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Clinical and laboratory experience of chorionic villous sampling in Nigeria

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Abstract

Background: Chorionic villous sampling is a first trimester invasive diagnosis procedure that was introduced in Nigeria <2 decades ago.

Objective: The objective of the following study is to review experience with chorionic villous sampling in relation to clinical and laboratory procedures, including general characteristics of women, indications and outcome, complications, laboratory analysis and learning curve.

Materials and Methods: Descriptive study of chorionic villous samplings between 2005 and 2012. Clinical and laboratory data were extracted from records. The women had trans-abdominal or trans-cervical procedure after counseling. Deoxyribonucleic acid extraction was by boiling method and molecular diagnosis by restriction fragment length polymorphism or quantitative fluorescence polymerase chain reaction. Analyzed data were presented using simple frequency tables.

Results: A total of 426 women were analyzed. The major indications were Sickle cell anemia (97.2%), gender determination (1.9%) and aneuploidy (0.7%) respectively. Most procedures (71.2%) were done between 11^{+0} and 13^{+6} weeks by trans-abdominal approach (88.7%). Overall success at the first sampling was 98.8%. Error in laboratory diagnosis recorded in 3 (0.7%) pregnancies, while 5 (1.2%) were reanalyzed due to maternal decidua/inadequate fetal sample (0.7%) or failure of amplification (0.5%) respectively. Primary sex ratio was 5 (XY): 3 (XX). Down syndrome was the most common aneuploidy diagnosed with a detection rate of 66.7%. Learning curve was evident from reducing the incidence of abortion, number of aspirations and increasing success at the first attempt and villi yield.

Conclusion: The present study shows acceptance and utilization of chorionic villus sampling and also demonstrates its safety and reliability.

Key words: Chorionic villous sampling, clinical, down syndrome, laboratory, sickle cell disease

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Introduction

Chorionic villous sampling is the gold standard for the first trimester prenatal diagnosis.[1] Ultrasound guided chorionic villus sampling (CVS) for early and rapid antenatal diagnosis of sickle cell disorder was introduced in Nigeria in the early 1990s, with successful implementation in two main centers involved in the procedure.[2-5] Previous publications focused on different aspects of the procedure, with emphasis on its application in the prenatal diagnosis of sickle cell disease. The scope has however gradually increased to include common aneuploidies of autosomes and sex chromosomes, gender determination and rare genetic conditions.

It is estimated that about 25-30% of the Nigerians carry the sickle cell gene and about 100-150,000 children are delivered annually with serious sickle cell disorder.[2,6,7]

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Down syndrome, which is the most common chromosomal abnormality, has incidence of 1 in 865 live births.[8] Unfortunately, genetic disorders such as sickle cell disease are associated with high perinatal, infant and maternal morbidity and mortality. The occurrence of genetic disorders generally places a significant psychological and financial burden on the affected individual, families and the society that has to provide for supportive therapies, rehabilitation and continuing existence.

The determination of the genetic status of the fetus such as hemoglobin genotype or karyotype in early pregnancy using CVS provides an opportunity for the desiring parents to have early trimester termination of severely affected pregnancies or to prepare for the birth of the child. Post natal care is better planned and outcome optimized when the couple have prior knowledge of the presence of a congenital disorder.

CVS yields cells that are rapidly proliferating during culture and also capable of fast replication with polymerase chain reaction (PCR) technology. Its major benefit is that it offers an opportunity for a first trimester diagnosis and decision.[4,5] Although CVS is traditionally believed to imply only the clinical aspect of the procedure, it is however not completed until the samples are analyzed in the laboratory to produce the result. Most recent analyses utilize molecular techniques. The safety and reliability of procedure as well as the accuracy of laboratory results are well-documented, when procedures are performed by experienced operators.[9]

In Nigeria, challenges in chorionic villous sampling could be in the aspect of logistics and manpower. These include molecular laboratory support, trained gynecologist, counselors and equipment. The number of gynecologists and molecular diagnosis centers that offer comprehensive genetic testing is limited, thus contributing to the dearth of studies on this subject.

The need to provide a comprehensive update of the procedure justifies this study, which examines our experience in chorionic villous sampling over 8 years period. It examines the procedure and laboratory protocols, with emphasis on the baseline general characteristics of the pregnancies, indications and outcome, complications, laboratory analysis and outcomes and learning curve. In respect of chromosomal abnormalities, the detection rates and primary sex ratio were discussed. Reference was made to previous publications from the same center.

Materials and Methods

We conducted a retrospective observational study on all women that had CVS at High Rocks Fetal Medicine and Genetic Diagnosis Centre, Lagos, Nigeria between 1st January, 2005 and 31st December, 2012. All procedures were conducted after 11 weeks of gestation in women that fulfilled the inclusion and exclusion criteria. Procedures were performed by a specialist in Fetal Medicine and Genetics, whereas laboratory analyses were done by trained molecular analysts/scientists and counseling offered by genetic counselors.

Study criteria

Included were CVS performed above 11 weeks of gestational, both parents have the A and either S or C allele in their hemoglobin genotype or has a high risk for chromosomal disorder based on nuchal translucency measurements and advanced maternal age. Excluded from the study were plural pregnancies and unresolved vaginal bleeding/blighted ovum.

Ethical approval/consent

Ethical approval for a comprehensive study on chorionic villous sampling was obtained from the ethical committee of the Olabisi Onabanjo University Teaching Hospital, while the management board of High Rocks Fetal Medicine and Genetic Diagnosis Centre consented to the participation of their patients and access to records for the study. All women signed informed consent form after pre procedure genetic counseling.

Counseling

Non directional counseling was offered before (pre procedure) and after (post procedure) the entire process by trained genetic counselor. Pre procedure counseling discusses the mode of inheritance of the condition, the steps in invasive procedures, risks associated with it especially procedure-related miscarriage in the center and globally, reliability of molecular diagnosis and post procedure management options. Post procedure counseling is done after the result is available. It provides further detail on the management options available. This includes guidelines for the care of a child with a particular defect as well as an option of termination, both legal and medical. In both forms of counseling, the couple takes responsibility for the decision made.

Technique

Pregnancy was dated using the last menstrual period or based on the early pregnancy scan. Each woman completed questionnaire containing enquiries about biosocial data before undergoing the procedure.

In all cases, preliminary ultrasound scan was done to confirm viable singleton pregnancy, gestational age, placenta location and any other incidental findings that may impact on the procedure and also to decide on the choice of route of biopsy. The procedures were conducted under continuous ultrasound guidance, ensuring that the tip of the needle is continuously viewed.

In transabdominal CVS, the abdomen skin was routine cleaned with hibitane and draped in the supine position. About 5-10 ml of 1% xylocaine was locally infiltrated into the abdominal wall layers. Two techniques were used during the study period. In the first technique, a minor stab incision was made on the skin, followed by the introduction of the Rodeck's transabdominal biopsy forceps. This involves passing 16-18 gauge trocar and cannula down into the placental tissue, withdrawal of the trocar and followed by the introduction of Rodecks biopsy forceps. The forcep jaw is opened, rotated 360° clockwise and anti-clockwise, closed and withdrawn with the villi grasped. The second technique involves the use of aspiration needles set made up of gauge 16-18 mm trocar and cannula. A 'give sign' signified entry into the placenta tissue. The cannula is withdrawn and replaced with a longer but smaller gauge aspiration needle and stylet (18-20 mm). This was moved to and fro a few times within the placenta before the stylet is removed. A 10-20 ml syringe preloaded with either ethylenediaminetetraacetic acid (EDTA) or heparin was connected to a connection tube which was in turn connected to the aspiration needle. Chorionic villi were aspirated by creating negative pressure.

In transcervical approach, the cervix was exposed with bivalve speculum and held with volsellum while the biopsy retrieval instruments are passed in carefully. The Rodecks biopsy forceps is opened and close as it moves forward and backward in the placenta. All procedures were done under continuous ultrasound visualization with a 3.5-5.0 MHz sector transducer. The women were requested to rest for 30 min and avoid sexual intercourse for 2 weeks.

The retrieved villi were immediately flushed into a petri dish containing EDTA or heparin in saline and examined under low power inverted microscope for confirmation. Maternal decidua was removed with dissecting forceps and cleaner villi transferred into a fresh petri dish, a process repeated several times, until a clean villi sample was obtained. The final clean samples were compared with a reference photographic standard, to derive the wet weight. The sample was analyzed or stored in ultralow freezer (−20°C).

Laboratory analysis

Deoxyribonucleic acid (DNA) was extracted from chorionic villi, maternal and paternal blood samples by boiling method. In this protocol, boiling was used to achieve denaturation of protein in conjunction with trypsin. Molecular analysis was achieved using Amplified Refractory Mutation System PCR for sickle cell anemia (SCA). In this technique, the production of multiple copies of a particular DNA by the PCR machine is prevented when there is no complementary allele and vice versa. This enables a clear distinction between the A and S allele in a given sample. Quantity Fluorescence PCR describes the use of specialized kit that offers molecular assay for the rapid detection of chromosomes 13, 18, 21, X and Y aneuploides by quantitative fluorescent PCR. These chromosomes are identified by the amplification of selected short tandem repeats and the gender determining sequences Amelogenin-SRY.

The sample for Angelman syndrome was analyzed in Europe.

Standard operating procedures were ensured to guarantee quality assurance, accuracy and reliability of results. These included repeated cleaning, washing and examination of samples under a microscope to eliminate maternal decidua contaminants, calibration of equipment especially micropipettes, strict adherence to manufacturers guidelines on reagent storage, handling and preparation and proper documentation. Known samples were used as positive controls for confirmation of results, while negative control was to rule out contaminants. Analysis was repeated where there is ambiguity of results.

Definitions

Bleeding was defined as loss of blood from the sampling site subjectively assessed to be more than 2.5 ml or with clots; blood loss from the cervix that is subjectively assessed to be more than 5 ml. Abortion refers to spontaneous cessation of fetal heart beat after the procedure. Infection was defined as the occurrence of low grade fever without localized uterine or adnexa tenderness. Rupture of membranes is the obvious leakage of amniotic fluid or decreased measurable amniotic fluid on ultrasound examination.

Data retrieval and analysis

Relevant data were extracted from the procedure notes. Pregnancy was monitored through telephone calls, short mail messages and internet mails to physicians and patients. The patients were particularly counseled to notify us of any unusual event. Data were entered into computer software, analyzed and presented as simple frequency tables.

Results

Four hundred and thirty three (two) women were counseled, of which 7 were excluded based on the inclusion and exclusion criteria. These are 3 twin pregnancies, 3 threatened abortions and 1 blighted ovum. The study therefore involved 426 viable singleton pregnancies.

Baseline biosocial and obstetric parameters in the women sampled are summarized in Table 1. About a third (35.4%) of the women were between 26 and 30 years age group, while collectively, those below 35 years were in the majority (70.8%). The maternal age range was 23-47 years with a mean of 30.9 + 3.6 years. Para 3-4 was highest (51.9%) and ≥ para 5 were least (4.5%). Majority of procedures were done between 11 and 13 weeks (71.2%), while 7 (1.6%) were performed after 18 weeks. Christianity was the predominant (83.0%) religion. All of them had

Table 1: Baseline biosocial and obstetric parameters

Parameters	Number (*N*=426)	Percentage
Maternal age (years) (Mean: 30.9, Range: 23-47)		
21-25	39	8.9
26-30	151	35.4
31-35	113	26.5
31-35	88	20.6
>41	36	8.5
Parity (Mean: 3.3, Range: 0-6)		
1-2	186	43.7
3-4	221	51.9
>5	19	4.5
Gestational age (weeks)		
11-13	303	71.2
14-17	116	27.2
>18	7	1.6
Religion		
Protestant	68	15.9
Catholic	102	23.9
Anglican	184	43.2
Islam	51	11.9
Others	21	4.9
Economic level		
Low	42	9.9
Middle	223	52.3
High	161	37.8
Educational level		
Secondary	102	23.9
Tertiary	324	76.1

either secondary or tertiary education and majority (90.1%) were either middle or high income earners.

The most frequent (97.2%) indication was sickle cell disorder in the parents [Table 2]. Fetal hemoglobin genotype distribution after molecular analysis showed that hemoglobin genotype AS was the most common (49.5%), followed by AA (28.5%) and SS (20.3%). AC and SC constituted 1.4% and 0.2% respectively.

The second most common (1.9%) indication was maternal desire to determine fetal gender. 6 out of 8 (75%) women in this group were from the Middle East countries and 2 (25%) were Nigerians. The fetal sexes showed 5 males (XY) and 3 females (XX). Three (0.7%) pregnancies were evaluated for suspected chromosomal abnormality based on the nuchal translucency scan and advanced maternal age/history of Down syndrome in family. Two fetuses with Down syndrome were diagnosed (detection rate = 66.7%). One was in a woman below 35 years and the second woman was above 35 years of age. The one fetus evaluated for possibility of Angelman syndrome was in a 42-year-old woman with previous birth of an affected child. The fetus was unaffected.

Table 2: Indication and outcome of procedure in the fetuses

Indication/outcome	Number	Percentage
Sickle cell disorder	*n*=414	97.2
Fetal outcome		
Hemoglobin genotype AA	118	28.5
Hemoglobin genotype AS	205	49.5
Hemoglobin genotype SS	84	20.3
Hemoglobin genotype AC	6	1.4
Hemoglobin genotype SC	1	0.2
Chromosomal disorder	*n*=3	0.7
Fetal outcome		
Trisomy 21	2	66.7
Trisomy 18	-	-
Trisomy 13	-	-
Gender determination	*n*=8	1.9
Fetal outcome		
Male	5	62.5
Female	3	37.5
Other genetic disorders	*n*=1	0.2
Fetal outcome		
Angelsman syndrome	-	-

AA=118; AS= 205; SS= 84; AC= 6; SC= 1

Table 3 summarizes the complications recorded. Bleeding from the abdominal entry point was the most common (2.1%). In none of these cases was pregnancy compromised. Spontaneous bleeding per vaginam, which ended as abortion within 1 week was reported in 4 (0.9%) pregnancies. Rupture of membranes occurred in 1 (0.2%) case, but pregnancy was carried to term and delivered of a healthy baby.

Table 4 presents the summary of experience with performing CVS over 8 years. The number of procedures was lowest (21 or 4.9%) at inception, but drastically increased to become the highest number/year (87 or 20.4%) in 2008. Thereafter, the number of cases remained at 40-59/year between 2009 and 2012. Transcervical approach was used between 2005 and 2008. All procedures were transabdominal from 2009. The highest proportion (14.3%) of repeat procedure was in 2005. In 2006 and 2008, it was 2.2% and 1.7% respectively. From 2009, the study reported 100% success at first attempt. The mean number of needle insertion in transabdominal procedures is inversely related to the weight of villi. In 2005, average of 5 insertions yielded average of 25 mg of villi, while in 2012, average of 1.5 insertions produced average of 35 mg of villi.

In one of the cases of laboratory diagnosis error, the actual genotype was AC instead of AS. The laboratory procedure was repeated in 5 (1.2%), of which 2 (0.5%) were due to failure of amplification and in three cases, the sample was heavily contaminated with maternal decidua, with inadequate fetal villi present [Table 5].

Discussion

Our series shows that chorionic villous sampling was utilized by the educated and economically advantaged. We have previously reported that provision of subsidy remains a feasible way to facilitate utilization by women in the lower socio economic stratum.[10]

There have been occasional reports of blighted ovum or threatened pregnancy between counseling and procedure as was revealed in this series.[5,11] The possibility of this should form part of counseling. Transcervical approach was discontinued in 2009, partly because of its associated higher risks of abortion and also because of believes that transabdominal approach has a better outcome.[12] This differs from the conclusion of the 2nd International Conference on CVS in Birmingham in 1986, that "the best technique of CVS is not yet agreed".[13] In our series, two different transabdominal techniques were used. The earlier technique using the Rodecks forceps suffered two major disadvantages compared with more recent needles. They were of larger calibers and the tips were non echogenic. The latter needles have increased visibility under ultrasound scan and this is known to reduce the risk of complication.[9] On the contrary, a similar study of over 30 years duration, suggest that techniques does not have any influence on outcome.[1] Evidences from a recent study have been reported to show preference for transabdominal CVS.[12]

The distribution of indications demonstrate the burden of sickle cell disorder, being the most serious single gene defect affecting blacks population[6,14] In Nigeria, about 100-150,000 deliveries yearly are affected with the condition and about 25% of the population carry the trait.[2,3,6] The World Health Organization recommendation in support of prenatal diagnosis also positively influenced the acceptance of CVS in the first trimester as a feasible method of control.[6] In terms of hemoglobin genotype distributions, the study established a pattern that differs from the distribution in the population in south western Nigeria.[7] Hemoglobin genotype SS was more predominant that was reported in the adult population study. This may be explained by the high prevalence of hemoglobin F that has a positive beneficial effect on oxygen carriage and ultimately fetal growth and survival. Hemoglobin genotype AS which was most predominant could be due to heterogeneous genetic advantage conferred by malaria endemicity in the tropics.

There is a general perception that chromosomal abnormality is rare in Nigeria. In the contrary, the incidence of Down syndrome in Nigeria compares with incidences world-wide.[8] The detection rate of 66.7% is not a true representation of the population figure because only a small proportion of high risk pregnancies had CVS. It is however a pointer to what the picture could be in the general population. Religious and socio cultural inclinations often discourage women from finding out the true status of the fetus after being screened positive.[5] In spite of this, the rate is within the range of rates in other centers and therefore strongly supports the introduction of screening and diagnosis in pregnancy in the country.[15-17]

Although only 2 Nigerians did CVS for gender determination, the fact that it was the second most common indication might suggest the importance attached to gender within the Nigerian community. With improved awareness, it is likely that requests for it would increase in future. Our

Table 3: Complications of CVS

Complications	Number (*N*=426)	Route		Percentage
		TA	TC	
Abortion	4	2	2	0.9
Bleeding	9	4	5	2.1
Rupture of membranes	1	-	1	0.2

TA=Transabdominal; TC=Transcervical; CVS=Chorionic villous sampling

Table 5: Laboratory analysis

Parameter	Number (*N*=426)	Percentage
Laboratory diagnosis error	3	0.7
Repeated laboratory analysis	5	1.2
Failure of amplification/PCR	2	0.5
Maternal sample/inadequate fetal sample	3	0.9

PCR=Polymerase chain reaction

Table 4: Summary of experience in performing CVS over 8 years

Year	Number	Route		Repeat procedure (%)	Abortion (%)	Mean insertion	Weight of villi
		TA	TC				
2005	21 (4.9)	17	5	3 (14.3)	1 (4.8)	5.0	25
2006	45 (10.6)	35	10	1 (2.2)	1 (2.2)	3.5	30
2007	73 (17.1)	51	22	(0.0)	(0.0)	2.0	35
2008	87 (20.4)	75	12	(0.0)	1 (0.0)	1.5	40
2009	48 (11.3)	48	-	1 (2.1)	(0.0)	2.0	35
2010	40 (9.3)	40	-	(0.0)	(0.0)	2.0	35
2011	59 (13.8)	59	-	(0.0)	1 (1.7)	2.0	25
2012	53 (12.4)	53	-	(0.0)	(0.0)	1.5	35

TA=Transabdominal; TC=Transcervical; CVS=Chorionic villous sampling

study is probably the first to report primary sex ratio in Nigeria. In spite of the limitation arising from study size, it has shown that we could use the opportunity of CVS for other indications to determine a more likely primary sex ratio in future.

Complications in the study were defined based on the criteria that were previously established and used and this makes for objective comparison.[5] Bleeding in transabdominal procedure was the most common in the study but it was of no serious consequence on pregnancy continuation and outcome. Abortion rate was within the figures from other centers worldwide.[18] In terms of yearly distribution however, they were mainly in the 1st years of this series, with transcervical procedures. This justifies our change in approach to transabdominal as recommended in a similar study.[18] Continuous ultrasound guidance could account for the low number of membrane rupture.

It is instructive to observe that the need for repeat CVS and number of abortion/year declined significantly after the 1st year in the series. Furthermore shown is gradual reduction in the number of needle insertions with a concomitant increase in the villi yield, while all procedures became transabdominal from 2009. These are demonstrations of improving experience and proficiency over time. It has been suggested that proficiency is attained after 50 cases of CVS, done under careful ultrasound guidance and using echogenic tip needles.[11] We presumed that economic reason was responsible for the decline in number of procedures after 2009. This may justify government support in form of subsidy and improved awareness.

With the difficulty in accessing statistics of laboratory diagnosis errors, we are unable to compare our laboratory diagnosis error rate with other centers. While there are recognized causes of error in molecular diagnosis such as occurrence of rare molecular events, it could also arise from factors such as wrong sample labeling and handling and wrong interpretation. These latter factors will probably be more predominant in the earlier stages of the learning curve. We had since commenced and recommended repeat CVS, strong adherence to standard laboratory procedures and use of variable number of tandem repeat technique when direct sickle hemoglobin mutation gives heterozygote genotype. Counseling should indicate the risk of laboratory diagnosis error before sampling is carried out.

Conclusions

The acceptance and utilization of CVS is beginning to increase especially among pregnant women whose fetuses are at risk of SCA, as well as among an increasing population of women concerned about the possibility of fetal chromosomal and genetic disorders. There is however still a large population of Nigerians, who are unable to access the service due to cost and lack of awareness. Our experience up to date attests to the safety and reliability of the procedure and results and should encourage clients. A firmer scientific conclusion about the overall safety and reliability would however require a comparison of our complication rates with the general population and established molecular laboratories.

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