EDITORIAL

Tapping The New Horizons In Prenatal Screening: Maternal Blood For Cell Free DNA Detection

1. The data from first trimester abortions, still births and neonatal deaths indicates an alarming prevalence of chromosomal abnormalities.[1] Moreover, in a region like subcontinent, where marriages between cousins have prevailed for long and the rate of consanguinity is high, there is a significant prevalence of various genetic disorders.[2] The convention to date in prenatal screening pivots around either high resolution ultrasonographic examination for fetal anomalies, invasive procedures such as amniocentesis or chorionic villus sampling and blood/urine biomarker measurements including unconjugated estriol, Alpha feto protein (AFP) and others. There is, without a shadow of doubt, an emerging need for more sensitive, robust and clinically more yielding early markers with broader coverage of genetic defects in pregnancy.[3] The expansion of diagnostic molecular techniques have made it possible to replace the conventional invasive techniques.[4] Circulating cell free DNA (cfDNA) is a fragmented and slightly denatured DNA fragment (50-280 bp) released into circulation after broken cells are shed into the blood circulation subsequent to cellular damage or some denaturing process.[5] Advances in nano molecular diagnostics can decipher the tiny signatures on their surfaces, be it some cancerous process or some genetic anomaly from feto-maternal mix up of blood. cfDNA overtime has become detectable to depict the changes in genetic structure of fetal diseases very early in the course of pregnancy.

2. The concept of cf DNA detection probably was well conceived by the end of last century, however the clinical translation for its detection from maternal blood and placenta got a punching trigger in the last decade when enrichment techniques for cf DNA collection for prenatal genetic testing evolved.[6] In addition to now accessible molecular biotechnology, the feasibility of prenatal conduct of test is better matured and improvised to supersede the conventional and invasive investigations as highlighted in above discussion. Interestingly this novel technique may have an edge over conventional testing as reports have suggested maternal incidental findings during noninvasive prenatal testing for fetal aneuploidies.[7]

3. The conventional paradigm of in vogue radiological and pathological methodologies though seems antiquated, would still be commanding the skies for quite some time in near future given the handy nature of technologies, coupled with financial limitations to support newer technologies and lack of expertise especially in developing economies. Other emerging challenges for cfDNA testing implementation in prenatal workup are the limited infrastructure with obvious constraints of human resource in molecular domain, absence of harmonization of preanalytic practices across institutions comprising reproducibility of testing, minimum role of multi-disciplinary team approach, and lack of social state support system for prenatal diagnosis. Moreover, novel and emerging molecular technologies like sequencing, microarrays and multiplexed PCRs remain underutilized due to the health economy of our country. Developing countries with existential issues associated with loads of medical illiteracy coupled with ongoing population outburst seems to lag behind in adopting contemporary biotechnologies and bioinformatics.[8] Similarly, another factor which can possibly appear in introducing cfDNA use in prenatal screening could be the glorifying ignorance among conventionally trained medics who may need to learn and advocate the simpler molecular techniques to identify fetal aneuploidies.[9] The same author in an earlier study indicated that there will always be the possibility of other chromosomal aberrations apart from trisomy 13, 18 and 21 leading to a false negative outcome requiring appropriate pre-test genetic counselling and rightful interpretation of any such investigation by a trained medical genetic specialist and molecular pathologist.[10]

4. Social and psychological impacts of undesirable pregnancy outcomes and their non-amenability to treatment, compounded by the lack of a social state support system for the disabled warrants innovative and ingenious solutions for prenatal screening. The direct and indirect cost of incorporating radiological and biochemical tests leads multiple false positives leading to invasive procedures like CVS and amniocentesis as highlighted by Bianchi *et al*.[11] The same author highlighted positive predictive value and sensitivity of cfDNA testing to be greater than 80-90%, which is almost 10 times more than conventional approach which can obviate requirement of invasive CVS and amniocentesis thus rightsizing cost and procedural nuisance among pregnant subjects.[12] The American College of Medical Genetics and Genomics (AMCG) after acknowledging the need of prenatal screening with cfDNA has even given a next-level statement by recommending this methodology as the gateway to whole genome /exome sequencing in fetuses which can become a

game changer in prenatal screening.[13] Pakistan with a documented population growth rate of 2.2%, rapid and haphazard urbanization and rapidly challenging healthcare economics faces up to 80/1000 and 20/1000 cases with positive maternal AFP screen positive and combined testing incorporating hCG, ME and AFP cases of Trisomy 21 respectively.[14] cfDNA based prenatal screening can reduce false positives and further optimize cost and patient concerns.

5. Provided ethical concerns causing additional abortions among few, the authors opined that this technique has the muscle to replace the conventional prenatal screening especially the biochemical modes. The tide of conventional diagnostics seems to be turning in favor of innovative nano tools allowing non-invasive methodologies for prenatal genetic disease detection. It is anticipated that incoming times will soon witness cfDNAs entering the routine prenatal screening. It's about time that this technology be incorporated in pre-natal screening in our country for reducing unnecessary invasive procedures and ensuring early diagnosis. There is a pressing need for better education for health professionals and genetic counsellors, incorporation of multidisciplinary team approach and general awareness in masses regarding acceptability of prenatal screening.

REFERENCES

1. Blue NR, Page JM, Silver RM. Genetic abnormalities and pregnancy loss. Semin Perinatol 2019; 43(2): 66-73.
2. Hafeez A, Ijaz A, Chaudhry N, Ali O, Khadim MT. Diagnosis of inherited metabolic disorders by selective metabolite testing: three years experience at a tertiary care center in Rawalpindi. J Pak Med Assoc 2020; 70(1): 53-7.
3. Lewis C, Choudhury M, Chitty LS. Hope for safe prenatal gene tests. A content analysis of how the UK press media are reporting advances in non-invasive prenatal testing. Prenat Diagn 2015; 35(5): 420-427.
4. Robson SJ, Hui L. National decline in invasive prenatal diagnostic procedures in association with uptake of combined first trimester and cell-free DNA aneuploidy screening. Aust N Z J Obstet Gynaecol 2015; 55(5): 507-510.
5. Chen E, Cario CL, Leong L, Lopez K, Márquez CP, Chu C, Li PS, et al. Cell-free DNA concentration and fragment size as a biomarker for prostate cancer. Sci Rep 2021; 11(1): 5040.
6. Sekizawa A, Purwosunu Y, Matsuoka R, Koide K, Okazaki S, Farina A, et al. Recent advances in non-invasive prenatal DNA diagnosis through analysis of maternal blood. J Obstet Gynaecol Res 2007; 33(6): 747-764.
7. Brison, N, Van Den Bogaert K, Dehaspe L. Accuracy and clinical value of maternal incidental findings during non-invasive pre-natal testing for fetal aneuploidies. Genet Med 2017; 19: 306-313.
8. Ali MM, Hamid M, Saleem M, Malik S, Mian NA, Ihsan MA, Tabassum N, Mehmood K, Awan F. Status of bioinformatics education in south asia: past and present. Bio-med Res Int 2021; 2021: 5568262.
9. Liehr T. Non-invasive prenatal testing, what patients do not learn, may be due to lack of specialist genetic training by gynecologists and obstetricians? Front Genet 2021; 12: 682980.
10. Liehr T, Lauten A, Schneider U, Schleussner E, Weise A. Noninvasive prenatal testing - when is it advantageous to apply. Biomed Hub 2017; 2(1): 1-11.
11. Bianchi DW, Chiu RWK. Sequencing of circulating cell-free DNA during pregnancy. N Engl J Med 2018; 379(5): 464-473.
12. Gregg AR, Van den Veyver IB, Gross SJ, Madankumar R, Rink BD, Norton ME. Noninvasive prenatal screening by next-generation sequencing. Annu Rev Genomics Hum Genet 2014; 15: 327-347.
13. Gregg AR, Gross SJ, Best RG, Monaghan KG, Bajaj K, Skotko BG, et al. ACMG statement on noninvasive prenatal screening for fetal aneuploidy. Genet Med 2013; 15(5): 395-398.
14. Rahman S, Obaid-Ur-Rahman M. Prevalence rate of Down's syndrome in Karachi resident women. Pak J Pharm Sci 2005; 18(2): 61-63.

Dr Sikandar Hayat Khan
Department of Pathology,
Combined Military Hospital, Multan Pakistan

Dr Ayesha Hafeez
Department of Pathology,
Combined Military Hospital Multan Pakistan

Dr Raja Kamran Afzal
Department of Pathology,
Combined Military Hospital Multan Pakistan