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Unexpected Prenatal Cytogenetic Results in Positive Maternal Serum Screening Cases

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Abstract

Maternal Serum Screening (MSS) in 1st and 2nd trimester of pregnancy is a known and voluntary accepted screening method for chromosome 18, 21 and Neural Tube Defect (NTD) in the general population. Every screening method is supported by a diagnostic test and hence, in screen positive (high risk) cases, confirmation of the chromosomal anomaly requires invasive procedures like Chorionic Villus Sampling (CVS), Amniocentesis or Cord Blood Sampling. Genetic Counseling before the sample collection plays an important role for the couple to make an informed choice for which the consent is obtained. Trisomy of Chromosome 13, 18, 21 are the common findings in high risk cases with positive MSS. Unusual chromosome anomalies also come as a surprise. The present study is of 1329 high risk maternal serum screen positive cases with average gestational age of 17-18 wks for whom Amniocentesis was done to rule out chromosomal aneuploidies only. Of the total 1392 cases, 82 abnormalities were observed. In 47 (57.32%) cases, expected chromosomal aneuploidy (Trisomy of chromosome 13, 18 and 21) were seen. Unexpected results were observed in 35 (42.68%) cases. The unexpected results included Monosomy, Trisomy of sex chromosomes, Translocation, Inversion of autosomal and sex chromosome, Deletion, Duplication, Isocentric, Marker chromosomes and derivatives. The high number of unexpected finding is sufficient enough to conclude the importance of Genetic Counseling and fetal Karyotyping in prenatal diagnosis.

Keywords: High risk pregnancies, chromosomal abnormalities, prenatal diagnosis.

Introduction

Maternal serum screening has been routinely offered to pregnant women from last half a decade. MSS is available in 1st trimester (Double Marker Test) and in 2nd trimester (Triple Marker Test and Quadruple Marker Test)[1]. Markers such as AFP, β-hCG, uE_3, PAPP-A and Inhabin - A are looked to estimate risk in ongoing pregnancies[2]. With current excitement and promises about gene therapy just being around the corner, there is no doubt of screening and prenatal diagnosis will remain the major areas of clinical genetics in the future[3].

Methods of prenatal diagnosis are divided into non-invasive and invasive procedure. Non-invasive methods include ultrasound and biochemical screening from maternal blood[4]. Maternal serum screening offers women the opportunity of early screening for fetal aneuploidy and option of earlier diagnosis. During pregnancy a chromosomal abnormality contributes to fetal morbidity and mortality[5]. Combination of different levels of biochemical markers, mention above, are used in the maternal serum screening test.

The rate of missed abortion due to chromosomal abnormality is estimated about 50%[6]. Prenatal screening for chromosomal abnormalities can be performed in the late first trimester (10 to 14 weeks) and in the early second trimester (15 to 20 weeks) or in both.

An expected abnormal result in prenatal diagnosis gives option for the life altering decision. The common expected abnormalities which are screen from maternal blood and detected by invasive procedure like amniocentesis are trisomy 21, 13 and 18[7]. Trisomy 21 (Down syndrome) is the most common chromosomal abnormality associated with significant risk of long-term morbidity[8]. It occurs with an estimated prevalence at birth of 1.2/1000 live births. Trisomies 18 and 13, which are usually lethal either in uterus or within the first years of life, occurs less frequents[6,7]. In screen positive cases the indications are first focus only on the expected outcomes for cytogenetic abnormalities. Apart from above all stated abnormalities the unexpected structural and numerical abnormities also responsible for the selection of quality life of a baby. Unexpected results may occur from the maternal serum screening as a high risk indication referred for expected results. Current study is a review of the expected and unexpected outcomes in the positive maternal serum screening.

Material and Methods

A total of 1329 cases received and referred for chromosomal analysis by amniocentesis for increased risks in 1st and 2nd trimester maternal serum screening (Double / Triple / Quadruple Test) were studied at Centre for Genetic Health Care, Mumbai. Amniotic fluid samples were collected in-house with informed

written consent. Additionally samples couriered from different parts of India were included in the study. Amniotic cells were cultured long term in the amniotic cells complete culture medium (Bio-AMF-2). Flasks were kept in the CO_2 incubator for 7-8 days to form sufficient colony for metaphases. It took on average 8 to 12 days for the colonies to grow. After sufficient colony formation, cells were observed under inverted microscope and change of medium was given for further division of the cells. After 24 hrs of change, colchicines were added and flaks were taken for harvesting. Harvesting was done by routine slandered protocol. This was followed by hypotonic treatment and fixative washes. Slide was prepared and kept for ageing to improve morphology of the chromosomes. Banding and staining was done by standard GTG banding protocol. Slides analyzed at 450 band level[9,10].

Results and Discussion

Of the total 1392 high risk pregnancies referred for genetic amniocentesis for maternal serum test screen positive, DMT contributed to a total of 234 cases while Triple and Quadruple test accounted for 1047 and 111 respectively. Abnormal results were obtained in 82 cases of which 47 (57.32%) were common chromosomal aneuploidies (Trisomy 13, 18 and 21) where as 35 (42.68%) cases had unexpected findings.

The cases were referred for the expected out comes like trisomy 13, 18, and the most common trisomy 21. Out of 1392 cases, 1310 (94.10%) cases were normal and in total 82 (7.25%) cases abnormalities found. Out of total 82 abnormal cases, expected chromosomal abnormalities observed in 47 cases (57.31%) while unexpected abnormalities observed in 35(42.68%) cases. In expected results trisomy 21 is the commonest trisomy and found in 38 cases (46.34 %), trisomy 18 in 8 (9.76%) cases and trisomy 13 is in one (15.85%) case.

The distributions of unexpected results are as follows, Monosomy of the sex chromosome in 2(2.44%) cases, trisomy of sex chromosome in one (1.22%), inversion of autosomal chromosome in 9(10.99%) cases, inversion of sex chromosome in 3(3.66%) cases, Translocation in 7 (8.54%), duplication, derivatives, deletion, marker chromosome, heterochromatin in one – one (1.22%) cases each and isocentric of sex chromosomes in 7(8.54%) cases.

Table-1
Data of maternal serum screening test at different gestational age with results

Screening test	Total no. of cases	Normal Results	Expected Results	Unexpected Results
DMT (11 to 13 weeks)	234	219	10	5
TMT (14 to 18 weeks)	1047	992	27	28
QMT (15 to 18 weeks)	111	99	10	2
Total	1392	1310	47	35

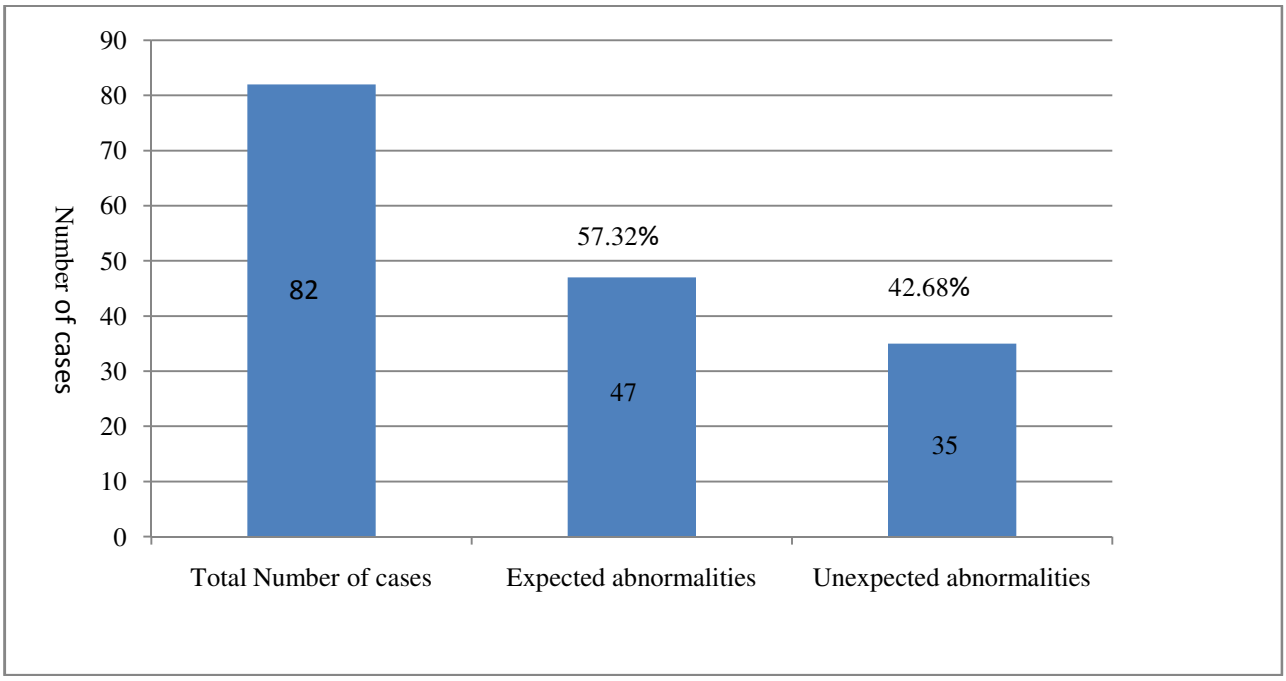

Figure-1
Expected and unexpected abnormalities in Amniocentesis for high risk MSS

Table-2
Chromosomal patterns with data of expected and unexpected results from positive maternal serum screening cases

Results with Syndrome	Chromosomal patterns observed	Total Number of cases
Expected Results observed		
Down's syndrome	46,**,+21	36
	47,**,t(4;6),+21	1
	47,**,inv(9),+21	1
Edward's Syndrome	47,**,+18	8
Patau Syndrome	47,**,+13	1
Total number of expected abnormalities		47
Unexpected Results observed		
Translocation	46,**,t(4;5)(q31.3;q35)	1
	46,**,t(9;21)(p13;q22)	1
	46,**,t(7;8)(q11.23;p21.3)	1
	46,**,t(4;6)(p16;p21)	1
	46,**,t(1;16)(p10;q10)	1
	45,**,t(15;21)(q10;q10)	1
	46,**,t(1;4)(p34;q31)	1
Inversions		
	46,**,inv(9)(p11;q12)	8
	46,**,inv(8)	1
	46,**,inv(*)	3
Isocentric		
	46,**,i(*)	7
Monsomy of sex chromosome	45,*	2
Tetraploidy	69,***	1
Trisomy of sex chromosome	47,***	1
Duplication	46,**,dup(9)	1
Derivatives	46,inv(*),der(14;21)(q10;q10)	1
Marker chromosome	47,**,+mar	1
Heterochromatin variation	46,**,1qh+	1
Deletion	46,**,del(*)	1
Total unexpected abnormalities		35

Discussion: Invasive procedures like amniocentesis are expensive, in this part; maternal serum screening plays an important role to screen the high risk population. In many studies it is concluded that Down syndrome is the most common genetic abnormality. Trisomy 21, 18 and NTD are screened in maternal serum screening[1,13]. The abnormalities apart from these are also detected and come as surprise in invasive procedure. Numerical unexpected abnormalities like Klinefelter and turner syndrome where the reproductive life and other problem associated are also important[11,12].

Structural abnormality also manifest as a clinical syndrome due to losses or gain of chromosomal material resulting in deletion or duplication. The fetus with reciprocal translocation is simple two ways translocation occurs between two chromosomes, usually in autosomes[14]. Other translocations are more complex ones or ones where sex chromosomes are involved. Fetus carrying this type of translocation may have the mental or physiological abnormality. Very unbalanced conception will abort even before prenatal diagnosis. If the fetus carries a de novo translocation, studies demonstrate that the risk for birth defects or mental retardation or both is in the range of 6-10%[15].

Some uncommon abnormalities like micro deletion may be surprise but are not detected by cytogenetic, FISH is preferred. Other structural abnormalities like inversion, insertion, duplication etc. have to be evaluated with reference to point of breakage and whether known genes have been disrupted. A risk of 9.4 % is quoted by counselors for De novo inversion resulting in phenotypic anomalies, but most of the time reviews of literature are the most useful guideline for decision making[16].

Conclusion

A major goal of screening tests is to achieve maximum accuracy and minimum harm at a low cost for common chromosomal anuploidy. Maternal serum screening in 1st and 2nd trimester is a known voluntary accepted method for screening of chromosome 21, 18 and NTD in the general population. Majority cases show normal fetal chromosomal pattern. Amongst the abnormal karyotypes, trisomy 21 and trisomy 18 are expected but unusual

chromosomal abnormalities also come as surprises. In the present study data revealed the incidence of unexpected result is relevantly high. The unexpected results mostly the structural chromosomal rearrangement may affect the quality of life of the fetus. The fetuses born with the structural abnormality can be mentally and or physically subnormal.

The data from study suggest that all positive maternal serum screening cases should be offered confirmatory diagnostic test (invasive procedure) for obtaining complete karyotype to rule out expected and any unexpected results. The couples should undergo pre and post test counseling for the same.

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