Assessment of the early risks of chorionic villus sampling

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A study was carried out to develop proficiency in performing chorionic villus sampling (CVS) and to determine whether the risk for miscarriage was so high as to preclude a randomized clinical trial comparing CVS with amniocentesis. A total of 202 women who had decided to have induced abortions volunteered to either undergo CVS (101 women) or be a control (101). There were no differences between the two groups in factors that may affect the rate of miscarriage. CVS was performed an average of 9.8 days before abortion. The rate of fetal loss was significantly higher in the CVS group ($p = 0.009$). An analysis of the results as a function of the physician's experience over time showed that there were distinct learning phases. It may take longer than is generally recognized to acquire the expertise necessary to perform CVS with the lowest risk possible. Caution should be exercised before diagnostic CVS is offered to women who plan to continue their pregnancies.

Dans le présent travail, on a pratiqué la biopsie des villosités choriales (BVC) afin d'y devenir plus habile et de savoir si le risque de fausse-couche est si grand qu'il interdise un essai comparatif de cette biopsie et de l'amniocentèse. De 202 femmes ayant déjà opté pour une interruption de grossesse, 101 choisissent de subir la BVC et 101 servent de témoins. Ces deux groupes ne diffèrent pas quant aux facteurs connus de fausse-couche. La biopsie précède l'avortement provoqué de 9,8 jours en moyenne. Le taux de mort foetale est significativement plus élevé ($p = 0,009$) dans le groupe biopsé que chez les témoins. L'analyse des résultats en fonction de la longueur de l'expérience du médecin met en évidence de nettes phases d'apprentissage. Le temps qu'on met à acquérir la compétence nécessaire pour pratiquer la BVC avec le minimum de risques est peut-être plus long qu'on ne le croit généralement. Il faut faire bien attention avant de proposer cette biopsie à la femme qui entend poursuivre sa grossesse.

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Genetic diagnosis in the first trimester by means of ultrasonically guided transcervical passage of a narrow-gauge plastic catheter to aspirate chorionic villi was first reported by Old and colleagues,[1] in 1982. As of August 1985 more than 7100 chorionic villus sampling (CVS) procedures had been performed in continuing pregnancies in 72 centres.[2-5] The main advantage of CVS is that it allows diagnosis in the first trimester: if a fetal abnormality is detected, abortion can be performed earlier than with amniocentesis in the second trimester. CVS will be performed primarily in women aged 35 to 39 years, and less than 1% will terminate their pregnancies.

There are now data that attest to the relative safety of amniocentesis in the second trimester. CVS should be shown to be as safe as amniocentesis before it is advocated as the preferred diagnostic procedure in low-risk pregnancies. One of the important questions to be addressed is the rate of fetal loss attributable to the procedure.

The likelihood of miscarriage varies with such factors as maternal age, length of gestation at the time of the procedure, cigarette smoking and use of alcohol. Since determination of the stage of gestation at which a miscarriage occurs will vary, depending on whether ultrasound is used to ascertain fetal loss, a controlled trial is required to determine which component of an observed miscarriage rate is attributable to CVS. The question of the relative safety and efficacy of CVS compared with amniocentesis ultimately can be answered only through a randomized clinical trial.

Before such a trial, however, a pretest is

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necessary for two reasons: to show that the procedure is not so hazardous that it should not be used in women who intend to continue their pregnancies; and to find the level at which the physician gains sufficient expertise to perform the procedure as safely as possible, so that the results of the randomized trial will not be prejudiced.

We undertook a preliminary study to develop our technical and laboratory competence with CVS and to establish whether the immediate risks of the procedure were so high as to deter us from proceeding with a randomized clinical trial.

Methods

Women who had been counselled and had chosen to terminate their pregnancies for social reasons returned to our clinic for clinical and laboratory assessment and contraceptive counselling. They were asked to participate in the study at that time, which was generally 5 to 14 days before abortion. The women who agreed to take part then chose to undergo CVS or be a control. Fortunately, adequate numbers of women volunteered for each group. The women then underwent a standard interview carried out by experienced senior nurses at the clinic. Information was gathered about the following factors, which may influence the rate of miscarriage: age, last normal menstrual period, parity, outcome of previous pregnancy, education, employment,[6] use of contraceptives in the 3 months before pregnancy, attempt to induce abortion during the pregnancy, cigarette smoking, use of alcohol and complications in the pregnancy. Although the questionnaire was not tested for validity, there was no apparent reticence on the part of the women to discuss smoking or use of alcohol or illicit drugs.

All the women underwent an ultrasound examination; those with an empty fetal sac or no fetal heartbeat were eliminated from the study. CVS was then performed. The women received routine care, and the study did not interfere with the scheduled abortion.

The weight of the specimens was assessed by means of visual comparison with full-scale standard photographs of specimens of known weight prepared in the laboratory. The amount of villi was estimated with microscopy at low-power magnification. The villus material was then separated and processed to obtain direct chromosome spreads by means of standard procedures.[7] Before consenting to CVS women had been told that they would not receive the results.

All of the women were interviewed again immediately before abortion to record complications that had occurred between visits, and another ultrasound examination was done to confirm the presence of a fetal heartbeat and to measure fetal growth.

The study was approved by the Children's Hospital of Eastern Ontario Research Committee and the Ethics Committee of Ottawa Civic Hospital.

Statistical significance was assessed with a two-tailed Fisher's exact test.

Results

A total of 262 women agreed to participate in the study; 19 (7%) were found to have an empty fetal sac or no fetal heartbeat and were eliminated from the study. Of the remaining 243 women, 103 had chosen to undergo CVS and 140 to be controls. Concern that we might disseminate confidential information prevented us from contacting them to remind them of their follow-up appointment. As a result, 39 controls did not appear for the appointment and were eliminated from the study. Of the 39, 36 had induced abortions and 3 continued to term. Only two women in the CVS group were similarly excluded; one did not undergo the second ultrasound examination before her induced abortion, and the other decided to have an abortion sooner elsewhere. Therefore, there were 101 patients in each group.

The demographic characteristics of the two groups were similar, and unpaired statistical analysis did not reveal any significant differences in mean maternal age, length of gestation, socioeconomic status, marital status, parity, frequency of previous induced abortion, cigarette smoking, use of alcohol, use of contraceptives in the 3 months before pregnancy or complications during pregnancy. There were also no significant differences in 5-year age groups, 1-week intervals of gestation at the time of entry into the study or location of the placenta.

There were 10 fetal losses (9.9%) in the CVS group, as determined by absence of fetal heartbeat (in 8 cases) or miscarriage before the follow-up ultrasound examination (in 2). There was one fetal loss (1.0%) in the control group, as determined by absence of fetal heartbeat. The difference was significant ($p = 0.009$).

There was no difference in parity, use of contraceptives in the 3 months before pregnancy, socioeconomic status, frequency of previous induced abortion, smoking or use of alcohol between the women with fetal loss and all those in the CVS group. However, there was a difference in location of the placenta. The observed and expected numbers of various locations were as follows: anterior, 4 and 3.9, posterior, 1 and 4.1, fundal, 2 and 0.1, and cervical, 3 and 1. The difference between the observed and expected values was significant for the posterior site ($p = 0.04$) and the fundal site ($p = 0.02$).

Significantly more women in the CVS group (14) than in the control group (1) reported vaginal bleeding during the follow-up period ($p = 0.0006$) (Table I). The mean length of this period was similar for the two groups (9.8 ± 0.3 days and 9.7 ± 0.3 days respectively), as was the number of

women in each 3-day subdivision of the interval.

No difference was noted in lack of normal fetal growth during the follow-up period between the two groups. This probably reflects the relative insensitivity of ultrasound in detecting growth failure over such a short time.

Since difficulties and complications with a new procedure are most likely to occur when it is first used, and its risks may decrease with time, the results were analysed as a function of experience over time. CVS was performed by two physicians. Over the same time, physician 1 performed 74 procedures, and physician 2 performed 27. Physician 1's procedures were divided into three successive periods (Table II). This person tended to obtain larger samples and to require fewer attempts as he gained experience. However, this did not reflect time-related changes, since physician 2 did not show the same trends. Physician 1's ability to obtain samples that could be karyotyped also increased with experience. This did not reflect laboratory experience, since the technologists had consistent results throughout the study period when given a minimum of 5 mg of villus material.

Of the 10 fetal losses in the CVS group, 8 occurred after each physician had gained experience from performing the procedure in 24 women who later had induced abortions. Seven occurred after the procedures performed by physician 1 in period 2 (Table II). During this period he was obtaining more consistent samples but still often required more than one attempt.

The data for physician 1 were examined to determine whether there was a relation between length of gestation, number of attempts required, number of samples that could be karyotyped, mean weight of villi and rate of fetal loss. There was no difference in the number of samples that could be karyotyped between the samples obtained before 8 weeks' gestation and those obtained thereafter. The rates of fetal loss after procedures performed before and after 8 weeks' gestation were 19% and 8% respectively; the mean sample weights were 14.9 and 18.6 mg respectively. Although these differences were not significant, the results support the current practice of performing CVS after 8 weeks' gestation.

Table I—Reported complaints during the follow-up period in the women who underwent chorionic villus sampling (CVS) and in the controls

Complaint	No. of women: CVS group (n = 101)	No. of women: Control group (n = 101)
Vaginal bleeding	14	1
Cramps	10	6
Vaginal discharge	3	2

Discussion

In our study the women who underwent CVS had a significantly higher rate of fetal loss during the follow-up period than those in the control group. The major factors that may affect the rate of miscarriage were similar in the two groups. In addition, all the pregnancies were judged to be normal on the basis of results of ultrasound examination, and none of the women reported that they had attempted to terminate the pregnancy. The rate of fetal loss in our control group was comparable to that expected in pregnancies con-

Table II—Results of CVS

Result	Physician 1: Period 1 (n = 24)	Physician 1: Period 2 (n = 24)	Physician 1: Period 3 (n = 26)	Physician 2 (n = 27)
	No. of procedures			
No. of attempts required per procedure				
1	4	11	17	6
2	11	9	5	8
3	9	4	4	13
	Mean no. of attempts per procedure			
	2.2	1.7	1.5	2.3
	No. of procedures			
Amount of villi obtained (mg) per procedure				
≤ 5	15	8	3	14
6–10	3	2	2	4
> 10	6	14	21	9
	Mean amount of villi obtained per procedure, mg			
	7.1	21.2	28.0	11.1
	% of samples			
Karyotype obtained	50.0	91.7	100.0	70.4
	No. of losses			
Fetal loss after CVS	2	7	0	1

firmed by ultrasonography at the same time of gestation.[8,9] It is therefore reasonable to conclude that CVS can cause significant fetal loss immediately after the procedure, even when there is no evidence of puncture of the chorionic membrane. There is no apparent reason to expect a different result if CVS were performed under similar conditions in women between 35 and 39 years of age, although the background rate of fetal loss might be higher.

In the CVS group, location of the placenta was the only variable that differed significantly between the women with fetal loss and those without. The small numbers preclude any firm conclusions, but fundal location may present difficulty simply because of the limited length of the catheter and the distance from the physician. The cervical location was somewhat overrepresented and could carry more risk because of proximity to where the catheter enters and a more direct angle of approach. This question merits close scrutiny as larger numbers of women are studied.

Our rate of fetal loss is not without precedent, but in certain experienced hands the rate is significantly less than 9.9%. In centres where over 300 procedures have been performed, fetal loss rates in continuing pregnancies are generally lower than those in less experienced centres, and rates are often highest in centres just beginning to offer the service.[5] Our study provides useful information concerning this risk. Most centres gain initial experience in pregnancies that are to be terminated and then perform CVS in continuing pregnancies once a certain level of success in obtaining villi is reached. Before our study, CVS had been performed in 17 women immediately before scheduled induced abortion, with a high rate of success in the later cases. Once the study began, the success rate immediately decreased to 50%; we attributed this decrease to hesitancy on the part of the physician because, for the first time, the possibility of causing a miscarriage was a concern. In period 2, physician 1's rate of success increased to 92% because of more aggressive puncture of the chorion frondosum. However, there was an unacceptably high rate of fetal loss. In period 3 the success rate was 100%, and there were no fetal losses.

The standard criteria for offering diagnostic CVS generally include a specific rate of success in obtaining villi (e.g., 25/30). Physician 1's results in period 2 clearly show that one can be successful in obtaining tissue and still have a high rate of fetal loss. There is therefore a possibility that current criteria for offering diagnostic CVS may result in unnecessary fetal loss and, furthermore, may prejudice the results in the initial stages of a randomized trial comparing CVS and amniocentesis. Although some obstetricians may have the opportunity to gain adequate experience by performing CVS at the time of induced abortion, perhaps at experienced centres, the patients are often under general anesthesia; this may preclude comparison of results with those of the diagnostic situation.

We believe that our approach has the advantage of ensuring adequate proficiency and safety before CVS is offered to women who plan to continue their pregnancies. Since a woman might decide to continue her pregnancy after undergoing CVS in a study like ours, it is still necessary to have an initial trial period of sampling at the time of induced abortions. However, this risk should be small if patients are selected carefully. The alternative, in many cases, is to begin offering CVS to women who plan to continue their pregnancies before an adequate level of proficiency is attained. It may take far more time to become proficient at CVS than to become successful at obtaining villus material.

Conclusion

Our study was intended as a preliminary assessment of the possible risks of CVS. We have shown that there can be significant loss due to the procedure. In addition, it may take more time to acquire expertise in CVS than is generally recognized. The final answer as to the efficacy and safety of CVS as compared with amniocentesis must await the results of a randomized trial.

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