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Will Cell Free Fetal DNA (NIPT) With Obstetrical Ultrasound Be Replaced As First Line Screening Program For All Antenatal Women To Eliminate Chromosomal Abnormalities?

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Abstract: *Prenatal diagnosis of fetal anomalies& their clinical outcome at an early gestational age,with non-invasive screening tools- sonography and maternal blood cell free fetal DNA, proved to be a new biomarker. Establishment of new algorithm in perinatal biology.*

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I. Introduction

In each conception there is a risk of chromosomal defect. It is estimated that at least 10% to 15% of conceptions are chromosomally abnormal. Among 3% to 4% are evident as birth defects. Birth defects result from the interaction between the genetic makeup of the embryo and the environment in which it develops. The basic developmental information is encoded in genes but the genotype is subjected to environmental influences that can be observed phenotype.Despite considerable advances and research over past several decades; the etiology of more than half of the human congenital abnormalities remain unknown.

INCIDENCE OF BIRTH DEFECT IN INDIA

Disorder	Incidence	Birth/year
Congenital malformation	1:50	6,78,000
Chromosomal Diseases	1:166	1,60,000
Down Syndrome	1:800	34,000
Trisomy 13	1:6,500	4100

These are the numbers retrieved from Birth defects registry of India.

Why screening ?

- Desire to have a normal baby.
- Chromosomal abnormality are relatively common, occur spontaneously and sporadically.
- Increase in numbers of women-giving birth later.
- Newborn with chromosomal abnormalities pose a considerable financial, social and emotional strain on the family.
- Prepare for birth of an abnormal infant.
- Desire to have a normal baby.
- Chromosomal abnormality are relatively common, occur spontaneously and sporadically.
- Increase in numbers of women-giving birth later.
- Newborn with chromosomal abnormalities pose a considerable financial, social and emotional strain on the family.
- Prepare for birth of an abnormal infant.

METHODS OF PRENATAL DIAGNOSIS

Noninvasive test

- Bio-chemistry-Maternal Serum screen
- Ultrasonography
- Isolation of fetal cells from maternal circulation

Invasive test

- Amniocentesis
- Chorionic villus sampling
- Cordocentesis
- Pre implantation genetic diagnosis
- Fetoscopy

Journey to rule out abnormal pregnancy, Initially it was screened for Trisomy 21 because of long life span and quality of life issues.

Year	Screening technique	Detection rate	specificity
1966	**Amniocentesis**		
1970	**Age alone**		
1980	**Era of biochemical screening test**		
	AFP		
	Triple screen	**72%**	**5%false +ve**
	Quad test	**79%**	**5%false +ve**
	Panta screen	**83%**	**5%false +ve**
1980	**Chronic villus sampling as diagnostic test**		
1990	**Ultrasonography & biochemical test**		
	First trimester anomaly scan	**80-85%**	**5%false +ve**
	Sequential screening	**90-94%**	**3%-5%false +ve**
2010	**Ultrasonography, biochemical test with NIPT (material serum cell free fetal DNA)**	**98%**	

Conventional screening methods

Strategy	Analytes	Detection rate
First trimester screen	NT, PAPP-A, free B- HCG	79-87%
NT	NT alone	64-70%
Triple test	MSAFP, free B-HCG, UE3	61-70%
Quadruple test	MSAFP, Free B-HCG, UE3, Inhibin –A	74-81%
Integrated Screen	First Trimester Scan & Quad Test	94-95%
Stepwise sequential screen	First Trimester Screen and quad test 1% offered diagnostic test	90-95%
Contingent sequential screen	FTS &Quad test	88-94%
Cell free fetal DNA(high risk pregnancy)	No analytes	98%

Based on a 5% positive screen rate

ULTRASOUND –AN EFFECTIVE SCREENING TOOL

- In recent years dramatic advances in ultrasound technology- including improved spatial and contrast resolution, 3&4 dimensional imaging, harmonic imaging, new- improved ultrasound scanning probe, improved digital review work station made easy to diagnose subtle anatomic defects.
- Advance communication media, collaborative studies and refinement of guidelines has made ultrasonography a popular screening technique in Obstetric prathinctice.

CELL FREE FETAL DNA (NIPT)

- Cell free fetal DNA is discovered by Dennis Lo in 1997.
- Fetal DNA comes primarily from the placental cell apoptosis.
- Fetal DNA is 5-25% of the total cell free DNA.
- Fetal DNA clears rapidly from maternal circulation soon the baby is delivered.
- NIPT is primarily designed to screen for the common trisomies of chromosomes 21, 18 and 13 in singleton and twin pregnancies.

High quality first trimester screening services significantly enhancesautonomy of pregnant women:
Ultrasonography

Ultrasound machines are forming pictures using sound waves. Ultrasound has revolutionized the care of women during pregnancy. Most of the anatomical abnormalities are detected with high end machines.

CellfreefetalDNA

Noninvasive prenatal single blood test that uses cutting edge technology to screen pregnant woman for chromosome abnormalities within 10 gestational weeks.

SUPERIORITY OF NEWER TECHNIQUES

- Anomalies which were not diagnosed in first trimester are now diagnosed in first trimester due following improvements:
- Greater accuracy-sensitivity, specificity, positive predictive value
- Less risk to fetus and mother-pregnancy loss, maternal infections
- Low cost
- More targets- All typesoftrisomies, gene mutations, micro-deletion, single gene disorder, whole genome sequencing, Rh typing,maternal and paternally inherited alleles …..etc

Goal of Obstetric scan with NIPT

- Enable a high detection rate of fetal abnormality
- Reduce false positive results
- Reduce exposure of fetus to risk
- Easily reach to every mother.

Summary

- Targeted anomaly scan is a golden screening tool to rule out anatomical abnormalities in utero fetus.
- With that NIPT cell free fetal DNA performs well as an advanced screen for whole chromosome aneuploidy.
- Economic consideration will likely dictate whether its use can be expanded to all risk populations or whether it can be applied routinely for all antenatal patients.
- Conventional first trimester screening and NIPT provides complementary information regarding risk of chromosomal abnormalities.

II. Conclusion

With usage of high end sonography machine in obstetric practice& interrogation of NIPT into clinical care has identified a new aspect of perinatal biology. With the advent of advances in sonography, it has now become possible to reveal earliest anatomical and physiological changes of fetus. Cell Free fetal DNA is a new biomarker that can provide information about the placenta and potentially be used to prognosticate clinical problem and outcome of fetus.

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