each year (Brandenburg et al., 1991a). Two different techniques of chorionic villus sampling can be used, the transcervical and the transabdominal approach. Transcervical (TC) CVS is performed between 9-11 weeks, transabdominal (TA) CVS is carried out after 11 weeks of pregnancy. For both methods continuous ultrasound guidance is mandatory. A diagram of both methods is given in fig. 1 and fig. 2.

A minimum of 10 mg chorionic tissue is required for karyotyping. The results are known within 5-10 days.

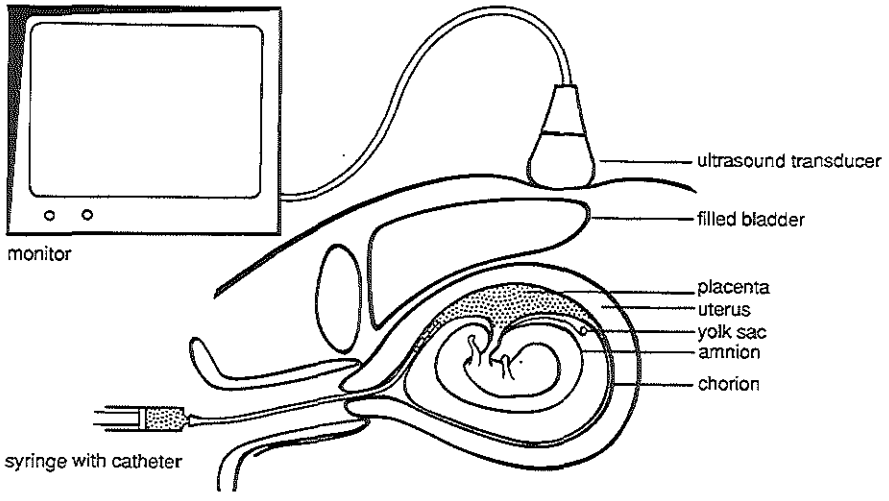

Fig.1 transcervical chorionic villus sampling.

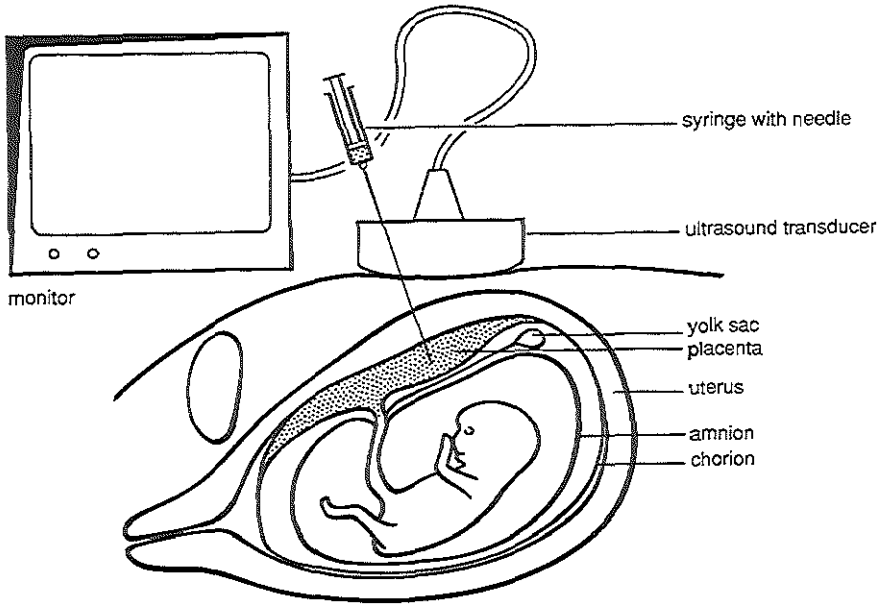

Fig. 2 transabdominal chorionic villus sampling.

Discrepancies between direct chorionic villi chromosome studies and fetal cells are caused by cell lines of non-fetal origin, present as a mosaic or even in all cells (Simoni et al., 1985; Leschot et al., 1987; Sachs et al., 1990a). Mosaicism is reported in 1-2% of samples (Leschot et al., 1989). Mosaic cell lines of trisomy 3, 7, 16 are always of non-fetal origin and 45,X cells in more than 90%. The recognition of false mosaics, which represent the great majority, is possible by examining cultures of the samples. In most cases mosaicism is confined to the cytotrophoblast (Crane and Cheung, 1988; Sachs et al., 1990a).

Contamination by maternal cells in case of cell culture of an XX fetus should always be considered, additional amniocentesis is only rarely necessary.

Fetal loss rates after CVS are higher than after amniocentesis since CVS is performed 4-6 weeks earlier in pregnancy. Older women have a high spontaneous abortion rate in early pregnancy which affects the post-procedure fetal loss rate (Jahoda et al., 1987).

Various studies have been performed to estimate the procedure related fetal loss after CVS. Some studies report an excess abortion risk of CVS compared with amniocentesis between 3% and 5% (Hogge et al., 1985; Brambati et al., 1987; MRC Working Party on the evaluation of CVS, 1991) However, in the latter (a multicentre study), data from centres that only had limited experience with the procedure were included.

Several studies report a similar abortion rate after CVS as after amniocentesis (Crane et al., 1988; Green et al., 1988; Canadian Collaborative CVS-Amniocentesis Clinical Trial Group, 1989; Rhoads et al., 1989).

Factors that influence the fetal loss rate after CVS include the experience of the operator (Brambati et al., 1987), the sampling method (Philip et al., 1991) and maternal age (Jahoda et al., 1987, 1989). A recent review of literature concluded that transcervical CVS had a 1.7% higher total fetal loss than amniocentesis, whereas the fetal loss rate of transabdominal CVS was the same as after amniocentesis (Philip et al., 1991). Jahoda et al. (1987, 1989) stressed the role of maternal age in estimating the abortion risk after CVS. Women over 36 years had a fetal loss rate up to 28 weeks of 6.1% compared to 3.1% in younger women.

CVS for women of advanced maternal age is not performed in the Rotterdam centre until 12 weeks of pregnancy because of a higher spontaneous abortion rate before that time (Cohen-Overbeek et al., 1990).

It appears that the risk of obstetric complications after 20 weeks of pregnancy does not differ between a 1st trimester CVS group and a 2nd trimester amniocentesis group (MRC Working Party on the evaluation of chorion villus sampling, 1991; Rhoads et al., 1989).

The rate of congenital abnormalities was also similar in both groups. This was confirmed by the study of Kaplan et al. (1990). Recently, an association between CVS and limb reduction deformities was suggested. Five of the infants born to 289 women who underwent early CVS displayed a limb abnormality (Firth et al., 1991). CVS in these cases was performed very early in gestation (56-66 days) during the phenocritical stage of development. Monni et al.(1991) reported an incidence of transverse limb reductions of 0.07%. In our centre an overall incidence of 0.075% was established. The incidence was 0.14% in the group that was sampled before 11 weeks and 0.04% in the group that was sampled after 11 weeks (Jahoda et al., in press).

By performing TACVS in advanced maternal age at 12 weeks a low abortion rate is achieved and the risk to the fetus is minimized. A genetic termination of pregnancy can then still be performed as an out-patient procedure.

2.2 Utilization of prenatal diagnosis in women of advanced maternal age in the southwest region of the Netherlands between 1984-1989.

Introduction.

The uptake rate of prenatal diagnosis in women of advanced maternal age in our region was initially studied between 1978 and 1984 and reported in 1985 (Thomassen-Brepols, 1985). At that time amniocentesis was the only method of prenatal diagnosis for women of advanced maternal age. Late in 1983 the technique of chorionic villus sampling was introduced in our centre directly after its clinical applicability was demonstrated (Simoni et al., 1983; Ward et al., 1983).

In the Netherlands the age limit for advanced maternal age was reduced from 38 to 36 years in 1984. From 1985 onwards a substantial number of 36 and 37-year-old women visited our centre for prenatal diagnosis. Both the introduction of CVS and the reduction of the age limit might effect the utilization of prenatal diagnosis. Furthermore, during the past ten years medical information has become more accessible to the public. Increased awareness of the higher risk of chromosomal abnormalities in women of advanced maternal age and therefore a growing uptake of prenatal diagnosis was expected. In addition, an increasing number of women postpone childbearing because of their career (Kessler et al., 1980; Holloway and Brock, 1988). This will result in a rise in the number of older women who may use prenatal diagnostic facilities.

In this study the following questions were addressed:

(i) has the pregnancy rate in women of advanced maternal age gone up in our region during the last six years;
(ii) has the uptake rate for prenatal diagnosis in this age group increased during the same period;
(iii) can a relationship be established between maternal age and uptake rates.

Material and Methods.

The centre for prenatal diagnosis in Rotterdam covers the Southwest region of the Netherlands with approximately 45.000 births per year. Advanced maternal age was defined as 36 years or older at the gestational age of 20 weeks. The number of births provided by the Central Bureau for Statistics (CBS) was given per maternal year of age at the time of delivery. It follows that not all women who were 36 years at the time of delivery were entitled to have prenatal diagnosis. Of the women who were 36 years at that time only (52-20)/52 (62%) were included in the study.

All women of advanced maternal age who lived in the Rotterdam Region and underwent prenatal diagnosis at our centre between January 1984 and January 1990 entered the study.

The following data were collected: maternal age, date and type of procedure and place of residence. Uptake rate graphs were constructed from these data. Data analysis was performed by logistic regression.

Results.

The total number of women of 36 years and older at a gestational age of 20 weeks is given in Table 1. An overall increase from 1668 women in 1984 to 2264 women in 1989 is seen. This rise occurred in all age groups with the exception of the group of women of 46 years and older.

Table 2 shows the increase in percentage of deliveries in elderly women in our region during the study period.

A statistically significant increase of utilization of prenatal diagnosis was established for women of 36 and 37 years of age. This resulted in a significant increase in the overall uptake rate ($p<0.001$) (Table 3). The relation between maternal age and the uptake rate is seen in this same table. The highest age group shows the lowest uptake rate.

Table 1. Number of women of 36 years of age or more at a gestational age of 20 weeks in the Southwest Region of the Netherlands between 1984 and 1989.

age	1984	1985	1986	1987	1988	1989
36*	317	357	389	401	442	433
37	404	423	453	466	514	540
38	280	330	322	374	385	358
39	169	204	240	225	282	271
40-45	446	436	541	531	614	622
≥46	52	70	72	66	60	40
Total	1668	1820	2017	2063	2297	2264

(Data from the CBS)

*Only 62% of women who were 36 years at the time of delivery were 36 at a gestational age of 20 weeks.

Table 2. Number and percentages of deliveries in older women (36 years of age or more at 20 weeks gestation) in the Southwest Region of the Netherlands.

year	N	%
1984	1668 / 37658	4.4
1985	1820 / 38296	4.7
1986	2017 / 40309	5.0
1987	2063 / 39629	5.2
1988	2297 / 40192	5.7
1989	2264 / 40117	5.6

(Data from the CBS)

Table 3. Percentages uptake of prenatal diagnosis between 1984 and 1989 in the Southwest Region of the Netherlands in women of advanced maternal age.

	1984	1985	1986	1987	1988	1989	p-value
36	3.9	35.0	51.2	66.0	61.5	65.6	<0.001
37	19.0	24.6	46.4	43.6	39.1	40.5	<0.002
38	45.0	46.7	52.5	47.3	37.7	48.0	n.s.
39	36.0	44.1	42.1	46.7	41.8	36.5	n.s
40	24.1	17.8	19.4	19.9	22.8	29.7	n.s.*
overall	32.4	30.9	39.6	42.1	38.7	42.9	<0.001

*data of 1989 not included for calculation of p-value.

Discussion

The total number of eligible women for prenatal diagnosis in our region increased during the study period. As expected, the number of women who gave birth at the age of 36 or more decreased with advancing maternal age. The low number of women of 36 years in Table 1 is caused by the fact that only 62% of the women, who were 36 at the time of delivery, were entitled to prenatal diagnosis (Material and methods). The percentage of elderly gravidas increased from 4.4% in 1984 to 5.6% in 1989, this is in agreement with other studies that reported an increasing number of older gravidas (Fonteyn and Isada, 1988; Berkowitz et al., 1990; Baird et al., 1991). In 1984 prenatal diagnosis became accessible to women of 36 and 37 years of age. Therefore, the utilization in this group shows an acute rise. Women of 38 and older, who were entitled to prenatal diagnosis during the previous years, did not demonstrate an increase in utilization during the study period. In the group of very advanced maternal age (>40 years) no increase in the uptake rate was seen until 1989. Further data have to be awaited to demonstrate whether this rise is continuing. The overall uptake rate appeared to have increased during the study period. However, it must be realized that this rise is only caused by an increase in the group of 36 and 37 years of age as no increase could be established for the older group apart from a rise in 1989 of the very advanced age group.

The uptake rate for prenatal diagnosis depends largely on two factors. Firstly, the obstetrician's attitude towards prenatal diagnosis plays a major role when patients are counselled (Lippman-Hand and Cohen, 1980; Lippman-Hand and Piper, 1981; Bernhardt and Bannerman, 1982; Bell et al., 1984). A study concerning the referral patterns amongst obstetricians in New York State (USA) indicates that as many as 47% never referred a patient for amniocentesis. In this same study it appeared that the obstetricians who did refer patients for prenatal diagnosis were younger and fewer of them were catholics (Bernhardt and Bannerman, 1982). A survey amongst

women of advanced maternal age in Ohio (USA) who did not undergo prenatal testing, revealed that 24.7% of the women had never heard of the test (Volodkevick and Huether, 1981). In a study from Queensland it was concluded that 49% of the referred patients raised the question of prenatal diagnosis themselves with their doctor (Bell et al., 1984).

In the Netherlands a lawsuit against an obstetrician who had not informed a 43-year old gravida about her increased risk for Down's syndrome in her offspring was won by the woman (Editorial Ned Tijdschr Geneesk, 1986). This verdict might affect the percentage of obstetricians that mention the possibility of prenatal diagnosis but it is assumed that the effect on the referral pattern is limited in obstetricians who are not in favour of prenatal diagnosis.

The second factor that plays an important role in the utilization of prenatal diagnosis is the socio-economic status of the women (Thomassen-Brepols et al., 1982; Bell et al., 1984; Knott et al., 1986;). Amongst black women from rural areas in Georgia the uptake rate was reported to be as low as 0.5% as opposed to 60% uptake in white urban counties during the same period (Sokal et al., 1980). Likewise, a significantly higher number of Asian women in the London area refuses the offer of prenatal diagnosis compared with European women (Knott et al., 1986).

In Rotterdam the uptake rate for prenatal diagnosis in women of advanced maternal age amongst the ethnic minorities was 4% in 1981 whereas 25% of the Dutch women were tested (Thomassen-Brepols et al., 1982). Accordingly, a survey under non-pregnant graduates between 38 and 43 years of age in the early years of prenatal diagnosis showed that 83% would opt for prenatal diagnosis when pregnant (Bundey, 1978).

A remarkably low uptake at the age above 40 is noted in our study despite the increased risk of chromosomal anomalies. This can be explained by the high percentage of women of very advanced maternal age that belong to ethnic minorities (Brandenburg et al., 1992).

Information about prenatal diagnosis to ethnic minorities therefore needs special attention. One should not be too pessimistic about the results of this effort. In Atlanta a group of black women of low socio-economic status received extra attention regarding information on the facilities for prenatal diagnosis; 61% of them elected to undergo the procedure (Marion et al., 1980).

The freedom of choice to undergo prenatal diagnosis can only be guaranteed if eligible women are well-informed. Proper information to the medical profession and mothers of advanced age should be a matter of concern since the number of eligible women is growing.

2.3 **Chorionic villus sampling; sampling approach, utilization, and acceptability.**

2.3.1 *Sampling approach.*

Introductory remarks.

It was the transcervical approach which was almost exclusively used at the time that first trimester CVS was introduced for prenatal diagnosis of chromosomal, metabolic and DNA disorders (Simoni et al., 1983; Jahoda et al., 1985; Sachs et al., 1988).

The transabdominal access was initially an alternative to those women in whom the transcervical approach was contraindicated e.g. when cervicitis or cervical stenosis was present or in whom the pregnancy had progressed beyond 12 weeks of gestation. Furthermore, TACVS was used in the second and third trimester when rapid karyotyping was important, in particular when fetal abnormalities were established by ultrasound (Pijpers et al., 1988a; Hogdal et al., 1988).

It became obvious that the transabdominal route had certain advantages over the cervical route: the procedure is less embarrassing to the patient, the cervix (difficult to disinfect) is avoided, the rate of post procedure blood loss is reduced since the cervix is no longer traumatised by a tenaculum. Furthermore, the procedure can be performed when the patient has an empty bladder and is therefore less time consuming since many of the patients needed to drink and wait to obtain sufficient bladder distension for TCCVS. Contractions of the uterus which cause frequently a delay at TCCVS pose hardly ever a problem at TACVS.

Monni et al. (1988) reported 71 patients who had undergone TCCVS as well as TACVS (in different pregnancies). All women gave preference to TACVS.

In our centre it was established that the fetal loss rate after CVS depends largely on maternal age and timing of the procedure (Jahoda et al., 1989). In the group of advanced maternal age (≥36 years) the fetal loss rate (<28 weeks) was 6.2% after TCCVS and 5.8% after TACVS when sampled before 12 weeks.

The fetal loss rate drops to 2.4% after TACVS when the sampling takes place after 12 weeks (Jahoda et al., 1991). This is explained by the high pre-TACVS abortion rate (Cohen-Overbeek et al., 1990).

Transabdominal chorionic villus sampling after 12 weeks seems therefore to be the method of choice for prenatal diagnosis in the first trimester in women of advanced maternal age.

2.3.1.1 *Transabdominal villus sampling in early second trimester: a safe sampling method for women of advanced age.*

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Published in Prenatal Diagnosis 1990;10:307-311.
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Summary

Transabdominal chorionic villus sampling (TA-CVS) was performed in 707 viable singleton pregnancies to exclude chromosomal abnormalities. Maternal age ranged between 36 and 49 years (mean 37.9 years); gestational age varied between 10.2 and 18.3 weeks (mean 13.3 weeks). In 639 women (90.4 per cent), a sufficient amount of chorionic tissue (≥ 10 mg) was obtained after one needle insertion; in 66 women (9.3 per cent) two insertions were needed. An abnormal chromosome pattern was established in 19 cases (2.9 per cent). Vaginal bleeding or spotting within 28 days after TA-CVS occurred in 11 cases (1.5 per cent). The completed follow-up of 678 chromosomally normal pregnancies showed an overall fetal loss rate of 2.6 per cent before 28 weeks. The overall perinatal mortality was 0.9 per cent. When relating fetal loss to gestational age at TA-CVS, this was 6.6 per cent in women sampled before 12 weeks against only 1.8 per cent after 12 weeks. At the same time, the percentage of fetal loss occurring within two weeks following the procedure was 75 and 30 per cent, respectively. It is suggested that these data reflect the decline in spontaneous abortion rate during this particular period of pregnancy. It is concluded that TA-CVS is an effective procedure which, when performed after the natural decrease of fetal loss, appears to be a safe option for women of advanced maternal age.

Key words Maternal age Fetal loss CVS in early second trimester

Introduction

The technique of transabdominal chorionic villus sampling (TA-CVS), first reported by Smidt-Jensen and Hahnemann (1986) for first-trimester pregnancies and by Nicolaides et al. (1986) for second-trimester pregnancies, has currently become the method of choice in more than 10% of all CVS procedures (Jackson, 1989). TA-CVS has been claimed to be safer with respect to bacterial contamination of uterine contents (WHO Consultation, 1986) and also simpler and more practical than transcervical CVS (Maxwell et al., 1985; Nicolaides et al., 1986; Brambati et al., 1988).

Advanced maternal age, which is the most common indication for prenatal diagnosis, is associated with a significantly higher fetal loss rate following transcervical CVS (TC-CVS) (Jahoda et al., 1987). This paper provides information on the efficacy and safety of TA-CVS in women from 36 years onwards.

Materials and methods.

TA-CVS was performed between March 1987 and October 1988 in 707 viable singleton pregnancies of mothers of advanced age to exclude chromosomal abnormalities. Maternal age ranged between 36 and 49 years (mean 37.9 years). Gestational age was determined from the last menstrual period and ultrasound measurement of fetal crown-rump length. All women were HbsAg negative.

In each case, TA-CVS was carried out as an office procedure without local anaesthesia under continuous ultrasound monitoring (Hitachi-EUB 340, curved-linear array transducer with carrier frequency of 3.5 MHz) using a 12 cm long 20 gauge needle without stylet (TSK supra, biopsy cut), as recently reported by Pijpers et al. (1988a). A maximum of two needle insertions was performed per session. Each woman left the office 20-30 minutes after the procedure with instructions to limit her activities during the next 24 hours. TA-CVS was contraindicated in the presence of vaginal bleeding within 7 days of the procedure or intestinal loops situated between the uterus and abdominal wall on ultrasound examination. Anti-D gamma-globulin (75 mcg) was routinely administrated to all Rh-negative non-sensitized women. Cytogenetic investigations were performed as described by Sachs et al. (1988). In the case of a chromosome anomaly, selective abortion was carried-out by means of suction curettage up to 15 weeks of gestational age. Beyond that time, prostaglandin induction was instituted. Continuing pregnancies were followed up by means of a questionnaire concerning short- and long-term complications prior to 28 weeks of gestation. For statistical analysis the Fisher exact test was used. For assessment of fetal loss before 28 weeks the 80 per cent confidence interval was used.

Results.

TA-CVS was performed between 10.2 and 11.6 weeks in 121 women (17.5 per cent), between 12.0 and 14.6 weeks in 477 women (67 per cent), and between 15.0 and 18.3 weeks of gestation in 109 women (15.5 per cent) (late booking).

In 639 women (90.3 per cent) a sufficient amount of chorionic tissue (≥ 10 mg) was obtained after one needle insertion; in 66 (9.3 per cent) two insertions were necessary. In the remaining two women, TA-CVS failed during the first session. The gestational age was 11.3 and 12.1 weeks. One underwent a successful TA-CVS procedure one week later; the other had amniocentesis instead, because of obesity and a retroverted uterus with a fundal placenta. The amount of chorionic tissue obtained for cytogenetic analyses varied between 10 and 100 mg (mean 20.8 mg). An abnormal karyotype (Table 1) was established in 19 cases (2.9 per cent), one of which

Table 1. Abnormal cytogenetic results following TA-CVS in 707 mothers aged 36 years and more.

Karyotype	No
Trisomy 21	11
Trisomy 18	4
47,XXY	2
47,XXX	1
46,X,der(Xp+)	1*

* not confirmed in fetal tissue (Sachs et al., 1988).

could not be confirmed in fetal tissue (Sachs et al., 1988). All 19 women requested termination of their pregnancy; one additional termination was carried-out for psychological reasons. Three of these terminations were performed between 16 and 18 weeks gestation. Eighty-two women (11.6 per cent) were Rh-negative and received anti-D gamma-globulin. Bleeding or spotting within 28 days after TA-CVS occurred in 11 cases (1.5 per cent), two of which experienced bleeding longer than 7 days. Transient lower-abdominal discomfort was documented in 72 cases (10.2 per cent). The completed follow-up of 687 chromosomally normal pregnancies showed an overall fetal loss rate of 2.6 per cent (N=18) before 28 weeks. Beyond this gestational age the perinatal mortality was 0.9 per cent (N=6). When relating fetal loss to gestational age at TA-CVS, this was 6.6 per cent (N=8)(80 per cent confidence interval 3.7-9.5) in women sampled before 12 weeks. In women undergoing the TA-CVS procedure beyond 12 weeks the fetal loss rate was 1.8 per cent (N=10) with 80 per cent confidence interval 1.1 - 2.5 (Table 2). This difference is statistically significant ($p = 0.006$). When relating to the number of needle insertions at one session, no statistically significant difference could be established between the fetal loss rate following one (2.2 per cent) and two needle insertions (3 per cent). Seventy-five per cent of the fetal loss cases were observed within two weeks following TA-CVS when the procedure was performed before 12 weeks against 30 per cent when the procedure was carried-out beyond 12 weeks of gestation.

Table 2. Fetal loss rate in continuing pregnancies of mothers of advanced age related to gestational age at TA-CVS.

Gestational age in weeks at TA-CVS	N women	N fetal loss	%	80% confidence interval
< 12	120	8	6.6	3.7-9.5
≥ 12	567	10	1.8	1.1-2.5
Total	687	18	2.6	

Discussion.

TA-CVS can be considered an effective method for prenatal diagnosis allowing adequate chorionic tissue to be collected in nearly 100% of cases during one session. The low incidence of short-term complications such as vaginal bleeding (1.5 per cent) has also been reported by others (Lilford et al., 1987; Brambati et al., 1988; Smidt-Jensen and Hahnemann, 1988; Pijpers et al., 1988a). When assessing the procedure-related fetal loss rate, the spontaneous abortion rate in women of advanced age should be considered. Lippman et al. (1984) described a spontaneous abortion risk in a group of women older than 35 years as varying from 5 to 9% between 9 and 11 weeks and decreasing to 1-5 per cent between 12 and 16 weeks. We observed a significant reduction in fetal loss rate if TA-CVS was performed from 12 weeks of gestation (1.8 per cent against 6.6 per cent before 12 weeks). A similar marked drop in spontaneous abortion rate during this period of pregnancy has been reported in pregnancies without any invasive procedure (Liu et al., 1987). The significant decline in spontaneous abortion rate during the late first trimester of pregnancy is also expressed by our finding that when TA-CVS was performed before 12 weeks of gestation, fetal loss mostly (75 per cent) occurred within 2 weeks following the procedure, whereas this was only the case in 30 per cent when TA-CVS was carried-out beyond that gestational age. This observation is clearly related to the decline in spontaneous abortion rate described in women of advanced age (Lippman et al., 1984; Gustavii, 1986).

TA-CVS performed at 12-13 weeks' gestation still allows termination of pregnancy as an office procedure as is demonstrated in our study and recommended by others (McGovern et al., 1986; Robinson et al., 1988). When the fetal loss rate was related to the number of needle insertions no significant difference between one or two needle insertions could be established. It can be concluded that TA-CVS is an effective procedure, which when performed after the natural decrease of fetal loss rate, appears to be a safe option in advanced maternal age.

Acknowledgements.

We wish to thank W.C.J.Hop, M.Sc. who kindly provided the statistical analysis. The skillful technical assistance of Mrs.Cardi v.d.Berg is gratefully acknowledged.

2.3.1.2 *Transcervical (TC) and transabdominal (TA) CVS for prenatal diagnosis in Rotterdam: experience with 3611 cases.*

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Published in Prenatal Diagnosis 1991;11:559-561.
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Summary.

Data from 3611 consecutive CVS (TC.n=1780; TA.n=1831) were analysed with emphasis on influence of maternal and gestational age at CVS on the fetal loss rate <28 weeks. For TC-CVS the gestational age varied from 9.3-11.6 weeks, for TA-CVS from 9.3-20 weeks. Sampling efficacy at first attempt was 86.5 per cent and 95 per cent respectively. In 4.6 per cent an abnormal result was established. In older mothers (n=2362) the fetal loss rate was significantly higher ($p<0.05$) when sampled before 12 weeks (TC-CVS 6.2 per cent, TA-CVS 5.8 per cent). When the CVS (TA) was performed after 12 weeks the fetal loss rate decreased to 2.4 per cent.

In 1079 younger women the fetal loss rate remained low (TC 2.8 per cent; TA <12 weeks 1.8 per cent; TA >12 weeks 1.7 per cent) and was not influenced by gestational age at the time of sampling. We concluded both methods safe and reliable when the choice of application considers maternal age.

Key words CVS Fetal loss rate Maternal age Gestational age.

Introduction.

Since the introduction of first-trimester prenatal diagnosis on chorionic villi by Simoni et al. in 1983, chorionic villus sampling (CVS) has become a widespread alternative to second-trimester amniocentesis. In this study we report our experience with 3611 consecutive cases of CVS (TC-CVS.n=1780; TA-CVS.n=1831). Since the major indication (65.5 per cent) for CVS in women is advanced maternal age, attention was particularly focused on this group of women. The procedural risk was evaluated with emphasis on variables which might influence the fetal loss rate, such as maternal age, the number of uterine entries, and gestational age at CVS.

Patients, methods and results.

Data were obtained on blood group, Rh factor, eventual Rh sensitization and

HbsAG in all 3611 women. In 1780 women with negative cervical mucus culture, a TC-CVS was performed using a Portex or Angiomed catheter with ultrasonic guidance provided by a real-time sector scanner (Diasonics DFR1, frequency carrier 3.5 MHz). The 1831 women scheduled for TA-CVS were seen by the same team employing a modified "free-hand" method (Holzgreve et al., 1987). A 20-gauge needle without a stylet and with a biopsy cut was used; ultrasound guidance was provided by a Hitachi EUB-340 curved linear-array real-time scanner (frequency carrier 3.5 MHz). An adequate sample was obtained at first attempt of TC-CVS in 86.5 per cent and of TA-CVS in 95 per cent. The average amount of chorionic tissue withdrawn was 21 and 23 mg, respectively. The gestational age at TC-CVS varied from 9^{3}-11^{6} weeks (mean 10^{1}) whilst at TA-CVS the upper limit was extended to 20 weeks for late bookings (9^{3}-20 weeks; mean 12^{2}).

The cytogenetic studies were performed using Simoni's direct method with FdU synchronisation according to Gibas et al., 1987 and Sachs et al., 1988. Results were available within a few days; 1-2 weeks were required for the biochemical and/or DNA-studies. All Rh-negative non-sensitized women received a single dose (75 mcg) of anti-D gamma-globulin.

An affected fetus was established in 165 pregnancies (4.6 per cent); these and five other pregnancies (psychosocial reasons) were terminated. One fetus at risk for metachromatic leucodystrophy, and one at risk for Niemann Pick III were diagnosed as unaffected in chorionic villi but detected as affected in cultured amniotic fluid cells. With one exception (parents refused amniocentesis), all abnormal fetal karyotypes were confirmed on fetal tissue after termination whilst all newborns were of the expected karyotype (Table 1). The fetal loss rate was significantly higher ($p<0.05$) in mothers at advanced age when sampled before 12 weeks of gestation, which is in accordance with the expected higher spontaneous abortion baseline in older women (Gustavii, 1984; Jahoda et al., 1989; Cohen-Overbeek et al., 1990). The fetal loss rate in this group of women was 6.2 per cent for TC-CVS and 5.8 per cent in TA-CVS (Table 2). When TA-CVS in older mothers was carried-out after 12 weeks, the fetal loss rate was 2.4 per cent. The fetal loss rate after TA-CVS in younger mothers was not influenced by gestational age (Table 2).

Follow up.

The pregnancy outcome after 28 weeks showed 3.15 per cent (n=98) premature deliveries with an overall perinatal mortality of 0.93 per cent (n=29). None of the 26 (0.83 per cent) congenital malformations diagnosed after birth could have been detected by CVS or ultrasound during the procedure.

Conclusions.

The fetal loss rate in the group of older mothers can be decreased by postponing the procedure beyond the natural drop in the spontaneous abortion baseline.

Summarizing our experience with transcervical and transabdominal CVS and analysis of chorionic tissue, we can confirm the reliability, safety, and efficacy of this method.

Table 1. Outcome of 3611 pregnancies after CVS for prenatal dagnosis.

	N	TC-CVS (%)	*N*	TA-CVS (%)
Selective abortion (abnormal result)	114	(6.4)	51	(2.78)
Termination for other reasons	4	(0.22)	1	(0.06)
Overall fetal loss < 28 weeks	80	(4.8)	47	(2.64)
Lost to follow-up	3	(0.2)	-	-
Ongoing pregnancies > 28 weeks	-	-	208	(12)
Delivered < 37 weeks	37	(2.3)	61[#]	(4.0)
Delivered > 37 weeks	1545*	(97.6)	1466*	(96.0)
Perinatal death	15	(0.95)	14	(0.9)

[#]1 IUFD in twins at 31 weeks.
*including six pairs of twins.

Table 2. Relation between gestational age at TC- and TA-CVS and abortion rate for 2362 mothers aged 36 years or more and in 1079 younger mothers.

		Gestational age at CVS			
		< 12 weeks Fetal loss		> 12 weeks Fetal loss	
	Type of CVS	N	%	N	%
Mothers aged < 36 years	TC	18	(2.7)	-	-
	TA	2	(1.8)	5	(1.7)
Mothers aged > 36 years	TC	62	(6.2)	-	-
	TA	11	(5.8)	29	(2.4)

2.3.2 *Utilization.*

Introductory remarks.

With the introduction of CVS in early pregnancy, a first trimester abortion can be carried-out in case of an abnormal result. This has major consequences since an early abortion is less traumatic than a mid-trimester termination. Furthermore, a first trimester abortion is to be preferred for economic as well as logistic reasons compared with a termination in the second trimester which requires hospitalization of several days. It is, therefore, important to be informed about the utilization of CVS as well as the effect that CVS has on the uptake of prenatal diagnosis. The hypothesis that more women will make use of prenatal diagnostic facilities because an early abortion is more acceptable than mid-trimester termination will be tested in this subchapter.

Effect of chorionic villus sampling on utilization of prenatal diagnosis in women of advanced maternal age.

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Published in Clinical Genetics 1992;41:239-242.
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The effect of the introduction of chorionic villus sampling on the utilization rate of prenatal diagnosis in advanced maternal age was studied during the period 1 January 1985 - 1 January 1991. On the first of January 1984, the age limit for prenatal diagnosis in The Netherlands was lowered from 38 to 36 years of age, but it lasted until 1985 before women of 36 and 37 years made use of the facilities for prenatal diagnosis. The overall uptake rate during the studied period increased significantly, but only because of the increased uptake rate in the group 36 and 37 years. In the maternal age group of 42 years and older, an uptake rate as low as 15.9% was established. This was mainly determined by the relatively high percentage (73.0%) of women from ethnic minorities in this age group. The number of CVS procedures increased significantly during the study period, but the utilization rate was not influenced, since the number of amniocenteses decreased accordingly. An increase in acceptability of prenatal diagnosis by women of advanced maternal age due to early testing and early termination of pregnancy could not be substantiated in the present study.

Key words : advanced maternal age - chorionic villus sampling - prenatal diagnosis - uptake rate.

In the mid-eighties, two major changes involving prenatal diagnosis took place in The Netherlands.

Firstly, in 1984 chorionic villus sampling (CVS) became available for clinical use, soon after the publications in 1983 by Ward et al. and Simoni et al. It was expected that since this test was performed earlier in pregnancy and results were obtained faster than after amniocentesis, prenatal diagnosis would become acceptable to more women of advanced maternal age. A higher uptake rate was therefore anticipated. Secondly, in the same year the age limit for prenatal diagnosis in women of advanced maternal age was reduced from 38 to 36 years of age.

In this study the following questions were addressed: a) Has there been an increase in the uptake rate for prenatal diagnosis since 1985; b) Has a shift occurred from amniocentesis towards CVS during the same period; c) What was the uptake for prenatal diagnosis relative to advancing maternal age; d) Did a relationship exist between maternal age and the nature of the procedure (CVS or amniocentesis)?

Material and methods.

In the Netherlands, approximately 35% of all confinements take place at home, under the care of a midwife or general practitioner (Kleiverda et al., 1990). All these deliveries involve low risk patients. All births in primigravidas over 35 years of age and in multigravidas over 40 years of age take place in a hospital. Around 80% of all women of advanced maternal age in Rotterdam including suburbs deliver in one of the hospitals in the Rotterdam region.

All women of advanced maternal age who delivered in one of the six District hospitals or the University Hospital in Rotterdam between first January 1985 and first January 1991 were included in the study[1]. Advanced maternal age was defined as 36 years or more at twenty weeks of gestation. A total of 2045 records was analysed. The calendar year and maternal age at the time of the procedure and the nature of the procedure were evaluated retrospectively for both women who underwent prenatal diagnosis and those who did not. Uptake rates were calculated for all women together per year of maternal age and per calendar year, using the ordinary χ^2-test and the χ^2-test for trend proportions (Armitage and Berry, 1987).

[1]During the years 1989 and 1990 data from three District hospitals plus the University Hospital were studied. Three hospitals denied the disposal of information because of changed laws on patients privacy.

Results.

Fig. 1 shows the uptake rate for prenatal diagnosis between 1985-1990. There is a statistically significant increase ($p<0.001$) in uptake for prenatal diagnosis from 36.3% in 1985 to 48.9 % in 1990.

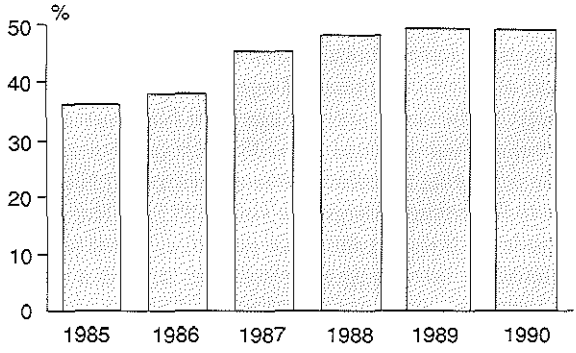

Fig.1 .Uptake of prenatal diagnosis in women of advanced maternal age between 1985 - 1990

The uptake for prenatal diagnosis relative to maternal age is presented in Fig. 2. A maximum uptake rate at the age of 40 was observed; this was followed by a decrease afterwards. At maternal age of 43 and older, the uptake rate for prenatal diagnosis is as low as 15.9%. The percentage of women originating from Turkey, Morocco and the Cape Verde Islands was 73.0% at the age of 42 years and older as opposed to only 15.5% in the age group of 36 - 42 years. When women of ethnic minorities are excluded, the uptake rate in the age group of 42 years and older increases from 15.9% to 41.2%. The uptake at maternal age 36-37 years increases from 22.3 % in 1985 to 50.5% in 1990, whereas at maternal age of 38 years and older the uptake rate virtually remains unchanged. Fig. 3 illustrates the initially slow growth

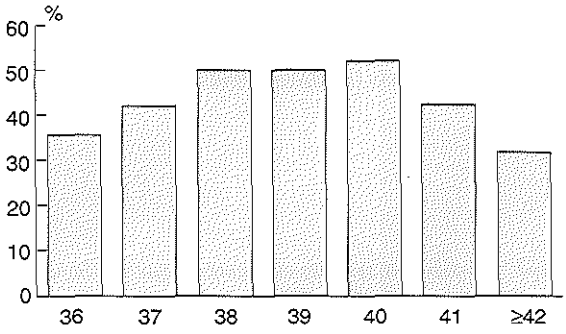

Fig. 2. Uptake of prenatal diagnosis during the years 1985 - 1990 in each maternal age group.

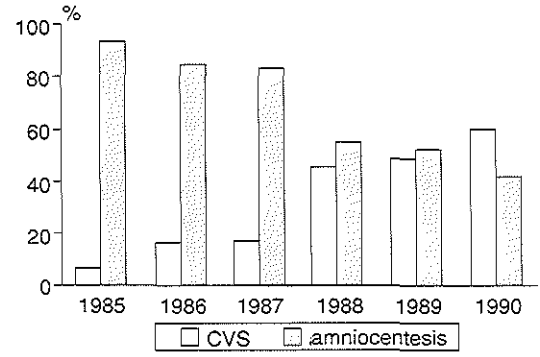

Fig. 3. Percentages of CVS and amniocentesis between 1985 - 1990 in women of advanced maternal age.

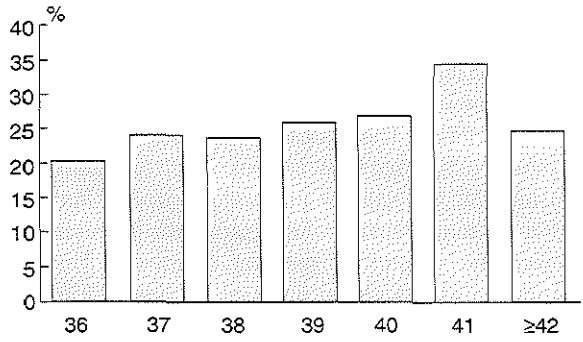

Fig. 4. Percentage that CVS represents of all procedures performed between 1985 - 1990 in women of advanced maternal age.

of the share that CVS represents in all procedures performed in women of advanced maternal age. Only since 1988 a substantial proportion of procedures (44.9%) is represented by CVS, with a concomitant drop in the number of amniocentesis procedures. In 1990, more CVS procedures than amniocenteses were performed. Fig. 4 shows that the percentage of CVS procedures does not significantly change relative to maternal age.

Discussion.

Between 1985 and 1991, the overall uptake rate in women of advanced maternal age who delivered in one of the Rotterdam hospitals was subject to a significant rise. However, this increase was due to the rising uptake in the age group of 36-37 years.

In women of 38 years and older, the uptake remained virtually unchanged. These data suggest a time delay between the introduction of a lower age limit for prenatal diagnosis (editorial Ned Tijdschr Geneesk, 1986) and the actual implementation of this change in policy by referring physicians.

From various studies it is known that the physician's attitude to prenatal diagnosis is of importance for the referral rate as most women learn about the possibilities of prenatal diagnosis from their physicians (Bernhardt and Bannerman, 1982; Bell et al, 1984). This may also explain the observation that the introduction of CVS had no significant impact on the overall uptake rate in women of advanced maternal age. It is understandable that an obstetrician who does not favour prenatal diagnosis in general for religious or ethical reasons, will still refer very few eligible patients, despite the fact that the newly introduced method (CVS) results in a diagnosis in the first trimester.

The uptake rate for prenatal diagnosis increased up to the age of 40 years. Beyond that age, despite a higher genetic risk, a lower uptake rate is noticed. This is in agreement with an earlier study by Adams et al. (1981). The low uptake rate in the maternal age group of 43 years and older may be determined by the fact that this group harbours relatively more women from ethnic minorities. In other studies a lower uptake for prenatal diagnosis has been reported amongst non-white women of advanced maternal age compared to white women in the same age group (Sokal et al., 1980; Marion et al., 1980). The reasons for this poor attendance may be several fold. Women of ethnic minorities tend to seek medical attention relatively late in pregnancy, which may be too late for prenatal diagnosis. Furthermore, there is a socio-cultural and/or language barrier which causes the physician or midwife to refrain from discussing the subject of prenatal diagnosis. Finally, many Muslim patients object to prenatal diagnosis on religious grounds. Of interest is that only a small number of the Muslim patients are aware of the fact that the Koran allows pregnancy termination up to a gestational age of 12 weeks. This would make CVS the procedure of choice when chromosomal abnormalities have to be excluded.

During the study period of 1985-1990, both the absolute number and the percentage of CVS-procedures were subject to a significant rise. This rise was not caused by a higher number of patients requesting prenatal diagnosis, but by a shift from amniocentesis towards CVS. The first few years following the introduction of CVS a hesitation towards CVS was noticed both among patients and referring physicians. This was understandable from the point that the reliability, acceptability and procedure related risk had yet to be established. After 1987, for many patients the advantages of an early result became obvious since the risk of the CVS-procedure appeared to be acceptably low.

Still, in a recent study we demonstrated that a considerable number of women who underwent amniocentesis were delayed in their referral to our centre by several weeks as a result of the delay in counselling by the physician (Brandenburg et al., 1991b).

Based on the increasing risk with age of chromosomal abnormalities, a rise was expected in the number of requests for CVS with advancing maternal age. This

could not be substantiated in the present study, since no age-related trend in the use of CVS could be detected. Again, this may be determined by the relatively high percentage of non-autochthones in the very advanced maternal age group. It must be realised that this study was undertaken among patients who had antenatal care in an urban hospital near our centre and therefore had easier access to prenatal diagnosis facilities. We expect that the uptake rates, as concluded in this paper, are higher than in the rest of our region, although the impact of a lower percentage of women of ethnic minorities outside the city will probably outweigh this effect.

It can be concluded that chorionic villus sampling is accepted as a rapid, reliable and safe method for prenatal diagnosis in autochthone women of advanced age. It must, however, be stated that this is only true for women who already opt to undergo prenatal diagnosis. The hypothesis that prenatal diagnosis has become acceptable to more women of advanced maternal age because of the shift towards the first trimester must be abandoned.

2.3.3 *Acceptability.*

Introductory remarks.

Two studies concerning the acceptability of CVS are presented here. The acceptability of CVS by the patient as well as by the referring physician is reflected by the number of patients referred for the test. The increase in the number of CVS procedures since its introduction late 1983 in our department supports our belief that CVS has become a well-accepted method for prenatal diagnosis for women of advanced maternal age.

2.3.3.1 *Acceptance of chorionic villus sampling in the southwest region of the Netherlands: a 5-year evaluation.*

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Published in American Journal of Medical Genetics 1991;41:236-238.
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Abstract.

The acceptance of chorionic villus sampling (CVS) for monitoring pregnancies at-risk for chromosomal and genetic disorders was studied from its introduction in the Centre for Clinical Genetics in Rotterdam in 1984 until 1988. Special attention was given to the increasing acceptance in the group with advanced maternal age (12.6% CVS in 1984, 53% CVS in 1988) and the group with a high genetic risk (42.7% in 1984, 84.2% in 1988). The odds growth rate in CVS was 1.64 and 1.67 respectively, which was not significantly different. The relatively limited use of CVS at advanced maternal age is most likely determined by the fact that a considerable number of patients are referred too late in pregnancy to have the option of CVS.

Keywords: advanced maternal age, high genetic risk, prenatal diagnosis, amniocentesis, chorionic villi biopsy.

Introduction.

Chorionic villus sampling (CVS) for early diagnosis of fetal genetic disease was introduced in our department in 1984. It was demonstrated earlier that ultrasound-

guided CVS allows rapid and accurate chromosomal and biochemical analysis of fetal material in the first trimester of pregnancy (Simoni et al., 1983). Chromosome results are available within 7 to 10 days. Therefore, a rapid increase in the number of patients opting for CVS rather than for amniocentesis in the 16th week could be expected. However, as with all newly introduced techniques, it took some time before both patients and referring physicians had gained sufficient information to make a balanced choice between CVS and amniocentesis and for the physicians to refer the patient early enough for the CVS procedure.

The aim of the present study was to determine the acceptability of CVS in relation to amniocentesis, expressed by the increase of CVS use over amniocentesis during the period 1984 - 1988.

Material and methods.

The regional Centre for Clinical Genetics in Rotterdam serves the southwest region of the Netherlands. This area covers approximately one quarter of the total number of deliveries in the Netherlands, which in 1988 was nearly 180,000. The data of all patients referred to our Centre between 1984 and 1988 were collected. The patients were distributed each year according to 5 groups of indication (Table 1).

For each year and for each group the percentage of patients in which CVS had been the procedure for prenatal diagnosis was calculated. In group III (risk of neural tube defects) amniocentesis had to be performed for alpha-fetoprotein determination. Group IV (recurrent chromosome anomaly) was considered to be of little interest, since this group represents only approximately 2.5 % of all referred patients. Group V was not studied in detail, since this group consisted of patients with either a very low genetic risk (maternal anxiety) or a sonographically detected anomaly later in pregnancy. In the latter, where AFP determinations could add to the diagnosis, amniocentesis was performed. If only a chromosome abnormality was suspected transabdominal CVS was performed. In these situations there was virtually no patients' choice as to what procedure was preferred, so for the acceptability of the CVS procedure this group is of limited interest. Attention was focused on the group of advanced maternal age (AMA; group I) and the group with high genetic risk (HGR; group II) in respect to utilisation of CVS. The increase in uptake of CVS in the AMA and the HGR group was studied by means of a logistic regression analysis to compare the odds growth rate. The odds growth rate represents the figure by which the odds (percentage uptake (p)/100-p) is multiplied for each year. For instance, an odds growth rate of 1.64 means that each year p/100-p increases with 64%.

Results.

In 1984 12.6% of all procedures for AMA and 42.7% of all procedures of HGR were performed by CVS. The following years were characterized by a rise in CVS

resulting in a value of 52.2 % and 86.7% respectively in 1988 (Tables 2, 3). The odds-growth rate was 1.64 per year (95 % confidence interval: 1.58-1.74) for AMA and 1.67 (95% confidence interval: 1.46-1.91) for HGR. There was no significant difference in the odds-growth rate between the AMA and HGR group. An increasing number of women was seen because of advanced maternal age (1984: 699; 1988: 1298), whereas the number of women with a high genetic risk remained virtually unchanged (1984: 124; 1988: 120).

Table 1. Indications for Prenatal Diagnosis.

Group	Specification
I: Advanced Maternal Age (AMA)	36 years or more at 20 weeks of gestation
II: High genetic risk (HGR)	a. Metabolic disease b. X-linked disease c.Parental translocation
III: Risk of neural tube defect (NTD)	
IV: Recurrent chromosome anomaly	
V: Others	

Table 2. The Growth of the Acceptance of CVS for Prenatal Diagnosis in Advanced Maternal Age between 1984 and 1988.

	CVS		Amniocentesis	
	N	%	N	%
1984	88	12.6	611	87.4
1985	198	19.4	822	80.6
1986	328	26.5	909	73.5
1987	519	37.4	867	62.6
1988	688	53.0	610	47.0

Table 3. The Growth of the Acceptance of CVS for Prenatal Diagnosis in Pregnancies at High Genetic Risk between 1984 and 1988.

	CVS		Amniocentesis	
	N	%	N	%
1984	53	42.7	71	57.3
1985	59	45.0	72	55.0
1986	85	59.0	59	41.0
1987	88	71.6	27	28.4
1988	101	84.2	19	15.8

Discussion.

Evans et al. (1989) predicted that during the 1990s the diagnostic techniques for fetal genetic disease will be mostly completed by the end of the first trimester or early second trimester of pregnancy. Indeed, within 5 years after introduction of CVS in our department, CVS constituted nearly 90% of procedures performed for high genetic risk. This high percentage is probably explained by the fact that most women in this group will have had genetic counselling before a subsequent pregnancy, resulting in an early referral for CVS.

In spite of major advantages of CVS over amniocentesis as a method of sampling fetal material for chromosome analysis (Spencer and Cox, 1987, 1988; Sachs et al., 1988; Jahoda et al., 1989) the number of CVS procedures for advanced maternal age did not increase at the rate we had anticipated. After 5 years of performing CVS, this method only represented approximately 50% of the procedures for AMA.

Two reasons for the difference in acceptation of CVS between the high genetic risk group as opposed to the advanced maternal age group could be given: (1) Patients with a high genetic risk usually have been counselled by a geneticist and therefore visit a centre for prenatal diagnosis early enough in pregnancy to take advantage of CVS; (2) Women with high genetic risks may feel that the earlier result after CVS as compared to amniocentesis offsets the perceived increased risk of CVS over standard amniocentesis.

Recent studies suggest there is no statistical difference in the fetal loss rate between women undergoing CVS and undergoing amniocentesis (Rhoads et al., 1989; Canadian Collaborative CVS-amniocentesis Clinical Trial Group, 1989).

The increased number of referrals of women of advanced maternal age is most likely determined by the lowering of the age limit for prenatal diagnosis from 38 to 36 years of age in 1984.

It seems that many women, especially those at advanced maternal age, could have benefitted from a very early referral in their pregnancy so as to allow them to

gain realistic information about the pro's and con's of CVS. Most studies on CVS indicate that an early result and a less traumatic procedure (vacuum aspiration) for pregnancy termination are major factors for couples in their decision to opt for CVS (Spencer and Cox, 1987, 1988; Sjörgen and Uddenberg, 1989).

Acknowledgements

We would like to thank Professor M.F. Niermeijer and Professor E.S. Sachs for their helpful comments. The expert statistical analysis provided by P.G.H.Mulder, M.Sc., is gratefully acknowledged.

2.3.3.2 *Prenatal diagnosis in advanced maternal age. Amniocentesis or CVS, a patients' choice or lack of information?*

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Published in Prenatal Diagnosis 1991;11:685-690.
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Summary.

Ninety-six women of advanced maternal age were interviewed about the way they obtained information on prenatal diagnosis and about how the decision was made as to what procedure was to be performed (Transabdominal Chorion Villus Sampling (TA-CVS) or amniocentesis). In the CVS group women visited their physician or midwife earlier in pregnancy (mean 7.1 weeks) than in the amniocentesis group (mean 10.7 weeks). The availability of prenatal diagnosis was not mentioned during the first antenatal visit in 55 % of women from the amniocentesis group as opposed to 25 % from the TA-CVS group. Approximately 40 % of women eligible to prenatal diagnosis did not receive any information from the referring body prior to counselling at our centre.

Only 29 % of women who underwent amniocentesis had actually chosen this procedure, 71 % was too late to undergo transabdominal CVS at 12 weeks.
It is concluded that information to the patient must be improved in order to ensure an early referral to a centre for Prenatal Diagnosis.

Key words: advanced maternal age, chorionic villus sampling, amniocentesis.

Introduction.

Chorionic villus sampling (CVS) has become a widespread and acceptable method of collecting fetal material for prenatal diagnosis (PND) in the first trimester of pregnancy (Ward et al., 1983, Simoni et al., 1983). The advantages of CVS are obvious in terms of early results because there are less emotional, social and medical impacts (Spencer and Cox, 1988, Cao et al., 1987). In 1988 only one-third of patients of advanced maternal age was referred to our centre for CVS, the remaining two-thirds being referred for amniocentesis. Three explanations could be given for the low CVS referral rate :
a. the post-procedural fetal loss rate is assumed to be higher for CVS than for amniocentesis, although several studies could not substantiate this (Rhoads et al., 1989,

Canadian Collaborative CVS-Amniocentesis Clinical Trial Group, 1989, Crane et al., 1988): b. the CVS procedure does not allow exclusion of neural tube defects; c. unfamiliarity with timing of CVS.
The objective of the present study was to establish the underlying reasons for the relatively low referral rate for CVS.

Patients and methods

Patients who visit the centre for prenatal diagnosis at the academic hospital in Rotterdam originate from the Southwest region of the Netherlands (approximately 45,000 deliveries per year). The region consists of the city Rotterdam plus suburbs and the country, which together represent nearly a quarter of the Netherlands. The women are referred by either a. the midwife with a private practice, b. the family doctor c. the gynaecologist (both from the Academic hospital Rotterdam as well as from the smaller hospitals in the region). Approximately 50 % of the referred women receive antenatal care with the family doctor or the midwife, 2.7% have antenatal care in the academic hospital (1989). The remaining women attend the antenatal clinic in a District hospital in the region.

An appointment for genetic counselling at our department was made as soon as a request for prenatal diagnosis had been received. Women with a language barrier that posed a problem to the answering of the questionnaire were excluded from the study. Counselling included the reason for prenatal diagnosis and the technique, timing and risks of amniocentesis and transabdominal chorion villus sampling (TACVS), so to allow a balanced selection between the two procedures. In our centre TACVS is performed at 12 weeks (Cohen-Overbeek et al., 1990) and amniocentesis at 16 weeks. The underlying reasons for the patients' choice as to which procedure was preferred were evaluated by a questionnaire survey. The questionnaire was completed face-to-face with an investigator.

The questionnaire included the following questions :
a. level of education, a scale from 1 (primary school only) to 7 (university training completed) was used; b. age; c. domicile; d. menstrual age at the time of the first prenatal visit to the physician or midwife; e. menstrual age at the time the issue of PND was brought up; f. the referring body (physician or midwife) who provided the medical information about PND; g. the nature of information given by the referring body; h. menstrual age at the time our department was contacted; i. the reason for the final decision as to which procedure was to be performed following counselling at our department.

During the period of September until November 1989, 96 out of 148 women of advanced maternal age (36 years and older) were randomly selected and interviewed. The reason for seeing only 96 of the referred patients was determined by the fact that three intake-clinics were run at the same time whilst there was only one investigator to complete the questionnaires.
The answers obtained from the questionnaires were standardised and adapted for

computerisation. For statistical analysis the χ^2-test and the Wilcoxon's two-sample test were used.

Results

The questionnaire was completed by all participants. Of these, 38 (39.6%) were given an appointment for amniocentesis at 16 weeks and 58 women (60.4%) opted for TACVS at 12 weeks.

Whereas there was no difference in both groups regarding age and level of education, the amnio group constituted a significantly higher number of patients from the greater Rotterdam area than from the regional area ($p<0.01$) (Table 1).

Table 2 shows the delay in referral to our centre. The first antenatal visit took place between 5 and 13 weeks of menstrual age in the amnio group (mean 7.9 weeks) and between 5 and 11 weeks of menstrual age in the CVS group (mean 6.5 weeks). This time difference is statistically significant ($p < 0.01$).

Table 1. Domicile, age distribution and educational level in the amniocentesis group and in the TACVS group.

	Amnio group (N=38)	TA-CVS group (N=58)	p-value
Originating from the city of Rotterdam and suburbs (%)	47.3	15.4	< 0.01
Mean age (years)	37.6 (range 35-44)	37.4 (range 35-41)	N.S.
Mean educational level (scale 1-7)	3.5 (range 1-7)	3.7 (range 1-7)	N.S.

Table 2. Delay in referral of women of advanced maternal age.

	Amnio group (N=38)	TA-CVS group (N=58)	p-value
1st antenatal visit (wks)	7.9 (5-13)	6.5 (5-11)	< 0.01
1st discussion of PND (wks)	10.7 (7-16)	7.1 (7-12)	< 0.001
% of women < 12 wks at that time	76	100	
Mean time interval between information and counselling (wks)	2.6	2.2	N.S.
Menstrual age at counselling (wks)	13.4 (9-17)	9.3 (6.5-14)	< 0.001
Mean delay between 1st antenatal visit and counselling (wks)	5.5	2.7	< 0.001

PND=prenatal diagnosis

In 95% patients from the amnio group and in all patients from the CVS group this first visit took place before 12 weeks of menstrual age.
In the amnio group the mean time at which the issue of prenatal diagnosis was brought up by the referring body or patient was 10.7 weeks (range 7-16 weeks) and in the CVS group 7.1 weeks (range 7-12 weeks). This difference is statistically significant ($p < 0.001$).

The availability of prenatal diagnosis was not mentioned during the first antenatal visit in 55 % of patients from group A as opposed to 25% in the CVS group.

The mean time interval between the patient receiving information from the referring body on the issue of PND and the actual appointment in our department was not essentially different between the two groups, 2.6 weeks in the amnio group and 2.2 weeks in the CVS group ($p=0.28$).

In the amniocentesis group, PND was mentioned by the referring body before the menstrual age of 12 weeks in 76% of cases.

The mean menstrual age at the time of counselling for PND in our centre was 13.4 weeks (range 9-17 weeks) in group A and 9.3 weeks (6.5-14 weeks) in the CVS group. 3 women who were over 12 weeks of age opted for TACVS for reasons of an early result.

The mean delay between the first antenatal visit and the actual counselling in our centre was 5.5 weeks in the amnio group and 2.7 weeks in the CVS group. This difference is statistically significant ($p < 0.001$).

Table 3. Source of information about the availability of prenatal diagnosis.

	Amnio group (N=38) %	TA-CVS group (N=58) %
Family doctor	26	39
Midwife	29	13
Gynaecologist	45	48

In the amnio group information on the availability of PND was provided by the general practitioner in 26%, by the midwife in 29% and by the gynaecologist in 45% (Table 3). For the CVS group the percentages were 39%, 13% and 48% respectively.

The nature of the information on methods of PND provided by the referring body to the patient is presented in Table 4. No information was provided in 42 % of patients from group A and 40 % in group B.

Regarding the ultimate procedure selection, 28.9% of the women in the amnio group opted for amniocentesis for reasons of a slightly lower abortion risk compared to CVS or ruling out a neural tube defect (Table 5). The remaining 71.1% underwent amniocentesis since pregnancy had progressed too far to allow any selection.

Table 4. Information on method of prenatal diagnosis provided by referring physicians (or midwives) to women of advanced maternal age.

	amniocentesis (N=38)	TA-CVS group (N=58)
No information (referred only)	42	40
Information on amniocentesis	24	9
Information on CVS	-	19
Information on both methods	26	28
Previous information from other sources	8	4
	100 %	100 %

Table 5. Reasons for having amniocentesis in amnio group (N = 38).

	%
Assumed lower procedure risk	10.5
Exclusion of neural tube defect	18.4
Late referral	71.1

Discussion.

From our study it becomes clear that the majority of patients of advanced maternal age does not have the choice which procedure, TACVS or amniocentesis, will be performed.

Not many patients are well-informed about the need of early referral if CVS is requested. Moreover, an early visit to the physician or midwife does not necessarily result in a timely referral to a centre for PND. It is essential that the consulted physician has proper knowledge of the time and nature of the procedure and the procedure related risks. Time differences between the amniocentesis group and CVS group were observed with respect to the first antenatal visit, the timing of information on PND and the first actual appointment at our centre. In the CVS group women tend to visit their physician or midwife earlier in pregnancy compared with the amniocentesis group.

The issue of PND was first brought up in the CVS group at around 7.1 weeks, and in the amniocentesis group at around 10.7 weeks. Patients from the amniocentesis group do not only see their physician later in pregnancy, they also discuss the option for PND at a relatively later stage, resulting in a mean time difference in appointment for the procedure between the two groups of 4.1 weeks. The reason as

to why the issue of PND is brought up later in pregnancy in the amniogroup needs further investigations. A possible explanation could be found in the fact that a higher percentage of the amnio group originates from the greater Rotterdam area were the family doctor usually does not provide the obstetric care but refers to either midwife or gynaecologist.

We have come to the conclusion that our efforts to provide better information to both patients and physicians must continue to achieve a more efficient referring system for women of advanced maternal age to a centre for PND.

2.4 Conclusions.

In this chapter several aspects of prenatal diagnosis in women of advanced maternal age were reviewed. The uptake of prenatal diagnosis by elderly women has reached a plateau in the last six years. In the group of women of 36 and 37 years of age an increase in utilization is seen, probably because it was only recently that for this group prenatal diagnosis became accessible. The introduction of CVS had no effect on the utilization of prenatal diagnosis. The percentage of women who opt for CVS is still growing. Therefore, a lower percentage of women will elect amniocentesis.

It appeared from our study that most women who decided on prenatal testing are poorly informed about the possibilities and limitations of CVS. Many women make their booking appointment too late in pregnancy (>12 weeks) and will therefore not be considered for CVS.

The reason that CVS is not carried-out in our centre before 12 weeks is based on the high spontaneous abortion rate amongst elderly gravidas early in pregnancy. CVS at 12 weeks or later can only be safely performed transabdominally. When sampling takes place at this gestational age, the risks to the fetus will be limited.

Chapter 3

Abnormal cytogenetic results following prenatal diagnosis in women of advanced maternal age.

Introductory remarks.

An abnormal fetal karyotype is a distressing event for the future parents. It is important, therefore, that specialized medical care and psychological support is provided (Donnai et al., 1981; Frets et al., 1990).

Before CVS became available mid-trimester abortion was the only means of terminating an affected pregnancy. Prostaglandins (PG) have been used for genetic terminations since the early seventies (Blumberg and Golbus, 1975). Until late 1983 terminations in our centre were carried-out through intra-amniotic instillation of PGF2α. Serious complications were never reported. From 1984 onwards synthetic PGE derivate Sulproston (Nalador®) was administered either intramuscularly or intravenously. Side effects include gastro-intestinal disturbances and painful uterine contractions. Approximately 2-3% of immature fetuses are born alive (Reyburn and LaFerla, 1986). Incomplete expulsion of the placenta can be expected after induced immature delivery; curettage is therefore recommended soon after the placenta is delivered.

Prostaglandins may be contra-indicated or may only be used with great caution in case of asthma, hypersensitivity to PG, a uterine scar, liver or kidney diseases, epilepsy (Brandenburg et al., 1990), or diabetes mellitus. In these cases instillation of a hypertonic salt solution combined with an intravenous oxytocin drip may serve as an alternative.

First trimester prenatal diagnosis has opened the possibility of terminating a chromosomally abnormal pregnancy by means of out-patient vacuum-curettage. In our department first trimester abortions are performed under paracervical block with 1% Lidocaïne, mostly combined with an anxiolytic agent e.g. Midazolam (Dormicum®). Women beyond 13 weeks of gestation will receive 500 µg Sulproston intramuscularly some hours prior to the evacuation to facilitate dilatation of the cervix. In this way late first trimester abortion is thought to be less traumatic than a mid-trimester pregnancy termination. This might be even more so because maternal bonding becomes stronger as pregnancy progresses (Campbell et al., 1982). A less traumatic procedure may influence the ultimate decision whether or not to become pregnant again.

In this chapter, two aspects of abnormal cytogenetic results are discussed. Firstly, a study is presented on reproductive behaviour related to late first and mid-trimester genetic termination (3.1). Secondly, sub-chapter 3.2 focuses on women who wished to continue their pregnancy despite an abnormal cytogenetic result.

3.1 *Reproductive behaviour and prenatal diagnosis following genetic termination of pregnancy in women of advanced maternal age.*

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Accepted in Prenatal Diagnosis.

Summary.

One hundred and fifty-one women of advanced maternal age who underwent genetic termination of pregnancy (TOP) were studied for their reproductive behaviour and the type of procedure for prenatal diagnosis in a subsequent pregnancy.

A total of 59 women (39%) decided on a next pregnancy. In all continuing pregnancies prenatal diagnosis was performed of which 75% consisted of chorion villus sampling (CVS). Reproductive behaviour following a genetic termination was negatively correlated with maternal age and parity. Both reproductive behaviour and the choice to undergo a diagnostic procedure in the next pregnancy were independent of the type of diagnostic procedure in the previous affected pregnancy.

Key words: Advanced maternal age, genetic termination, amniocentesis, chorion villus sampling.

Introduction.

During the last six years a shift has taken place in many centres from second trimester amniocentesis towards first trimester chorionic villus sampling (CVS). This shift, which applies to both women of advanced maternal age and to women undergoing biochemical or DNA-tests implicates that a higher incidence of chromosomal abnormalities will be found after CVS as compared to amniocentesis (Hook et al., 1988). Spontaneous fetal loss as a result of a chromosomal abnormality causes different incidences of Down's syndrome and other chromosome abnormalities at CVS, at amniocentesis and at birth, (Hook, 1978a; Milunski, 1986). As much as 30% of Down's syndrome fetuses diagnosed at amniocentesis will end in fetal loss, as was concluded from a study in women who elected not to have their affected pregnancy terminated (Hook 1978b, 1983). Moreover, rare lethal chromosomal abnormalities diagnosed at CVS, may not be seen at amniocentesis (Wyatt, 1983). Therefore, in women of advanced maternal age CVS will be associated with a higher rate of pregnancy terminations than amniocentesis.

Based on these considerations, the following questions were addressed: (i) what was the reproductive behaviour following a genetic termination; (ii) to what extent was the choice of diagnostic procedure in a next pregnancy influenced by the type of procedure in the previous affected pregnancy.

Patients and methods.

The medical records of women of advanced maternal age (≥38 years until 1984, ≥36 years after 1984) who underwent amniocentesis or CVS between 1st January 1980 and 31st December 1989 at our centre were studied. For each case, the nature of the diagnostic procedure, the gestational age at the time of the procedure, the obstetric history, the cytogenetic results and the gestational age at the time of pregnancy termination were documented. Information on the time lapse between termination of the affected pregnancy and a next pregnancy, the decision to undergo prenatal diagnosis in the next pregnancy and the type of diagnostic procedure was obtained from the family doctor or directly from the patient. Enrolment into the study was stopped on 1st July 1991.

All data were computerized with the SSPS system and analyzed by means of the Cox proportional hazards survival analysis (inverted for cumulative incidence) and Pearson's chi-square test.

Results.

Complete follow-up was obtained in 151 pregnancies, of which 105 were terminated following an abnormal genetic finding at amniocentesis and 46 following an abnormal CVS result.

Mean maternal age in these two groups was 39.4 years (± 2.5 yrs (SD)) and 39.7 years (± 2.8 yrs (SD)), respectively. A total of 59 women (39%) became pregnant again, 43 (41.0%) of which following termination of an affected pregnancy diagnosed at amniocentesis and 16 (34.8%) following CVS (Table 1).

Table 1. Reproductive behaviour and prenatal diagnosis after termination of pregnancy for genetic reasons.

	after amniocentesis		after CVS		
	N	(%)	N	(%)	P
Genetic termination	105		46		
Subsequent pregnancy	43	(41.0)	16	(34.8)	NS
Prenatal diagnosis	36	(83.7)	12	(75.0)	NS
CVS	27		9		
amniocentesis	9*		3		

* 2 of the amniocentesis were done in 1983 before CVS was available.
CVS chorionic villus sampling

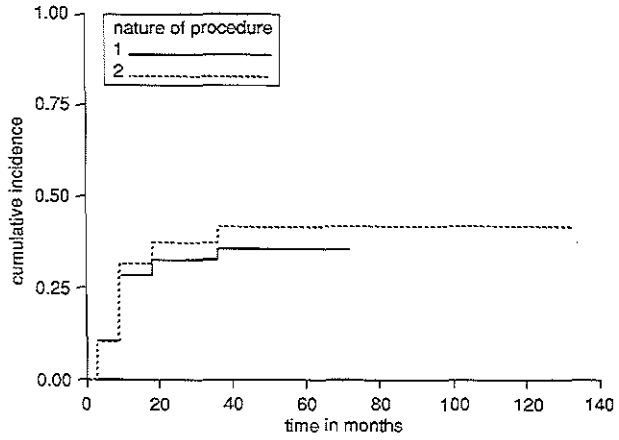

Fig. 1. Cumulative incidence of subsequent pregnancies following a genetic termination.
1 = after CVS; 2 = after amniocentesis

Figure 1 gives the cumulative incidence of subsequent pregnancies after genetic termination related to CVS and amniocentesis. No significant difference could be established between the two procedures.

Figures 2 and 3 demonstrate that the cumulative incidence of subsequent pregnancies is significantly lower in older women ($P<0.001$) and at higher parity ($P=0.005$).

Eleven women experienced an early spontaneous abortion in their subsequent pregnancy; the number of women which would have opted for prenatal diagnosis is unknown.

Prenatal diagnosis was performed in 48 ongoing pregnancies. CVS was again requested by 9 out of 12 women (75%) who had previously undergone CVS and by 27 out of 36 women (75%) who had previously undergone amniocentesis. The three women who underwent amniocentesis after CVS in the previous pregnancy had been postponing their visit to our centre till 13-14 weeks of pregnancy for unknown reasons. From the nine women who requested again amniocentesis, six feared the higher post CVS abortion rate and three women visited us too late to be considered for CVS.

Discussion.

Within the follow-up period, a large number of women of advanced maternal age (61%) who had experienced a termination of pregnancy for genetic reasons did not become pregnant again. Genetic termination is a traumatic experience to all members of the family (Black and Furlong, 1984; Frets et al., 1990) and can therefore affect the decision on a future pregnancy. We realize however, that not all women

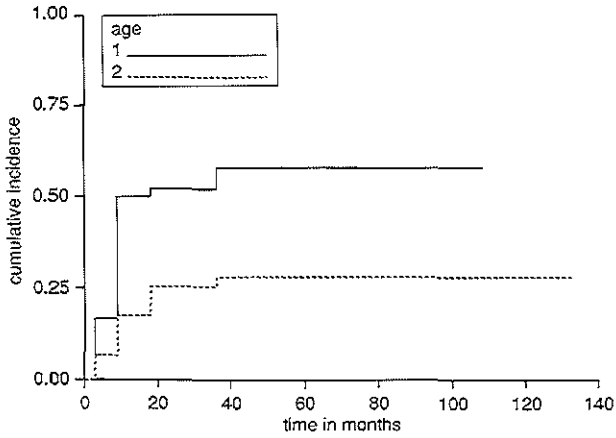

Fig. 2. Effect of maternal age on cumulative incidence of subsequent pregnancies following a genetic termination.
1 = 36-38 years; 2 = 39 years and older.

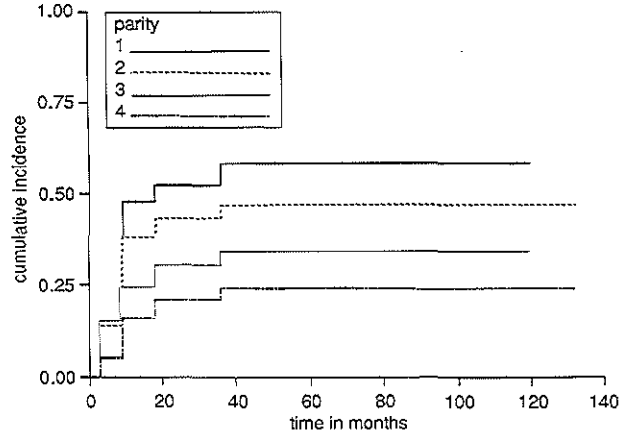

Fig. 3. Effect of maternal parity on cumulative incidence of subsequent pregnancies following a genetic termination.
1 = para 0; 2 = para 1; 3 = para 2; 4 = para 3 and higher.

who decided on a next pregnancy will become pregnant. Reduced fertility because of advanced age and possible post termination complications could also play a role. On the other hand, in a group of women of comparable maternal age who experienced a spontaneous fetal loss after prenatal diagnosis 60% percent achieved a next pregnancy (Brandenburg et al., in press), which is 20% higher than after termination of pregnancy for genetic reasons.

We could not establish a difference in reproductive behaviour after post-CVS or

after post-amniocentesis termination of pregnancy. Obviously, CVS does not facilitate the decision on a future pregnancy. When women achieve a next pregnancy there is a preference for CVS both following a previous amniocentesis and a previous CVS.

When looking at the effect of maternal age on the cumulative incidence of a subsequent pregnancy it was apparent that at the age of 36-38 years a maximum of 57.5% of women becomes pregnant, whereas the figure is only 27.9% in women of 39 years and older. This marked negative effect of maternal age on reproductive behaviour may be explained by the age-related reduction in fertility (Stein, 1985; Van Noord-Zaadstra, 1991). Maternal age is positively correlated with maternal parity which in our study also had a negative effect on reproductive behaviour. The presence of one or several children could make couples less motivated to again go through the stress of prenatal diagnosis.

It can be concluded that more than half of the women who underwent termination of pregnancy for genetic reasons did not achieve a new pregnancy. The gestational age at which prenatal diagnosis in the affected pregnancy was performed had no bearing on their decision. All women elected to undergo prenatal diagnosis in the subsequent pregnancy. The majority (75%) requested CVS independent of the type of invasive procedure in the previous affected pregnancy.

3.2 Continuation of pregnancy in the presence of a prenatally diagnosed chromosome abnormality.

Women who seek prenatal diagnosis because of advanced maternal age are referred to our centre by their family doctor, gynaecologist or midwife. Only few women make an appointment of their own accord. Referring physicians will only briefly discuss the issue of prenatal diagnosis since extensive counselling will follow in our centre. During the counselling the attitude of the couple towards termination of pregnancy in case of an abnormal fetal karyotype, is considered. If the couple is against termination on religious, moral or ethical grounds, they are strongly advised to refrain from prenatal diagnosis. If the couple insists on undergoing a test, amniocentesis or CVS will be performed. This is a situation which occurs only once or twice a year on a total of more than 2500 requests for prenatal diagnosis (1991). At the time of the first counselling, approximately 5% of the women who are referred to our centre will not yet have made up their mind regarding termination of pregnancy in case of an abnormal result.

Between 1984 and 1991 a total of four women of advanced maternal age decided to continue their pregnancy despite the presence of a chromosomal abnormality. Table 1 presents the continuing pregnancies related to the total number of abnormal karyotypes during the same period and the nature of the diagnostic procedure. Only 1.5% of serious chromosomally abnormal pregnancies were continuated as opposed to 10.7% of pregnancies with a sex chromosome abnormality. Abnormalities of sex chromosomes cause less serious and less visible abnormalities which influences the decision to continue the pregnancy. No continuing pregnancies were found in the CVS group. Table 2 shows the characteristics of the four women who continued the pregnancy with an abnormal fetal karyotype.

Table 1. Number of continuing pregnancies relative to the total number of abnormal karyotypes and the nature of the diagnostic procedure (1984-1990).

	amniocentesis N (%)	CVS N (%)
trisomies and other severe chromosome anomalies	1/66 (1.52)	0/71 (0)
sex chromosome anomalies	3/28 (10.71)	0/12 (0)
all chromosome anomalies	4/94 (4.26)	0/83 (0)

Continuation of a chromosomally abnormal pregnancy is exceptional. We hypothesised that because of less well-developed maternal bonding in early pregnancy, continuation of a chromosomally abnormal pregnancy following CVS would be less likely. This turned out to be correct and is in agreement with Verp et al. (1988), who reported that 97.6% of chromosomally abnormal pregnancies established at CVS

Table 2. Characteristics of patients who continued their affected pregnancy.

case number	year of procedure	maternal age (yrs)	obstetric history	chromosome results after amniocentesis
1	1984	40	G III P II two healthy infants	47, XXX
2	1984	43	G V P IV two healthy infants	47, XXY
3	1985	39	G IV P II Ab I two healthy infants	47, XXY
4	1989	38	G III P II no live infants	47, XX + 21

were terminated as opposed to 78.1% terminated after amniocentesis. Drugan et al. (1990), however, could not demonstrate a significant difference in the number of terminations between the CVS group (82.8%) and the amniocentesis group (72.4%).

In our series, termination took place in 95.7% of pregnancies with a chromosomal abnormality diagnosed at amniocentesis and in all pregnancies with an abnormal fetal karyotype diagnosed at CVS. All three women who continued their pregnancy despite a sex chromosome aneuploidy, stated that at the time they made the right decision. They added that they would have opted for termination if a more severe abnormality had been found. The only woman who decided to continue a trisomy 21 pregnancy experienced an intra-uterine death at 26 weeks.

3.3 **Conclusions.**

Following the diagnosis of an abnormal fetal karyotype, most women will decide to have their pregnancy terminated. Termination during the first trimester of pregnancy is less traumatic and could therefore result in a more positive attitude towards a next pregnancy. However, no difference in reproductive behaviour could be established between women who had experienced a termination of pregnancy after CVS and those who had gone through a mid-trimester termination after amniocentesis. Only 40% became pregnant again, which is partially explained by the reduced fertility in older women.

On the basis of the low number of continuing pregnancies with a chromosomal abnormality, it seems that the policy of counselling couples before the actual procedure allows women only to undergo the test when all aspects of a possible fetal chromosomal disorder have been considered.

Chapter 4

Spontaneous fetal loss after prenatal diagnosis in women of advanced maternal age.

Introductory remarks.

Early spontaneous abortion has long been looked upon by physicians as an unimportant obstetric event, which only causes a grieving reaction in pathological conditions (Friedman and Gladstein, 1982; Leon, 1986). It has become known, however, that a grieving reaction occurs in nearly all women who lost a fetus or infant, independent of the gestational age at which the loss took place (Peppers and Knapp, 1980; Leppert and Pahlka, 1984). Studies on psychodynamics of fetal loss after prenatal diagnosis demonstrate a relation between gestational age and mood disturbances (Black, 1989; Black, 1990). Patients who undergo prenatal diagnosis are usually counselled for the increased risk of a spontaneous abortion as well as for the possibillity of selective termination. It seems that women who are psychologically prepared for fetal loss demonstrate a less overwhelming grief reaction than women who did not anticipate fetal loss (Leon, 1986). Most women who have gone through a spontanous abortion, without having had prenatal diagnosis, experience feelings of guilt because they consider something wrong with themselves (Leppert and Pahlka, 1984). These feelings of guilt are less pronounced after a spontaneous abortion following prenatal diagnosis because there is an explanation for the loss. Nevertheless, most women who lost a pregnancy after prenatal diagnosis have feelings of guilt because a wanted pregnancy was put at risk. Some of the women report depressions or reduced social and sexual activities for longer than six months (Black, 1990).

We hypothesised that a changed state of mood will effect the decision to become pregnant again. Furthermore, by delaying the next pregnancy, women of advanced maternal age may pass beyond their fertile period.

In this chapter we will study the effect of spontaneous fetal loss after prenatal diagnosis on reproductive behaviour and the utilization of prenatal diagnosis in a subsequent pregnancy.

4.1 Reproductive behaviour following spontaneous loss of a pregnancy after prenatal diagnosis.

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Accepted in Clinical Genetics.

Summary.

Hundred and fifty-eight women of advanced maternal age with complete follow up who experienced spontaneous fetal loss after prenatal diagnosis were studied for reproductive behaviour as well as prenatal diagnosis in a subsequent pregnancy. A higher rate of pregnancies amongst women who experienced an early spontaneous abortion after chorionic villus sampling (CVS) was expected compared with women who lost a pregnancy at a later stage after amniocentesis.

Of the 92 women who underwent CVS in a previous pregnancy 57 (62%) became pregnant again. From the 66 women who underwent amniocentesis in the pregnancy that ended in fetal loss 34 women (52%) chose for a subsequent pregnancy. The cumulative incidence of subsequent pregnancies was significantly influenced by maternal age but not by parity or the method of prenatal testing. Most women who decided on a new pregnancy opted for prenatal diagnosis. There was a preference for amniocentesis in case of a previous CVS. However, the reverse was not the case.

Introduction.

Prenatal diagnostic procedures are associated with a low degree of fetal loss. For amniocentesis the loss is approximately 0.5%-1% (Sachs et al., 1982; Tabor et al., 1986) and for chorionic villus sampling (CVS) 1.5%-1.7% (Jahoda et al., 1985; Philip et al., 1991). The rate of fetal loss is higher at 9-12 weeks than at 16-17 weeks gestation. This is due to the higher incidence of spontaneous abortion in early pregnancy, in particular amongst older women. (Stein, 1985; Simpson, 1990). In this group the spontaneous abortion rate between the intake visit when fetal viability was proven and the date of transabdominal CVS at 12 weeks was as high as 6.8% (Cohen-Overbeek et al., 1990).

Fetal loss after first trimester CVS is thought to be less psychologically traumatic than after second trimester amniocentesis (Black, 1990). A severe grief reaction may nevertheless occur after both events. This is particularly so for women of advanced maternal age since it may be their last pregnancy. The loss of a pregnancy

may be such a traumatic event that they may relinquish the idea of further offspring or refuse prenatal diagnosis in a subsequent pregnancy.

We hypothesised that after a less traumatic event more women would choose for a subsequent pregnancy. Furthermore, we were interested in the percentage of women who would again opt for prenatal diagnosis despite the disappointing experience with prenatal testing. We expected a preference for CVS after previous amniocentesis and for amniocentesis when CVS had been performed earlier.

The objective of the present study was to determine the effect of spontaneous fetal loss following CVS or amniocentesis on reproductive behaviour and the choice of prenatal diagnosis in a subsequent pregnancy.

Patients and methods.

The study included all files of women of advanced maternal age (≥ 38 years until 1984, ≥ 36 years after 1984) who underwent amniocentesis or CVS in the Rotterdam centre between January 1st 1980 and December 31st 1989. The number of previous pregnancies and deliveries, the type of diagnostic procedure and the gestational age at the time of the procedure as well as the occurence of fetal loss was documented for each case by the same invesigator. Information about the time interval between fetal loss and a subsequent pregnancy, the decision to undergo prenatal diagnosis in this pregnancy and the choice of diagnostic procedure was collected from the record when the patient had returned to our centre during her subsequent pregnancy. Additional information was obtained from the family doctor or directly from the patient by telephoning her. Enrolment into the study ended on July 1st 1991, so the shortest follow up was 1.5 years.

All information was computerized and analyzed by means of the Cox proportional hazards survival analysis (inverted for cumulative incidence) and Pearson's chi-square test.

Results.

During the study period 183 women of advanced maternal age lost a pregnancy in which prenatal diagnosis had been performed. Complete follow-up was obtained in 158 women, 92 of whom experienced fetal loss after CVS and 66 following amniocentesis. Of the women who were lost to follow up 15 had undergone CVS and 10 amniocentesis. Twenty-four were lost to follow up because they could not be traced; only one woman refused to provide information. The mean maternal age of the women in the study group who had undergone CVS was 38.1 (SD ± 2.1) years and 38.6 (SD ± 2.0) years of those who had undergone amniocentesis.

Fifty-seven (63%) out of 92 women who had post-CVS fetal loss became pregnant again and 34 (52%) out of 66 women after post-amniocentesis fetal loss (Table 1). Figure 1 shows the cumulative incidence of subsequent pregnancies following post-CVS and post-amniocentesis fetal loss. The pregnancy incidence following post-CVS and post-amniocentesis fetal loss was not statistically different.

Table 1. Subsequent pregnancy and prenatal diagnosis (PD) after fetal loss in previous pregnancy with PD.

	after amniocentesis		after CVS		
	N	%	N	%	P
Patients with fetal loss after P.D.	66		92		
Subsequent pregnancies	34	(52.0)	57	(62.0)	0.85 (NS)
Spontaneous abortions	6		8		
T.O.P.	1		3		
Ongoing pregnancies	27		46		
PD	25	(92.6)	37	(80.4)	0.56 (NS)
CVS	14	(56.0)	12	(32.4)	
Amniocentesis*	11	(44.0)	25	(67.6)	

* 1 patient got pregnant again before 1983, when CVS was not yet available.
TOP Termination of pregnancy for social reasons.
CVS Chorionic villus sampling. PD Prenatal diagnosis
NS non significant.

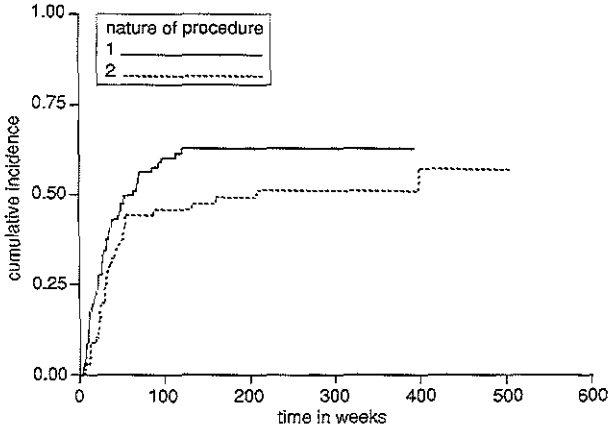

Fig. 1. Cumulative incidence of subsequent pregnancies following procedure-related fetal loss. 1=after CVS; 2=after amniocentesis.

Figures 2 and 3 demonstrate a significantly lower cumulative incidence of subsequent pregnancies in older women ($p < 0.001$) independent of parity.
Eleven early spontaneous fetal losses occurred in the 57 pregnancies following post-CVS fetal loss leaving 46 pregnancies for further analysis.
Seven early spontaneous fetal losses occurred in the 34 pregnancies following post-amniocentesis fetal loss leaving 27 pregnancies for further analysis.

Prenatal diagnosis in a subsequent pregnancy was performed in 37 out of 46

women (80.4%) who had previously undergone CVS and in 25 out of 27 women (92.6%) who had previously undergone amniocentesis. This difference was not statistically significant. In the post-CVS group, 25 out of 37 women (67.6%) preferred amniocentesis as opposed to 12 out of 37 women (32.4%) preferring CVS. In the post-amniocentesis group, 14 out of 25 women (56%) requested CVS and 11 out of 25 women (44%) requested amniocentesis.

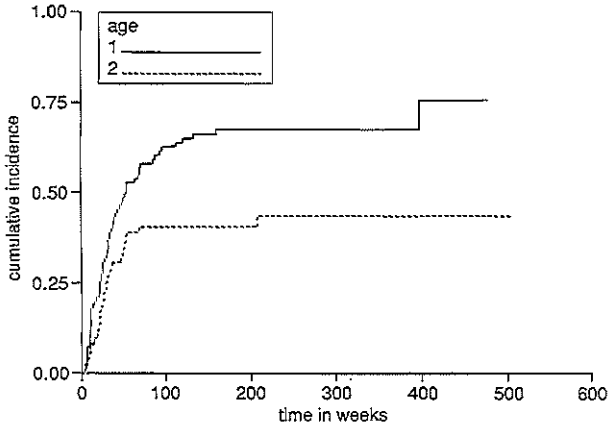

Fig. 2. Effect of maternal age on the cumulative incidence of subsequent pregnancies following procedure-related fetal loss. 1=age 36-38 years; 2=39 and older.

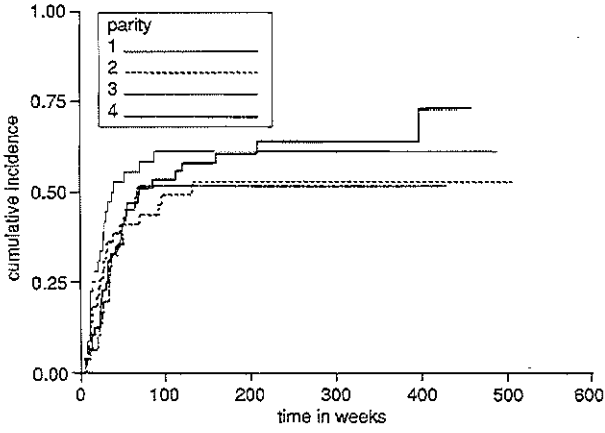

Fig. 3. Effect of maternal parity on the cumulative incidence of subsequent pregnancies following a procedure-related fetal loss.
1=para 0; 2=para 1; 3=para 2; 4=para 3 and higher.

Eleven women, of which nine following a post-CVS fetal loss and two following a post-amniocentesis fetal loss did not request prenatal diagnosis in a subsequent pregnancy. The age of these women was not higher compared with the total study group. The parity was significantly lower than in the total study group (1.0 and 1.5 respectively).

Discussion.

Women who have experienced a spontaneous fetal loss after prenatal diagnosis may not become pregnant again. This was the case in 42% of the women in our study. The chance of becoming pregnant was significantly influenced by maternal age but independent of parity and type of test in the previous pregnancy.

The inverse relationship between the cumulative incidence of subsequent pregnancies and maternal age may be determined by the reduction in reproductive capacity with advancing maternal age (Stein 1985; van Noord-Zaadstra et al., 1991). The lack of any relationship with parity was surprising since in women with a higher parity a lower cumulative incidence of pregnancies was expected. It seems that in spite of the traumatic experience of fetal loss some women are still strongly motivated to start a new pregnancy. A speculation is that more women in this group might have a new partner. This hypothesis, however needs further study. The fact that the type of test performed in the previous pregnancy had no effect on the incidence of women who became pregnant again, suggests that fetal loss after amniocentesis is not more traumatic than after CVS.

The vast majority of women who elected to start a subsequent pregnancy chose to have prenatal diagnosis again (85%). Also this choice was not influenced by the type of diagnostic procedure in the previous pregnancy. The choice as to which procedure was to be performed in the subsequent pregnancy was left to the patient. If fetal loss had occurred following CVS, amniocentesis was preferred in the next pregnancy. This preference for a different test was not evident in women who experienced fetal loss after amniocentesis. This may be so because women seem to have doubts about the safety of CVS in a subsequent pregnancy. This is partly explained by the fact that early CVS data were included at a time when the safety and reliability of the procedure still had to be proven.

It can be concluded that the influence of CVS on reproductive behaviour in women who experienced a spontaneous fetal loss after prenatal diagnosis is smaller than anticipated. Since CVS is thought to be less traumatic both emotionally and physically as compared with amniocentesis, it seems that reproductive behaviour does not reflect any difference in the impact of fetal loss after CVS and amniocentesis.

4.2 Conclusions.

This study demonstrates that a high percentage of women of advanced age does

not become pregnant again after spontaneous fetal loss following prenatal diagnosis (42%). However, this was considerably lower than in the group of women who underwent a genetic abortion (61%) (sub-chapter 3.1). In both groups no difference in reproductive behaviour could be established between women who underwent CVS and those who underwent amniocentesis. It can be concluded from both studies that a selective termination of pregnancy is more traumatic than a spontaneous abortion following prenatal diagnosis. This is not in agreement with the study of Black (1990) who found no differences in distress levels between the two groups of women but it was emphasised that the sample size was too small to draw definite conclusions.

Continuing attention should be given to the support of those women who have lost a pregnancy, either through selective or spontaneous abortion following prenatal diagnosis.

Chapter 5

Advanced maternal age and twin pregnancy.

Introductory remarks.

Twin pregnancies are more common in elderly gravidas than in younger women (Goldstein and Stills, 1983). There is a three-fold higher incidence at age 35-39 years compared with women below 20 years (Tas, 1990).

In the Netherlands the number of multiple pregnancies has risen. This is due to an increasing number of women of advanced maternal age, a more liberal use of ovulation stimulating drugs and the introduction of in-vitro fertilization and embryo transfer programmes (Tas, 1990).

Prenatal diagnosis in twin pregnancies poses several problems.
Firstly, there is a slightly higher procedure-related fetal loss rate in twin pregnancies compared with single pregnancies (NICHD Study Group, 1976; Pijpers et al., 1988b; Palle et al., 1983; Pruggmayer et al., 1990; Anderson et al., 1991). Secondly, one twin having a chromosomal anomaly is more probable than the probability of both twins being affected (Table 1), which raises the discussion with the parents about a selective continuation before performing an invasive prenatal procedure. The parents must be informed about the possibility of losing the unaffected fetus. Selective termination of an anomalous fetus in a multiple pregnancy is considered ethically appropriate by most health care professionals, ethicists and clergy (Evans et al.,1991).

Another aspect of prenatal diagnosis in multiple pregnancies is the identification of either fetus. The use of intra-amniotic dye (methylene blue during the first years of amniocentesis, later Indigo carmin) is recently abandoned in our centre because an association was demonstrated between fetal exposure to methylene blue and intestinal obstruction (Nicolini and Monni, 1990; van der Pol et al., 1992). Identification of the amniotic sacs is presently made by ultrasound only. Transabdominal chorionic villus sampling in twin pregnancies was started in 1988 in our centre, at first in patients with high genetic risks and later also in older women. TACVS offers advantages over amniocentesis because selective reduction early in pregnancy gives less complications than a selective feticide in the second trimester (Berkowitz et al., 1988).

In this chapter we present the Rotterdam experience with prenatal diagnosis in dizygotic twin pregnancies of older women during the period 1980-1990 (5.1).

In sub-chapter 5.2 a quantitative assessment of the risks and probabilities of the pregnancy outcome with and without prenatal diagnosis in twin pregnancies are discussed.

Table 1. Rate of Down's syndrome (DS) and all chromosome anomalies (ACA) in dizygotic twins at amniocentesis.

maternal age (years)	One fetus affected %	No fetus affected %	Both fetuses affected %	
36	DS	0.99	99.00	<0.01
	ACA	1.98	98.01	0.01
37	DS	1.27	98.72	<0.01
	ACA	2.41	97.57	0.01
38	DS	1.61	98.39	0.01
	ACA	2.92	97.06	0.02
39	DS	2.06	97.93	0.01
	ACA	3.61	96.35	0.03
40	DS	2.62	97.36	0.02
	ACA	4.49	95.45	0.05
41	DS	3.32	96.65	0.03
	ACA	5.69	94.28	0.08
42	DS	4.23	95.73	0.05
	ACA	7.13	92.74	0.14
43	DS	5.33	94.60	0.07
	ACA	8.59	91.20	0.20
44	DS	6.72	93.16	0.12
	ACA	9.50	90.25	0.25
45	DS	8.45	91.35	0.20
	ACA	11.63	87.98	0.38
46	DS	10.55	89.13	0.31
	ACA	14.21	85.19	0.59
47	DS	13.09	86.42	0.50
	ACA	17.36	81.72	0.92

Based on Ferguson Smith, 1983.

5.1 The Rotterdam experience.

In this sub-chapter all pregnancies of women of advanced maternal age in which prenatal diagnosis had been performed between the 1st of january 1980 and the 31st of december 1990 are presented. The following subjects will be discussed:
a) maternal age; b) fetal loss below 28 weeks of gestation; c) the incidence of congenital anomalies; d) cytogenetic results.

All amniocenteses were carried-out between 164 and 175 weeks. A 20 gauge 3.5 inch needle was used. Twenty ml of amniotic fluid was drawn from either amniotic sac for karyotyping and alphafetoprotein (AFP) assays.

All TACVS procedures were performed with a 20 gauge needle without stylet (TSK Supra) under continuous ultrasound guidance (sub-chapter 2.3).

Diamniotic twin pregnancies of 150 women of advanced maternal age were monitored. TACVS was performed in six twin pregnancies. In the remaining 144 twin pregnancies amniocentesis was performed. Table 2 provides the fetal outcome of twin gestations after amniocentesis.
Details of 8 pregnancies ending in abortion before 28 weeks are given in table 3. None of these fetuses displayed congenital anomalies. In three pregnancies trisomy 21 was diagnosed in one twin.

Table 2. Fetal outcome after amniocentesis in 144 twin pregnancies.

	N (%)
Spontaneous loss of pregnancy <28 weeks	8 (5.6)
Discordant results with subsequent selective abortion	3 (2.1)
Congenital abnormalities (percentage of infants)	5 (1.7)

N=number of pregnancies

Table 3. Characteristics of eight twin pregnancies resulting in premature delivery after amniocentesis.

Case no.	maternal age years	parity	gest.age at delivery (weeks)	complicating factors
1	37	primi	20	-
2	40	multi	20	cervical incompetence, stitch
3	38	multi	24	PROM at 17 weeks
4	37	primi	28	preeclampsia, plac.abruption
5	37	primi	21	PROM at 17^{2} weeks
6	38	primi	19	PROM at 18^{4} weeks
7	36	multi	24	PROM at 17 weeks
8	37	multi	19	PROM at 18 weeks cervical incompetence, stitch

The first case involved a 36 year old primigravida who underwent selective feticide of a trisomy 21 fetus by air embolization at 19 weeks. Premature rupture of the membranes (PROM) occurred at 26 weeks. After a hospitalization of 4 weeks fluid leakage had ceased. A healthy male infant of 2640 g was delivered at 38 weeks. (Pijpers et al., 1989). The second patient was a 38 year-old gravida with a twin pregnancy also discordant for Down's syndrome. At 19 weeks 2 ml potassium chloride was injected intracardially to the affected fetus. The pregnancy continued uneventfully resulting in delivery at term of a 2360 g female infant who is presently doing well. The third patient was a 42 year old gravida who underwent selective feticide at 18 weeks because of discordancy for trisomy 21. Two ml of potassium chloride was again administered intracardially to the affected fetus. The pregnancy was complicated by PROM at 22 weeks, probably because of rupture of the amniotic sac of the dead foetus. At 34 weeks a ceasarean section was performed because of placental abruption. A 1400 g male infant was delivered who is currently doing well.

A congenital anomaly other then trisomy 21 was found after birth in five out of 144 twin pregnancies in which amniocentesis had been performed (288 fetuses).

Two twin brothers suffered from a spastic pylorus. Following surgery they were free of symptoms.

A case of jejunal atresia was established in a 2730 g female infant born at term. This infant had been exposed to dye (Indigo carmin) at amniocentesis. The twin sister (3800 g) showed no congenital anomalies. One male infant was born at term with multiple congenital anomalies after an uneventful IVF twin pregnancy. He had a cheilognatopalatoschizis, absent ear drums and absent eyeballs. The combination of these defects makes Fraser syndrome a likely diagnosis. The co-twin had no anomalies.

The fifth case was a prenatally diagnosed anencephalic male fetus. Because of the possible risks to the remaining twin after selective feticide and because of the lethal nature of the condition we refrained from intervention. The twin was born at 35 weeks. The co-twin weighed 2200 g. and had no congenital anomalies.

The details of the twin pregnancies in which CVS was performed are given in table 4.

Table 4. Fetal outcome in six twin pregnancies after chorionic villus sampling.

maternal age	gestational age at sampling (weeks)	pregnancy outcome
41	12	delivered at 34 weeks; both infants A + W
38	11	IUD at 14 weeks co-twin delivered at term: A + W
37	12	delivered at term: A + W
37	13	delivered at term: A + W
38	12	delivered at term: A + W
38	12	delivered at term: A + W

A + W = alive and well
IUD = intra-uterine death

5.2 A quantitative estimation of the effect of prenatal diagnosis in dizygotic twin pregnancies in women of advanced maternal age.

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Revised form submitted for publication.

Summary.

Counselling of women of advanced maternal age with a twin pregnancy is complicated by the great variety in pregnancy outcome and the various ethical values of the future parents. Twelve possibilities of pregnancy outcome are presented for six age groups between 35 and 45 years of age using data from the literature. Variations in the fetal loss rate after the diagnostic procedure appeared to exert more effect on the fetal outcome probabilities than variations in the fetal loss rate after selective feticide. This study emphasises that the individual circumstances of elderly gravidas influence the decision to undergo prenatal diagnosis in a twin pregnancy.

Introduction.

Centres for prenatal diagnosis are increasingly faced with the problem of prenatal diagnosis in twin pregancies in elderly women, since the incidence of dizygotic twin conceptions increases with maternal age and the number of elderly gravidas is still rising (Stein, 1985; Redwine and Hays, 1986; Pijpers et al., 1989). Prenatal diagnosis in twin pregnancies is technically quite feasible using modern real time ultrasound and its reliability and safety have been demonstrated in many studies (Taylor et al., 1984; Pijpers et al., 1988b; Anderson et al., 1991; Pruggmayer et al., 1992). The most probable abnormal result after prenatal diagnosis in a twin pregnancy is an abnormal fetal karyotype of one of the two fetuses (discordancy). The risk that both fetuses are affected is extremely small (Table 1 of 5.1).

When selective feticide was not yet feasible, most parents elected to terminate the pregnancy if a chromosomally abnormal fetus was found (Redwine and Hays, 1986). Selective feticide at 18-20 weeks is associated with a considerable risk to the remaining twin. Fetal loss rates as high as 25% have been reported (Golbus et al., 1988). The risk appears to be much lower when selective feticide is carried-out at 12-13 weeks (Redwine and Hays, 1986; Berkowitz et al., 1988). Subsequently, transabdominal chorionic villus sampling (TACVS) at 12 weeks became the method of choice

in twin pregnancies in our centre.

Counselling of parents about prenatal diagnosis in a twin pregnancy has to take into account the differences in ethical attitudes of the parents. Some parents may consider the birth of (at least) one normal child as their principal goal. These parents are prepared to accept a certain risk of having one chromosomally abnormal child and do not easily accept the risk of prenatal diagnosis or selective termination. Some of these parents may have been waiting for a pregnancy for years, for instance after infertility treatment. On the other hand, some parents seek prenatal diagnosis because they primarily want to prevent the birth of a chromosomally abnormal infant. For these parents the risk of the diagnostic procedure is of less importance. The parental attitudes may be somewhere in between these two options.

The decisions to opt for prenatal diagnosis may also be influenced by the wish to be reassured about a normal pregnancy which will reduce anxiety during the remaining period of the gestation (Asch et al., 1991).

This paper is concerned with the problem of parental decision-making in relation to prenatal diagnosis in dizygotic twin pregnancies and tries to delineate the different phases and options. Our hypothesis that TACVS is to be preferred because early selective feticide results in less fetal loss of the remaining twin was also tested.

Methods.

The options and effects of transabdominal chorionic villus sampling (TACVS) in a twin pregnancy of a 40-year-old woman are considered. The dilemma is schematically presented in fig. 1. The square at the extreme left denotes the decision whether to perform TACVS or not. It is assumed that if an abnormal fetal karyotype after TACVS is found, selective abortion of the affected fetus and termination of the pregnancy in case of two affected fetuses will be performed.

The pregnancy outcome is defined as the number of infants that is alive just prior to the start of labour (which excludes perinatal deaths) and their karyotypes. The probability of best pregnancy outcome is defined as the sum of the probability of one infant without a chromosomal abnormality and the probability of two infants without a chromosomal abnormality. A summary of the probabilities of events during the course of a twin pregnancy as used in this study is given in table 1. The probabilities of the pregnancy outcomes with and without TACVS can be estimated by calculating the path probabilities of the decision tree in figure 1 (Weinstein et al., 1980).

The prevalence of abnormal karyotypes depends on maternal age. Age-dependent prevalences of chromosomal abnormalities at 10 weeks' and 18 weeks' gestation have been determined in large numbers of singleton pregnancies (Hook et al., 1983; Hook et al., 1988). For a 40-year-old woman, the prevalence of an abnormal karyotype at TACVS at 12 weeks of pregnancy is approximately 3.0%. This is based on linear interpolation of the regression-smoothed age-specific prevalences of abnormal

Table 1. Summary of the probabilities of risks in a dizygotic twin pregnancy up to 28 weeks with and

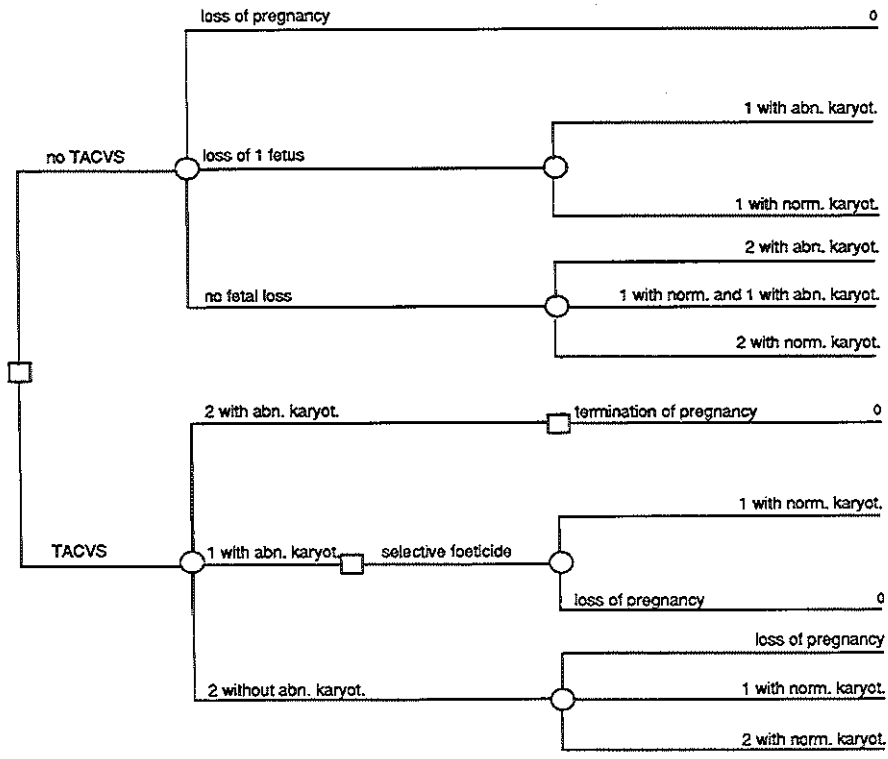

Fig. 1. Decision tree for prenatal diagnosis in a dizygotic twin pregnancy in women of advanced maternal age. The square at the left denotes the choice whether or not to perform prenatal diagnosis. The chance nodes (circles) represent the events that may follow this choice.

without TACVS in a 40-year-old woman, perinatal deaths excluded.

RISKS	PROBABILITY
Abnormal karyotype in one fetus at TACVS	3.0%
Abnormal karyotype in one infant at birth	1.6%
IUD of one fetus	2.5%
Loss of pregnancy with TACVS	7.0%
Loss of pregnancy without prenatal diagnosis	5.0%
Loss of remaining fetus after selective feticide at 12-13 weeks	15%

TACVS : transabdominal chorionic villus sampling.
IUD : intra-uterine death.

karyotypes of 3.1% at ten weeks and 2.3% at 18 weeks of gestation. The prevalence of chromosomal abnormalities in singleton live births at this maternal age is 1.6% (Hook et al., 1983). This percentage is also used in the present study for twin preg-

nancies, although a duration of a twin pregnancy is on average 4 weeks shorter (Pijpers et al., 1988a; Anderson et al., 1991).

We used fetal loss rate data from the multicentre study of Pruggmeyer et al. (1992), because this study provides the most recent and complete results of genetic amniocentesis in twin pregnancies.

In twin pregnancies the spontaneous loss rate of pregnancy after amniocentesis is approximately 5.8% (Pruggmeyer et al., 1992). The spontaneous loss rate after TACVS will be higher, because this procedure is performed earlier in pregnancy. The excess fetal loss following TACVS and amniocentesis, however, is the same (Philip et al., 1991). In singleton pregnancies a pooled estimate of spontaneous loss rate after TACVS was calculated to be approximately 3.3% (Heckerling et al., 1991). A pooled fetal loss rate after amniocentesis in singleton pregnancies was found in this same study to be 2.8%. The difference of 20% agrees with the data from our own centre where we established a fetal loss rate of 1.5% after amniocentesis and of 1.8% after TACVS (Jahoda et al., 1990). Based on this difference the spontaneous pregnancy loss rate in twin pregnancies following TACVS was estimated to be 20% higher than the loss rate of 5.8% after amniocentesis resulting in an approximately 7% loss rate after TACVS in twin pregnancies. Since the excess fetal loss rate with TACVS in singleton pregnancies was recently calculated to be 1% (Philip et al., 1991), we assumed a 2% excess risk in twin pregnancies resulting in a 5% fetal loss in twin pregnancies without prenatal diagnosis. This is in agreement with the 4.6% fetal loss established in twin pregnancies by Prömpeler et al.(1989).

The risk of intra-uterine death (IUD) of one fetus in a twin pregnancy is approximately 5.8% (Pruggmeyer et al., 1992). It is assumed that the risk of spontaneous intra-uterine death of one fetus is not increased by the performance of prenatal diagnosis, only the risk of complete pregnancy loss is raised (Pijpers et al., 1988a; Pruggmeyer et al., 1992). In dizygotic twin pregnancies the risks to the surviving co-twin are very small and therefore not taken into account (Hagay et al., 1986).

Most data on selective feticide at 12-13 weeks of gestation concern multiple pregnancies after assisted ovulation. The risk of loss of the remaining fetus is on average 15% (Loucopoulos and Jewelewicz, 1982; Donner et al., 1990).

TACVS will be considered in this study as a test with >99.5% specificity and sensitivity. This is justified because the results of chorionic villus sampling are highly accurate. In our centre, follow- up of pregnancy outcome revealed no false positive results and no false negative results in 3000 cases, although in some cases villi cultures had to be awaited (Sachs et al., 1990a). Indeterminate results (e.g. chromosomal mosaicism) that necessitated amniocentesis were observed in less than 1% of the analyses.

Results.

The probabilities of the twelve possible pregnancy results with and without TACVS in women with a dizygotic twin pregnancy were calculated with the use of

the data from the literature and our own centre (Methods) in the pathways of fig. 1. The results are presented in table 2. The probability of two infants with an abnormal karyotype and the probability of one infant with an abnormal karyotype (and the co-twin lost) are very low. For a 40-year-old woman, these percentages are 0.02% and 0.04%, respectively. For the computation of these probabilities we assumed that, apart from the incidences of abnormal karyotypes at TACVS and at birth, the risks of TACVS and selective abortion are the same for all ages. The data in table 2 indicate that maternal age has a considerable effect on the probability distribution of pregnancy outcome. For a 35 year old woman the 0.9% risk of a discordant twin is prevented by TACVS with a 2.1% higher probability of complete pregnancy loss. For a woman of 45 years the 9.3% probability of the birth of a discordant twin is prevented with 4.9% higher chance of pregnancy loss.

Table 2. Distribution of pregnancy outcomes* with and without TACVS in women with ages ranging from 35 to 45 years.

age	TACVS	no live infants	1 ak + 1 lost	2 ak	disc. twin	1 nl + 1 lost	2 nl
		%	%	%	%	%	%
35	–	5.0	0.01	0.002	0.9	2.5	91.6
	+	7.1	0	0	0	3.5	89.1
37	–	5.0	0.02	0.005	1.4	2.5	91.1
	+	7.2	0	0	0	4.6	88.2
39	–	5.0	0.03	0.01	2.3	2.5	90.2
	+	7.4	0	0	0	6.1	86.5
40	–	5.0	0.04	0.02	2.9	2.5	89.6
	+	7.5	0	0	0	7.2	85.2
41	–	5.0	0.05	0.04	3.6	2.5	88.8
	+	7.7	0	0	0	8.7	83.6
43	–	5.0	0.08	0.1	5.8	2.4	86.6
	+	8.4	0	0	0	12.8	78.8
45	–	5.0	0.1	0.3	9.3	2.4	83.0
	+	9.9	0	0	0	19.5	70.6

* perinatal deaths excluded. TACVS: transabdominal chorionic villus sampling; ak: abnormal karyotype; nl: normal karyotype ; disc: discordant twin.

A computation was made for a lower fetal loss risk following selective feticide and for a higher risk of fetal loss following TACVS. If the risk of selective feticide decreases from 15% to 5%, the probability of the birth of one or two infants with a normal karyotype increases only from 92.4% to 93.0% for a 40-year-old woman. This means that the 2.9% risk of the birth of a discordant twin is prevented with a 2.0% higher chance of complete pregnancy loss. On the other hand, if the excess fetal loss after TACVS is not 2%, as we assumed in our study but 3%, the probabili-

ty of the best pregnancy outcome decreases for a 40-year-old woman from 92.4% to 91.5%.

In our approach we did not explicitly consider the situation of mosaicism requiring amniocentesis. It can be estimated that this occurrence has only a very small effect on the risk of complete pregnancy loss. Even if mosaicism, necessitating amniocentesis, would occur as often as 10%, the risk of complete pregnancy loss in a 40-year-old woman only increases from 7.5% to 7.6%.

Discussion.

A quantitation of the effect of TACVS on the probability distribution of the pregnancy outcome in women of advanced age was attempted.

Since the birth of one or of two infants with an abnormal karyotype is extremely rare, these pregnancy outcomes are of minor importance in genetic counselling of women with dizygotic twin pregnancies. Parents will consider both the birth of one and of two infants without chromosomal abnormalities as the best pregnancy outcome compared with the other possible outcomes. These considerations imply that the decision whether or not to undergo prenatal diagnosis is for the greater part determined by the probabilities and the parents' attitude towards the relevant pregnancy outcome categories: 1) the birth of one or two infants without chromosomal abnormalities; 2) the loss of the entire pregnancy and 3) the birth of a discordant twin. The desirability of prenatal diagnosis decreases when the parents consider the birth of a discordant twin a less serious event than the loss of the pregnancy. A 35 year old woman may opt for prenatal diagnosis only if she strongly rejects the possibility of discordant twins. However, for a 45 year old woman prenatal diagnosis may be the best option except when she feels that the birth of a discordant twin is not essentially different from one or two infants without chromosomal abnormalities.A 35 year old woman may opt for prenatal diagnosis only if she strongly rejects the possibility of discordant twins. However, for a 45 year old woman prenatal diagnosis may be the best option except when she feels that the birth of a discordant twin is not essentially different from one or two infants without chromosomal abnormalities.

Variations in fetal loss rate after selective feticide has a smaller effect on the probability distribution of pregnancy outcomes than variations in pregnancy loss rate after TACVS. It can therefore be concluded that in centres that have limited experience with TACVS, amniocentesis has a preference over TACVS in twin pregnancies in women of advanced maternal age. In twin pregnancies with high genetic risks TACVS should be considered as the method of choice.

Many future parents learn about the presence of a twin pregnancy during ultrasound at the first visit to a centre for prenatal diagnosis. Therefore, in most instances the counselling will be done by a gynaecologist. A major problem of genetic counselling in twin pregnancies is the large number of possible pregnancy outcomes. A further complicating element in this respect is that parental attitudes towards these outcomes may differ considerably. These factors necessitate a careful individual

evaluation of the attitude of parents towards the effects of prenatal diagnosis. It is insufficient in our view to confine this information to the excess risks of prenatal diagnosis. Providing key information about the probabilities of the pregnancy outcome is the most important element in this process. Considering only three pregnancy outcomes may serve as a starting point of this process of genetic counselling in a dizygotic twin pregnancy.

5.3 Discussion.

Since prenatal diagnostic procedures in twin pregnancies are associated with a higher abortion risk than in single pregnancies and since selective termination in discordant twin pregnancies involves the risk of morbidity and mortality in the remaining co-twin (Redwine and Hays, 1986; Golbus, 1988) counselling of parents needs special attention. The most probable abnormal outcome after prenatal diagnosis in a dizygotic twin is discordancy. The risk that both fetuses are affected is very low in women under the age of 45 (table 1, subchapter 5.1). Before selective continuation became an option in discordant twins, most parents opted for termininations of pregnancy (Antsaklis et al., 1984; Redwine and Hays, 1986). If parents reject the possibility of selective feticide in case of discordancy, and accept one infant with Down's syndrome, as may be the case after a long period of infertility or after in vitro fertilization, the best option is to refrain from prenatal diagnosis because the probability of two affected fetuses is too low to justify TACVS.

The precise risks for the remaining fetus after selective termination is still not well established. Too many different techniques are described in the literature to allow comparisons regarding fetal loss and fetal morbidity. Twelve selective terminations are summarized in one publication from ten different authors, six different methods were used. (Redwine and Hays, 1986). In this group one abortion occurred three weeks after the procedure, three infants were born between 27 and 30 weeks. Two of these died of prematurity. Eight infants (75%) were born between 34 and 40 weeks and are alive and well.

In a series of nine selective terminations in dizygotic twins between 18 and 22 weeks (Golbus et al., 1988) three different techniques were used. Apart from premature deliveries (30.0 - 34.4 weeks) no fetal loss or morbidity is reported.

Larger series of selective terminations concern reduction procedures in multifetal pregnancies after use of ovulation stimulating drugs (Evans et al., 1990). In this series as many as 5/22 (23%) ended in loss of both twins. Seventeen pregnancies progressed to term, two of which resulting in intra-uterine death of one twin. No fetal morbidity was reported.

It is suggested that less complications can be expected when selective termination is carried-out around 12 weeks of pregnancy rather than at 18 weeks or more (Redwine and Hays, 1986; Golbus et al., 1988; Evans et al., 1990), because less necrotic tissue is present in utero. The maternal risks of selective termination are limited. The development of maternal disseminated intravascular coagulopathy

(D.I.C.) when thromboplastic agents from the retained dead fetus reach the maternal circulation has so far only been seen in the second and third trimester after spontaneous fetal demise.

Maternal D.I.C. has not been reported after selective termination (Redwine and Hays, 1986), allthough this complication can theoretically not be excluded. Since maternal D.I.C. is not seen in the first trimester after fetal death it seems advisable to perform selective feticide early in pregnancy.

The other possible hazard to the mother could be the psychological impact of the selective termination. It is understandable that a selective feticide at 18 to 20 weeks is more distressing than at 12 weeks (Theut et al., 1989) since maternal bonding advances with gestational age. As yet we do not know the psychological impact of a continuing pregnancy following feticide of one twin. The grieving process after the loss of a child in the second trimester is comparable to the grieving at the loss of a child born at term (Leon, 1986). The grieving process at the loss of an unborn child that has to be carried until the co-twin is born will be very different from any other situation. Psychological follow up is indicated to estimate the effects of such an experience. In case the situation becomes very confusing to the parents it may be necessary to consult a psychologist, who is experienced in supporting couples after genetic terminations.

Further studies are necessary to evaluate our assumption that early prenatal diagnosis and subsequent early selective feticide will reduce fetal loss and morbidity of the remaining twin as well as maternal risks and anxiety.

General conclusions

In this thesis several aspects of prenatal diagnosis in women of advanced maternal age were studied. The effects of the increasing number of elderly gravidas, the lowering of the maternal age at which prenatal diagnosis became accessible and the introduction of chorionic villus sampling, were evaluated. It appeared that the number of gravidas older than 36 years has been increasing in our region by 0.3% each year since 1984. The yearly increase of women who visited our centre for prenatal diagnosis because of advanced age was higher than 0.3% because also women of 36 and 37 years are entitled to prenatal testing since 1984.

Chorionic villus sampling was introduced in our department at the end of 1983. In 1984 CVS was an established method of prenatal testing. Five years later 50% of the procedures for advanced maternal age and approximately 90% of the procedures for high genetic risks consisted of CVS.

In the early years of CVS most procedures were performed transcervically. Since it appeared that the fetal loss rate was lowest when sampling took place after 12 weeks, transabdominal (TA) CVS in elderly gravidas became the procedure of choice. Notwithstanding the fact that CVS is performed later in pregnancy than in most other centres, many women make the first visit to our centre too late in pregnancy to be allowed a choice between amniocentesis and TACVS. We have come to the conclusion that our efforts to provide information about recent developments in prenatal diagnosis to both the medical profession and to the future parents must continue. Information to ethnic minorities needs special attention since most of these women have a limited knowledge of increased risks for chromosomally abnormal offspring and the availability to detect these abnormalities. Furthermore, most Muslim patients are unaware of the fact that in case of an abnormal result, a first trimester abortion is allowed according to the Koran.

Termination of pregnancy in the first trimester is thought to be less traumatic than in the second trimester. This difference, however, was not expressed by the percentage of women who became pregnant again after a genetic termination of pregnancy. Both women who had undergone a mid-trimester abortion and women who had experienced a first trimester abortion became pregnant again in approximately 40% of cases. Women who lost a pregnancy after prenatal diagnosis had been performed, conceived in approximately 60% of cases. In de latter group there was also no difference between CVS and amniocentesis. Further psychological studies are needed to establish to what extent early termination of pregnancy is less traumatic than mid-trimester abortion.

The difference in reproductive behaviour between those women who experienced a spontaneous abortion and those whose abortion was induced, suggests that it might be more traumatic to decide upon the abortion of a chromosomally abnormal fetus, than it is to experience the spontaneous loss of a fetus after prenatal diagnosis.

The advantage of CVS in obtaining the result early in pregnancy seems more

obvious for the vast majority of women with normal test results since they can be reassured 4-6 weeks earlier than after amniocentesis.

Twin pregnancies in elderly gravidas create a special problem in prenatal diagnosis. When an abnormal result is present, the twin will most likely be discordant for the abnormality. The possibility and risks of selective feticide must be discussed with the parents before an invasive procedure is undertaken. The probability that both fetuses display a trisomy 21 is too low (e.g. 0.02% in a 40-year old woman) to justify prenatal testing. Counselling older women with a twin pregnancy should therefore include assessment of the parental attitude towards a discordant twin.

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Summary

Chapter 1

The objectives of the study, to identify the effects of recent developments on prenatal diagnosis in women of advanced maternal age are presented in this chapter. Pregnancy and its possible complications in older women are reviewed in chronological order, with emphasis on spontaneous abortion and chromosomal abnormalities.

Chapter 2

In this chapter the role of chorionic villus sampling in women of advanced maternal age is discussed. The techical aspects of the sampling procedures are reviewed. Attention is given to the timing and route of CVS, as well as the acceptability and utilization of CVS. The first paper focuses on the safety of TACVS in older women. TACVS is a safe procedure when sampling is carried-out after 12 weeks of pregnancy. In the second paper the effect of maternal and gestational age on pregnancy outcome after CVS is studied. When TACVS in elderly gravidas took place before 12 weeks of pregnancy a fetal loss rate of 5.8% was found; when TACVS was performed after 12 weeks the fetal loss rate was 2.4%. In younger women the timing of sampling did not influence the fetal loss rate.

A yearly increase in the number of CVS procedures is reported both in our region and in the Rotterdam hospitals. These results are presented in the third and fourth paper. It is demonstrated that the uptake of prenatal diagnosis was not affected by the introduction of CVS. In the last paper we will discuss the possible reasons for women to visit our centre too late to have the option of TACVS.

Chapter 3

In this chapter some aspects of abnormal cytogenetic results after prenatal diagnosis are discussed. The methods of second trimester pregnancy termination and first trimester abortion as applied in our department are reviewed.

Continuation of a chromosomally abnormal pregnancy is an exceptional situation. No pregnancy with an abnormal fetal karyotype was continued after CVS, whereas four women continued their pregnancy despite a chromosomally abnormal fetus detected at amniocentesis during the same period. A paper is presented regarding the reproductive behaviour of women who had undergone a genetic termination of pregnancy. Sixty-one per cent of a group of women of advanced maternal age did not become pregnant again following pregnancy termination for genetic reasons. However, all women who achieved a subsequent pregnancy, again underwent prenatal diagnosis.

Chapter 4

The reproductive behaviour of women who lost a pregnancy in which prenatal diagnosis had been performed, is discussed in this chapter.

Fourty-two per cent of a group of women of advanced maternal age did not become pregnant again. Twenty-five per cent of the women who did become pregnant decided against prenatal diagnosis in this subsequent pregnancy.

Chapter 5

In this chapter, attention is given to prenatal diagnosis in twin pregnancies in elderly gravidas. The data of the twin pregnancies between 1980-1990 from our centre are presented.

Since the probability of selective feticide is relatively high and because the risk of the loss of the remaining twin is considerable at 18-20 weeks, transabdominal chorionic villus sampling is considered an alternative. A study is presented regarding the effect of prenatal diagnosis in twin pregnancies on the probabilities of various pregnancy outcomes.

Counselling of older gravidas with a twin pregnancy should concentrate on the attitude of the future parents towards a discordant twin. In some individual cases refraining from prenatal diagnosis may be the best policy when a twin pregnancy has been diagnosed.

Samenvatting

Hoofdstuk 1

Het doel van de studie, het vaststellen van de effecten van een aantal recente veranderingen op het gebied van de prenatale diagnostiek, wordt in dit hoofdstuk uiteengezet.

De mogelijke complicaties van een zwangerschap op oudere leeftijd wordt in chronologische volgorde besproken met de nadruk op het spontane abortus risico en chromosomale afwijkingen.

Hoofdstuk 2

In dit hoofdstuk wordt de rol van de chorion villus sampling bij vrouwen van gevorderde maternale leeftijd belicht. De technische aspecten van de methoden van prenatale diagnostiek worden besproken. Speciale aandacht wordt gegeven aan de timing en de techniek van CVS (transcervicaal of transabdominaal). Voorts wordt gekeken naar de mate waarin CVS geaccepteerd wordt door patienten en verwijzers en op welke schaal CVS wordt toegepast. Het eerste artikel bespreekt de veiligheid van TACVS. Wanneer de ingreep na de twaalfde week werd verricht werd een laag abortus risico vastgesteld. In het tweede artikel wordt het effect van maternale leeftijd en tijdstip van de ingreep op de uitkomst van de zwangerschap bestudeerd. Wanneer TACVS bij oudere zwangeren voor de twaalfde week werd verricht werd een fetal loss van 5.8% gevonden, wanneer TACVS na 12 weken werd verricht was de fetal loss rate 2.4%. Bij jongere vrouwen werd de fetal loss rate niet beinvloed door het tijdstip waarop de ingreep plaats vond. Een jaarlijkse toename van het aantal CVS procedures, zowel in de gehele regio als binnen de Rotterdamse ziekenhuizen, wordt beschreven in het derde en vierde artikel.

Het wordt aannemelijk gemaakt dat de introductie van CVS geen invloed heeft gehad op het percentage oudere zwangeren dat van de mogelijkheid tot prenatale diagnostiek gebruik maakt. Het laatste artikel bespreekt een aantal redenen waarom zoveel vrouwen te laat in de zwangerschap naar onze afdeling komen om nog in aanmerking te kunnen komen voor TACVS.

Hoofdstuk 3

In dit hoofdstuk wordt een aantal aspecten van een afwijkende uitslag na prenatale diagnostiek besproken. De methoden van afbreking in het eerste en tweede trimester zoals die in onze kliniek worden uitgevoerd, worden nader bekeken.

Continuering van een zwangerschap waarin een chromosoomafwijking is vastgesteld is een uitzonderlijke situatie. In de periode tussen 1984 en 1990 continueerden vier vrouwen een zwangerschap nadat bij vruchtwateronderzoek een chromosoomafwijking was vastgesteld. Er werden geen chromosomaal afwijkende zwangerschappen gecontinueerd na CVS. In dit hoofdstuk is een artikel opgenomen waarin onderzocht werd hoeveel vrouwen die een genetische afbreking hadden ondergaan weer

zwanger werden. Van de vrouwen die een afbreking op genetische indicatie ondergingen, werd 61% niet meer zwanger. Alle vrouwen die weer zwanger werden ondergingen prenatale diagnostiek .

Hoofdstuk 4

Het zwangerschapspercentage en de bereidheid om weer prenatale diagnostiek te laten verrichten bij vrouwen die een zwangerschap ongewild verloren na prenatale diagnostiek wordt in dit hoofdstuk besproken. 25% van de vrouwen die weer zwanger werden liet geen prenatale diagnostiek verrichten in de volgende zwangerschap.

Hoofdstuk 5

In dit hoofdstuk wordt aandacht besteed aan prenatale diagnostiek bij tweelingzwangerschappen van oudere zwangeren. De tweelingen van oudere moeders uit de periode 1980-1990 van onze kliniek worden gepresenteerd.

Wanneer een selectieve foeticide verricht wordt bij een discordante tweeling is het risico op verlies van de andere foetus aanzienlijk bij 18-20 weken. CVS lijkt hier een alternatief te bieden. Het artikel dat in dit hoofdstuk is opgenomen bestudeert de invloed van prenatale diagnostiek (TACVS) op de waarschijnlijkheidsfrequenties van de verschillende zwangerschapsuitkomsten bij tweelingen.

De counselling van oudere zwangeren met een tweelingzwangerschap dient rekening te houden met de persoonlijke gevoelens van de aanstaande ouders ten aanzien van discordantie voor een chromosoomafwijking. In bepaalde individuele situaties kan afzien van prenatale diagnostiek bij vrouwen van gevorderde maternale leeftijd met een tweelingzwangerschap de beste keuze blijken.

Dankwoord

Iedereen die heeft bijgedragen aan het tot stand komen van dit proefschrift wil ik graag op deze plaats bedanken.

In de eerste plaats gaat mijn dank uit naar mijn promotor Prof.Dr.J.W. Wladimiroff voor zijn niet aflatende steun en interesse. Ook zijn hulp bij het vertalen naar leesbaar Engels is van grote waarde geweest.

Mijn tweede promotor Prof.Dr.E.S.Sachs ben ik veel dank verschuldigd voor haar waardevolle bijdragen en voor de inwijding in de beginselen van de genetica.

Mijn dank gaat uit naar Prof.Dr.H.Galjaard die door zijn kritische vragen en zijn inspirerende persoonlijkheid een belangrijke invloed heeft gehad op dit proefschrift.

Prof.Dr.M.F.Niermeijer wil ik bedanken voor zijn goede adviezen en het op korte termijn oplossen van mijn vaak brandende vragen. Ik hoop dat we nog lang buren blijven op de D-vleugel.

Voor hun bereidheid zitting te nemen in de promotiecommissie wil ik graag bedanken Prof.Dr.N.J.Leschot en Prof.Dr.C.H.Rodeck.

Veel heb ik te danken aan Dr.M.G.J.Jahoda, initiator van de prenatale diagnostiek in Nederland. Ik ben er trots op dat ik van haar "de prenatale" mocht leren in een bijzonder prettige sfeer.

De collega's van de " 24-ste", Frans Los, Peter in 't Veld, Jan van Hemel, Dicky Halley, Wim Kleijer en Robert-Jan Galjaard, alsmede de analisten (m/v) en secretariële staf ben ik veel dank verschuldigd voor de fantastische samenwerking.

Mijn collega's van de prenatale, Patricia Stewart, Titia Cohen, Rik Quartero, Roger Heydanus en Nicolette den Hollander wil ik graag bedanken voor hun hulp, collegialiteit en bijdrage aan de goede sfeer op onze afdeling.

Bedanken wil ik ook Anne-Marie Westerveld en Edith van Leeuwen voor de assistentie die zij verleenden bij vele honderden ingrepen, waarbij de patiëntes allemaal persoonlijke aandacht kregen.

Ook de collega's van 8-Zuid, Frans Huikeshoven, Kees ten Hoope en de artsassistenten, alsmede de verpleegkundige en administratieve staf wil ik hartelijk bedanken voor hun bijdragen.

Jan van der Meulen van de afdeling klinische besliskunde wil ik danken voor de vele uren die hij besteedde aan mijn ogenschijnlijk eenvoudig beslisboompje over tweelingzwangerschappen.

Theo Stijnen van de afdeling biostatistiek en epidemiologie dank ik voor zijn hulp bij vele van de statistische analyses.

De secretaresses, die voordat ik mijn eigen PC had, veel werk hebben verzet en ook daarna nog onmisbaar bleken wil ik hartelijk bedanken. Eveline François en Sylvia Breur, zonder jullie hulp was het nooit gelukt.

Alle patiënten die op welke wijze dan ook hebben bijgedragen aan de kennis over prenatale diagnostiek op leeftijdsindicatie wil ik graag bedanken.

Lieve papa en mama, het is gelukt je dochters tot zelfstandige vrouwen op te voeden. Bedankt voor alles wat je mij hebt meegegeven.

Lieve Lous, ook jou wil ik graag bedanken. Zonder de stabiliteit die jij in mijn leven hebt gebracht was het allemaal veel moeilijker geweest.

Curriculum Vitae

1952	Geboren te Amsterdam.
1971	Eindexamen HBS-B aan het Montessori Lyceum te Amsterdam.
1978	Artsexamen aan de Vrije Universiteit te Amsterdam.
1978-1979	Assistentschap chirurgie in het Ziekenhuis Amstelveen. (Dr.A.Nederveen).
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1983-1984	Assistentschap gynecologie en verloskunde in het Hippolytus Ziekenhuis te Delft (B-opleiding, Dr.O.J.S. van Hemel).
1984	Inschrijving in het specialistenregister.
1984-1985	Fellowship oncologie in het Antoni van Leeuwenhoekhuis te Amsterdam (Dr.E.Aartsen).
1985-1987	Consultant Obstetrics and Gynecology, Bahrain Defence Force Hospital, Bahrain.
1987-	Gynecoloog in dienst van de Stichting Klinische Genetica Rotterdam (Prof.Dr.H.Galjaard),werkzaam in de prenatale diagnostiek (Prof. Dr. J.W.Wladimiroff) binnen de afdeling gynecologie en verloskunde van het Dijkzigt ziekenhuis, Erasmus Universiteit te Rotterdam (Prof.Dr.A.C.Drogendijk).