EDITORIAL

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Prenatal Screening for Genetic Disorders: Indian Scenario

India is one of the most religiously and ethnically diverse countries in the world, with highly religious societies and cultures. It is also a breeding point for genetic diversity due to strict breeding practices leading to the accumulation of deleterious genetic variations. The prevalence of birth defects in India is approximately 64.4 per 1000 live births. India being a country of 1.4 billion people is also having a high birth rate and hence a large number of infants with genetic disorders are born every year, almost half a million with malformations and 21,000 with Down syndrome.

Genetic diseases add a huge burden on the population of any country in the form of mammoth costs for the management of morbidities associated with diseases. The best policy to reduce the burden of genetic disorders and congenital disabilities is antenatal screening and newborn screening. Universal prenatal screening is advisable for common genetic disorders and congenital anomalies such as Down syndrome, beta-thalassemia, and neural tube defects.

Several prenatal-screening tests are now available for Down syndrome, but knowledge about the appropriate timing of the test and the need for pre- and post-test counseling may not be up to date among the primary care physicians. In addition, the diagnostic tests for many of the genetic disorders available in India are at a relatively nascent stage. Antenatal diagnostics are available for a few genetic diseases that too in very few hospitals. There is also a considerable degree of confusion regarding the selection of prenatal screening tests in each case. Moreover, there is no nationwide consensus regarding the nature and timing of these prenatal screening protocols. In the absence of any definite guidelines and the additional gaps in the awareness regarding the appropriate prenatal screening in the country, the optimum benefits of these screening protocols are not reaching the population.

Genetic disorders with significant prevalence in India are beta-thalassemia, Down syndrome, and neural tube defects. These diseases pose significant morbidity to the population and hence require population-based prevention programs. The risk of developing beta-thalassemia in a child is 25% if both parents are carriers of beta-thalassemia. Screening of couples for most of the hemoglobinopathies including beta-thalassemia can be done during a pre-pregnancy stage or at the first antenatal visit preferably during the first trimester. Cation exchange high-performance liquid chromatography (CE-HPLC) is the recommended screening test for the detection of the carrier state of hemoglobinopathies such as beta-thalassemia and Sickle cell anemia, through quantification of HbA2, HbF, HbS, HbD, and HbQ. The criteria to detect beta-thalassemia carrier state is a decreased red cell index [mean cell volume (MCV) < 80 fl and mean cell Hb (MCH) < 27 pg] in association with HbA2 ≥ 3.5%. Prenatal diagnosis of beta-thalassemia requires detection of genetic mutation in both parents before testing the DNA of the fetus obtained through chorionic villus sampling (CVS).

Neural tube defect is one of the most common congenital malformations which can be easily prevented by preconceptional administration of folic acid supplementation. Ultrasonography detects necessarily 100% cases of anencephaly at 12–14 weeks of gestation. Other forms of neural tube defects such as meningocele, encephalocele, and open spina bifida can be detected at 16–20 weeks of gestation with specific pointers such as lemon and banana signs. India urgently requires to develop infrastructure through education and motivation of pregnant women for antenatal follow-up and standard of care practices through training of healthcare workers for diagnosis of neural tube defects using ultrasonography and maternal serum alpha-fetoprotein.

Down syndrome is also one of the common genetic diseases accounting for 15–30% of total cases and is the most common cause of intellectual disability. Prenatal screening of Down syndrome includes demographic factors such as maternal age as well as multiple biochemical and ultrasonographic parameters, which collectively achieve a detection rate of 99%. It is most commonly screened through double marker test, triple test, and quadruple test with or without nuchal translucency (NT). Modifications such as sequential testing or the addition of ultrasonographic parameters such as nasal bone can further add to the detection rate. Furthermore, for a definitive diagnosis of suspected cases, an examination of fetal sample is required, which requires chorionic villous sampling (CVS) during the first trimester, or amniocentesis/cordocentesis during the second trimester. These invasive procedures have an inherent risk of abortion and hence health professionals require special training and experience to successfully perform.

With fetal tissues obtained through invasive procedures, chromosomal fluorescent in situ hybridization (FISH) analysis and karyotyping are done for the detection of common aneuploidies. Furthermore, a recent technology-based method based on the cytogenetic microarray (CMA) can be used to analyze chromosomes at a much greater resolution. The cytogenetic microarray can be even considered in prenatal testing of high-risk cases even with normal USG findings. However, all prenatal testing methods and screening procedures including CMA need good supportive counseling facilities.

Cell-free fetal DNA (cffDNA) analysis (also known as noninvasive prenatal test or NIPT) of the maternal plasma is one of the latest tests, which has shown a detection rate of 99–100% of Down syndrome cases. However, with occasional false-positive results, false-negative prenatal tests, and no results in about 2–6% of cases, ccfDNA analysis is still considered a screening test only. Furthermore, an NIPT screen positive case still has to be confirmed by invasive testing before deciding the fate of the fetus.

It is a burning need of the hour to develop guidelines for appropriate screening and diagnosis of common genetic disorders/congenital disabilities in India. Moreover, screening of pregnant women and newborn babies for diagnosis of inherited genetic diseases should be necessarily done in all districts to provide comprehensive clinical care. Amniocentesis and fetal karyotyping should be offered to pregnant women who screen positive for fetal aneuploidy. If invasive testing is being done for pregnancy, cytogenetic microarray testing can

be offered after cost discussion. Moreover, we need to establish genetic diagnostic units in government hospitals, producing skilled clinicians in the areas of human genetics (biochemical genetics, cytogenetics, molecular genetics, clinical genetics, and comprehensive clinical care). Furthermore, accurate pre- and post-test genetic counseling in simple and easily understandable language should be offered essentially.

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