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PARENTAL DECISION AFTER GENETIC COUNSELING FOR PRENATAL DETECTION OF SEX CHROMOSOMAL ABNORMALITIES

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ABSTRACT

The study was undertaken to evaluate the importance of Genetic counseling in prenatally detected fetal sex chromosomal abnormality observed through amniotic fluid culture or chorionic villi sampling. We also evaluated the impact of pre and post test genetic counseling on the parental decision. The sample population included a total of 1793 women who were referred for prenatal genetic testing with mean gestational age of 16 weeks for amniocentesis and 11 weeks for Chorionic villus sampling (CVS), to rule out chromosomal aneuploidies, from 2006 to 2011. All the patients were offered pretest counseling and after informed written consent was obtained from the patients. CVS and amniocentesis procedure was done under sonography guidance as per standard protocol. The fetal Karyotype was done and the result obtained was tabulated and analyzed statistically. Out of 1793 cases, frequency of sex chromosomal abnormalities was 0.84%. Sex chromosomal variants were observed in 1.004% cases. After posttest counseling, termination of pregnancy was decided by 86.7% of the women with fetal sex chromosomal aneuploidies, while 13.3% decided to continue with the pregnancy. Genetic Counseling helped the patients to understand the consequences of the outcome which in turn helped them to take informed desired action.

KEYWORDS : Sex Chromosomal Abnormalities, Amniocentesis, Fetal Karyotype, Genetic Counseling, Prenatal Diagnosis.

Genetic amniocentesis is a safe routine diagnostic procedure offered to women who are at a risk of genetic disorder which can be diagnosed prenatally. The identification of chromosomal alterations remains, undeniably, one of the major indication of prenatal diagnosis by Chorionic villus sampling (Rhoads et al., 1989) or amniocentesis (Engel et al.,1980). Today 1st and 2nd trimester maternal serum screening test for chromosome 13, 18, 21 and neural tube defect (NTD) is available. Added to this today, is evaluation of almost all the pregnancies by sonography for fetal well being and anomalies. Many ultrasound markers for chromosomal disorders are now known which needs to be confirmed by fetal Karyotypes. Also there are some gray areas in the fetal ultrasound evaluation which need confirmation of a syndrome. Consequences of autosomal aneuploidies always involve delay in mental developmental which may be associated with physical defects. While sex chromosomal aneuploidies or mosaic cell lines are otherwise normal, they may have slightly lowered IQ but always have problems associated with sex organ development. Genetic counseling by a trained geneticist, is thus essential for the couple to make informed choice, as any lapse in understanding can lead to irreversible action. Prenatal diagnosis not only helps in obstetric management but also in further evaluation for recurrent risks and reproductive options in future. Genetic counseling is also a pre requirement for genetic fetal tissue sampling and is offered as pre test and post test counseling. In pre test counseling, couple is explained about the benefits, limitation and associated risk of 0.5 -1% miscarriage in the obstetric procedures and laboratory procedures. In post test counseling it is usually the interpretation of the result and availability of safe management options. In case of abnormal or variant karyotype, further need of confirmation whenever required is discussed and the consequences of continuation or termination of pregnancy is mentioned. The counseling is always non directive. The present study was conducted to evaluate the importance for Genetic counseling in prenatally detected fetal sex chromosomal abnormality (SCA). We also attempted to evaluate the impact of pre and post test genetic counseling on the parental decision.

MATERIALS AND METHODS

Present study involved analysis of fetal Karyotypes obtained from amniotic fluid samples or chorionic villus sampling (CVS) of 1793 women between the age group of 18 and 45 for a period of five years from 2006 to 2011. The sample population included those that were referred for invasive procedure on account of positive markers for aneuploidies through maternal serum

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screening, abnormal ultrasound evaluation or medical history. The patients were counseled (pre-test counseling) and informed written consent was obtained before the procedure. In amniocentesis 15-20 ml of fluid was aspirated and transferred into two tubes pre-labeled with patient name and code. In CVS villi were aspirated by transcervical or transabdominal route and subjected to short and long term cultures. The tissue was cultured and processed to prepare Karyotypes by GTG banding. Total of 20 metaphases were analyzed and 3 were karyotyped using 'Cytovision' karyotyping software. Sex of the fetus was not disclosed as per PCPNDT act (Pre-Conception and Pre-Natal Diagnostic Techniques act). However in case of sex chromosomal abnormality, couples were told about the involvement of sex chromosomes and consequences were explained on the basis of the involved chromosome. In cases having fetal chromosomal abnormalities, post-test counseling was offered. Data of Parental age, previous pregnancy history, history of infertility, assisted reproduction and ultrasound abnormalities was also collected. In patients with past history of ambiguous genitalia or known sex chromosomal anomaly, ultrasound phenotypic and genotypic correlation was recommended. The data obtained was analysed to see the effect of these factors on the parental decision. Fetal Karyotype data was analyzed by calculating frequency statistics. Whenever necessary, the results were compared by two-tailed Fisher's exact test, calculated online at http://www.graphpad.com. The difference was deemed significant with $P < 0.05$.

RESULTS

The mean gestational age when invasive procedure was done was 16 weeks for amniocentesis and 11 weeks for Chorionic villus sampling. The indications for the prenatal test were positive markers for aneuploidies through maternal serum screening tests, abnormal ultrasound findings and previous abnormal pregnancy history. Out of these 1793 cases subjected to fetal karyotyping after CVS / genetic amniocentesis, frequency of sex chromosomal abnormalities (SCAs) was found to be 0.84%. The SCAs included trisomies, monosomies, mosaics and translocations involving the 'X' or 'Y' chromosome. Sex chromosomal variants were observed in 1.004% cases. Theses variants were 46,X,inv(Y). Amongst these SCAs, the most frequent was monosomy X (53.3%). The types of sex chromosomal abnormalities and their frequencies are tabulated in Table 1.

We did not find correlation of increased frequency of SCAs with advanced maternal age as the average maternal age was 30.47 ± 3.38. Average age of the mother with different types of fetal sex chromosomal abnomalies is tabulated in Table 2. The average maternal age with fetuses with sex chromosomal trisomies was slightly higher as compared to those with other sex chromosomal abnomalies, but this difference was found to be statistically insignificant. Thus our studies indicate that there is no association of advanced maternal age with rise in fetal sex chromosomal abnormalities.

All the 1793 cases were offered pre-test counseling. Fifteen cases with fetal sex chromosomal abnormalities were offered post-test counseling. After post test counseling, termination of pregnancy was decided by 86.7% of the women with fetal sex chromosomal an euploidies, while 13.3% decided to continue with the pregnancy. Pregnancies that were terminated included eight Turner's syndromes with 45,X karyotype; two with

Table 1 : Frequency of Fetal Sex Chromosome Abnormalities

Fetal Sex Chromosomal abnormality	No. of cases	Frequency
45,X	08	53.3%
47,XXY	02	13.3%
47,XYY	03	20%
46,XY,t(X;2)	01	06.7%
45,X/46,X,i(Xq)	01	06.7%

Total Cases: 1793
With SCAs: 15 (0.84%)
Variants: 18 (1.004%)

Table 2 : Fetal Sex Chromosome Abnormalities and Maternal Age

Fetal Sex Chromosomal abnormality	No. of cases	Average Maternal Age
45,X	08	30 ± 2.25
47,XXY	02	32 ± 8.5
47,XYY	03	33 ± 3.5
46,XY,t(X;2)	01	25
45,X/46,X,i(Xq)	01	26

Total Cases: 1793
With SCAs: 15 (0.84%)
Average maternal age: 30 ± 3.9

Table 3: Fetal Sex Chromosome Abnormalities and Parental Decision

Fetal Sex Chromosomal abnormality	No. of cases	Pregnancy outcome: Terminated (T)	Continued (C)
45,X	08	T -100%	C - 00%
47,XXY	02	T -100%	C - 00%
47,XYY	03	T – 33%	C – 67%
46,XY,t(X;2)	01	T -100%	C - 00%
45,X/46,X,i(Xq)	01	T -100%	C - 00%

Total Cases: 1793
With SCAs: 15 (0.84%)

Klinefelter's syndrome with 47,XXY karyotype; one with Turners mosaic with 45,X/46,i(X) karyotype and one translocation with 46,XY,t(X:2) karyotype. Amongst those with 47,XYY two decided to continue with the pregnancy while one decided termination of pregnancy. Table 3 demonstrates the different termination rates for each SCA type. Frequency of continuation and termination of pregnancies with different fetal SCAs in given in table 3.

DISCUSSION

We observed that the couples' decision of opting for termination or continuation of the pregnancy in prenatally diagnosed SCAs of the fetus depends on the likely severity of the manifestation of symptoms of the abnormality. However other factors such as previous miscarriages, previous problems with infertility, the number of previous healthy children and whether the pregnancy was assisted or spontaneous did not influence a couples' decision. These findings are in accordance with that of Holmes et al., (1987). The decision on pregnancy termination for SCA may be related partly to the genetic counseling strategy, which explains varying rates in the literature (Abramsky et al., 2001; Holmes et al., 1987; Hall et al.2003 and Mansfield et al.1999). We observed that the other factors that influenced the couples' decision to continue or terminate pregnancy included economic, social and psychological issues which are involved in raising the child with SCA and its future life as an adult. However temporal period did not influence decision making though studies of Yon-Ju Kim et al., (2002) indicate so, because of limited number of affected samples in the present study. According to our study termination rate was 86.7%. Termination rates following prenatal diagnosis of sex chromosome abnormalities have been reported to be in a very wide spectrum ranging from 12.7 to 86.5% in various studies (Yilmaz et al., 2008).

47,XYY: Though XYY individuals are reported to show aggressive behavior, mental retardation is unlikely, and the individual can lead a normal life. The couples in our study opted for continuing with the pregnancy. These findings are also similar to those of Sheng-Wen Shaw et al., (2008).

47, XXY: Pregnancy termination was opted by all the parents, as the consequences of fetal sex chromosomal aneuploidy was un acceptable to the couples due to unpredictable risk of low IQ, hypogonadism and infertility.

Studies of Sagi et. al. (2001) shows that the differences in rate of termination and continuation of pregnancies reflected in the studies of various researchers may be related to differences in cultural norms and values.

45,X: In the present study all cases of fetal monosomy X and structural abnormality of X chromosome, the couple opted for termination of pregnancy after post test counseling. This was due to parental concerns of having a child with primary amenorrhea due to poor development of sex organs, ovarian dysgenesis, secondary amenorrhea, short stature and occasionally associated cardiac and renal abnormalities. Interview analyses of Sagi et al. (2001), showed that the main reason behind the decision to terminate the pregnancy was associated with the parents' fear of non-specific abnormality of the child, and concerns about abnormal sexual development. Our findings are also similar to the studies of Brun et. al.(2004); Christian et. al. (2000); Sagi et. al. 2002; and Sheng-Wen Shaw et al. (2008).

Structural SCAs: All women decided to continue the pregnancy when the fetus was detected with inversion Y. Coincidently these women had bad obstetric history earlier to the current pregnancy and opted to continue with the pregnancy. One couple with X; 2 translocation in the fetus opted for termination of the pregnancy after post-test genetic counseling. The maternal age being 25 years, they decided to terminate the pregnancy because they had chances of opting for more pregnancies. Studies of Young Joo Kim et al. 2013, reported association of some fetal SCAs with advanced maternal age, but did not conclude because of small sample size. In our study, the average maternal age of those with fetal SCAs was 30.47 ±3.9. Thus our study indicates that there is no association of advanced maternal age and fetal SCAs.

CONCLUSION

Interpretation of the reports in prenatal diagnosis is important and genetic counseling by trained professional is essential as sex chromosomal abnormalities mostly comes a surprise in prenatal Karyotyping. Lapse in understanding the consequences can lead to irreversible actions. If there is Post test counseling in Sex chromosomal abnormalities, outcomes in clinical, reproductive and intellectual development are varied and so patients decision varies. Further to this the parental decision to terminate pregnancy, is also influenced by economic, social and psychological issues which are involved in raising child with SCAs and also on cultural norms and values.

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