INTRODUCTION

Every woman has a risk that her fetus/baby has a chromosomal defect.

"Recent evidence suggests that maternal age can be combined with fetal nuchal translucency and maternal serum biochemistry (free b-hCG (beta unit of human chorionic gonadotropin) and pregnancy-associated plasma protein (PAPP-A)) at 11-14 weeks to identify about 90% of affected fetuses."

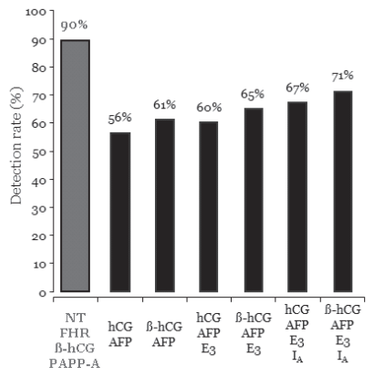
Let us understand the maternal serum biochemistry-free b-hCG and pregnancy-associated plasma protein (PAPP-A) marker in detail for better understanding of the recent concepts where maternal serum biochemistry is an integral part of 11- 14 weeks scan.

Initially before about 40 years it was only the maternal age on which was the factor considered of the screening for the Trisomy / aneuploidy.

We adhered to the dogma of the 35 years of age or equivalent risk; since the maternal age of pregnant women has increased & increasing in India. In the last 20 years, the cut-off age for invasive testing has therefore increased from 35 to 38 years. In screening by maternal age with a cut-off age of 38 years, 5% of the population is classified as 'high risk' and this group contains about 30% of Trisomy 21 babies.

In the late 1980s, maternal age and the concentration of various Fetoplacental products in the maternal circulation -Triple marker test was introduced to select high risk group with better detection rate than age factor alone . At 16 weeks of gestation the median maternal serum concentrations of a-fetoprotein (AFP), unconjugated estriol (uE3), human chorionic gonadotropin (hCG) (total and free-b) and inhibin-A in Trisomy 21 pregnancies are sufficiently different from normal to allow the use of combinations of some or all of these substances to select a 'high-risk' group. This method of screening is more effective than maternal age alone and, for the same rate of invasive testing (about 5%), it can identify about 50-70% of the fetuses with Trisomy 21.

In the 1990s, instead of screening in 2nd trimester, 1st trimester screening was introduced. Prof Kypros Nicolaides from Fetal Medicine Foundation Kings college, London introduce screening by a combination of maternal age and fetal NT thickness at 11-13+6 weeks of gestation. This method has now been shown to identify about 75% of affected fetuses for a screen-positive rate of about 5%. Subsequently, maternal age was combined with fetal NT and maternal serum biochemistry (free b-hCG and PAPP-A) in the first-trimester to identify about 90% of affected fetuses with false positive rate of 3%.Introduction of other ultrasonography markers like fetal nasal bone improves the detection of Trisomy 21 up to 95 %.



From above graph it is very evident that inclusion of chemical markers in maternal evaluation plays important role in improving the detection rate of Trisomy 21.

Sequential screening

* Every woman has a risk that her fetus/baby has a chromosomal defect.
* The background or a priori risk depends on maternal age and gestation.
* The individual patient-specific risk is calculated by multiplying the a priori risk with a series of likelihood ratios, which depend on the results of a series of screening tests carried out during the course of the pregnancy.
* Every time a test is carried out the a priori risk is multiplied by the likelihood ratio of the test to calculate a new risk, which then becomes the a priori risk for the next test.

SERUM BIOCHEMISTRY

Trisomy pregnancies are associated with altered maternal serum concentrations of various Feto-placental products.

The gestational age used for the calculation of biochemical risk must be derived from the CRL and is calculated automatically by the various software's available today on the basis of the CRL at the time of the 11 - 13+6 week's scan.

Maternal serum free b-hCG and PAPP-A are the two main chemical markers evaluates for the fetal aneuploidy today and PlGF (maternal serum placental growth factor) for the prediction of preeclampsia during the pregnancy.

There is no significant association between fetal NT and maternal serum free b-hCG or PAPP-A in either Trisomy 21 or chromosomally normal pregnancies and therefore the ultrasononographic and biochemical markers can be combined to provide more effective screening than either method individually (Spencer et al 1999). Six prospective screening studies have confirmed the feasibility and effectiveness of combining fetal NT and maternal serum free b-hCG and PAPP-A. In the combined data on a total of 38,804 pregnancies, including 182 with Trisomy 21, the detection rate for Trisomy 21 at a 5% false positive rate was 86% (Nicolaides 2004). Screening in the first trimester by a combination of maternal age, fetal NT, FHR and serum free ß-hCG and PAPP-A identifies about 90% of Trisomy 21 pregnancies for a false positive rate of 3%

* The measured concentration of free ß-hCG and PAPP-A is influenced by the machine and reagents used, gestational age, maternal weight, ethnicity, smoking status and method of conception.
* In the calculation of accurate patient-specific risks it is necessary to make adjustments in the measured free ß-hCG and PAPP-A. Each measured level is first converted to a multiple of the expected normal median (MoM) specific to a pregnancy of the same gestation, maternal weight, smoking status, ethnicity and method of conception.
* In Black women the PAPP-A level is about 60% higher than in White women. Failure to take into account ethnic origin would result in substantial underestimate of the true risk of Trisomy 21 in Black women.
* In women who smoke and those conceiving by IVF serum PAPP-A is decreased and this could be misinterpreted for increased risk for Trisomy 21 and a substantial increase in false positive rates.

The level of free b-hCG in maternal blood normally decreases with gestation. In Trisomy 21 pregnancies free b-hCG is increased. The level of PAPP-A in maternal blood normally increases with gestation and in Trisomy 21 pregnancies the level is decreased. For a given gestation, each b-hCG and PAPP-A level represents a likelihood ratio that is multiplied by the a priori risk to calculate the new risk. The higher the level of b-hCG and the lower the level of PAPP-A are associated with the higher the risk for Trisomy 21. Normal handling of samples is only likely to minimally effect the risk assessment of chromosomal anomalies.

However, careful attention should be paid to minimise the increase of free-beta hCG levels in samples shipped as whole blood.

CHEMICAL MARKERS WITH CHROMOSOME ABNORMALITIES:

	βhCG	PAPP-A
T21	↑	↓
T18	↓	↓
T13	↓	↓
Triploidy (paternal)	↑↑↑	↓
Triploidy (maternal)	↓↓	↓↓
Sex chromosome abnormalities	→	↓

In normal euploid pregnancies the average free β-hCG is 1.0 MoM and PAPP-A is 1.0 MoM

In Trisomy 21 compared to euploid pregnancies:

* The difference in biochemical markers is greater at 11 than at 13 weeks
* The difference in fetal NT is greater at 11 than at 13 weeks