

## PRENATAL DIAGNOSIS OF GENETIC DEFECTS

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**T**HE development of early prenatal diagnostic tests for certain foetal malformations has been a significant achievement in recent years. Congenital abnormalities and genetic diseases including chromosomal alterations and metabolic disorders can be detected in the foetus through improvements in the techniques of tissue culture, cytological methods and biochemical assays<sup>1-5</sup>. Prenatal identification of such abnormalities, followed by medical termination if required, is now a well established and accepted procedure in most countries<sup>6-8</sup>. Such aberrations have been associated with :

(a) Advanced maternal age—the risk of giving birth to a child with chromosome aneuploidy, especially trisomy 21, increases with the age of the mother. At 35 years of age, the risk is about 1 in 240, followed by a steep rise to 1 in 50 at 40 years of age and above.

(b) Translocation or other chromosomal anomalies present in either parent: they may result in an unbalanced arrangement in the offspring. This can be suspected in couples with a history of repeated foetal loss or sterility.

(c) Occurrence of the defect in a previous child, or family history of congenital defects.

During the last 10 years, the number of requests for prenatal chromosomal analysis has increased considerably in the developed countries<sup>9-11</sup>

An extensive survey by Laxova<sup>11</sup> had given the incidence of genetic abnormalities detectable by prenatal diagnosis to be consistently about 5%, indicating that 95% of the women considered at risk had been examined. In spite of the fact that analysis of amniotic fluid and of cultivated foetal cells can provide a firm diagnosis for essentially all chromosomal disorders, together with many of the inborn errors of metabolism and neural tube defects<sup>1,12-14</sup>, mid-trimester amniocentesis at 14-16 weeks of pregnancy is at

present available to only a small proportion of the women at risk. In the United States less than 3% (about 5,000) of such women underwent amniocentesis in 1975<sup>15</sup>. Since the first report of perinatal detection of chromosomal aberrations in 1966<sup>16,17</sup>, the monitoring of 14,000 pregnancies had been reported from the USA and Western-Europe until 1978. In a population with about 3 million births each year, at least 5% of the babies, or 150,000 are born to women 35 years of age and older. If amniocentesis is confined only to those who are 40 and older (1% of all births), this would still comprise at least 30,000 women in the above survey to whom test should be offered for the reason of maternal age alone.

### INCIDENCE AND RECURRENCE RISK FOR CHROMOSOMAL DISORDERS

The incidence of chromosomal aberrations, as 1 in 200 live born, had been earlier established in various newborn surveys<sup>18</sup>. However, the reported frequencies of diseases due to a single gene mutation, and to a combination of environmental and polygenic factors show considerable variations in different surveys. This may be explained by the wide differences in the selection of the population, the method of investigation and the criteria used for classification. If all available diagnostic methods could be applied on a large scale, following the cases until advanced age, the incidence of congenital disorders may even be higher than what is now assumed<sup>19-21</sup>.

In India, chromosomal aberrations have been found to occur in about 3-4% live births in the surveys of newborn, in populations from the referral hospitals of large cities like Calcutta, Bombay and Delhi. Rural populations, by and large, do not avail of hospital services and thus studies of this type are liable to give erroneous

results. Results in surveys from all parts of the country appear to be consistently similar. Thus the frequency of Down's syndrome is about 1-2 per 1000 births in most reports<sup>22-24</sup>. A higher incidence has been claimed in areas with high background irradiation<sup>25</sup>.

At the global level, the occurrence of chromosomal anomalies in a newborn population, not at special risk, is 0.5% and the frequency of individual chromosomal aberrations varies from 1 in 700 to less than 1 in 10,000. Most of them arise from errors during gametogenesis or at the time of fertilization. The number of chromosomal anomalies, especially of trisomy 21, has been found to increase with maternal age, as seen in several retrospective studies<sup>26-38</sup>. This observation was confirmed from prospective studies based on prenatal monitoring of midtrimester pregnancies<sup>39-44</sup>.

Advances in diagnosis of chromosomal and metabolic diseases have now established that only about 25% of the cases inherited can be attributed definitely to chromosomal changes and/or deleterious gene defects<sup>10,42,45-54</sup>. From the frequency of chromosomal anomalies in human conceptions and disregarding preimplantation losses, only a few embryos with unbalanced chromosome complements are estimated to survive beyond the neonatal period. The rest die mostly as spontaneous abortions or in the perinatal period<sup>9,45,55,56</sup>. However, the high prenatal mortality is not evenly distributed among all types of chromosome anomalies<sup>45</sup>. Sex chromosome anomalies remain the commonest abnormality in both detectable abortions and in newborn surveys. It is thus likely that surveys of all ages would also display a similar pattern.

Walter *et al*<sup>57</sup>, surveyed the cytogenetics of mental retardation. Some acentric fragments could be associated with Klinefelter variants or Turner's, sometimes in a mosaic form with normal cell line<sup>58-63</sup>. In India, approximately 25% of the male and 33% of the female cases of sex chromosomal abnormalities have shown mental disorders as a secondary manifestation<sup>61</sup>.

Spontaneous abortions form an excellent source of data for evaluation of possible associa-

tion among chromosome abnormalities since at least half of them have abnormal karyotypes<sup>64</sup>. Alberman *et al*<sup>65</sup> detected a ten-fold increase in Down's syndrome among liveborn siblings of trisomic spontaneous abortions. Boue and Boue<sup>66</sup> showed that three fourths of all abortions occur in women with history of a previous trisomy.

In the prospective studies, the risk figures for women of 35 years and older were considerably higher than those in most retrospective studies. Part of this discrepancy might be accounted for by foetal wastage between amniocentesis and birth<sup>48</sup>. Polani *et al*<sup>43</sup> have suggested that many women who are referred for amniocentesis are high risk samples of their age group. Probably the most important reason for the difference between retrospective and prospective studies is the fact that former are liable to underestimation, being based on a selection of liveborns with clinical features of Down's syndrome. A number of liveborns are therefore missed and the same is true for the affected babies who die in the perinatal period<sup>66-68</sup>.

#### INCIDENCE AND RECURRENCE RISKS FOR VARIOUS CATEGORIES OF CONGENITAL DISORDERS

Of the more than 3000 different congenital disorders at present identified, some are caused by chromosomal aberrations<sup>55,70-72</sup> while several hundred malformations are attributed to a combination of unknown environmental and polygenic factors<sup>73,74</sup>. The overall incidence of congenital disorders among live born has been estimated to be 4-6%<sup>75-81</sup>. The usual incidence of major malformations in newborn surveys is 2 to 2.5%<sup>75,77,79,83</sup>. Most of them are limited to specific anatomical areas. Although a number of them are easily detected shortly after birth yet many only become apparent later in childhood or even adulthood. It is therefore not surprising that data derived from a registry for handicapped children and adults and from a large scale surveillance system over a longer period of time, reveal a higher incidence of congenital malformation than newborn surveys. In 48,000 individuals over a period of 21 years an incidence of

3.58% for "multifactorial congenital malformations" was found<sup>81</sup>.

Most congenital malformations are of unknown origin. The most common ones, such as congenital heart diseases, spina bifida, anencephaly, cleft palate and/or cleft lip, and club-foot, are usually defined as "multifactorial" to indicate that their etiology depends on a combination of polygenic predisposition and of environmental factors<sup>73,75,84,85</sup>. Epidemiological studies have given valuable information about the frequency of certain malformations and their distribution in relation to geographic area, ethnic group, social class, infections, time of birth, nutrition, sex, age and parity<sup>86-89</sup>. However, few have contributed to a better understanding of their etiology. It is known that a proportion of recurrent abortion is associated with abnormalities of female reproductive tract which are presumably unrelated to chromosomal abnormalities<sup>90-91</sup>.

Earlier surveys in India, of both live and still birth indicate an incidence of a major congenital anomaly in about 2%, a frequency comparable to the world figure<sup>92</sup>. Goravalingappa and Nashi<sup>93</sup> found 31.27 per 1000 births in Karnataka but malformations were greater (120 per 1000) in stillbirths.

The incidence of neural tube defects, which include conditions like meningocele, anencephaly and spina bifida, has importance in preventive diagnosis. It occurs in numbers from as high as 8/1,000 in some geographic areas like South Wales or Belfast to less than 2/1,000 in regions in Japan, Africa and South America<sup>75,85,94,95</sup>. Usually, the recurrence risk in siblings and in children from an affected parent is related to the frequency of the particular malformation in the general population<sup>96</sup>. The risk for neural tube defects, for instance, matches the actual incidence in England and Wales among newborns as 4.5/1,000<sup>75</sup>. On the other hand, Kleijer *et al*<sup>97</sup> found a recurrence risk of 1.9% in the Netherlands where the occurrence among newborn is about 2/1,000<sup>47</sup>. A high number has been noted in certain parts of India<sup>92</sup>. Major malformations like anencephaly, spina bifida, hydrocephalus, neural tube defects, cleft lip and

palate, talipes, polydactyly, defects of cardiovascular system and gastro-intestinal tract occur in 2% of births in India<sup>98-114</sup>. Of these, the neural tube defect can be detected prenatally through the measurement of serum alfa-fetoprotein levels in the maternal blood<sup>115</sup>. Other congenital malformations similarly detectable include certain cardiac, skeletal and intestinal defects.

#### INCIDENCE AND RECURRENCE RISK FOR SEX—LINKED DISEASES

Antenatal detection of sex of the foetus is a relatively easy procedure involving study of uncultured amniotic fluid for X and Y chromatin and is carried out with success in most laboratories. However, it has occasionally been misused for the selective destruction of female infants as a part of medical termination. The only justifiable indication of sex determination is for the detection of X-linked disorders.

According to McKusick's catalogue<sup>116</sup> about 200 genetic disorders are included as sex linked traits. The X-linked inheritance is established for more than 100 diseases and is highly probable in other cases. Duchenne's progressive muscular dystrophy and haemophilia are more common (300 per 10<sup>6</sup>) than all other X-linked disorders together (200 per 10<sup>6</sup>). In other instances, like X-linked haemophilia, the molecular defect is known, but not expressed in cultured skin fibroblast or amniotic fluid cells.

Immunological tests have improved the accuracy of carrier detection of severe haemophilia A or B at 15-22 weeks of gestation<sup>117-121</sup>. The plasma levels of antihemophilic factor (factor VIII), measured by coagulation assay (VIIC) are subnormal whereas those of the antigenic determinants of a molecule biochemically related to it (VIII RAg) are normal or even increased. The ratio of VIIC to VIII RAg may also be reduced in hemophilic carriers. Determination of this ratio, together with family data, has aided in the detection of the carrier state<sup>122</sup>. Collection of foetal blood by foetoscopy and analysis by DNA hybridisation, as has been carried out in  $\alpha$ -thalassaemia, have now opened up new possibilities<sup>123</sup>.

In USA and Canada, a total of 115 prenatal sex determinations had been carried out in pregnancies at high risk for X-linked disease in 1973<sup>8</sup>. In 1978, this number had increased to 433<sup>124</sup>. A similar number must have been monitored in Western Europe, where by the end of 1974 the main centres had carried out 280 prenatal sex determinations<sup>41</sup>. The majority was concerned with pregnancies at risk for Duchenne's muscular dystrophy and haemophilia, which in series account<sup>9</sup> for 40%. The remaining 20% were pregnancies at risk for other X-linked disorders, such as agammaglobulinemia, adrenal aplasia, diffuse cerebral sclerosis, chronic agranulomatosis, Lowe's syndrome, retinitis pigmentosa and some types of X-linked mental retardation, deafness and blindness.

### CONCLUSIONS

Prenatal diagnosis thus would contribute to positive genetic counselling only if the diagnosis of the disease is definite in the parents in case of both chromosomal or metabolic disorders. This stresses the importance of establishing adequate diagnostic facilities for genetic diseases. The procedure itself is easy and the risk, in experienced hands, minimal. For example, Milunsky<sup>125</sup> recorded 73 misdiagnosis in a worldwide review of 22,000 amniocentesis. In a survey of 2,100 amniocentesis<sup>126</sup> one maternal and 12 foetal deaths were reported. Four years of collaborative work in the USA, where 1,040 diagnostic amniocentesis were matched with controls, showed no difference in the foetal loss in the two groups<sup>127</sup>. The overall risk of loss related to the procedure may be 1 in 500 to 1,000. However, in India, the 2% loss observed<sup>128</sup> is expected to be greater due to non-availability of ultrasound in most centres.

It is to be hoped that with improved facilities like the use of prenatal amniocentesis and other diagnostic methods, prenatal diagnosis of congenital and genetic defects will be helpful in preventing any increase in the genetic load.

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## ANNOUNCEMENT

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