GeneFocus

Prenatal Screening for Sex Chromosome Aneuploidies: Is it Justified?

Shubha R Phadke

Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow, India

Correspondence to: Dr Shubha R Phadke *Email:* shubharaophadke@gmail.com

Abstract

Prenatal screening and testing for common genetic disorders and termination of affected pregnancies is widely accepted as one of the best strategies to reduce the burden of these disorders in the population. However, one has to consider the justification for doing prenatal screening for disorders which may be common but do not have significant disability associated with them. This article outlines the drawbacks of doing antenatal screening especially non-invasive prenatal screening (NIPS) for sex chromosome aneuploidies.

Key words: Non-invasive prenatal screening (NIPS), sex chromosome aneuploidies

Introduction

Non-invasive prenatal screening (NIPS) is a technical marvel and a revolution in screening for chromosomal disorders. Historically, Down syndrome due to trisomy 21 has been a prototype for antenatal screening and diagnosis. Starting from maternal age as the screening strategy, screening test has achieved more than 99% sensitivity and can be offered to all pregnant women (Gil et al., 2014). With use of next-generation sequencing based technology, NIPS achieved acceptance due to very high sensitivity as compared to other screening tests on mother's blood, namely double marker and quadruple marker screens usually done along with fetal ultrasonographic evaluation. Ease of testing and applicability at very early gestation are considered great advantages along with decreased need of invasive testing. The increased applicability resulted in the use of the test for other chromosomal aneuploidies including those of sex chromosomes and screening as early as 10 weeks of gestation. Superficially, this appears a win-win situation, though it is flouting the basic principles of population-based screening which are still applicable. A significant proportion of conceptuses with trisomy 21 are spontaneously aborted before 16 weeks and early screening test may detect them which is not necessary. Secondly, screening is usually done for common disorders while trisomy 13 and 18 are not common and being rare, the positive predictive value for these are significantly lower as compared to that for trisomy 21. Being usually lethal, the burden of these disorders is perceived relatively less as compared to that of rearing a child with trisomy 21 with lifelong disability due to mental handicap. Thirdly, NIPS includes sex chromosome aneuploidies, and guidelines by the American College of Medical Genetics and Genomics (ACMG) also strongly recommend this (Dungan et al., 2023). However, individuals with these disorders usually do not have major disability or significant morbidity.

It is time to ponder upon the recommendations and current practices of NIPS even if cost is not the issue. It may be an over-enthusiastic screening strategy for rare disorders like trisomy 13 and 18 and for sex chromosomal anomalies.

NIPS for sex chromosome aneuploidies

The most common sex chromosome aneuploidies are 45,X (Turner syndrome), 47,XXY (Klinefelter syndrome), 47,XYY (XYY syndrome), and 47,XXX, which have birth frequencies of approximately 1 in 2500, 1 in 500 to 1 in 1000, 1 in 850 to 1 in 3000, and 1 in 1000, respectively. As everyone knows, these are non-lethal abnormalities and there is no significant mental or physical handicap in most of them (Sait and Phadke, 2021). Most of the individuals with 47,XXX and 47,XYY will

go undetected throughout life. The reproductive issues in cases with 45,X and 47,XXY have solutions in this era of assisted reproductive techniques. Hence, these are not the candidates suitable for inclusion in antenatal screening test, as the only option after prenatal diagnosis is termination of the pregnancy. If detected in prenatal diagnosis by amniocentesis, there is a challenge for the genetic counsellor and dilemma for the family. But that is unavoidable and counselling should be positive. The available information about outcomes of 47,XXX and 47,XYY on the internet shows some increased prevalence of reproductive problems and behavioural problems, respectively. The families posed with such challenge have a lot of anxiety and may terminate the fetuses with such sex chromosomal abnormalities or may have issues with emotional bonding or difficulty while bringing up the child.

Though we say that nondirective counselling should be done and the decision of termination should be of the family, understanding the long term outcomes of such variations (without significant clinical abnormalities) is beyond the capacity of lay persons. Hence, prenatal screening for such common aneuploidies without grave significance should not be offered and aneuploidy of sex chromosomes should not be included, just because it is technically possible. The argument against this could be that we shall be failing to diagnose 45,X and 47,XXY. But even if these aneuploidies are detected in amniotic fluid karyotype/ microarray, we communicate that the possible problems are short stature, cardiac anomaly, hypogonadism, and infertility, all of which are manageable.

Prenatal screening is mostly done with the objective of prevention of the birth of a child with disability. Termination of pregnancies with isolated sex chromosomal abnormalities is not justified and hence screening tests should not include these. It leads to undue anxiety and unnecessary termination of pregnancies.

NIPS in the first trimester

The argument for first trimester NIPS is that it enables early reassurance for the pregnancy. But the primary objective of prenatal screening and diagnosis is to prevent the birth of a child with disability and lifelong burden associated with it and not reassurance. No prenatal test can give the assurance of a healthy baby. As half of trisomy 21, more than half of trisomy 13/ 18 and most of monosomy X are spontaneously aborted during the first trimester, it is advisable to do screening after the first trimester. Many of us have experienced that by the time the NIPS report comes as positive, USG already is showing hydrops or cystic hygroma in many cases. This leads to unnecessary guilt on the mother of taking the decision of aborting the pregnancy which was likely to get aborted on its own or at least would have got diagnosed in the antenatal ultrasonogram (USG) at around 13 to 14 weeks.

NIPS for other aneuploidies

Most fetuses with trisomy 13 and 18 have some USG-detectable anomalies and may be picked up simultaneously. Due to the rarity of these conditions, possibility of their getting detected by USG, and the low positive predictive values of screen positive cases, including trisomy 13 and trisomy 18 in the screening panel also needs reconsideration. The prevalence of other rare autosomal trisomies (RATs) being very low, the positive predictive values are too low to be included for screening in the low-risk population. A positive NIPS result creates undue anxiety, increases the need for invasive testing and poses a dilemma for the family. The comprehensive review by Lannoo et al. (2023) has tabulated all the information about predictive values for screening for RATs and various issues related to that. It is an eye-opener for clinicians and provides the list of research issues in this area.

The better option

It may be better to do NIPS only for trisomy 21 at 16 to 18 weeks of gestation and combine it with maternal serum alpha fetoprotein assay, which is still very important (Racusin et al., 2015; Siddesh et al., 2017) and ultrasonography for malformations. One-stop screening for genetic disorders antenatally should be convenient and not a burden. As NIPS is still too costly to be advocated for population-based strategy, quadruple/double marker screening followed by chromosomal analysis by cytogenetic microarray on amniotic fluid is a cost-effective strategy as it may miss some fetuses with trisomy 21 but will detect other chromosomal imbalances of clinical significance (Phadke et al., 2017).

Secondly, in the name of 'non-directive counselling' we should not create and pose dilemmas for the pregnant woman and let her face the difficult decision-making with her limited knowledge of medical disorders and ability to understand the complexities of uncertain outcomes. No amount of genetic counselling can give an accurate picture about the life of an adult with Klinefelter syndrome and Turner syndrome. During pregnancy the mother is emotionally labile and very sensitive about the baby in the womb. The screening programs should be such that the dilemmas in front of the family are minimal and the screening program should be only for the disorders for which we feel termination of the pregnancy is ethical.

Thirdly, as screening programs (with the good intention of improving outcome of the pregnancy) for genetic disorders, preeclampsia, etc. are increasing, they are causing an immense burden of the logistics of testing, providing appropriate pre and post-test counselling, understanding counselling issues, and facing uncertainties. Due to unavailability of genetic counsellors, involvement of social workers in counselling for prenatal screening, and the time constraints of the clinicians, the families usually do not get adequate and clear information during pre-test counselling. There are limited studies available in published literature documenting the magnitude of anxiety generated in the family due to prenatal screening, but all of us have the experience of seeing 'would-be mothers' scanning the internet at night and losing sleep over the screening test results. We have to see how to minimize the anxiety and try to keep the woman happy and cheerful during pregnancy. Outcome of most pregnancies is good, but it will not be incorrect to say that most of the pregnant women spend a significant time worrying about the possibility of chromosomal disorders.

Even those who refuse screening tests carry the burden of anxiety. In addition to improving pre-test counselling, as a medical genetics society we need to decide what to offer. The emotional burden of the tests for preventing disorders (very rare trisomy 18 and 13 and common sex chromosomal anomalies with satisfactory outcome) should not be more than the advantage of prevention. We need to carefully reconsider what we want to offer in screening tests. And last but not the least, research on the effect of screening tests on the emotional health of pregnant women is needed.

Conclusion

Prevention is better than cure. But in the case of prenatal screening the method of prevention of genetic disorders is termination of pregnancy. Though this option is justified and acceptable to many of us and the lay persons, wisdom and ethics should be the responsibility of the clinician who is offering the test. So, the medical genetics community has to take a decision about which disorders need to be included in the screening program. The severity of the disorder in terms of outcome and high prevalence should be points to consider while choosing the disorders to be included in NIPS. Hence, sex chromosomal abnormalities and trisomy 13/18 should not be included.

'We should not offer more and make the pregnant woman suffer!'

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