ORIGINAL ARTICLE

FEASIBILITY AND SAFETY OF TRANSABDOMINAL CHORIONIC VILLUS SAMPLING

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Background: Chorionic Villus Sampling (CVS) is the technique of choice for prenatal diagnosis prior to 12 weeks gestation. The objective of this study was to determine the feasibility, and pattern of complications following first trimester Trans-abdominal Chorionic Villus Sampling (TA-CVS). **Methods:** This was a descriptive study conducted in the Obstetrics and Gynaecology Department Military Hospital (MH) Rawalpindi from Jan 2007 to July 2008. Couples at risk of giving birth to a child with genetic disorder were identified and counselled. Trans-abdominal Chorionic Villus Sampling was done using double needle technique under ultrasound guidance. Immediate and late complications were followed up. Data was analysed using SPPS-10. **Results:** On 200 cases chorionic villus sampling was done as an outdoor procedure. Most common indication was thalassaemia trait 75 (37.5%). Most procedures were done between 12–13 weeks. All placental positions including 104 (52%) posterior and 71 (35.5%) anterior were approachable. Most aspirations were easy, however, in 30 (15%) the aspiration was difficult. Overall success rate was 100%. In 158 (79%) of the cases sample yield was good. One (0.5%) patient had vaginal bleeding and three (1.5%) had placental haematoma formation. Most patients (84%) experienced mild pain during the procedure. The procedure related miscarriage occurred in 2 (1%) patients while another patient developed this complication after 6 weeks. **Conclusion:** First trimester TA-CVS is an accurate and safe invasive prenatal diagnostic procedure. Placentas in almost any position can be approached without any significant risk to mother and the foetus.

Keywords Prenatal diagnosis, thalassaemia, chorionic sampling

INTRODUCTION

Trans-abdominal Chorionic Villus Sampling (TA-CVS) is associated with a lower rate of procedure associated miscarriage than Trans-cervical (TC) and the former is becoming more popular. Chorionic Villus Sampling is the technique of choice for prenatal diagnosis prior to 12 weeks gestation.[1] Chorionic Villus Sampling is performed as an ambulatory procedure.[2] In experienced hands CVS is a safe procedure with overall foetal loss rate of 0.5–1.5%. The data for CVS is inconsistent partly because of the different methods used to obtain chorionic villi.

The most common indication for cytogenetic testing by CVS is an increased risk of foetal aneuploidies due to advanced maternal age, family history, or abnormal first trimester screening for Down's syndrome. Chorionic Villus Sampling has been recommended for prenatal diagnosis in high risk groups by the US Preventive Services Task Force and the Society of Obstetricians and Gynaecologists Canada, in conjunction with the Canadian College of Medical Geneticists.[3] The Cochrane Pregnancy and CDC have also published recommendations on prenatal counselling about CVS that are consistent with these recommendations.[4]

Haemoglobinopathies constitute a major health problem in the Indo-Pak subcontinent.[5] Thalassaemia is the commonest single gene disorder in Pakistan, and each year there are more than 3,500 new affected births.[6] In the absence of any method for achieving complete care and treatment being expensive, prenatal diagnosis and selective termination of an affected foetus is a feasible option to decrease the disease load.[3] National utilisation of prenatal diagnosis for haemoglobin disorders is far lower than expected. A high proportion of referrals are still made in the second trimester and after the birth of an affected child. The findings point to serious shortcomings in present antenatal screening practice and to inadequate counselling resources. The major concern of any prenatal diagnostic procedure is the frequency of procedure associated pregnancy loss. In past 20 years there have been wide discrepancies between quoted risks of invasive prenatal diagnostic procedures. We conducted this study to evaluate the feasibility and safety of TA-CVS.

MATERIAL AND METHODS

This study was conducted at Obstetrics and Gynaecology Department of Military Hospital Rawalpindi in collaboration with Armed Forces Institute of Pathology from February 2007 to July 2008. A total of 200 cases were enrolled using convenience sampling.

Patients included were those having children with thalassemia major, both partners having thalassemia trait, previous history of giving birth to child with Down's syndrome, cystic fibrosis, Duchene muscular dystrophy or haemophilia; and non-viable pregnancy, obvious foetal and placental anomaly, triplet or high order pregnancy, and gestation more than 18 weeks.

Informed consent was taken after counselling. Patient's demographic details, obstetric and family history recorded in a Performa designed for the study. Rhesus status was noted in every case. Ultrasound scan was done to determine the foetal viability, gestational age, number of foetuses, their chorionicity, placental position and the presence of fibroid uterus. For ultrasound guided TA-CVS the needle was inserted using either a free-hand technique. A co-axial chorion biopsy needle set 18G×165 mm outer needle and 20G×200 mm inner needle was used. Once the inner needle was in place, the plunger of the attached 20 ml syringe was pulled back to about 15 ml mark to create a suction force. In case of a poor yield of the sample, a second or rarely a third aspiration attempt was made through the same outer needle left in place. Pain was rated as mild, moderate and severe.

A post-aspiration ultrasound scan was done to see the foetal well being, any haematoma formation, or placental separation. The patient was allowed home 30 minutes to one hour after the procedure. No prophylactic antibiotics were used. Follow-up was done after 1 week at the time of report collection. Miscarriage was defined as loss within 6 weeks of procedure. Rhesus prophylaxis with anti-D immunoglobulin was offered following each procedure in Rh-negative mothers. All patients were examined at the time of report collection for vaginal bleeding or miscarriage. Out of 200 cases, 89 were booked in our unit and had regular follow-up till delivery. Remaining 111 cases were contacted 6 weeks after CVS for any untoward events.

Data was analysed using SPSS-11. Descriptive statistics were applied. Mean and SD was calculated for all quantitative variables.

RESULTS

The total number of cases included in the study was 200 consecutive women in our study, who underwent TA-CVS. Table-1and 2 gives the demographic features of women exposed to CVS. Most patients were from lower classes and had ethnicity of being Punjabi or Pathan.

Indications for CVS are shown in Table-3. Table 3 also shows gestational age as well as placental position. In 85% (170) the aspiration was deemed easy. A good sample was obtained in 158 (79%) cases (Table-4).

In 90% (180) cases, the procedure was successful in the first attempt at aspiration. In only two cases more than 2 attempts were required and the outer needle had to be reinserted. Adverse events were minimal (Table-5), 83% (166) had mild pain at the time of procedure, 99.5% (199) patients had no episode of vaginal bleeding. Only 1.5% (3) women had haematoma formation following the procedure. One sixty-six (84%) experienced mild pain during procedure. Only 1.5% (2) women had a miscarriage following the procedure. Thick abdominal wall and posterior placentas were the main causes of difficulty with procedure. Foetal loss was defined as loss within 6 weeks of procedure and was determined to be 1.5% (3). Out of these 2 (1%) occurred within a week. Out of the total 200 cases 74 (37.5%) foetuses were diagnosed to be suffering from thalassaemia trait. Forty-two (21%) foetuses had thalassaemia major, 50 (25%) of foetuses with no thalassaemia and we picked up 3 cases of Down's syndrome (Table-6).

Table-1: Characteristics of women having CVS

Parameter	Number	%
Age		
19	4	2
20–30	165	82.5
31-40	30	15
>40	1	0.5
Mean	26.97±4.24	
Body mass index		
18.5 to<25	146	73
25 to<30	53	26.5
≥30	1	0.5
Social Class		
Upper	30	15
Middle	52	26
Lower	118	59
Consanguinity		
1st cousin	128	64
2nd cousin	46	23
Distant relatives	6	3
Unrelated	20	10
Background		
Urban	147	73.5
Rural	53	26.5

Table-2: Distribution by education and parity

Educational Status	Number	%
Nil to Primary	82	41
Middle	13	6.5
Matriculation	11	5.5
Intermediate	64	32
Graduate	24	12
Postgraduate	6	3
Parity		
Nil	2	1
1–2	118	59
>2	80	40

Table-3: Indications for CVS, gestational age and placental position

	Number	%
Reason for CVS		
Thalassemia	168	84
Cystic fibrosis	6	3
Down's syndrome	26	13
Gestational age (Weeks)		
10	3	1.5
11	13	6.5
12	60	30
13	64	32
14	28	14
15	12	6
16	15	7.5
17	2	1
18	3	1.5
Placental Position		
Anterior	71	35.5
Posterior	104	52
Fundal	25	12.5

Table-4: Characteristics of CVS

	Number	%
Ease of aspiration		
Difficult	30	15
Easy	170	85
Reasons for difficult procedure (n=30)		
Thick abdominal walls	11	36
Posterior placenta	13	45
Anterior Fibroid	2	06
Anxious patient	4	13
Sample Adequacy		
Good	158	79
Adequate	42	21

Table-5: Procedure related adverse events

Severity of Pain	**Number**	**%**
Mild	166	83
Moderate	34	17
Vaginal bleeding		
Yes	1	0.5
No	199	99.5
Haematoma Formation		
Yes	3	1.5
No	197	98.5
Miscarriage		
Within 7 days	2	1
Within 40 days	1	0.5
No miscarriage	197	98.5
Number of attempts		
1	180	90
2	15	9.5
>2	2	1

Table-6: Final diagnosis as indications for CVS

Final diagnosis	**Number**	**%**
No thalassaemia	50	25.0
Thalassaemia trait	75	37.5
Thalassaemia major	42	21.0
Inconclusive results	1	0.5
Trisomy 21 present	3	1.5
No trisomy 21	23	11.5
No delta 508 mutation	1	0.5
Homozygous cystic fibrosis	5	2.5
Total	**200**	**100**

DISCUSSION

Chorionic villus sampling has emerged as the only safe invasive prenatal diagnostic procedure prior to the 14th week of gestation. Over 2 decades of experience has demonstrated the accuracy, efficacy and safety of CVS.[7]

Majority of invasive prenatal diagnostic procedures in the west are performed for individuals deemed to be at high risk for Down's syndrome. Brambati B *et al* performed CVS on 1,844 women, aged 18–48 years, at 13–20 weeks gestation whose primary indication was chromosomal anomalies and single gene defects in 85% and 15% of cases respectively.[8] In our study majority were done to pick up Thalassaemia Major by TA-CVS to allow timely termination in 1st or early 2nd trimester at a time when privacy is higher. Complication rate along with maternal tension is decreased due to early voluntary termination of pregnancy.[9] Thalassaemia is the commonest single gene disorder in Pakistan, 5–7% of our population (8–10 million) are carrying genes of thalassaemia minor. They do not need blood transfusions themselves but due to by chance marriage of two such persons, they may give birth to a child with thalassaemia major who will need regular blood transfusions for the rest of his life.

There was a very high incidence of consanguineous marriages in the population studied. Regarding ethnicity 100% of Pathan couples were in a consanguineous marriage. May be repeated family marriages through generations caused thalassaemia trait individuals to come together in a marriage. The cases referred for antenatal diagnosis of cystic fibrosis were also Pathans. All the remaining couples had CVS after the tragic birth of a thalassaemia major child. Majority of patients were poorly educated and belonged to lower socioeconomic class. Despite these odds, with proper guidance they made it to a tertiary care centre.

Prenatal diagnosis through early foetal sampling has played a pivotal role in prevention of genetic disorders.[9] Since all sampling procedures are ultrasound guided, therefore these are generally very safe for the foetus as well as the mother. Chorionic villus sampling has given a new dimension to prenatal diagnosis. The best time for CVS appears to be around 12–13 weeks. Most Islamic scholars in Pakistan have a consensus of opinion that Islam permits termination of a pregnancy before 17 weeks of gestation if the foetus is found to have a serious abnormality.[6] Over 90% of the couples are willing to accept the test and terminate the pregnancy before 17 weeks.[6]

Majority (75%) of TA-CVS in our study were performed at 12–14 weeks of gestation like other studies.[10] Most of the studies on procedure related complications of CVS use amniocentesis as a control group. The background risk in cohort of women undergoing CVS will always be higher than in amniocentesis. As amniocentesis is always performed in later gestation the risk of spontaneous miscarriage is lower. There is a considerable source of bias as they are not comparing 'like with like'. Many control studies[11] have taken normal antenatal patients who have had no invasive procedures as a control in an attempt to quantify the background risk.

There was not a single case of failed attempt or inadequate sample at TA-CVS in this study. In large studies the failure rate is 0.07%. The bench mark for proportion of unsuccessful CVS attempts is set at 0.3%. In one case in our study the lady was obese and had multiple fibroids. The difficult CVS finally ended successfully at 35 minutes. Other reasons for difficulty in procedure were an anxious patient and posterior placenta. Unlike other studies[12], we did not find previous caesarean section a risk factor for difficult procedure. The international data on multiple number of needle insertions is heterogenenous varying between 1.4% and 26%. In our study outer needle was only entered >2 times in only 2 cases. Aspiration was done with inner needle twice in 9% and only once in 90% (n=180) of the cases. This data is comparable to a very large study by

Brun JL *et al*[13] from France. They examined 10,741 singleton pregnancies after 11 weeks and concluded that CVS is feasible, accurate and safe[14] in this landmark study. All attempts at sampling were successful except eight (0.07%). The rate of foetal loss at <28 weeks was 1.64% in all pregnancies and 1.92% when CVS was performed before 13 weeks. Advanced maternal age was the single factor significantly associated with foetal loss.[13] We also noted a link between increasing maternal age greater than 30 years and miscarriage. Previous reports on the rates and predictors of foetal loss after CVS has been limited by conflicting rates that have been reported using different definitions of foetal loss and lack of adequate control groups. Loss rate ranging from 0.2–2.6% have been reported. Like most others we did not have a control group. Loss of pregnancy is the most serious complication after CVS. The overall rate of foetal loss is 0.5–2.0%.[14] The result of this study also conforms to other data.

The largest meta-analysis for 29 studies for complications with CVS was performed by Mujezinovic and Alfirevic[10]. The aim of study was to compile a systemic review of complications related to CVS and to provide a benchmark data for counselling and performance and assessment. Pooled pregnancy losses were classified as within 14 days of procedure; within 24 weeks of gestation and/or total. The benchmark was 0.7%, 1.3% and 2%. Our results are at par with these set standards. The meta-analyses was a mix-up of both Transvaginal CVS and TA-CVS. In the study by Odibo *et al*[11] African–American maternal race was linked to foetal loss. In our small study we could not make any association with ethnicity. All three cases of foetal loss belonged to different ethnicity –Punjabi, Pathan and Saraiki. The study[11] also showed link between two or more aspirations/needle insertions. In only one of our three losses there were 2 aspirations. There was also a history of pre-procedural bleeding in one of the cases. The same link has been established by Odibo *et al*[11] in a large case control retrospective study of >5,000 cases over a 16 year that evaluated the rate and risk factors for foetal loss after CVS. Two of the ladies who aborted in our study were >32 years of age which was more than the mean age of the group. This finding is in agreement with Brun *et al*[13] but at variance with Odibo *et al*[11]. The latter group found age <25 years to be a risk factor. Limb reduction defects have been linked to early CVS before 10 weeks of pregnancy and poor technical expertise[15,16] and was not an issue in our study. In order to assess the safety and accuracy of early amniocentesis (9–14 weeks) compared with CVS, the Cochrane Pregnancy and Childbirth Group Trials Register and Cochrane Controlled Trials Register were searched.[4] Combined total pregnancy loss in the early amniocentesis group was 6.2% compared to 5% in the CVS group.

Bleeding and spotting are uncommon and may result due to direct damage to placental edge. Only one patient had an episode of vaginal bleeding which got settled with bed rest whereas up to 6% of cases occurred in studies carried out by Brambati[17], MRC European trial[18], and Jackson[19].

Among women 38 years of age on average, CVS appears to entail a greater risk of foetal loss than amniocentesis. The best estimates come from two recent Canadian and European trials of CVS and amniocentesis.[20–22] The European reported a rate of 9% spontaneous foetal loss before 28 weeks gestation in the CVS group and 6% in the amniocentesis group. The Canadian trial reported a rate of total foetal loss (including induced abortions of 16.9% in the CVS group and of 15.2% in the amniocentesis group. For these two trials, the combined odd ratio for foetal loss before 28 weeks gestation after CVS, compared with amniocentesis is 1.32.

In our study, practically all positions of placenta were sampled without much difficulty, and it was found to be most feasible for use in routine practice.

Only 3 (1.5%) patients had retrochorial haematoma formation which resolved in a few days. No case of infection including chorioamnionitis occurred in our study. In a study by Ahmed H[6] the rate of chorioamnionitis was 0.37%. An estimated 0.8% excess risk for foetal loss associated with CVS compared with amniocentesis did not reach statistical significance.[23–25] Although CVS is more difficult to master than amniocentesis, the risk for foetal loss shrinks as the experience of the practitioner grows.[26,27]

The study by Ahmad H[28] concluded that TA-CVS appears highly effective and safe and might be offered as a valuable alternative to early as well as mid trimester amniocentesis.

Almost all the couples in our study were identified retrospectively when they already had at least one affected child. In communities where family size is small, retrospective identification of the couples and the offer of prenatal diagnosis are unlikely to reduce the incidence of thalassaemia major. By contrast, when final family size is large, retrospective counselling may lead to either cessation of reproduction or prenatal diagnosis and this can reduce the affected birth rate by up to 50%. Further reduction in birth rate of affected children would require prospective identification of at risk couples. There is a need to increase the utilisation of prenatal diagnosis for thalassaemia by addressing various impediments, including lack of awareness, high cost, poor access, delay in seeking help and advice against the test. The study proved that in experienced hands, first trimester trans-abdominal CVS is an accurate and safe invasive prenatal diagnostic procedure.[29]

Wax *et al*[30] carried out a study to assess anticipated and perceived pain associated with TA-CVS.

They concluded that TA-CVS is associated in majority of patients with moderate perceived pain.[30] In experienced hands CVS is a safe procedure. Mild and transient post procedure pain due to uterine cramps is common. Most (83%) of patients in our study had mild abdominal pain following the procedure.

A service for prenatal diagnosis of Beta Thalassaemia was introduced in Pakistan in May 1994. During the first 3½ years of the service, 300 couples requested the test. A total of 319 CVSs were done between 10 and 16 weeks of gestation, 5.4% had a spontaneous abortion within two weeks of the CVS. The children born had no error in the prenatal diagnosis. Now much lower procedure associated miscarriage rates are being offered like in our study. One year after the start of the service, interviews with 141 couples with an affected child showed that 72% knew of the availability of prenatal diagnosis.[6] The main reasons for non-utilisation of prenatal diagnosis were the cost of the test and fear of undergoing the test. This study demonstrates that prenatal diagnosis is feasible and acceptable in a Muslim country such as Pakistan.[28] The same is true for Iran.[31]

Baig SM *et al*[31] conducted a study in southern Punjab to initiate awareness, screening and characterisation of the mutations causing thalassaemia as well as a genetic counselling program mainly in the districts of Faisalabad and DG Khan to establish prenatal diagnosis. A cooperative trend and a positive attitude toward the prevention of beta-thalassaemia were noticed in the families with affected children and in the general population.[31]

The results of our low institution-specific foetal loss, and complication rates are comparable to larger studies of outstanding interest. The gap between CVS and amniocentesis has narrowed to be insignificant in experienced hands[32] provided the operator has required skill. CVS is harder to learn and has a steeper learning curve. In less experienced hands the risks of all procedures can be significant.[33] Patients' decisions are easily influenced by reported risks.

CONCLUSION

First trimester TA-CVS is an accurate and safe invasive prenatal diagnostic procedure at gestation <15 weeks and should be considered the gold standard. When a definitive first trimester prenatal diagnostic test is warranted, the procedure of choice is CVS.

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