Non-invasive prenatal test: advantages, limitations and future

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INTRODUCTION

At the present time, a pregnant woman who wants to know if her fetus is affected by any kind of genetic disorder has two options, either a non-invasive test, like an ultrasonography or maternal serum markers, which gives a risk score of being affected, or an invasive test, like amniocentesis or chorionic villus sampling, which gives a definitive result about the fetus possible genetic alterations at the molecular level. However, both have benefits and drawbacks. As a result, neither is used as a single test offered to every pregnant woman.

The discovery of cell-free fetal DNA (cff-DNA) in maternal plasma by Lo et al (1997) opened a door to the development of a non-invasive prenatal test (NIPT) designed to be able to give a final diagnosis. Up to now, NIPT, despite having a high accuracy in detecting trisomies 13 (Patau's syndrome), 18 (Edward's syndrome) and 21 (Down's syndrome), as well as sex chromosomes aneuploidy, is still not a diagnostic.

AIMS

1. To describe and compare non-invasive and invasive prenatal tests currently used in a clinic.
2. To research the knowledge of the new non-invasive prenatal test.

METODOLOGY

Review based on reading current papers.

INVASIVE AND NON-INVASIVE TESTS

NON-INVASIVE TESTS

They might be used first to determine if a more invasive test needs to be performed.

✓ They usually do not cause any physical pain, to the mother or the fetus.

✖ The tests have a false-positive rate of 2-3% and false-negative rate of >5%.

Maternal age

Figure 1

Ultrasonography

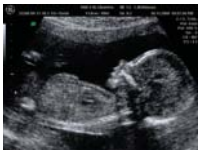

Figure 2. www.centromedicobidasoa.com

Maternal serum markers

Figure 3. http://abcnews.go.com

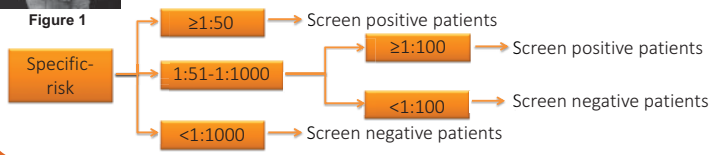

Figure 4. Nicolaides KH, et al. (2012)

INVASIVE TESTS

Tests are usually performed on women identified to be at risk for aneuploidies. They are needed to diagnosis any genetic disorder

✓ They present higher accuracy respect to non-invasive screenings.

✖ There is 1% greater risk of miscarriage.

Chorionic villus sampling (CVS)

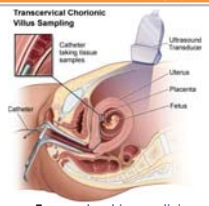

Figure 5. www.hopkinsmedicine.org

- Carried out between 10 to 12 weeks.
- The cells come from placenta tissue

Amniocentesis

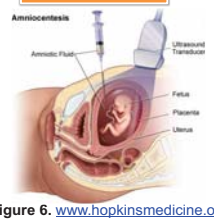

Figure 6. www.hopkinsmedicine.org

- Carried out between 15 to 20 weeks.
- The cells are shed by the fetus in the amniotic fluid.

NON-INVASIVE PRENATAL TEST (NIPT)

METHODS

A. Quantitative methods

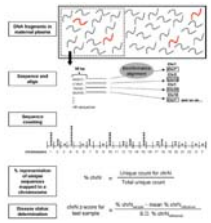

Figure 7. Chiu RW, et al. (2008)

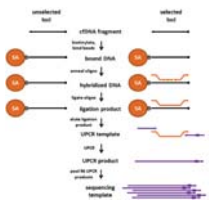

Figure 8. Sparks AB, et al. (2012)

Massive Parallel Shotgun sequences all cff-DNA in maternal plasma.

Digital Analysis of Selected Regions only sequences loci from chromosome of interest by including a targeted amplification step.

B. SNP-based methods

Prenatal Support algorithm determines fetal copy number using parental genotypes. The algorithm gives an individualized risk score for each sample.

Next-generation Aneuploidy Test Using SNPs algorithm calculates the risk score for each patient taking into account parental genotype data and inheritance patterns.

ADVANTAGES

✓ NIPT has higher sensitivity, specificity and false-positive rates than maternal serum screenings.

✓ NIPT gives results as earlier as 9 weeks of pregnancy without needing multiple blood samples.

LIMITATIONS

✖ NIPT can detect trisomies 13, 18 and 21 and sex chromosome aneuploidies.

✖ NIPT is still not a diagnostic test.

✖ NIPT hardly detects mosaicism confined to the placenta.

✖ False positive and false negative results can occur.

✖ It is unclear if NIPT can be performed in low risk population, multiple gestations and/or obese women.

✖ It is necessary that each sample passes a DNA quality control for results to be given.

FUTURE: improvements that should be implemented before performing as a diagnostic test:

1. To magnify the accuracy of both sequencing and results.
2. To develope an enrichment method of cff-DNA.
3. More research about the isolation and concentration of cell fetal DNA.
4. Further investigation about how mosaicism and maternal weight can affect the test results.
5. Regulations about the performance and quality of developed method.

ACOG STATEMENT

❖ NIPT should be accompanied by genetic counselling.

❖ There is the necessity to emphasize that NIPT is not still a diagnostic test.

❖ NIPT would be offered to women in one of the following groups:

A prior pregnancy with trisomy or parental balanced robertsonian translocation.

Women ≥35 years old.

Increased risk of aneuploidy found in non-invasive screening.

CONCLUSION

- Currently, although NIPT can reduce the number of unnecessary invasive diagnostic procedures in some cases, it is still not a diagnostic test.
- NIPT is thought to be a secondary screen procedure, performed after high-risk of aneuploidy has been found, because of its higher detection rate and lower false positive rate.
- At the present time, it has not been proved whether or not one method is better than the other.
- Further investigation and experiments are needed for NIPT to become a widespread non-invasive diagnostic test.
- NIPT costs must be minimized and guidelines about quality control and test warranty should be reported.

REFERENCES

- Lo et al. Presence of fetal DNA in maternal plasma and serum. *Lancet* (1997)
- ACOG Committee Opinion 545. *Obstet Gynecol* (2012).
- Nicolaides KH et al. Noninvasive prenatal testing for fetal trisomies in a routinely screened first-trimester population. *Am J Obstet Gynecol* (2012)