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Role of Interventional Procedure in Current Obstetrics

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Abstract

Objective: The main purpose of this study was to elucidate the main clinical indications, diagnostic yield and complications regarding interventional procedures.

Study Design: An observational, prospective study was conducted on all women who underwent amniocenteses and chorionic villus sampling between February 2015 and January 2018.

Methods: All samples which came to the Genetics laboratory, obtained by invasive procedures (amniocentesis and chorionic villous sampling [CVS]), performed during pregnancy, between February 2015 and January 2018 were included in the study. Maternal demographics, indication for amniocentesis, types of chromosomal aberration, gestational age at the time of amniocentesis and procedure-related complications during pregnancy data were analyzed using SPSS (version 20.0).

Results: A total of 192 samples were included in the study. 16 women underwent CVS, the main indication being ultrasound detection of cystic hygroma. 176 women underwent amniocentesis for various indications. The commonest indication for amniocentesis was ultrasound marker positive for aneuploidy 85 (44.3%) followed by ultrasonographically detected malformations 34 (17.6%). Fluorescence *In situ* Hybridization (FISH) was also performed in 73 cases for rapid results and the most common indication being ultrasound soft marker positive followed by maternal serum screening positive (MSS). Abnormal karyotypes were obtained in 15 cases (7.9%) . The clinical indications with highest positive predictive values were parent carrier of chromosome abnormality (40%) and ultrasonographically detected malformations (17.6%). There was only one woman with twin gestation (DCDA) and severe polyhydramnios, who post-amniocentesis went into preterm labour within 48 hours of the procedure (0.4%).

Conclusions: At a referral centre like ours, where high risk women and women referred from outside are mainly catered to, we found that amniocentesis based abnormal ultrasonographic findings, is a time tested proven technique with very low complication rates in detection of chromosomal abnormalities.

Keywords: Amniocentesis, Chorionic villous sampling, Chromosomal abnormalities.

Introduction

Interventional procedures are the definitive diagnostic modalities to rule out various genetic aberrations. CVS, has an advantage of earlier detection than amniocentesis, but high miscarriage rates, requirement of greater technical expertise and ambiguity in the results like

mosaicism has led to decrease in its popularity in comparison to amniocentesis for detection of chromosomal abnormalities. Amniocentesis, in modern obstetrics has played a leading role as an invasive diagnostic procedure for the detection of chromosomally abnormal fetuses [1 & 2].

The screening programs not only cause anxiety while waiting for the test results but also puts the family in a difficult situation when the result is 'false positive'. The situation becomes even worse when the screening results are 'false negative' as there are no therapeutic options for chromosomal abnormalities The aim is, therefore, to select screening and diagnostic tests that are both accurate and safe and can be done early in pregnancy to allow the choice of termination of pregnancy.

For a long time, prenatal aneuploidy screening was based solely on maternal age and, therefore, that was the main indication for amniocentesis. The introduction of combined biochemical and ultrasound markers changed the paradigm of prenatal diagnosis: no longer should maternal age per se be considered [3].

However, the definite diagnosis of chromosomal abnormalities in the antenatal period is still only possible through invasive techniques. Cytogenetic methods like karyotype play a crucial role in prenatal diagnosis. FISH is employed for the rapid detection (24 to 48 hours) of most common aneuploidies, such as trisomies of chromosome 13, 18, 21 as well as the X and Y chromosomes on non-cultivated cells with interphase nuclei.

The main objective of this study was to characterize a population of pregnant women submitted to amniocentesis in a tertiary hospital, and to assess the diagnostic yield regarding fetal karyotype as well as procedure related complication.

Materials & Methods

Study Objectives – To describe the main clinical indications, diagnostic yield, types of chromosomal abnormalities and complications regarding interventional procedures.

Study Design – Observational, prospective study was performed after obtaining clearance from Institutional Ethical Committee.

Study Period – February 2015 and January 2018.

Sample Size – A total of 192 samples were included in the study. 16 women underwent CVS, and another 176 women underwent amniocentesis for various indications.

All pregnant women who were detected to have soft markers or structural abnormalities detected on USG performed at our tertiary care centre or referred from outside with abnormal maternal serum markers were enrolled in the study. NT scan at 11 to 13+6 weeks followed by anomaly scan at 18 to 20 weeks were performed, where carefully soft markers for aneuploidy were looked for. If any abnormality was detected at either scans, the women were subjected to invasive procedures.

Informed written consent for amniocentesis as well as genetic analysis was obtained from the patient and the attenders prior to performing the procedure. Maternal demographics, indication for amniocentesis, no. of times needle inserted, puncture through or away from placenta, gestational age at the time of amniocentesis was noted in the proforma.

All procedures were performed under ultrasound guidance by senior staff obstetricians with special training in invasive procedures. Amniocentesis was performed with a 20-Gauge needle and, in the majority of cases, 15-20ml of amniotic fluid was collected. Further evaluation on procedure-related complications during pregnancy were noted. Any ill-effects due to the procedure was observed. Post-procedural miscarriage rate was defined as spontaneous abortion or fetal demise (within two weeks of

procedure) after amniocentesis. Fetal loss and premature rupture of membranes within 2-weeks of procedure were also noted.

Investigation for chromosomal anomalies was routinely performed by cytogenetic analysis and FISH. The traditional "gold standard" for prenatal diagnosis of chromosome abnormalities is metaphase analysis by GTG-banding method or G-bands. For FISH analysis, AneuVysion (Vysis) commercial DNA test kits for enumeration of chromosomes 13, 18, 21, X and Y were used. All amniotic fluid samples and also CVS samples were processed and analyzed according to a standardized protocol.

All the data was tabulated in a master-chart and statistical analysis was performed using SPSS (version 20.0).

Results

The distribution of maternal age at the time of the procedure is shown in Table I. Overall, 80% of the procedures were performed in women aged below 35 years and only 20% of the women aged above 35 years (Table 1).

Regarding the clinical indications for amniocentesis, the most frequent was ultrasound soft markers of aneuploidy (44.3%), followed by ultrasonographically detected malformations (17.7%); positive maternal serum screening (15.6%), either first trimester combined screening or

second trimester triple screening or integrated screening; maternal age ≥ 35years (14.5%) previous child with chromosomal abnormality (2.08%); parent carrier of chromosome abnormality (2.6%); single gene disorder (2.6%) and maternal anxiety (1.6%) (Table 2). Sixteen women underwent CVS, the main indication being ultrasound detection of cystic hygroma. Only 2 samples came out to be positive for Turner Syndrome and were terminated as per parents' decision. The other two samples came positive for Down syndrome and triploidy each; the indication for intervention being increased nuchal thickness.

Out of 190 karyotypes obtained, 15 presented chromosomal abnormalities (7.8%). Of those, 12 showed numerical aberrations. Six had trisomy 21 (50%), 2 showed monosomy X (16%), 2 had triploidy (16%), 1 presented trisomy 18 (8.3%) and 1 had triple X (8.3%) (Table 3). Down syndrome constituted 50% of the aneuploidies observed in this study. Among structural aberrations, 2 had translocation and 1 had derivative chromosome (Table 4). The clinical indications with highest positive predictive values were parent carrier of chromosome abnormality (40%) and ultrasonographically detected malformations (17.6%).

In order to get rapid diagnosis, some pregnant women with gestational age ≥ 20 weeks accepted fluorescence in situ hybridization (FISH). FISH was done on 73 uncultured amniotic fluid specimens using probes located at chromosome 13, 18, 21, X and Y. Aneuploidy was detected in 4 of them which also came positive in karyotype (Table 5).

The amniocentesis was mainly done between 16- 18 weeks (34%) followed by 19-21 weeks of gestation (32%). In three cases, amniocentesis was performed before 15 weeks, where there was gross ultrasonographic malformation and parents wanted termination of pregnancy. All CVS procedures were carried out between 12-14 weeks (Table 6).

Regarding the outcome of pregnancy after amniocentesis, one woman with twin gestation (DCDA) and severe polyhydramnios, who post-amniocentesis went into preterm labour within 48 hours of the procedure (0.4%) representing a post procedure miscarriage rate. Though there were two risk factors for the miscarriage, one was polyhydramnios and other was twin pregnancy. 4

pregnancies ended in miscarriage (< 28 weeks gestation), one at 15 weeks (CVS was done at 12 weeks for megacystis of bladder) and three others were found to have absent cardiac activity at 23 weeks (hydrops), 24 weeks (triploid) and 25 weeks (triploid) of gestation. Amniocentesis was done at 18 weeks, 19 weeks and 21 weeks respectively. The pregnancies terminated were mainly with abnormal karyotype and those which belonged to the category where multiple abnormalities were detected in USG.

Discussion

All pregnant women who were detected to have soft markers or structural abnormalities detected on USG performed at our tertiary care centre or referred from outside with abnormal maternal serum markers were offered invasive prenatal testing. Though chorionic villus sampling technique has benefits of early detection still amniocentesis is more popular because; less ambiguity in the results, simple technique and procedure related miscarriage is significantly less [4].

Regarding clinical indications for invasive testing, our results are similar to other published series [5 & 6]. Ultrasound markers of aneuploidy (44.3%) and ultrasonographically detected malformations (17.7%) are the most frequent indications for cytogenetic study representing 62% of all clinical indications. For few decades, triple marker was the only marker associated to Down syndrome and represented the main clinical cause for referral for invasive diagnostic procedures. Nowadays, a much more individualized risk assessment is performed in most countries [7]. Biochemical markers, combined with nuchal translucency and further ultrasound markers, such as nasal bone, ductus venosus and tricuspid regurgitation, are progressively replacing maternal age and triple marker alone as standard method for prenatal screening [8 & 9]. In our study we saw that even biochemical markers showed poor predictive value than ultrasound markers of aneuploidy and ultrasound detected malformations. It is clearly revealed that amniocentesis performed for positive prenatal screening has decreased, opposed to the invasive testing performed because of ultrasound detected markers and malformations. Nevertheless, the total number of amniocenteses performed did not decline but has increased with more obstetricians getting trained in antenatal sonography and with advent of advanced sonography machines with 3D and 4D technology; the total number of referrals kept steadily increasing. Even the introduction of Non-invasive prenatal testing (NIPT) could not replace or significantly decrease the number of amniocentesis done because of the cost of NIPT and still being a screening test.

During the study period, of the 192 samples studied, cytogenetic results were obtained in 99% of the cases. There were two culture failures where no growth was seen even after three weeks; one of which could be attributed to late gestational age i.e. 33 weeks [10]. As the amniocentesis was mainly performed earlier in pregnancy when live fetal cells are more in number, the culture failure rate was less as compared to other studies [11]. This is in good agreement with the current literature and reaffirms that prenatal cytogenetic diagnosis in amniotic fluid samples is a highly reliable method to obtain fetal karyotype [12 & 13].

In our series, chromosome abnormalities were noted in 7.8% of the cases which is in concordance with the reported literatures [6,11]. Analyzing the frequency of chromosome abnormalities for each clinical indication, parental chromosomal rearrangements presented the highest PPV (40%) followed by ultrasonographically detected malformations (17.6%). This is also in agreement with literature data, confirming ultrasound examination important role in prenatal diagnosis screening for

chromosomal anomalies [5, 8, 12]. Maternal serum screening still has a role in prenatal screening because in few cases, the fetus is not positive for soft markers or the USG operator is not able to pick up the soft marker. The PPV of positive prenatal serum screening (10%) was higher than quoted in other literatures [12 & 13]. The possible reason could be a referral bias.

There were found 12 karyotypes with numerical aberrations in the 190 karyotypes. The largest number of identified numerical aberrations were autosomal chromosome aneuploidies. It was found 6 trisomies of chromosome 21 (Down syndrome), 1 trisomy of chromosome 18 (Edwards syndrome), 2 showed monosomy X (16%), 1 presented trisomy 18 (8.3%), 1 had triple X (8.3%) and 2 showed triploidy (16%). The most frequent numerical chromosome aberration was Down syndrome (51.4%) (Figure 1). There were about 3 karyotypes with structural chromosomal aberrations. One had balanced translocation; one had unbalanced translocation and one had derivative chromosome 9. During the study period, there were 4 cases of polymorphic variants. Two cases of 9qh+ and 2 cases of 1qh+; all of them were included in normal karyotype as these are considered as variants without any phenotypic consequences.

The traditional reported amniocentesis-related pregnancy loss, quoted by most of practitioners when counseling women, has been stated as 1% [7, 13]. However, recent studies suggest lower procedure-related fetal loss rates. A systematic review and meta-analysis, that reported a miscarriage rate of 0.81% in the women who underwent amniocentesis, concluded that procedure-related risk of miscarriage is much lower than currently quoted risk of additional 1% [14]. A retrospective cohort study compared the fetal loss rate in women who underwent a mid trimester amniocentesis with the fetal loss rate of those women that did not have any invasive procedure and reported a fetal loss rate attributable to the invasive procedure of only 0.13% [15]. The risk figure for pregnancy loss following amniocentesis that has long been quoted in North America, based on expert opinion, is 0.5% [16]. In our study, post procedural miscarriage rate was of 0.4%, comparable to available literature numbers [13, 17-20]. Our study is limited by its small size; therefore a study with more number of cases should be conducted for better analysis. However, the findings were in concordance with the studies done on large sample.

Conclusion

Our study aimed to analyze the clinical indications, outcomes and procedure related complications in our tertiary centre throughout a 3 year span. Along these years, despite a meaningful shift in aneuploidy screening, with maternal serum marker declining as referral for invasive procedures, amniocentesis remained a valuable, reliable method for cytogenetic analysis, with recognized clinical indications. With the advent of advanced sonography and obstetricians getting specialized in fetal sonography the detection rate of even minor soft markers have increased which has lead to shift in the indication for amniocentesis. In this study almost every pregnant woman have undergone amniocentesis whose risks estimated by screening tests were considered high. It is encouraging to observe that the women are now better aware of possible chromosomal abnormalities in the babies and their implications.

Counseling is complex and important questions as procedure-related complications and associated fetal loss have been inconsistently reported, with significant variations from study to study. But majority of recent publications have lent support to the view that miscarriage risk, due to an invasive procedure (such as chorionic

villus sampling or amniocentesis) per se, is very low as we found in our study too.

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