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REVIEW OF CHORIONIC VILLUS SAMPLING IN PRENATAL DIAGNOSIS

O. A. O. Oloyede*, J. A. Akinde, E. E. Emuveyan**, M. O. Ibidapo***, T. A. Adewole******
Departments of Obstetrics & Gynaecology, *Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University Teaching Hospital, Sagamu , **Lagos University Teaching Hospital, Idi-Araba, Lagos, ***Department of Medicine, Lagos University Teaching Hospital, Idi-Araba, Lagos and ****Nigerian Institute of Medicine Research, P. M. B. 2013, Yaba, Lagos.

ABSTRACT

Advances in biotechnology with the introduction of the ultrasound scan and the application of polymerase chain reaction has made fetal medicine an interesting field of study. The fetus can now be easily assessed and its genetic constitution determined with relative ease and degree of accuracy, in the process referred to as prenatal diagnosis.

Invasive prenatal diagnosis continues to be the gold standard in pregnancies at increased risk of congenital abnormalities with chorionic villus sampling being one of the principal methods of prenatal diagnosis. Although not widely available in most developing countries, chorionic villus sampling is the procedure of choice for prenatal diagnosis with the principal advantage over others, of its being done in the first trimester. This review summarizes the historical perspective, timing, route and methodology of sampling, looks at the complications and draw backs of the procedure and also examines the controversial aspects of the procedure. Its utilization is advocated in developing countries.

KEYWORDS: Prenatal diagnosis (PND), Chorionic villus sampling (CVS), Polymerase chain reaction (PCR).

INTRODUCTION

Prenatal diagnosis of inherited fetal disorders has undergone rapid and revolutionary changes in recent years with the introduction of diagnostic ultrasound and improvement in imaging capabilities[1]. Hitherto difficult procedures are now better done under continuous ultra sound guidance. Coincidentally, the advances in the field of molecular genetics complimented these technological advances and facilitated an easier diagnosis of most fetal inherited abnormalities.

Prenatal diagnosis means trying to discover what medical problems a fetus has while in utero. An early pick up of such problems allows both parents and the attending physician, the opportunity of planning the management of the pregnancy. The risk of therapeutic abortion is also simplified and reduced by mother choosing that option[2]. Unnecessary anxieties are therefore relieved which is another major benefit of early PND[3].

The anomalies that could be diagnosed by PND are broadly classified into structural, genetic, chromosomal and those due to viral infection. They occur in approximately 2 out of every 100 pregnancies. Furthermore, their distribution is influenced by ethnicity and as such the diagnostic option employed is similarly influenced. For example, Sickle cell disease is predominant in Africans, á-Thallassaemia in South East Asia, Cystic fibrosis in Caucasians and Tay sachs Disease in the Ashkenazi Jews. More often than not, these anomalies are excluded by the various diagnostic methods rather than confirmed. The unpredictability of their occurrence however, is still a source of anxiety to most couples. Despite this, the risk and burden of being affected is worrisome enough to justify the introduction of PND in modern medicine[2].

The genetic constitution of the fetus can be obtained from different methods, which may carry some risk to the pregnancy[1,2]. These methods include

I. Chorionic villus sampling (CVS)
II Amniotic fluid sampling (Amniocentesis)
III Fetal blood sampling (Cordocentesis)

The usefulness of the information obtained and the substantial risk of the fetus having a major problem of some sort may justify the risk associated with these procedures[1].

The review focuses on the Chorionic villus sampling as a method of prenatal diagnosis.

Chorionic Villus Sampling

Chorionic villus sampling (CVS) is a method of obtaining trophoblastic tissue with the aid of biopsy forceps or cannula passed through the abdominal wall or the cervical canal.

The possibility of harvesting chorionic tissue has been known for over decades following attempts to obtain biopsies under direct vision through the hysteroscope. The methodology was considered crude and therefore not introduced into clinical practice[4]. Subsequently, attempts were made to harvest exfoliated trophoblast cells from the internal os by means of a simple throat swab. This method was also precluded from clinical practice because of the heavy contamination by maternal decidual tissue.

Working independently, the technique of transcervical

*Correspondence: Dr. O. A. O. Oloyede

villus aspiration was first developed in the Tietung hospital of an iron and steel company in Mainland China by a group of Chinese investigators in the early 1980s[5]. The technique was however, not ultrasound guided. The next public report of a transcervical villus aspiration came from the Society Union, where it was used in clinical practice for fetal sexing, in fetuses at risk of sex-linked disorders and for a number of enzyme assays[6]. The technique was initially introduced to the West on an experimental basis prior to termination of pregnancy at St. Mary's High Hospital in London and was done without ultrasound guidance. It soon became obvious that better results could only be obtained when aspirations are done under ultrasound guidance[7]. Further research led to the development of the Transabdominal method for obtaining chorionic villus tissue[4].

The success reported from St. Mary's Hospital was to serve as an encouragement for a wider application of chorionic villus sampling in many countries like the Britain, Italy, Scandinavia, France and the USA within the last 14 years[4]. Its popularity is also boosted by the fact that it provides a much earlier and faster result than amniocentesis with lesser risks of intervention if the fetus is affected[1].

In sub Saharan African, CVS was introduced first in Nigeria in 1987 through the report of WHO informal consultative group on Hereditary Diseases programme[3,8]. Then it was proposed for the control of sickle cell diseases in Africa. This innovation suffered a set back because of the dearth of gynaenocologists skilled in fetal Chorionic villi sampling, as well as the absence of good laboratory back up for the analysis of sample[9]. Initial attempts at overcoming these teething difficulties were unsuccessful due to the high cost of training staff abroad[3]. Quite often many of them, found alternative engagements while on sponsorship abroad or had problems adjusting to the local environment on completion of training or settled in job areas where the skill could not be put to use[3]. By 1993, these difficulties were resolved with the on-the-spot- training of two young resident obstetricians by two experienced obstetrician invited from London[3]. Prior to that a clinical pathologist had been trained on the applications of polymerase chain reaction technology.

Scope of Conditions Diagnosed

CVS is the method of prenatal diagnosis of wide array congenital conditions. These include:

A. **Genetic Abnormalities** – They constitute the largest volume of abnormalities diagnosed by CVS. World wide, the genetic disorder of haemoglobin – sickle cell disease and the thalassaemia (á and β) are the most common single gene disorder and carries enormous morbidity[1]. Sickle cell disease is also the first genetic abnormality to be diagnosed in sub Saharan Africa using the CVS[3,5]. Cystic fibrosis, unlike sickle cell disease is the most predominant single gene inherited disorder in the U.K[1,2]. It is probably best to combine CVS with molecular and biochemical studies for efficient prenatal diagnosis of CF. Another example of conditions that can be diagnosed is Muscular dystrophy using the process of 'reverse genetics'.

B. **Chromosomal Abnormalities** – Congenital anomalies due to chromosomal defects are also among the conditions diagnosed using CVS. In this group, the Down's syndrome or Trisomy 21 is the most cited. It has a strong association with maternal age and CVS is usually done after some initial screening tests. The other examples in this group are Trisomy 18, 47XXY and the fragile X syndrome.

C. **Metabolic Disorders** – There are different types of inherited metabolic disorders, many of which are very rare[1]. Tay Sachs disease is perhaps the only good example of conditions in the category. Apart from biochemicals like hexosaminidase A, Glycosidasis and others, diagnosis is also possible by DNA studies using linkage analysis and restriction fragment length polymorphisms[1,10].

The other varieties of congenital abnormalities due to structural defect like Neural tube defect, Cardiac defect, Skeletal dysplasia as well as those arising from viral organisms such as the Rubella, Toxoplasmosis and Cytomegalovirus are not routinely diagnosed using the CVS.

Timing of Sampling

Appropriate timing is very crucial to the success of the CVS. The optimum time of sampling is between the 10th and 12th week of gestation. It may however be done as from the 8th week till the 14th week of gestation[1,7].

Most workers believe that it is undesirable to perform a chorionic villus biopsy before 8th week of gestation because of the rapid embryonic development and organogenesis, which takes place prior to that time[4]. The fact the chorion frondosum is not clearly identi fiable prior to this time as well as the background risk of spontaneous abortion and limb deformities are also factors against sampling before 8th week[4].

Between the 10th and the 12th week, the chorion frondosum has been well formed (> 6mm thick) and there is a reasonable volume of tissue from which samples can be obtained. CVS is not encouraged after the first trimester because of the higher risks of abortion complications that may occur where this is done for affected fetuses. Moreover after the 20th week, other procedures like the cordocentesis may be preferable as it is associated with far lesser incidence of Cytogenic discordance.

Routes of Sampling

CVS can be done through any of the two favoured routes, namely, the transcervical and the transabdominal approach[1,2,11]. Historically, two other approaches namely the trans vaginal and the hysteroscopic have been described. In the early days, the transcervical approach was the more favoured route of sampling[11]. Nowadays, however, the transbdominal approach is been increasingly used where feasible, even through the accuracy of the two approaches are comparable[4,12].

The factors that guide any chosen route single or in combination are as follows:

(i) Site of placenta – The precise location of the placenta as determined by the abdominal scan determines the route of sampling. Generally, posterior or anterior placentas that are low lying or cover the internal os are best obtained through the transcervical method conversely, the transabdominal approach is recommended for fundal and anterior or

posterior placenta that occupy the body of uterus. In order to reach a posterior placenta, without penetrating the pool of liquor, an empty bladder is required[4]. In very rare cases of acutely retroverted uterus, vaginal manipulation can be done during sampling[4].

(ii) Thickness of the anterior abdominal wall – In the presence of a thick anterior abdominal wall, the transcervical approach may be more suitable[1].

(iii) Preference of the sampler – While it may be advisable for sampler to be comfortable with either technique, his preference occasionally determines the approach in situation where both approaches are suitable. The sampler's preference is often times a reflection of prior experience. Likewise the operator's experience is considered to influence the safety and success of medical procedures[13].

(iv) Presence of viral infection – The transcervical approach has been known to predispose to the transmission of Cytomegalovirus and Herpes simplex in affected mothers. In these cases, the transabdominal route is favoured[4].

Comparing the two approaches, the transabdominal approach has certain advantages over the transcervical namely,

(i) The risk of abortion is less than in the transcervical method[3,4,11,14,16].

(ii) It avoids the potentially contaminated vaginal area, thereby reducing the chances of transmitting viral organisms and other potentially life threatening infections to fetus[4,15].

(iii) It allows for multiple passages of forceps from a single entry point with less contamination from maternal decidua or cervical mucus[4].

(iv) The patients are saved from the embarrassment of lithotomy position and vaginal manipulations[4].

On the other hand, the following drawbacks are acknowledged

(i) There is less tissue yield per number of passages

(ii) It is technically more difficult

Methodology

CVS is a surgical procedure with both surgical and laboratory risks associated with it. It is important that the patient understands its nature and significance, and that she makes an informed decision to undergo the test[1]. A duly explained consent form must be signed. The pre CVS counseling must be non-directive, albeit warmly and calmly[3,4].

Routine abdominal ultrasound scanning is mandatory prior to the sampling session. The purpose is to confirm pregnancy status and suitability of patient for the procedure. The numbers of fetuses as well as the co-existence of any congenital abnormality or pelvic pathology like uterine fibroid are determined. More importantly it must answer the question as to the best route of sampling. Following the scan, the patient is appropriately positioned in either the supine or lithotomy position for routine cleaning and draping. In either method of approach, the sampling is done under continuous real time ultrasound scanning or guidance and using a convex or sector probe.

In the transabdominal approach, a local skin infiltration is done with 1 percent xylocaine down into the layers of the abdominal wall and followed by a stab incision at the identified point of entry. The introduction of the trocar and cannula is made easy by the combined effect of xylocaine infiltration and verbal assurances while the session is on. Following this, the trocar is withdrawn and the biopsy forceps introduced for sampling. The fewer the number of times that the forceps is introduced before adequate sample is obtained, the better and less risky the outcome. Two or three passages are often needed to obtain an adequare sample in this method[3].

In the transcervical approach, the cervix is exposed with the aid of the cuscos speculum and the anterior lip grasped with the volsellum. The biopsy forceps is gently introduced through the cervical canal into placenta tissue. Adequate sample is usually obtained with one passage of the forceps[3].

The type of instrument used in CVS could have a significant impact on the success rate of the Procedure[17]. Similarly, the ability to manoeurve the instrument within the uterine cavity without puncturing the gestational sac to see the tip of the instrument on ultrasoundscanning is particularly important[17]. In the transcervical biopsy, the chorion villi are obtained using the Rodeck biopsy forceps (RM surgical Development London). In the transabdominal approach the biopsy forceps (R.M Surgical Developments) is introduced through the cannula[3]. More recently, the aspiration cannula was introduced with the aim of simplifying the operation technique and to ameliorate pain and discomfort associated with the procedure. The Potex cannula was found to be more likely to yield inadequate sample and make the procedure more difficult or painful when compared with either the silver or aluminum cannula respectively[12]. Evidence has confirmed that an adequate sample was more likely to be obtained using small forceps than aspiration cannula in the transcervical approach. This is however, not strong enough to justify a change in practice for clinicians who have become familiar with the aspiration cannulas[12].

The patient is advised to rest for about 30 minutes after the procedure, take things easy for a few days and avoid sexual intercourse for up to ten days in order to minimize the risk of abortion[3]. She is also counselled to report to an obstetrician in case she notices vaginal bleeding, drainage per vaginam, fever or abdominal pain.

An insignificant feto maternal hemorrhage can be inferred from the demonstrated rise in alpha-fetoprotein immediately after the procedure[17]. Although, Kleihauer testing has not confirmed this, nevertheless, it seems prudent to still recommend anti-D prophylaxis for unsensitized rhesus negative mothers[4,18]. Moreover, the 0.1mls of fetal blood that is required to cause sensitization represents half of the total fetal blood volume at 9 weeks thereby making this possibility to be very remote[4].

Post result counseling and emotional support should be offered when necessary. The final decision on the fate of the pregnancy must however be left entirely in the hands of the couples after adequate information must have been provided[3].

Laboratory Analysis

Laboratory analysis of specimen is a major arm of CVS for PND. The samples obtained are examined under lower power inverted microscope and the villi are carefully dissected out of

maternal tissue contaminant. Chorionic villi have a characteristic fluffy, white appearance and float to the surface of the culture medium[4]. "Bush-like" villi with many sprouts will contain more mitotic figures than smooth "root-like" villi[19].

The clean villi are weighed (10-50mg) by comparing with a photographic documentation of reference standards[3,5,9]. The authenticated sample is to be transferred to the laboratory in saline medium. The tissues obtained are suitable for cytogenetic analysis as well as DNA and biochemical studies[1].

Chromosomal analysis can be done using any of the following methods.

(i) Direct preparation
(ii) Cell culture.

The direct preparation is the most suitable approach, nowadays as it has the advantage of rapid analysis and reporting within 48 hours. The cells analysed are those in metaphase using newer technologies like the polymerase chain reaction. (PCR) carried out on autogene thymocycler. Polymerase chain reaction (PCR) is a technique by which large amounts of specfic DNA fragments are produced from small amounts of complex template[20]. It has found useful application to numerous genetic disorders. Confirmed placenta mosaicism though rare, occur more frequently with direct preparation than the cell culture. Occasionally, there may be inconclusiveness of analysis as a result of failure of DNA amplification or technical reason[9,21]. The failure of DNA amplification may be due to a low DNA concentration or too much degradation of DNA, if RNAse or DNAse were inadvertently present in the reaction mixture or if there were some unknown inhibitory substances[9]. Worldwide this occur in 0.5% of cases.

The cell culture allows for the analysis of the fibroblast from the mesenchymal core of the villi. Analysis and reporting usually takes up to ten day or more.

The chorionic villi have also been found to be a reliable tissue for prenatal diagnosis of various metabolic disorders through the measurement of lysosomal enzymes and of various enzymes involved in inborn errors of amino acid, organic acid and nucleic acid metabolism[4,10].

Adverse Effects

The main concern about CVS has been that of safety of the procedure[1]. Complications occur in either the mother or the fetus.

Fetal Complications

The possible adverse effects or complication in the fetus are discussed below:

1. Abortion - The risk of procedure - induced abortion is about 2% (1in 50) during the first 12 weeks. Also the incidence tends to be higher following transcervical biopsies due to factors such as repeated aspiration, puncturing of amniotic sac, gestational age greater than 11 weeks, immediate bleeding and ultrasonic demonstration of a sub choral haematoma after the procedure[4,19]. Two patterns of abortions are recognized after invasive procedures. The first pattern, which occurs within 7 days, is characterized by initial bleeding followed by expulsion of the products[4]. The second variety occurs between the 2nd and 5th weeks after the procedure. This is characterized by severe oligohydramnios, loss of fetal heart rate and then abortion[4].

   While the first variety has been attributed to mechanical disruption during the procedure, the second pattern is presumed to be due to infection form organisms like Listeria, Chlamydia or Mycoplasma[4,22].
2. Structural Malformations - CVS has been widely reported to be associated with structural deformities such as tallipes, abnormal shortening or deformities of limbs digit, cleft lip and palate, gastroschisis, intestinal atresia and clubbed foot[1,2,12,23]. The occurrence of these defects is hypothesized on two theories namely, oligohydramnios following inadvertent puncturing of the amniotic sac and vascular disruptions[23]. Accumulated data has further shown that this risk is minimal or nil when the procedure is performed after 70 days of gestation[4].
3. Placenta Mosaicism - In this condition, the placenta has an abnormal karyotype while the fetus is chromosomally normal or vice versa. The incidence of confined mosaics is between 1 to 2 percent and is also found to be more commonly associated with direct preparation than with culture[1,4]. Their occurrences occasionally require additional invasive testing such as staining for antibody against fetal embryonic haemoglobin (HbE) and also add additional information about perinatal outcome while also alerting the practitioners to the possibility fetal genetic disorder[4].
4. Placenta Bleeding - This complication is seen more frequently with transcervical approach and also following multiple needle insertions.
5. Rupture of Membranes - Iatrogenic rupture of membranes leading to leakage of liquor may occur following either method. The tamponading effects of the anterior abdominal wall tend to reduce its severity when it occurs during the transabdominal approach. It is more obvious with transcervical approach. Rupture of membranes has been associated with the occurrence of structural abnormalities, infection and abortion.
6. Infection - The incidence of post chorionic villus sampling chorio ammionitis is low. From the transabdominal approach, it follows the introduction of organisms from the bowel that are inadvertently punctured. During the transcervical approach, the organisms are transformed from the vaginal flora.
7. Perinatal Effect - No distinct perinatal complication has been described by most workers
8. Long Term Infant Complication - A consistently normal development and school performance has been reported by a group of Chinese workers[24].

Maternal Complications

1. Psychological Effect - The psychological effect associated with CVS include the fear of revealing an abnormal pregnancy, dilemma of possible decisions about pregnancy continuation and / or fear of complications arising from pregnancy termination. Most times, the women are more concerned about a spontaneous abortion and waiting for the result than about a possible unreliable result[25],

Information is very vital towards allaying any of these anxieties. It is however, known that the unpredictability of the occurrence of these anomalies is still a major source of concern to a good number of couple. Despite these however, the psychological impact on women undergoing invasive procedures for fetal karyotyping does not constitute a major clinical problem[24].

2. Cellutitis - Infection of the subcutaneous tissue is a rare event that may follow poor antiseptic technique.
3. Hemorrhage - Bleeding may occasionally follow iatrogenic injury to blood vessels in the anterior abdominal wall or the highly vascularized cervix. Such bleeding is rarely significant enough to lead to the discontinuation of the procedure.
4. Anaesthetic Complication - Inadvertent intravascular injection of xylocane is another rare complication of CVS. It is largely prevented by exercising caution during skin infiltration.
5. Vaginal Bleeding - Vaginal bleeding is relatively uncommon after transabdominal biopsy occurring in less than 1% of cases, but not unusual following transcervical biopsy. While spotting may occur in about a third of biopsies done by the transcervical route, post procedural bleeding occurs much less frequently. The occurrence of a subchorionic hematoma is associated with bleeding for 7 or more days.
6. Rhesus Sensitization - Rise in maternal serum alpha fetoprotein (MS - AFP) has been consistently documented following CVS[23]. The size of MSAFP elevation is independent of technique used but more dependent on the quantity of tissue aspirated. Also the detection of MS AFP implies fetomaternal bleeding, and where the volume of blood is in excess of 0.1 mls, there is a very high probability of Rhesus isoimmunization.

It is suffice to say that necessary measures must be put in place to reduce the incidence of these complications. Some of these measures include[3,4,9]

(i) Proper patient selection taking into cognizance the exclusion criteria.
(ii) Adequate manpower training to reduce the incidence of intraoperative and laboratory errors.
(iii) Standard laboratory backup including uninterrupted electricity supply.
(iv) Preprocedural counseling to allay fears and anxieties.

CVS and other invasive procedures

These are two other invasive procedures to which CVS could be compared. These are:

(i) Amniocentesis
(ii) Cordocentesis

CVS however continues to be the gold standard because of obvious advantages namely,

1. I t is done in the first trimester when the risks of abortion is minimal, if there is the need to intervene.
2. It is a less invasive procedure, when compared with amniocentesis and cordocentesis.
3. The incidence of structural abnormalities and other complications are much less.
4. Results of laboratory analysis especially with the direct method are obtained faster than cell culture.

Exclusion Criteria

The following reason would exclude a woman from CVS[3,5,9],

(i) Unexplained bleeding per vagina
(ii) Presence of pelvic infection
(iii) Pregnancy below 8 weeks or thin placenta
(iv) Genotype AA
(v) Failure to obtain sample after three attempts.

Issues in CVS

These are several areas of controversy and debates on CVS.

Abortion

CVS for prenatal diagnosis has been widely speculated to be an encouraging factor to abortion. It must however be realized that there is already a high rate of indiscriminate abortions, 70 percent in a third of women who did not have access to PND[3]. With the introduction of PND, a lot of these fears of unknown are resolved and many less would have needed to undergo abortions.

Another area of concern also is the status of abortion law. In most developing countries where it is legally discouraged, offering women an insight into the unborn child might therefore be of little or no benefit. Contrary to this fact however, is that the establishment of the status and severity of the fetal anomaly might spur many nations into reviewing their abortion law with a view to preventing the delivery of handicapped children and the procurement of safe abortion where absolutely necessary.

Religion

Most of the established religious sects would frown at any attempt to determine the medical status of the unborn child, mainly because, it is believed that the abortion of even the affected fetus is sinful. It might be difficult to predict the attitude of religious group especially in developing countries where the CVS itself is still an innovation that is yet to be widely available. The influence of better education, improved financial status and modern information technology will however modulate the individual religious opinion when faced with the reality of the problem.

Cost

The cost of medical technology is increasing more rapidly than the economic growth of most countries[4]. CVS like most recent hi-tech related procedures in medicine attract a high cost. Right from the level of training to the acquisition of equipment and the conduction of sessions, the cost involved is enormous. This has posed as a major set back to the introduction and sustenance of the programme in most developing countries. Better financial status has been adduced as one of the reasons why most of the patients sampled in Nigeria are from Lagos[3].

Measure to reduce the burden of cost on the patient and the provider would include:

(i) Participation by government and non-governmental organizations.
(ii) Incorporation of programme into the National health insurance scheme.
(iii) Improvement of social factors such as electricity[3].

(iv) Reliance on direct preparation and performing culture only when the quantity and quality of metaphases is inadequate for confident diagnosis[4].

Technology / Expertise

The success of CVS or PND programs depends largely on two main pivots.

First, the sampling skill of the obstetrician, which is a product of adequate training and acquisition of experience. Training should preferably be tailored to the local environment. Trainees can more readily appreciate and adapt to the less than ideal conditions peculiar to their local environment[3]. Also it has been reported that technique learnt in the technologically advanced countries cannot be reproduced back home, where the practitioners are confronted with complexity of infrastructural deficiencies and different socio-cultural norms[3]. It is also acknowledged that centralization and restriction of CVS to limited number of experienced operators within centres is likely to have a positive influence on the safety and success of the procedure[13].

The second main point is that of a good laboratory support. This involves the use of advanced technology that can support PCR technology. In addition, the need for an uninterrupted supply of electricity is very crucial to the success of the procedure as the equipments are very sensitive to electrical fluctuations. It has been documented that such technology can be successfully transferred where there is will.

Medico-legal considerations

CVS like any other invasive procedures have medicolegal implications. Litigation could arise from complications of the procedure such as abortion or from laboratory report which may be false negative or false positive or inconclusive. False negative result occurs more commonly with direct preparation. An important measure put in place to protect the physician is the signing of a well informed consent form by the patient. The form states expressly that there is a margin of complication that may follow the procedure as well as error in the laboratory result.

CONCLUSION

Prenatal diagnosis of congenital anomalies is gradually becoming an indispensable aspect of modern medicine. It continues to be gold standard for pregnancies at risk of chromosomal aneuploidy or other genetic disease. Despite its associated risks, CVS is still widely acceptable as a good method of accessing tissues for PND. Secondary to the advantage of safe, early diagnosis, CVS appears to be the optimal choice for first trimester testing[20], Post sampling abortion is safe and less complicated than mid trimester abortion[3].

In Nigeria and other countries in the Sub Sahara Africa, there is the need to make the procedure more widely available and accessible to the generality of the population. This should be the immediate future goal. Realizing that funding is a major draw back, it is hoped that both government and non-governmental bodies will appreciate this and rise up to the challenge of subsidy.

In the developed countries, the immediate goal should be that of designing methods of painless and less traumatic sampling, compatible with higher yield of tissue.

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