Problem of Down's Syndrome

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Down's syndrome (DS) is the most common single chromosomal disorder and a frequent cause of mental retardation. The incidence of DS varies from 1 in 650 live births among western population to about 1 in 800 amongst Indians. However, between 65 and 80% of affected fetuses go in for abortion or still birth. Now with the increasing age of marriage there is likelihood of obstetricians encountering this problem more and more.

Risk of DS with Maternal Age

Maternal Age (Yrs)	Risk of DS
All ages	1 in 650
30	1 in 900
35	1 in 380
37	1 in 240
40	I in 110
44	1 in 37

Although the incidence of DS rises in babies of mothers more than 35 years of age since only a smaller proportion of pregnancies occur in women of this age group, most affected babies in India are born to younger mothers.

Morphological Features of DS (Trisomy 21)

Round flat face with prominent cheeks and high forehead, upward slanting palpaebral fissures, epicanthic folds, hypertelorism, a short nose, a broad and depressed nasal bridge, anteverted nares, a deformed philtrum, an open mouth, thin upper vermilion and broad everted lower lip, low set ears with prominent antihelix and deep concha, broad hands with simian creases, a short neck and cryptorchidism (Chen et al 1997.)

Types of DS (Genetic Abnormalities)

Trisomy 21	92-95%
(Due to nondysjunction)	
Translocation DS 14:21	3-5%
(About 9% when maternal age is less than 30)	
Other translocations	2%
Mosaic	1%

The maternal risks of Trisomy 21 is age related, being 1 in 1500 at 20 years rising to 1 in 37 at 44 years. The risk of recurrence of DS due to Trisomy 21 is about 1 in 100. The risk of translocation 14:21 recurring is about 1 in 10 if the mother has a balanced translocation and 1 in 50 if the father has the defect. Among Asian, there is 30% chance of recurrence of this due to autosomal dominant inheritance, which becomes sporadic

Antenatal Screening for DS

The first antenatal screening for DS was made in 1968 and screening on the basis of advanced age of women by amniocentesis was gradually introduced. The relationship between low maternal alpha fetoprotein (AFP) and DS was demonstrated in 1983. Subsequently raised maternal serum human chorinic gonadotrophin (hCG) and low unconjugated estriol (uE3) were also found to be associated with DS. These three biochemical markers were used together in 1988 and have become

widely adopted, particularly during 15-18 weeks. DS can be readily diagnosed by amniocentesis and karyotyping of the fetal cells in amniotic fluid. Unfortunatley this procedure carries a risk 0.5-5% of procedure related abortion. The cytogenetic analysis is also costly. Even employed as a usual policy of doing amniocentesis to all women at or above certain age, the identification of DS will at best be 30% and in practice only 14%; the majority still occur in women of younger age group (Chard, and Macintosh 1995).

Interesting observations were noted in comparitive study of serum β hCG, AFP with maternal age in DS screening in Asian population. High free β hCG and low AFP levels were found in 47 Asian DS Programmes. At a 5% false positive rate free β hCG alone would identify 46.8% of DS, age alone would detect 34.5% while AFP alone would detect 17%. Free β hCG, AFP MOM ratio detected 48.9% of DS. When combined with maternal age specific risk, free β hCG could achieve a 59.6% detection rate and AFP alone 42.6%. The detection rate for free β hCG / AFP MOM (Multiples of the normal median) ratio was 61.7% and that of free β hCG - AFP 63.8%. The false positive rate in all these instances was 5%.

Cardiff workers have suggested that DS screening is currently carried out using a combination of markers measured in maternal serum samples; these include maternal Serum alfa fetoprotein (MSAFP), total hCG, uE3 and free β hCG. Number of papers have compared the efficacy of different combinations of these markers. Some recommend MSAFP, total hCG & uE3 (Triple test) while others advocate MSAFP and free β hCG (double test). It is also shown that in such studies the accuracy of estimating, detection rate and false positive rate depend not only upon the method of calculation but also on age distribution of the affected mothers and the parameters used for calculating the patient's specific risk. They have shown that these effects can result in estimate errors of such magnitude that many observed differences in detection rate could be of significance - the same conclusion reached by Wright.

DS screening at an early gestational age (less than 18 weeks) could achieve a 68% detection rate with a false positive rate of 5% compared with a 59% detection rate for a 5.2% false positive rate when screened at a later gestation. Taiwan study show that the use of free β hCG in DS screening programmes can yield an improved efficacy in the detection of DS in an Asian population (Hsu, et al, 1997).

It has been found that maternal serum Inhibin A, a recently discovered marker for DS is significantly elevated in pregnant IDDM mothers when corrected for maternal weight.

Ultrasonogram (USG)

Several papers describe morphological abnormalities in the DS fetus which can be detected by USG during the second trimester.

USG features:

1.Thickened nuchal skin fold, 2. Cystic hygrome , 3.Duodenal stenosis, 4. Non immune hydrops, 5. Shortened long bones, 6. Sandal gap, 7. Macroglossia, 8.Increased Sandal gap, 9. Congenital heart disease.

A normal USG, however, does not rule out the presence of DS.

By observing subtle markers such as nuchal edema, suspicion as to the possibility of DS should be aroused. This is the observation of soft tissue thickening at the back of the neck: thickness of more than 5 mm may be the basis for a first trimester screening test with a detection rate of 80%. USG may become a useful complimentary investigation to biochemical tests with further refinements in the technology and access to well versed staff with reliable equipment (Chard,1995)

On the contrary USG in prenatal diagnosis of DS based on nuchal skin thickness may not be completely useful since this may occur is normal fetuses, it may vary with the attitude of the fetal head and can be produced artificially by the angle of the transducer. However, short femur (using increased BPD: femur length ratio as index) may be useful as ancillary screening method at 16 weeks.

Detailed USG requires great interpretative skill from the operator if unacceptable levels of false positive and false negative diagnosis are to be avoided (Stirrat, 1997).

Moreover, measurements of fetal nuchal translucency vary considerably between centers and could not be reliably incorporated into programmers (Haddow et al, 1998).

During the last decade, it was thought that chorion villus sampling (CVS) at 10-12 weeks may replace amniocentesis at 15 weeks or later for cytogenetic analysis. However the procedure related risk of CVS are more than those of amniocentesis. Hence the CVS may be confined to the diagnosis of single gene defect rather than chromosome defect.

Significant decrease in AFP values occur in DS due to decreased production. Lower levels of AFP can also be seen in :

1. Asian women 2. Vesicular mole, 3. Fetal death,
4. Increased Maternal weight, 5. Post maturity.

Prenatal diagnosis is indicated in the following

1.Pregnancy at or above 33 years. 2. Previous pregnancy with Trisomy 21 or other chromosomal lesion. 3.DS in a close relative., 4. Known translocation in either parent, 5. Family history suggestive of familial tendency to nondysjunction., 6. Low AFP levels in MSAFP Screening., 7. Lowered AFP, lowered uE3, increased hCG in maternal serum marker screening.

L. Down described Down's syndrome (Mongolism) in 1866. During more than a century many attempts were made for the antenatal diagnosis of this dreaded disease. Screening performance varies according to the choice of markers, viz, the double test AFP and hCG, the triple test-AFP, hCg and uE3 and the quadruple test AFP, hCG, uE3, Inhibin A, all in combination with maternal age.

The study of urinary markers and fetal cells in maternal blood is currently the subject of active research. The feasibility of diagnosing the major fetal chromosomopathies by culturing fetal cells later from maternal blood is also being tried.

Even though most of the cases go in for termination after confirmation, there are a few who survive and go in for a variety of corrective therapy. Improved social acceptance, better result with corrective cardiac surgery, seratonergic therapy for aggressive behaviour and Alzheimers disease, orofacial regulation therapy all emphasise the need for early diagnosis of DS patients and initiation of therapy at the appropriate time.

References:

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