

## CYTOGENETIC EVALUATION OF 1000 CASES OF CHORIONIC VILLUS SAMPLING

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**Background:** Chorionic villus sampling (CVS) is used routinely as a first trimester diagnostic procedure for fetal karyotyping in at-risk pregnancies. The success of the procedure is dependent on the experience of the operator performing it. The objective of this study was to determine the relationship between an operator-controlled clinical and laboratory setting and the safety and reliability of CVS service.

**Patients and Methods:** One thousand patients had a CVS procedure for a variety of indications, such as advanced maternal age, previous child with chromosome abnormality, etc. Both transcervical and transabdominal procedures were performed, according to placental location and uterine environment. For cytogenetic diagnosis, direct and short-term cultures were set up according to standard laboratory protocol.

**Result:** Cytogenetic results were obtained in 99.6% of studies with 94.5% normal (46,XX or 46,XY), with the remaining having a variety of numerical and structural chromosomal abnormalities. Maternal cell contamination was found in 2% of the first 262 cases, while the overall rate observed in the 1000 samples was 0.5%. Level II mosaicism was observed in 0.8% and level III mosaicism observed in 0.9% of cases, respectively. The overall rate of pregnancy loss of chromosomally normal pregnancies within 28 weeks of gestation was 2.8%. No limb reduction defects were seen in any infant post-CVS.

**Conclusion:** Our record demonstrates that experienced operators can deliver a safe and reliable CVS service. *Ann Saudi Med 1998;18(6):506-510.*

**Key Words:** Chorionic villus sampling, karyotypes.

Chorionic villus sampling (CVS) for first trimester fetal karyotyping is now a routine diagnostic procedure in at-risk pregnancies. A number of large collaborative studies throughout the world have documented the safety of the CVS procedure.<sup>1-5</sup> However, Ledbetter et al.<sup>3</sup> observed a nonsignificant increase of 0.5% to 0.8% in pregnancy loss rate in the CVS group compared to the amniocentesis group.<sup>3</sup> Contradictory findings of limb reduction associated with CVS have also been reported.<sup>6-9</sup> Based on the current data, it has been determined that CVS performed after 10 weeks of gestation, in the first trimester, is a safe, accurate and reliable prenatal test for detecting cytogenetic abnormalities.<sup>10</sup>

In the present study, we report our experience of 1000 CVS procedures performed in an operator-controlled clinical and laboratory setting. There were only two operators who performed the CVS procedures throughout

this study, with a single ultrasonographer. The CVS specimens were processed in the laboratory by the same small staff throughout the study.

### Patients and Methods

#### *Patient Preparation*

Prior to the physician entering the room, an initial ultrasound scan confirms fetal viability and number, gestational age and placental location, and assesses the uterine environment for the presence of any structural factors which may interfere with the procedure. The patient is asked not to void, so that the fluid in the bladder may be used as an angling tool for the position of the

TABLE 1. Summary of 1000 CVS procedures performed at the Genetic Institute of Florida (GIF).

Total CVS	TA	TC	CVS failed	Total pregnancy loss		Follow-up obtained
				SAB	TAB	
1000	446 (44.6%)	554 (55.4%)	2: no sample (0.20%); 2: no growth (0.20%)	28 (2.8%)	27 (2.7%)	1000

TA=transabdominal; TC=transcervical; SAB=spontaneous abortion; TAB=therapeutic abortion.

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placenta. The route of access for the CVS procedure, i.e., transcervical or transabdominal, may be influenced by the presence of pathogens, such as gonorrhea, chlamidia, and active herpes. In such cases, the transabdominal approach is done by using a 19 gauge, 3 1/2" needle that has been prepared with a heparin solution to prevent clogging. The total biopsy time is 5-7 seconds. With a transcervical CVS, a special Trophocan CVS catheter (26 cm) made by Portex is used, with an approximate sampling time of 10-12 seconds. Throughout the entire procedure, ultrasound visualization is constant. For the technically difficult procedure, certain efforts were employed to alter the placental angle. The most common method used in this study was to change the volume of urine in the patient's bladder to make the angle more favorable, and myometrial contractions were used to advantage to reshape the uterine wall behind the placenta. These may occur every 20-30 minutes. When a cervical CVS is preferred and if the initial angle is too steep for a smooth insertion of the catheter, a tenaculum may be used to grasp and gently pull the cervix in order to straighten the uterus. Maneuvering the speculum may also enhance the angle of entry. In cases where a cervical CVS is contraindicated and uterine or placental position are not optimal for an abdominal approach, digital manipulation of the uterus can be helpful in holding it in a more suitable position for the catheter.

After the CVS was successfully completed, the uterine environment was again assessed for the presence of any placental separation or hemorrhage. The fetal heartbeat was reconfirmed. The patients' tolerance was usually very good, with a majority of the patients able to leave immediately with few restrictions. Information on the outcome of the pregnancy was obtained on 95% of the patients from a questionnaire which was sent to the referring physician before the expected delivery date, or by telephone contact if this was not returned. Data was collected on fetal sex, birthweight, and congenital malformations. Statistical comparisons were made by chi-squared test, and a P-value of less than 0.05 was considered significant.

**Laboratory Procedure**

As a general laboratory policy, 20 mg or more of chorionic villi were requested, however, smaller amounts (2 mg-5 mg) were also processed. As soon as the sample was received in the laboratory, the villi were separated meticulously from the maternal decidua under a stereomicroscope. After separation, villi were processed for both direct (24-48 hours) and short-term (5-8 days) culture analysis, using a standard laboratory procedure. Briefly, for direct analysis, one-third of the villus sample was transferred into a 35-mm sterile Petri dish containing 3 mL of 50:50 mixture of Chang and Ham's F12 complete media with 1-2 drops of colcemid from a 22-gauge needle (stock conc. 10 µg/mL). The villi were incubated for 24-48 hrs at 37°C in a 5% CO<sub>2</sub> and 5% O<sub>2</sub> environment. At harvest, the villi were treated with prewarmed 1% sodium

citrate hypotonic solution for 20 minutes at 37 °C. The villi were then fixed in a 3:1 methanol acetic acid mixture. After the fixation, the villi were dissociated by a chilled 1:1 aqueous acetic acid solution and slides were prepared by a modification of Simoni et al.<sup>11</sup> The villus cell suspension was spread with a bent Pasteur pipette on a clean slide left at 37°C. The slides were aged at 60°C for one to several days and subsequently GTG-banded for chromosome analysis. A minimum of 4-10 metaphases

TABLE 2. Individual operator's performance in the outcome of CVS.

Operator	CVS performed	Post-CVS loss	P-value	Post-CVS loss with >1 insertion	P-value
A	295	12 (4.06%)		4 (33.3%)	
B	295	7 (2.37%)	0.24	1 (14.28%)	0.35
B	Next 410	6 (1.21%)			

TABLE 3. Number of post-CVS pregnancy losses in 1000 samples.

Case TA/TC	Gestation age	Result	Loss
7 TC/TC (twins)	11W4D	46,XY; 46,XY	SAB 20W
33 TC	11W	46,XX	Miscarriage 18W
74 TC	10W6D	46,XY	IUFD 27W
135 TC	10W	46,XY	Miscarriage 15W
166 TC	9W1D	46,XY	IUFD 21W
201 TC/TC (twins)	10W5D	46,XX; 46,XY	SAB 16W
208 TC	10W4D	46,XY	PROM 17W
218 TA/TC (twins)	10W6D	46,XX; 46,XY	PROM 23W
317 TC	9W4D	47,XY, +21	Miscarriage post-procedure
332 TA	11W6D	47,XX, +21	Miscarriage 18W
375 TA	9W6D	46,XY	IUFD 20W
443 TC	9W1D	46,XX	SAB 17W
566 TA	10W5D	46,XY	IUFD 17W
852 TC	10W6D	46,XX	IUFD 16W
34 TC	10W	46,XY	14W
78 TC	9W6D	46,XY	12W6D
86 TC	9W6D	46,XX	11W6D
211 TA	11W1D	46,XY	15W1D
216 TC	10W	46,XY	13W
290 TC	9W4D	46,XX/47,XX, +13	12W4D
779 TC	9W	47,XX, +18	10W
803 TC	9W5D	46,XY	13W?
887 TA	11W1D	46,XY	13W1D
911 TA	9W4D	46,XY	13W1D
931 TA	9W6D	46,XX, ((8;10)	13W6D
1046 TA	11W4D	46,XY/47,XY, +21	12W4D
1005 TA	10D	46,XX	15W

TC=transcervical; TA=transabdominal; PROM=premature rupture of the membrane; SAB=spontaneous abortion; IUDF=intrauterine fetal death; W=weeks; D=days.

TABLE 4. Mosaic and non-mosaic chromosome abnormalities observed in 1000 CVS samples.

Cytogenetic diagnosis	Total
Normal	949
Numerical abnormality	
Autosomal aneuploidy	
47,XX or XY, +21	14
47,XX or XY, +18	7
47,XX, +13	1
47,XY, +14	1
47,XY, +16	1
47,XX, +2	1
46,XY/47,XY, +21	1
46,XY/47,XX, +18	1
46,XX/47,XX, +13	1
46,XY/47,XY, +7	1
46,XY/47,XY, +5	1
46,XY/47,XY, +10	1
69,XXX	1
Sex chromosome aneuploidy	
47,XXY	1
45,X/46,XY	2
45,X/46,XX	1
46,XY/47,XXY	1
47,XXY, t(3;5) (q22; q13) mat	1
Structural abnormality	
Balanced	
45,XY, der (13;15) (q10; q10)	1
45,XX, der (15;22) (q10; q10)	1
45,XX, der (14;21) (q10; q10)	1
46,XX, t(8;10) (q24; q24) mat	1
46, XX, t(12;17) (p12; q21) pat	1
Unbalanced	
46,XX, der (21;21) (q10;10) +21	1
46,XY, der (8) t(8;10) (q24; q24) mat	1
46,XX, der (13) t(3;13) (q29; q22) mat	1
46,XX, add (18) (p11.3)	1
46,XX, del (10) (p15)	1
46,X, del (X) (p22)	1
46,XX/47,XX, i(12p)	1
46,XX/47,XX, +mar	1
Total	1000

were analyzed. The direct cultures were used to detect maternal cell contamination, confined placental mosaicism (CPM), and uniparental disomy (UPD).

For short-term cultures, cleaned pooled villi were incubated for 1 hour at 37°C in 1X Trypsin-EDTA solution, followed by a brief wash in HBSS and then incubated in collagenase solution (80-100 U/mL) for 45-60 minutes at 37°C. A minimum of 6-8 coverslips were set up on each sample in 100% Chang media, and a back-up flask was maintained until the case was completed. For cytogenetic diagnosis, 15-20 metaphases were analyzed with the routine GTG-banding technique. To differentiate between levels I, II, and III mosaicism, standard protocol used in amniotic fluid culture analysis was adopted.<sup>12</sup> Briefly, three levels of mosaicism are defined: Level I: a single abnormal cell in a coverslip; Level II: two or more cells with the same chromosome abnormality in a single

coverslip; Level III: two or more cells with the same chromosome abnormality found in multiple coverslips. For normal and abnormal karyotypic designations, the International System for Human Cytogenetic Nomenclature (ISCN) was followed.<sup>13</sup>

## Results

### Sampling Technique

Out of 1000 patients choosing CVS, 86.7% had the procedure for advanced maternal age; 6.6% were referred for a previous child with abnormal chromosome; 3.1% for maternal anxiety. The remaining 3.6% of patients had CVS for various reasons: translocation carrier (0.6%); recurrent abortion (0.5%); family history of mental retardation (0.8%); paternity testing (0.2%); teratogen exposure (0.2%); metabolic disorders (1.3%).

A successful sample was obtained in 996 patients (99.6%). A total of 446 patients (37.47%) underwent transabdominal CVS, while 554 patients (55.4%) underwent transcervical procedure (Table 1). Eleven patients (1.1%) had a second prenatal diagnostic procedure, either due to culture failure or mosaicism, 28 patients (2.8%) had spontaneous losses within 28 weeks of gestation, and 27 cases (2.7%) had a therapeutic abortion due to chromosomal abnormality. Table 2 gives the data on the spontaneous losses, which were mainly due to operator's inexperience. Table 3 summarizes the post-CVS pregnancy loss. Follow-up information after delivery of the child was obtained for 95% of patients. There were no recorded cases of limb reduction deformities in our population.

### Cytogenetic Diagnosis

1) Numerical and Structural Abnormalities: Normal chromosome results were obtained in 949 cases (94.9%). Table 4 summarizes both mosaic and non-mosaic chromosome abnormalities observed in 51 CVS cases (5.1%). Trisomy 16 was observed in one CVS sample, although follow-up amniocentesis revealed a normal chromosomal result with a normal outcome at delivery. In many cases, confirmation studies were performed on the abortus material, with no false-positives observed.

2) Level II and Level III Mosaicism: A total of nine cases out of 1000 samples were observed to show level III mosaicism of both autosomes and sex chromosomes. The results of level III mosaicism are summarized in Table 5. Two of these cases (C41 and C803), one with trisomy 13 and one with trisomy 21 mosaicism, either miscarried or resulted in fetal demise. One case of trisomy 7 mosaicism opted for therapeutic abortion despite reassurance of CPM. In the remaining two cases, one with trisomy 20 and the other with XYY mosaicism, follow-up amniocentesis was not recommended. Both of these cases had a normal outcome at the time of delivery. Table 6 summarizes data on the level II mosaicism observed in eight of 1000 cases (0.8%). In five of these cases, a follow-up amniocentesis

was recommended and the chromosome result in these cases were normal. The pregnancy outcome was also normal in the cases. In two cases of level II mosaics (C793 and C819) follow-up, amniocentesis was not recommended, due to strong suspicion of CPM. Both of these cases had a normal liveborn outcome.

3) Maternal Cell Contamination: Maternal cell contamination (MCC) occurred five times in the first 262 cases, and has not been encountered in the last 738 cases analyzed (0.5% overall). In four of these cases, only a single XX cell was found in XY analysis. Since MCC could not be detected in female fetuses, the overall rate would be twice the rate (0.5%) observed in the male fetuses, i.e., 1.0%.

### Discussion

Chorionic villus sampling was performed either transcervically or transabdominally in 1000 patients by two operators. The low pregnancy loss rate (2.3%) and a high culture success rate (99.6%) in our study is attributed to the coordination between the ultrasonographer, the operator and the laboratory staff.

A total of 28 out of 1000 patients (2.8%) who had CVS lost their pregnancy within 28 weeks of the procedure. These losses consisted of both normal and abnormal chromosome fetuses. Obstetrical problems, such as incompetent cervix, bicornuate uterus, and/or malignant hypertension in some of the patients in this group, may have played a role in spontaneous loss. The loss rate observed in this study is lower than the average loss rate of about 4% cited for CVS.<sup>8</sup> We did not observe any relationship between the loss rate and type of procedure (TA vs. TC).

The authors have observed that the learning curve for each individual physician was different, given the same use of ultrasound instrumentation, ultrasound technician, and the same training protocol for CVS sampling. The training protocol for CVS sampling required each physician to perform CVS on 50 non-continuing pregnancies. The differences observed between the two operators in our study with regard to procedure-related losses clearly indicates that the CVS procedure requires high technical skills. Although the authors failed to observe the difference as statistically significant, our data indicates that lack of high technical skills in CVS sampling may ultimately reflect on factors such as post-procedure loss, number of passes to obtain sufficient sample, sample size and repeat procedure. The importance of a technically skilled operator in the success rate of CVS was also recently addressed in other studies.<sup>14-16</sup>

The cytogenetic analysis success rate of 99.6% obtained in the first attempt is comparable to other reports.<sup>3</sup> Through repeat CVS of failed samplings, the success rate reached 100%. One case of full trisomy 16 without any normal cells was observed, which turned out to be a false-

positive. The follow-up amniocentesis in this case showed a normal chromosomal result with a normal liveborn child without intra-uterine growth retardation (IUGR). This was

TABLE 5. CVS cases with level III mosaicism.

Case #	Cytogenetic result	Follow-up amnio	Outcome
C41	46,XX/47,XX, +13	–	Miscarriage 4 weeks post-CVS
C204	46,XY/47,XY, +7	–	TAB
C214	45,X/46,XY	113 cells 46,XY	Normal male
C188	46,XY/47,XY, +5	53 cells 46,XY	Normal male
C233	46,XY/47,XY, +10	43 cells 46,XY	Normal male
C226	46,XY (long-term culture) 47,XY +20/48,XY, +20, +mar (direct culture)	Not recommended	Normal male
C475	46,XY/47,XYY	Not recommended	Normal male
C803	46,XY/47,XY, +21	–	IUFD 4 weeks post-CVS
C558	45,X/46,XY	23 cells 46,XY	Normal male

TABLE 6. CVS cases with level II mosaicism.

Case #	Cytogenetic result	Follow-up amnio	Outcome
C208	46,XX/47,XX, +13	42 cells 46,XX	Normal female
C514	46,XX/47,XX, +22	54 cells 46,XX	Normal female
C637	45,X/46,XY	20 cells 46,XY	Normal male
C665	45,XX, -19/46,XX	–	Miscarriage
C793	46,XX/46,XX, der (2) t(2;?)	Not recommended	Normal female
C819	45,X/46,XX/47,XXX	Not recommended	Normal female
C146	45,X/46,XX	47 cells 46,XX	Normal female
C779	46,XX/47,XX, +18	31 cells 46,XX	Normal female

clearly a case of CPM with a selective advantage of trisomy 16 cells in vitro. Rare trisomies, such as trisomy 7, 10 and 5, still pose a problem in CVS, although follow-up amniocentesis in such cases has revealed a normal result, proving that such trisomies are mainly confined to placenta. Studies of placental mosaicism and their pregnancy outcome are ongoing to classify these relationships.<sup>17-20</sup>

The incidence of level II and III mosaicism in our study was comparable to that reported in other large CVS collaborative studies.<sup>3-4</sup> Although the incidence of level III mosaicism was much higher than in amniocentesis (0.9% vs. 0.25%), the follow-up normal result with a normal outcome in all 13 cases in our study is reassuring that many of the low-level III mosaic findings in CVS are most likely due to CPM. Nevertheless, follow-up amniocentesis should be recommended in level III mosaic findings in CVS, irrespective of their percentage in the analysis. In our sample, MCC was found to be much lower (0.5%) than reported in other studies,<sup>3,20-22</sup> and the low rate of MCC was independent of the procedure, TA vs. TC. We believe that the laboratory procedure for cleaning the villi is an important factor in low MCC rather than the type of sampling technique, as is suggested in other reports.<sup>3</sup> However, direct CVS culture analysis can be utilized on all

adequate CVS samples to confirm the XX result on cultured villi.

In conclusion, the cytogenetic analysis of 1000 CVS samples in the present study reiterates that CVS is a safe, accurate and reliable first trimester technique for prenatal diagnosis in high-risk pregnancies. The success of the CVS is directly related to the experience of the operator and the laboratory handling of the sample.

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