

# CLINICAL PRACTICE

## Spontaneous abortion rate and advanced maternal age: consequences for prenatal diagnosis

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**Maternal age related and procedure-related fetal abortion rates were studied in 384 women aged 36 and over scheduled for transabdominal chorionic villus sampling (TA-CVS) at 12–14 weeks of gestation. The pre-TA-CVS abortion rate within 30 days of intake (at 6–10 weeks of gestation) rose from 1.9% at age 35–36 years to 10.9% at 40 years and older. Women entering in the 6th week of gestation had a greater probability of aborting before TA-CVS than women entering after day 48. 26 women aborted spontaneously before TA-CVS, the majority of abortions occurring at 10–12 weeks. TA-CVS was done in 346 women. 11 pregnancies were terminated because of genetic anomalies, and 8 women had spontaneous fetal loss. These findings justify delaying prenatal diagnosis in older pregnant women until 12 weeks of gestation.**

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### Introduction

The primary indication for first-trimester prenatal chromosome analysis is advanced maternal age.<sup>1,2</sup> Jahoda et al<sup>3</sup> found that transcervical chorionic villus sampling (TC-CVS) at 9–11 weeks of gestation was associated with a significantly higher spontaneous abortion rate in women aged 36 and older (7.2%) than in women aged under 36 (2.6%). Whether this higher abortion rate is procedure related or due primarily to a higher baseline rate of fetal loss at advanced maternal age is uncertain. The objective of the present study was to determine maternal age related and procedure related fetal abortion rates in older women scheduled for transabdominal chorionic villus sampling (TA-CVS) at 12–14 weeks of gestation.

### Patients and methods

384 pregnant women requesting first-trimester prenatal diagnosis between January and October, 1988, were included in the study. Admission criteria were: (i) maternal age 36 years or older at 20 weeks of gestation; (ii) a viable singleton pregnancy; (iii) gestational age not beyond 76 days; (iv) no indication for prenatal diagnosis apart from advanced maternal age. TA-CVS was scheduled as an outpatient procedure between 12 and 14 weeks of gestation.<sup>4</sup> After reconfirmation of fetal viability by ultrasound, the skin was disinfected and a 20-gauge needle without stylet was introduced into the chorion frondosum under continuous ultrasound guidance.

No local anaesthetic was used. The needle was attached to a 20 ml syringe filled with 5 ml saline. Chorionic tissue was obtained by moving the needle under continuous suction in a vertical and oblique direction. During each procedure the number of attempts and the amount of tissue collected were recorded. Non-attenders were contacted personally in order to establish the reason for failing their appointment.

In the event of a spontaneous abortion the gestational age at which this had occurred was documented. Continuing pregnancies were followed up by means of a questionnaire about short-term and long-term complications.

### Statistics

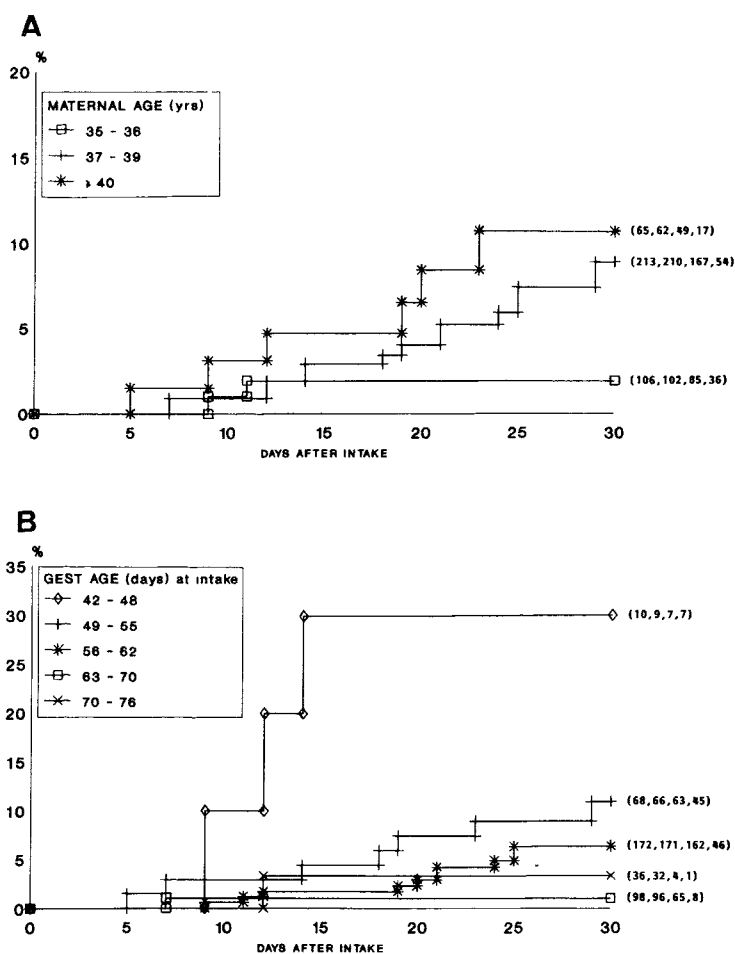
Cumulative percentages of women having a spontaneous abortion while being scheduled for TA-CVS were calculated with life-table methods.<sup>5</sup> The log-rank test was used to compare percentages between the different classes of gestational age and maternal age. In this analysis, women were considered removed from the study as soon as TA-CVS had been completed.

To assess the effect of the TA-CVS procedure on the spontaneous abortion rate, patients themselves partially served as controls. The composition of the control group depended on the variable interval between intake and the TA-CVS procedure. For example, if 2 patients, matched for maternal and gestational age at intake, waited 15 and 20 days, respectively, then the interval between day 16 and day 20 for patient 2 would serve as the control period for patient 1, who by then had already undergone TA-CVS. Cox regression<sup>6</sup> was used to compare abortion rates between those still waiting and those who had already undergone TA-CVS at various points of time. In this analysis the day of gestation at intake was considered the day of entrance into the study. Relative (post versus pre TA-CVS) abortion rates, adjusted for maternal age, were calculated.<sup>7</sup> *p* values given are two-sided. The limit of statistical significance was set at *p* < 0.05.

### Results

Maternal age of the 384 women ranged from 35 to 49 years (median 37 years) and maternal parity from 0 to 6 (median 1). Women were subdivided into five gestational

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Cumulative percentages of women aborting spontaneously while awaiting TA-CVS according to (A) maternal age and (B) gestational age at intake.

Numbers in parentheses denote number of women still being scheduled for TA-CVS on days 0, 10, 20, and 30 after intake.

age classes, 42-48 days ( $n = 10$ ), 49-55 days ( $n = 68$ ), 56-62 days ( $n = 172$ ), 63-70 days ( $n = 98$ ), and 71-76 days ( $n = 36$ ), and three maternal age classes, 35-36 years ( $n = 106$ ), 37-39 years ( $n = 213$ ), and 40 years or older ( $n = 65$ ). 5 women decided against prenatal diagnosis and 7 women did not undergo TA-CVS for technical reasons (retrochorionic haematoma, posterior placenta in a retroverted uterus, vaginal blood loss, HB<sub>A</sub>g positive). These women remained in the study up to the moment of withdrawal or cancellation.

There were 26 spontaneous abortions before TA-CVS. The percentage of women aborting while waiting for TA-CVS increased with advancing maternal age (figure, A). The percentage of women who aborted within 30 days after intake rose from 1.9% in the 35-36 years group to 10.9% in the group aged 40 and older (trend test:  $p < 0.05$ ). Women entering the study between day 42 and 48 of gestation had a greater probability of aborting before TA-CVS than those entering beyond day 48 ( $p < 0.05$ ; figure, B). The same observation was made when the comparison was adjusted for maternal age ( $p < 0.01$ ). No correlation could be established between the incidence of spontaneous abortion and past reproductive performance.

TA-CVS was carried out in 346 women, 6-54 days (median 26 days) after intake. Spontaneous abortion occurred in 6 women between 15 and 29 days after TA-CVS and in 2 women at 66 and 81 days. 11 pregnancies were terminated because of trisomy 21 ( $n = 6$ ), trisomy 18 ( $n = 2$ ), 47, XXY ( $n = 2$ ), or 47, XXX ( $n = 1$ ). The remaining 327 pregnancies progressed uneventfully up to 28 weeks.

CUMULATED NO OF DAYS PATIENTS WERE FOLLOWED AND NO OF ABORTIONS BEFORE AND AFTER TA-CVS FOR EACH WEEK OF GESTATION

Week	Age 35-36 (n=106)		Age 37-38 (n=213)		Age ≥ 40 (n=65)					
	Before TA-CVS		After TA-CVS		Before TA-CVS		After TA-CVS			
	R	A	R	A	R	A	R	A		
6	13	0	..	..	14	0	..	..	..	..
7	95	1	..	..	191	0	..	..	49	1
8	354	0	..	..	743	3	..	..	201	0
9	630	0	..	..	1186	1	..	..	358	1
10	705	1	6	0	1402	3	4	0	411	4
11	615	1	93	2*	1264	5	161	0	370	1
12	260	0	433	1*	500	3	882	2*	157	0
13	59	0	621	1	125	0	1232	2*	46	0
14	8	0	659	1+1*	35	1	1300	1	27	0
15	..	..	658	0	25	0	1299	1	11	0
16	..	..	658	0	8	0	1299	1	..	..
17	..	..	658	0	..	..	1291	1	..	..
18	..	..	658	0	..	..	1288	0	..	..
19	..	..	658	0	..	..	1288	0	..	..
20	..	..	658	0	..	..	1284	1	..	..
21	..	..	658	0	..	..	1281	0	..	..
22	..	..	659	0	..	..	1281	1	..	..
23	..	..	658	0	..	..	1274	0	..	..
24	..	..	658	0	..	..	1274	0	..	..
Total abortions	3		2+4*		16		6+4*		7	

R = Total no of days patients were monitored during a particular week of gestation.  
A = no of abortions

\*Induced abortions after TA-CVS

Subsequently, 1 woman suffered unexplained intrauterine death near term and 2 women were lost to follow-up.

The table shows the numbers of spontaneous and induced abortions before and after TA-CVS for each week of gestation in relation to maternal age. The women appeared to have a smaller risk of spontaneous abortion after than before TA-CVS, resulting in a maternal-age-adjusted relative abortion rate (post versus pre TA-CVS) of 0.10. This result, however, is severely biased because of the removal from the study of all chromosomally abnormal fetuses after TA-CVS. If all 19 abortions after TA-CVS are considered to have occurred spontaneously, the procedure led to a maternal-age-adjusted relative abortion rate of 1.66 (not statistically significant). Additional adjustment for gestational age at intake resulted in a relative abortion rate of 1.56.

Chorionic villus tissue was obtained after one sampling attempt in 307 women, including the 8 with spontaneous abortion after TA-CVS. In 1 woman the procedure was abandoned after one attempt, and a successful amniocentesis was carried out at 16 weeks. Two samplings were carried out in the remaining 38 women.

## Discussion

The safety of first-trimester invasive procedures has been assessed against the background risk of spontaneous abortion. Incidences of 2.1% and 3.3% have been reported.<sup>8,9</sup> However, the percentage of women of advanced maternal age in these studies was always less than 9%. Maternal age groups were differentiated in one study,<sup>9</sup> but the number of older women (over 40 years) was too small to allow any definite conclusions. The increase in chromosomal anomalies with advancing maternal age is more pronounced in populations undergoing CVS than in

populations referred for amniocentesis.<sup>10</sup> This strongly suggests a maternal age dependent rise in fetal loss rate between 9 and 16 weeks of gestation. Moreover, the incidence of chromosomally normal abortions also rises with advancing maternal age, with a steep increase after 36 years.<sup>11</sup>

The present study confirms that there is a steady increase in early loss of a previously viable pregnancy with advancing maternal age. This must be taken into consideration when planning first-trimester chorionic villus sampling in older women. Our study suggests that at advanced maternal age the risk of spontaneous abortion of a previously viable fetus in the first 12 weeks of gestation is greater than the chance of live birth of an infant with a chromosomal anomaly.

The decline in abortion rate is more pronounced between 6 and 7 weeks of gestation than later. The increased abortion risk for women entering the study in week 6 could be explained by the apparently high initial abortion risk for these women during weeks 7 and 8. At that time the abortion rate was 0.024 (3/124) abortions per day, whereas during the same period the abortion rate for women entering the study during week 7–8 was 0.001 (2/1509) abortions per day. This reduction in abortion rate is probably influenced by the ultrasound examination carried out at the intake visit. The exclusion, at that stage, of all non-viable pregnancies would explain the low abortion rate in patients entering during week 7–8.

A relation between gestational age at intake and abortion rate has also been observed in other studies in which early fetal viability was documented by ultrasound.<sup>12,13</sup> The only maternal age dependent data on fetal loss rates at given gestational periods presented in life-table style<sup>14</sup> were based on a cross-sectional study design and are therefore difficult to apply to a cohort under observation at a given stage of pregnancy. Moreover, in that study fetal viability was not verified by ultrasound. From the present study it has also become evident that a considerable number of pregnancy losses before TA-CVS occurred at 10–12 weeks of gestation. This coincides with the period surrounding the TC-CVS procedure and explains the relatively high spontaneous fetal loss rate after TC-CVS in the advanced maternal age group.<sup>3</sup>

In contrast to Regan,<sup>15</sup> we were unable to establish any relation between spontaneous abortion rate and past reproductive performance. This may be because non-viable pregnancies were disregarded in the present study: 50% of the spontaneous abortions in Regan's study would have fallen into this category.

We found no evidence for any adverse effect of TA-CVS on the abortion rate. The abortion rate after TA-CVS was not significantly higher than that before the procedure, even if it is assumed that all abortions would have occurred spontaneously. However, when all diagnosed chromosomal anomalies were excluded, the spontaneous abortion rate before TA-CVS was considerably higher than that observed after the procedure.

We suggest that these findings justify late first-trimester chorionic villus sampling in women of advanced maternal age because the spontaneous abortion rate and the procedure related abortion risk do not exceed the risk of fetal chromosomal abnormality. At 12 weeks of gestation termination is still feasible as an outpatient procedure. This approach will also be more cost effective, since a number of affected fetuses diagnosed early in the first trimester most likely would have aborted spontaneously by this time.

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## From The Lancet

### Health service reforms

Amongst the numerous evils which have been engendered by the Act of 1815, not the least obnoxious is the unnatural connection thereby formed between the science of medicine and the trade of the shopkeeper. It may, possibly, have been intended by the framers of that Act, that the apothecary who keeps an open shop should confine himself to the sale of medicines and other appurtenances of his art; but, as the Apothecaries' Company was founded on a radically false principle, so has every one of its acts, and all the consequences, tended to nothing less than the degradation and ruin of the profession. The occupation of the medical man should simply consist in the exercise of knowledge, and the administration of remedies. The instant that he encroaches on the domain of others, by keeping an open shop, for the sale of goods, he loses a great portion of the respect which naturally attaches to his profession, and is led, by the force of circumstances, to the committal of various acts that are totally inconsistent with the dignity of his calling. We would cite numerous examples of this fact, were it not too disagreeable a subject to dwell on.

(January 11, 1840)