

Abstracts - Free Papers (Papers from the Delegates)

β -Thalassemia Mutations: Diagnosis to Prevention

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β -thalassemia mutations in 72 heterozygous unrelated chromosomes & 36 individuals of β -thalassemia of homozygous nature originated from Gujarat were characterized. The samples were provided by one of the author working at Blood Bank Jalram Hospital, Baroda and Gujarat for molecular diagnosis. Using the amplification refractory mutation system (ARMS) technique we were able to detect mutations in all the 144 chromosomes, which includes 72 heterozygous chromosomes and 36 chromosomes where mutations were present on both the chromosomes. The recorded predominant mutations are IVS1-5 (G-C), -619bp, CD41/42, CD8/9 and IVS I-1 (G-T), which are in concordance of the previous reported mutations on Asian Indians. These mutations were accounting in 61.0, 13.8, 8.3, 5.5, 2.7 percentages respectively. However, CD 15 (C-T) was found the only mutation among the less common. Structural hemoglobin variants like β E (CD 26 G-A) and β D (CD121 G-C) were also found in Gujarat subjects. We have also characterized common α -thalassemia mutations among the β -thalassemia Major subjects by using Gap PCR. Gap PCR study was performed in 35 individuals. Out of 70 β -thalassemia chromosomes 5 chromosomes reveals $-\alpha^{3.7}/\alpha\alpha$ genotype (7.1%) while 3 chromosomes (4.3%) carries this mutation in homozygous state ($-\alpha^{3.7}/-\alpha^{3.7}$). This molecular diagnosis is useful for establishing the first trimester prenatal diagnosis program with a short panel of mutations based on direct mutation detection system at Gujarat. The diagnosis is useful for prevention of the birth of an affected thalassemia child in the Country.

PGD Using the FISH Technique for Detection of Chromosomal Aneuploidies and Translocations

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Chromosomal abnormalities like aneuploidies and translocations are one of the major causes of pre and post implantation embryo wastage reflected by decreased implantation and increased miscarriage. Hence, chromosomal evaluation of the embryos in these patients and the selection of normal embryos could increase the rate of pregnancy and healthy offspring. Preimplantation Genetic Diagnosis (PGD) is a recently developed technique using molecular genetics (FISH and PCR) in combination with in vitro fertilization (IVF-ICSI). It is also used for couples at high risk of transmitting sex-linked diseases. This reduces the physiological and mental stress of termination of an abnormal pregnancy. At Jaslok Hospital, we offer PGD using single blastomeres biopsied from 8-celled embryos obtained by the IVF-ICSI procedures. The blastomeres are analysed by FISH to rule out common chromosomal anomalies using the Vysis Multivysion PB / Aneuvysion probe kit and a Zeiss microscope with Metasystems software. Only normal embryos are transferred to the mother. For PGD, 60 blastomeres were biopsied from 15 cycles of 9 couples. After FISH analysis, 22 embryos confirmed normal for the chromosomes tested were transferred, resulting in 2 clinical pregnancies. Chromosome abnormalities detected in the blastomeres included triploidy, trisomy 13, 16 or 18, monosomy / tetrasomy 21, pentasomy

13, nullisomy 13 or 22, XXX and XXY. Some cells were anucleate, in which case a second blastomere was biopsied and tested. The couples tested were with a history of haemophilia (X-linked recessive disorder), mothers with low-grade mosaicism for Turner syndrome or Trisomy 21 and a carrier of a balanced translocation with a karyotype of 46,XX, t(1;3)(q24;q25). Centromeric and telomeric probes of the translocated chromosomes were used for FISH in this case. Embryos, which were either normal or balanced, showed 2 signals of each probe and were transferred to the mother. All other combinations of signals indicated an unbalanced karyotype, hence these embryos were not transferred. This is the first report from India on the use of FISH for PGD of chromosome aneuploidies and translocations.

To Study Sensitivity of Erythrocytic Indices for Diagnosis of Thalassemia Minor

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Complete Blood count (CBC) is most frequently asked test by a clinician and is most potential tool to suspect Thalassemia minor Formula based on indices were studied for their sensitivity Formulas were {1} $MCV - (5 \times Hb) - RBC - 3.4 < 0$ {2} $MCV/RBC < 13$ {3} $MCH/RBC < 3.8$ {4} $RBC > 5$ {5} $MCH \times MCV \times MCV/100 < 1530$. Blood samples were collected from university students for CBC and peripheral smear. The blood was analyzed for Hb A2 quantitative method. Iron deficiency anemia cases were excluded from study. Hb A2 more than 3.5 by quantitative method was criteria for diagnosis of Thalassemia minor. All five erythrocytic formulas were applied to study the sensitivity. It was observed that Formula 5 singularly had highest sensitivity of 73.62%. All five formulas in combination of any two, any three and any four were studied and highest sensitivity was found out. F2 and F5 had highest sensitivity (63.72%), F2, F4 and F5 had highest sensitivity (54.94%), F1 F2 F4 and F5 had highest sensitivity (46.15%) and all five formulas had sensitivity of 36.26 percent. Combined formula did not have better sensitivity than each individual formula, sensitivity was reduced with combination.

Isolation of Fetal Cells (Nucleated Erythrocytes) From Maternal Blood Non-Invasive Prenatal Approach

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Currently, the molecular geneticists are exploring non-invasive approach for prenatal and molecular diagnosis. Different fetal cell types are present in a pregnant woman, e.g. nucleated erythrocytes (NRBCs), lymphocytes and trophoblasts. Enrichment and purification methods are required for fetal DNA diagnosis. At CREMERE, we have successfully standardized this technique of separating NRBCs from maternal blood. Peripheral blood (2 ml) was obtained in EDTA bulb with informed consent from 40 pregnant women with 6-38 weeks gestation. The isolation of NRBCs is achieved by a discontinuous density gradient method using percoll. The lymphocytes with NRBCs were stained by Pappenheim method and the number of NRBCs per slide was counted. The distinct morphological features helped to differentiate NRBCs from the lymphocytes. Fetal NRBCs were detected between 8-24 weeks with maximum number between 8-18 weeks of gestation. This slide preparation is now ready for FISH diagnosis and single cell isolation using micromanipulator for PCR/PEP study. The great scope for this non-invasive approach is emphasized when the availability of invasive techniques and expertise are scarce in India.

A Followup of Prenatal Diagnosis in Down Syndrome

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In a preliminary attempt to follow up the efficacy of genetic counseling on prenatal diagnosis to parents who have had a down syndrome offspring, 96 couples were communicated, 66 % cases responded and it was noticed that 14.28% opted out of having another child. 7.42 % conceived of which 85.75 % had a normal pregnancy outcome and the rest either had abortion or MTP. Only 12 cases (19 %) had opted for PND, even in spite of the awareness of their having an increased risk of bearing a DS offspring.

Chromosomal Analyses from Fetal Lymphocytes and Amniocytes

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During the period 1991 through mid 2003, 1187 chromosomal analyses from fetal lymphocytes and from 1995 through mid 2003, 586 chromosomal analyses from amniocytes were performed at Surendra Genetic Laboratory, Chennai. The main indications for referral were advanced maternal age (= 35 years), triple screen positive, previous baby with Down's syndrome / chromosomal anomalies, previous baby with congenital anomalies, previous history of recurrent abortions, Intra Uterine Death (IUD), Still birth (SB), parent carrier of balanced rearrangement, structural anomalies seen during ultrasound examination. In fetal blood and amniocyte culture, 123 (10.4%) and 36 (6.1%) of the cases showed abnormal karyotypes respectively. Among the abnormal karyotypes in fetal blood, incidence of trisomy 18 was the highest-26% followed by trisomy 21 (21%), whereas in amniotic fluid, trisomy 21 was 40% followed by Trisomy 18 i.e., 16.7%.

Prenatal Diagnosis of Omphalocele Syndromes

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Omphalocele is a surgically treatable condition that can be isolated or may be associated with malformations. Present paper emphasizes the importance of prenatal detection of associated malformations that should be looked for in any fetus with omphalocele.

We report 21 cases of omphalocele associated malformations and syndromes and also review their autopsy findings. Out of 21 fetuses, five had OEIS (Omphalocele, Exstrophy cloaca, Imperforate anus, Spinal defects), two had Limb body wall complex (LBWC) and pentology of Cantrell each eight had associated neural tube defects, one had trisomy 18, 1 had achondrogenesis and two were unidentified syndromes.

Prenatal diagnosis of omphalocele should not be considered as the end of the diagnosis' but it indicates further investigations like level II USG for associated malformations, fetal echocardiography and amniocentesis or cord blood sampling for chromosomal analysis, since the prognosis for syndromic omphalocele is worse than isolated omphalocele.

Rapid Molecular Approaches for Aneuploidy Diagnosis

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Chromosomal abnormality is one of the major causes of mortality and morbidity in perinatal period. Conventional cytogenetics is the gold standard for chromosomal analysis. It assesses all chromosomes in one test. However, it is expensive, labor intensive and results are not available for 10-20 days with a failure rate (varies from laboratory to laboratory). The waiting period for results can be very stressful, especially in advanced pregnancy, newborns with ambiguous genitalia, newborns resembling known syndrome requiring surgical/intensive care management, preimplantation diagnosis, etc. Long delay of conventional method may not be acceptable to many parents and treating physicians. This is a typical picture with ultrasound detected malformations recognized in second half of pregnancy. Hence, there is a need for rapid alternative method. Interphase Fluorescence in situ Hybridization, Primed in situ Labeling & Quantitative Fluorescence PCR are such alternative techniques. These molecular approaches to study human chromosomes can be performed in 4 to 16 hours from receiving samples in our hand. We have worked on this subject for last several years and like to share our experience of application of molecular cytogenetics to tackle different clinical situations quickly, reliably and confidently. Our experience indicates that these techniques could play an important role in decision making particularly in above situations.

Determination of Down Syndrome by MAFP Marker Screening

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Evaluation of maternal alpha foeto protein (MAFP) has been entered in the diagnosis of genetic disorders since 1970. It is normally found in the blood stream of the mother tends to be elevated or lowered with certain chromosomal abnormalities.

Down syndrome (DS) is one of the most frequently occurring birth defect. There are different screening test, performed to determined the high risk pregnancies. An association between low level of MAFP, using ELECSYS 1010 systems. There was (7.02 ± 4.003) significantly low level of MAFP in cases of DS risk pregnancies.

The present study may be helpful to understand the screening specificity of the MAFP for the prenatal diagnosis of DS

Chromosomal Aberrations and Variations in Pregnancies of Indian Women - Management and Genetic Counselling

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Prenatal diagnosis of chromosomal disorders was performed in total 1136 pregnancies of Indian women. Out of these 1136 cases, 1054 were referrals for karyotyping of amniotic fluid (AF) samples and 82 for karyotyping of chorionic villus samples (CVS). The main indications for this study in these women were advanced maternal age (35.2%), previous history of Down Syndrome in the family

(25.35%), abnormal triple test (21.3%), abnormalities seen during ultrasound scanning (10.46%), previous child with congenital abnormalities or other chromosomal abnormalities (4.93%), heterozygosity diagnosed in one parent (1.67%), anxious parents (0.44%), exposure to drugs or radiation in the first trimester (0.35%). The cells from AF (at 16 to 18 weeks of gestation) or CVS (at 10 to 12 weeks of gestation) were cultured and eventually arrested at a stage of growth when there were enough cells at metaphase. Twenty-five metaphases were examined and at least four karyotyped.

Genotoxic Effect of Smoking on Human Gametes and Embryos

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Reproductive function is adversely affected by Tobacco. Studies have shown consistent, dose-related associations of smoking with delay of conception, augmented risk of abortion and early age of menopause. Current investigations have been aimed at understanding these destructive effects of smoking. Technologies have been useful for providing clinical data on reproductive outcome and biological material such as reproductive fluids, spare oocytes, spermatozoa and spare early embryos. Components of cigarette smoke, such as a heavy metal like cadmium, nicotine (a toxic alkaloid) and its metabolite cotinine, were detected in dose-relationship with smoking in ovarian granulosa cells and in follicular fluids and seminal plasma. This gonadal environment in smokers has been shown to be harmful to the growth and viability of their gametes; in addition, it induces genetic injury. Heavy weighed female and male smoking is associated in dose-relationship with reduced numbers of retrieved oocytes (8% to 17%); reduced density of ejaculated spermatozoa (by 13% to 18%) and alterations in the meiotic spindle leading to chromosomal errors in oocytes (diploidy) and in spermatozoa (aneuploidy). In oocytes of mice exposed during meiotic maturation in vitro to nicotine or cadmium, severe alterations of meiotic spindle structure and chromosome alignment were found.

Carcinogenic polycyclic aromatic hydrocarbon-Benzo(a)pyrene [V(a)P], is produced from cigarette combustion. Its reactive metabolite binds covalently to DNA, forming adducts. B(a)P-DNA adducts were detected, in high levels, in ovarian granulosa cells of smoker women, in spermatozoa of smoker males and in pre implantation embryos of smoking couples. Transmission of DNA-adducts to embryos was originated to be mainly by sperm. This may be related to many divisions occurring in spermatogenic cells and/or to a low capacity of mature spermatozoa to repair prezygotic DNA damage.

Spectrum of Neurodegenerative Disorders and Their Prenatal Diagnosis by Biochemical Assays

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Neurodegenerative disorders are associated with mental retardation and reduced survival. Diagnosis of these disorders is based on clinical features, MRI and enzyme estimation. We present the spectrum of these disorders diagnosed by enzyme estimation and the prenatal diagnosis performed from Oct. 2002 to Nov. 2003. Enzyme assays were done for 142 cases for Galactosemia, Metachromatic Leukodystrophy (MLD), Krabbe Disease, Mucopolysaccharidosis (Hurler, Hunter, Morquio A and MPS VI), Gaucher, Niemann Pick, Tay-Sachs, GM1 Gangliosidosis, Oligosaccharidoses and Pompe disease. Deficient enzyme levels were obtained in 18 cases. Of these, four had MLD and three Tay-

Sachs disease. Two cases each had Galactosemia, MPS 6, Hurler and Hunter disease and there was one each of GM1 Gangliosidosis, Sandhoff and Gaucher disease.

Enzyme estimation for prenatal diagnosis was done in 11 cases on Chorionic villi obtained at 11-13 weeks. The indications were, MPS in four cases, Niemann- Pick, Pompe and Galactosemia in two cases each, and Gaucher and Krabbe disease in one case each. Of these, only one had deficient enzyme activity for Pompe disease compared to a normal CVS sample.

This study shows that these disorders are not uncommon in India. Appropriate biochemical assays can effectively diagnose these rare disorders. However enzymatic confirmation of the disorder in the affected child is essential before undertaking prenatal diagnosis.

Cytogenetic Study in Couples with Repeated Fetal Loss and Its Potential for Prenatal Diagnosis

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Cytogenetic investigation was carried out in 1450 individuals comprising of 725 couples. All of them have experienced minimum 2–3 first trimester pregnancy loss. Of this, 3.86 % (56/1450) couples were found to have numerical and/or structural anomalies in either of the partners. Inversion (Y) was observed in 26.78 % (16/56) of cases. Reciprocal translocations was detected in 17.85 % (10/56) of the total cases followed by 14.27 % (8/56) in Robertsonian translocation. Mosaic maker chromosome was observed in 7.14 % (4/56) of the couples. Sex chromosome mosaic cell-line were observed in 5.35 % (3/56) of cases. Remaining cases were found to have polymorphism involving euchromatic & heterochromatic regions. Risk assessments involved in these couples are based on chromosome number and the region involved in structural rearrangements. Reassurance for a healthy child in subsequent pregnancies is offered in such cases by prenatal diagnosis / PGD / ART.

Unexpected Chromosomal Abnormalities at Prenatal Diagnosis

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We report four cases in whom prenatal diagnosis revealed an unexpected chromosomal abnormality. The prenatal diagnosis was done for indications like advanced maternal age, previous child with Down syndrome, low maternal serum alpha-fetoprotein and severe intrauterine growth retardation. When an unexpected chromosomal abnormality is encountered, the parents are faced with conditions, which they have never heard of and for which they are completely unprepared. The abnormalities included sex chromosome abnormalities, mosaicism for trisomies 6 and 12 and balanced structural rearrangement. Counseling for these conditions possess a great challenge because of their variability of prognosis and uncertainty in prediction of exact prognosis. In addition there is paucity of data on longitudinal studies of such prenatally diagnosed chromosomal abnormalities. This is further complicated by the fact that the phenotypic outcome of a prenatally diagnosed trisomic mosaic case may be influenced by factors like confined placental mosaicism and imprinting in uniparental disomy (UPD) secondary to rescue of an initial trisomy. Additional investigations like level II ultrasonography for malformations, fetal echocardiography, parent's karyotyping may be needed before counseling. This possibility of diagnosis of abnormalities other than for which prenatal diagnosis was done should be discussed briefly while counseling for prenatal diagnosis. Finally, all attempts should be

made to obtain cytogenetic confirmation on the abortus or the liveborn and their phenotypes should be studied by autopsy or examination, investigation and follow up of the baby after birth.

Prenatal Diagnosis and Genetic Counselling- Awareness and Impact

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Prenatal diagnosis was carried out on 425 patients at Genetics Department, Manipal Hospital, Bangalore. Of these, 253 (62.5%) patients were referred from the Foetal Medicine unit, Manipal Hospital, Bangalore, on detection of a foetal anomaly and 27 cases were found to have a chromosomal abnormality. Prenatal diagnosis was done on the remaining 152 cases (37.5%) after genetic counselling because of a prior history of genetic disorder in the family. 10 cases (6.5%) were detected to have chromosomal abnormality in this group. The impact of genetic counselling has led to a change in the timing of the procedural intervention and the referral patterns. This in turn, has resulted in an increased patient awareness and better overall outcome of genetic disorder management. The widespread cultural diversity in India has led to tailor made counselling to suit local customs and beliefs. Emphasis need to be laid on the primary care physician as the initial counselling a patient receives is imperative in the acceptance of genetic diagnosis and management.

Cytogenetic Studies in Pregnancies with Abnormal Fetal Ultrasound (USG) Examination

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Chromosomal anomalies have been found to be one of the major causes for congenital birth defects (CBD). CBD's can be identified in utero in early stage of gestation by USG. Cytogenetic analysis on such cases would enable to detect chromosomal anomalies, which is useful for appropriate genetic counselling. The aim of the present study was to analyse the significance of associated chromosomal abnormalities with various USG markers. Pregnant women visiting Mediscan systems from December 1997 to June 2003 were included in the present study. Five hundred and eighteen cases showed various abnormalities on USG examination. USG markers were classified as hard and soft based on whether it produces functional incapacity to the fetus. The association of chromosomal abnormalities with some of the major markers are listed as follows: increased nuchal thickness in 49 (10.3%), cystic hygroma in 28 (5.9%), echogenic bowel in 30 (6.3%), pyelectasis in 26 (5.5%) cases, micrognathia in 10 (2.1%), cleft lip and palate in 14 (3%), congenital heart defects in 45 (9.5%), ventricular septal defect in 31 (6.5%) and atrio ventricular septal defect in 25 (5.3%) of patients. Cytogenetic analysis was successfully performed on 474 cases using fetal blood sample, amniotic fluid or chorionic villus sample, by standard methods. Abnormal karyotypes were seen in 50 (10.5%) cases (numerical - 45 cases and structural rearrangements - 5 cases). Among numerical anomalies 16 cases (32%) had trisomy 18 (Edwards syndrome), 14 (28%) had trisomy 21 (Downs syndrome), 3 (6%) had trisomy 13 (Patau syndrome), 10 (20%) had sex chromosome anomalies (9 Turner/mosaic Turner and 1 Klinefelter syndrome) and 2 cases (4%) had triploidy (3n) chromosome number. The association of chromosomal anomalies with various USG markers are being analysed and this would help us to formulate specific structural anomalies detected on USG for fetal chromosomal analysis.

Utility of Information Brochure as a Part of Pretest Counseling for Down Syndrome

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Triple test is the most accepted method of Down syndrome screening. Screening tests are provided to asymptomatic persons and an additional diagnostic test may be needed for confirmation. With the aim of providing adequate pretest information to the patient we prepared a brochure about the information regarding Down syndrome, triple test and amniocentesis. We tested the utility of this information brochure by a questionnaire given to the pregnant and nonpregnant women.

Fifty eight pregnant patients attending our OPD for various reasons such as advanced maternal age, previous child with malformation and eighty one nonpregnant women were given the information brochure to read. They were asked to fill the questionnaire after reading the brochure. These questions tested their knowledge and attitude regarding Down syndrome and triple test. The brochure provides adequate information about Down syndrome and the utility of Down syndrome screening. The information is easily understood by most of the people. The understanding is better in the educated group. This and similar information in the local language should be used for pretest counseling.

Prenatal Diagnosis and Management of Mild Ventriculomegaly

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Mild ventriculomegaly is a management and counseling dilemma. Hence this retrospective observational study was undertaken over a period of 4 1/2 years. The surviving fetuses were followed up for 6-24 months. All fetuses found to have mild ventriculomegaly (LV + 10-15mm) from Jan 1999 to May 2003 were studied. Karyotype was offered to all, but particularly to those who showed some increase in size of the LV during the period of observation. There were 24 fetuses with MVM. 5/24 (21%) had unilateral ventriculomegaly. 19/24 (79%) had Bilateral ventriculomegaly. 4/5 (90%) with unilateral ventriculomegaly had term delivery and normal postnatal development. 1 insisted on a TOP. 4 of 19 with bil. MVM had other structural anomalies. One had CMV, one had VSD with 4q deletion. 10 of the 15 Bil. MVM were followed up and 80% had normal outcome. As noted in literature true isolated MVM and unilat. MVM had better prognosis.