Prenatal Screening: Perspective for the Pediatrician

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Pediatricians are the first contact of a child with genetic disorders such as Down Syndrome. After diagnosis, parents often express and wish that if it was possible to detect it during pregnancy and could it be avoided in the future pregnancy. This makes it essential that pediatricians should have some idea about the basic screening methods and strategy used during pregnancy.

Keywords; *Aneuploidies, Down syndrome, Prenatal diagnosis*.

Births with Down syndrome and other aneuploidies continue to occur with a prevalence of 1 in 925 [1]. Prenatal screening for fetal aneuploidies started early with triple test performed in the second trimester (a combination of alfa feto protein, conjugated estriol and beta human chorionic gonadotropin). In the last two decades, the focus of detection has shifted to the first trimester. Two serum markers (pregnancy associated plasma protein A and free beta human chorionic gonadotropin) and one marker assessed by ultrasound (nuchal translucency) are used to predict risk of aneuploidies. Prenatal screening has not been perceived as a health priority in developing countries. Chromo-somal and certain common malformations pose additional financial and social constraints in developing countries. In addition, serum screening may also direct attention and resource allocation to high-risk pregnancies complicated by pre-eclampsia/eclampsia and intrauterine growth retardation (IUGR) [2].

DEFINITIONS

Aneuploidies refer to numerical chromosomal aberrations. Common aneuploidies include Trisomy 21 (Down syndrome), Trisomy 18 (Edward syndrome) and Trisomy 13 (Patau syndrome). Sex chromosomal aneupoidy commonly screened for is Turner syndrome (XO). Risk ascertainment refers to the risk of having a child with any of the above mentioned aneuploidies. The likely risk computed in any pregnancy is illustrated in terms of a value for a given population having the same statistical measurements. Thus the risk computation of 1 in 150 means that if all demographic and biochemical parameters have the same statistical correlation, the likely possibility of a women carrying a fetus with abnormality would be 1 in 150.

An *a priori* risk means the baseline risk conferred on the woman either by age alone or as a result of biochemical screening. The risk increases as age increases due to a higher propensity for non-dysfunction. The risk of Trisomy 21 is 1 in 1667 at 20 years of age and increases to 1 385 at 35 years of age, and 1 in 30 at 45 years of age [3]. The risk calculation takes into account the gestational age at sampling, the status of the fetus-singleton/twinning, maternal weight, maternal diabetes, maternal smoking, and previous history of baby with trisomy 21. Incorporation of values of biochemical analytes along with the demographic data into a designated software generates a risk. Individual values of any analyte or factor are less predictive individually compared to the entire risk computed in a statistical manner incorporating all these factors.

Triple test and Quadruple test (addition of inhibin A) are used to compute risk of aneuploidies in the second trimester (16-20 weeks) [4]. Screening has now shifted to the first trimester and uses both serum and ultrasound markers. Nuchal translucency (NT) refers to the measurement of skin at the nape of the neck in the fetus in sagittal plane [5]. Integrated screening is the term used for assessing the risk in the first trimester followed by using this generated risk as *a prori* risk for the second trimester. The results of the first trimester are not disclosed before the final risk is generated. Contingent screening indicates that second trimester screening is subject (or contingent to) to risk generated in the first trimester [6]. ***Table* I** presents the performance characteristics of these tests [7-9].

TABLE I PERFORMANCE CHARACTERISTICS OF PRENATAL SCREENING MODALITIES

Test	*Timing (wks)*	*Sensitivity*	*False positive rate*
Triple	15-20	72-74%	5%
Quadruple	15-20	79-81%	5%
Serum integrated	10-13 & 15-19	86-89%	5%
Fully integrated with NT	Same as above 10-12	93-95%	5%

Like any other screening technique, confirmatory testing is required to evaluate the risk generated in the first trimester. Women demonstrating a high risk in the first trimester are offered chorionic villus sampling (CVS) and those demonstrating high risk in the second trimester are offered amniotic fluid sampling. In the integrated screening modality, those demonstrating high risk in the first trimester are offered CVS while those with low risk are asked to report later for screening of neural tube defects [10]. The risk cut-offs are carefully weighed against the risk of fetal loss due to amniocentesis and chorionic villus sampling [11]. Even the best modalities are limited in sensitivity and specificity for a confirmed diagnosis of aneuploidies. ***Table* II** depicts the timing and the procedures as an option for any parent.

A large number of these analytes are also being evaluated as potential tools for adverse pregnancy outcome such as pre-clampsia, IUGR and intrauterine demise [12]. More recently, noninvasive prenatal diagnosis as a screening test using next generation sequencing technology has been found to be highly accurate with sensitivity and specificity of upto 98-99% [13]. Despite the accuracy, the cost of the test presently is prohibitive as a screening test.

IMPORTANCE FOR THE PEDIATRICIAN

Pediatricians often face the responsibility of revealing the diagnosis to the parents and dealing with the emotional overture. They also have to deal with complications in the neonatal period (IUGR, congenital anomalies) and various comorbidities (hypothyroidism, recurrent otitis media, atlanato-axial instability, transient myeloproliferative disorders). The problems encountered in a child with Down syndrome are complex and require that the pediatrician liaises with a multidisciplinary team to adequately follow-up every child. Education regarding preventive strategies that reduce the burden of this disorder are of paramount importance.

CURRENT SCENARIO

Prenatal screening is common in developed countries. The biggest challenge in developing countries is late registration of pregnancy missing the opportunity of first trimester screening. Another challenge is the lack of correct recall of maternal age which forms the basis of ascertaining *a priori* risk of screening. With multiple birth orders and large family sizes, mothers tend to forget the date and at times even the year of their birth. A proportion of these women also do not remember the exact date of last menstrual period necessitating a dating scan for correct risk assignment. Since they do not register in the first trimester, this itself is a challenge. Even when women are registered in the first trimester of pregnancy, feasibility and availability of tests are important issues. Inclusion of nuchal translucency and nasal bone parameters improve detection rates and lower false positive rates in first trimester. However, these measurements require expertise and commitment.

The integrated mode of the screening is likely to pose even a bigger challenge because of the attrition between the first and second trimester. The second trimester is an

TABLE II PRENATAL SCREENING TESTS

Test/Procedure	*First trimester screening*	*Integrated prenatal screening*	*Serum integrated prenatal screening*
1st blood sample	9-13 wks	9-13 wks	11-14 wks
Nuchal translucency ultrasound	11-14 wks	11-14 wks	None
2nd blood sample	None	15-18 wks	15-18 wks
Results available	12-19 wks	15-19 wks	15-19 wks
Detection rate (accuracy)	80-85%	85-90%	80-90%
False positive rate	3.9%	2-4%	2-7%
Diagnostic test (if screen positive)	CVS 11-13 wks	Amniocentesis	Amniocentesis

CVS - Chorionic villous sampling.

opportune window for screening not only neural tube defects but also a wider spectrum of malformations [14]. It is very important for the pediatrician to stress upon the availability of the screening modality to fellow obstetricians as it is ultimately the pediatrician who has to deal with a child having disabilities.

The indecisiveness of families to opt for invasive testing after positive screening test is another hurdle delaying the test beyond the permissible time frame of the Prenatal diagnostic techniques (PNDT) act.

THE WAY FORWARD

Mandatory registration of births and deaths may help us overcome certain challenges. However this is likely to take some time till the current birth cohort registered by workers grows up to become sexually productive. Prenatal involvement of male partner is associated with beneficial outcomes such as higher first trimester antenatal visits, and abstinence from smoking and alcohol consumption [15,16]. This practice must be encouraged at least until female literacy and empowerment improve.

Gynecologists posted at primary and secondary level of care should be trained in methods of correct ascertainment of gestational age. Radiologists should also be roped in for encouraging early scanning and helping the gynecologists to effectively date the pregnancy. In our setting, the strategy should be to encourage early registration, improve availability of an early scan for gestational age assessment, provide serum screening to all who register within the stipulated period, and offer nuchal translucency and nasal bone measurement in screen positive group. A contingent approach in the first trimester is likely to be more feasible but is unlikely to become universal due to limited care-seeking during this period.

Resource allocation for such a program is justified by the excellent predictability of first trimester markers to predict adverse pregnancy outcomes. Apart from reducing the financial and social burden from the birth of a child with Down syndrome, it would help gynecologists to identify the subset of women who require closer surveillance and are at a greater risk of developing pre-ecclamsia, preterm birth, fetal demise and IUGR. These may also be selected for expert ultrasonic surveillance, both in first and second trimester

If we take the example of Delhi, approximately 3.6 lakh deliveries take place every year; 63% of these are institutional deliveries [17]. Further, the proportion of women who receive at least one antenatal care visit was 74.4% [17]. Considering this, approximately 75% of pregnant women would be accessible in the second trimester, a time when triple test coupled with a genetic sonogram would pick up more than 70% aneuplodies and a large number of structural defects. Taking Delhi as a model – by implementing screening strategies, approximately 245 births with Trisomy 21 could be prevented every year. We suggest that facilities for collection of samples for triple test should be available at most health facilities. Genetic sonograms currently should be offered in screen positive population, the high risk group and the affordable group. This is probably a trade-off of the limited resources to ensure the best possible yield.

Our second suggestion is implementation of first trimester screening in tertiary-care hospitals. The newer techniques in place can utilize dried blood spots which can be collected at any place and transported across without degradation of biochemical analytes. So the cost of machinery, personnel and expertise need not be duplicated, and the samples collected can be sent to a few centers that are committed and motivated to take up the task of screening. Nuchal translucency and nasal bone parameters can then be used in a contingent manner in the screen positive and high risk group. Preparedness to implement preventive strategies are important today for a better tomorrow.

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