2017

Prenatal Screening for Aneuploidy: Should cfDNA Replace Traditional Methods?

Rachel Watson
University of North Dakota

Prenatal Screening for Aneuploidy: Should cfDNA replace traditional methods?

Rachel Watson, PA-S
Department of Physician Assistant Studies, University of North Dakota School of Medicine & Health Sciences
Grand Forks, ND 58202-9037

UND School of Medicine & Health Sciences
University of North Dakota

Abstract

In 2011, advances in research in medical genetics led to the advent of prenatal cell-free DNA (cfDNA) or also known simply as non-invasive prenatal screening or testing (NIPS). This screen consists of analyzation of placental DNA circulating in maternal blood. NIPS has had a major impact on prenatal screening for aneuploidy. Mixed opinions and data exist as to whom this test is most appropriate for. The sensitivity and specificity of this screen in detecting common fetal aneuploidies has been well documented as superior to other screens in high-risk populations, but less so in low- risk obstetric populations. This paper will compare and contrast NIPS to more traditional screening methods such as first trimester maternal serum biochemical assay of human chorionic gonadotropin (hCG) and pregnancy associated plasma protein A (PAPP-A), and second trimester markers which include hCG, unconjugated estriol, inhibin A, and maternal serum alpha-fetoprotein.

Introduction

Screening for chromosome abnormalities prenatally is a complex topic and should be employed as an essential component of comprehensive obstetrical care. Various screening options are available to screen for the most common fetal aneuploidies, namely Trisomy 21 (Down syndrome), Trisomy 18, and Trisomy 13. Each screening tool has advantages and disadvantages, and informed decision making between patient and provider is essential for selection of which screen suits each patient, if any.

The traditional methods of screening will be compared to NIPS including gestational age at which these screens may be performed, sensitivity and specificity for Trisomy 13, 18, and 21, and for which populations these screens are most appropriate.

Statement of the Problem

With an increase in the amount of options for screening for fetal aneuploidy, awareness and understanding of the disadvantages and advantages of each screening tool is necessary in providing comprehensive obstetric care. Patients must first be counseled on the existence and possibility of fetal chromosome abnormalities; and informed decision making between patient and provider should ensue regarding which, if any, screening tool best suits the patient.

Research Question

Why should prenatal screening be offered? What are the current options for screening for fetal aneuploidy? Should NIPS replace standard screening for aneuploidy?

Literature Review

Why should prenatal screening be offered?

It is been well documented that the risk of carrying a fetus affected by any chromosome abnormality increases with maternal age.

Table 1. Risk of Chromosomal Abnormalities Based on Maternal Age at Term

Age at Term	Risk of Trisomy 21*	Risk of Any Chromosome Abnormality†
15‡	1:1,578	1:454
16‡	1:1,572	1:475
17‡	1:1,565	1:499
18‡	1:1,556	1:525
19‡	1:1,544	1:555
20	1:1,480	1:525
21	1:1,460	1:525
22	1:1,440	1:499
23	1:1,420	1:499
24	1:1,380	1:475
25	1:1,340	1:475
26	1:1,290	1:475
27	1:1,220	1:454
28	1:1,140	1:434
29	1:1,050	1:416
30	1:940	1:384
31	1:820	1:384
32	1:700	1:322
33	1:570	1:285
34	1:456	1:243
35	1:353	1:178
36	1:267	1:148
37	1:199	1:122
38	1:148	1:104
39	1:111	1:80
40	1:85	1:62
41	1:67	1:48
42	1:54	1:38
43	1:45	1:30
44	1:39	1:23
45	1:35	1:18
46	1:31	1:14
47	1:29	1:10
48	1:27	1:8
49	1:26	1:6
50	1:25	§

(ACOG, 2016)

What are the current options for screening for aneuploidy?

- ***First trimester screening***: Maternal serum hCG and PAPP-A + nuchal translucency ultrasound at 11 to 14 weeks
- ***Second trimester screening***: Quad screen analyzes four biochemical markers which include hCG levels, alpha-fetoprotein, unconjugated estriol, and dimeric inhibin A.
- ***Integrated/Sequential screening***: First trimester nuchal translucency study with ultrasound, hCG and PAPP-A levels, as well as a second trimester quad screen
- ***NIPT/cfDNA***: Analyzation of placental DNA circulating in maternal blood

Discussion: Should cfDNA replace traditional methods?

According to a survey published by the Journal of Maternal-Fetal and Neonatal Medicine in September of 2016, obstetric care providers identified NIPS as clinically superior to other screening tools (Brewer, Demers, & Musci, 2016). The survey stated that 81.5% of respondents believed that NIPS is a superior test in screening for aneuploidy regardless of maternal age. The survey also stated that most respondents would like ACOG to formally recommend this screening tool to all pregnant women, regardless of age.

Table 2. Characteristics, Advantages, and Disadvantages of Common Screening Tests for Aneuploidy

Screening Test	Gestational Age Range for Screening (Weeks)	Detection Rate for Down Syndrome (%)	Screen Positive Rate* (%)	Advantages	Disadvantages	Method
First trimester†	11–14‖	82–87	5	1. Early screening 2. Single test 3. Analyte assessment of other adverse outcome	Lower DR than combined tests NT required	NT+PAPP-A and hCG
Triple screen	15–22	69	5	1. Single test 2. No specialized US required 3. Also screens for open fetal defects 4. Analyte assessment for other adverse outcomes	Lower DR than with first-trimester or quad screening Lowest accuracy of the single lab tests	hCG, AFP, uE3
Quad screen†	15–22	81	5	1. Single test 2. No specialized US required 3. Also screens for open fetal defects 4. Analyte assessment for other adverse outcomes	Lower DR than combined tests	hCG, AFP, uE3, DIA
Integrated§	11–14, then 15–22	96	5	Highest DR of combined tests Also screens for open fetal defects	Two samples needed before results are known	NT+PAPP-A, then quad screen
Sequential‖ Stepwise	11–14, then 15–22	95	5	First-trimester results provided; Comparable performance to integrated, but FTS results provided; also screens for open fetal defects; analyte assessment for other adverse outcomes.	Two samples needed	NT+hCG+ PAPP-A then quad screen
Contingent screening¶		88–94	5	First-trimester test result: Positive: diagnostic test offered Negative: no further testing Intermediate: second-trimester test offered Final: risk assessment incorporates first- and second-trimester results	Possibly two samples needed	NT+hCG+ PAPP-A, then quad screen
Serum Integrated†	11–14; then 15–22	88	5	1. DR compares favorably with other tests. 2. No need for NT	Two samples needed; no first-trimester results	PAPP-A+quad
Cell-free DNA#	10 - term	99 (in patients who receive a result)	0.5	1. Highest DR for Down syndrome 2. Can be performed at any gestational age after 10 weeks 3. Low false-positive rate in high-risk women (or women at high risk of Down syndrome)	1. NPV and PPV not clearly reported 2. Higher false-positive rate in women at low risk of Down syndrome 3. Limited information about three trisomies and fetal sex 4. Results do not always represent a fetal DNA result	Three roughly equivalent molecular methods
Nuchal Translucency†	11–14‖	64–70	5	Allows individual fetus assessment in multifetal gestations Provides additional screening for fetal anomalies and possibly for twin–twin transfusion syndrome	1. Poor screen in isolation 2. Ultrasound certification necessary	US only

(ACOG, 2016)

Advantages of NIPS:

- High detection rates for the most common aneuploidies
- Can be performed any time after 10 weeks gestation
- Only one blood draw needed

Disadvantages of NIPS

- Only detects Trisomy 21, 18, and 13
- Mixed data on PPV in non high-risk populations
- Unreliable with multiples

Applicability to Clinical Practice

The research as stated in this review is highly applicable to clinical practice due to the fact that offering prenatal screening for aneuploidy to all women is an important part of providing comprehensive obstetric care. Physician Assistants in both the primary care setting and women's health setting may be providing obstetric care to patients, and knowledge of not only the existence of chromosome alterations but how to screen for them is of upmost importance in providing quality care. ACOG recommends offering screening to every pregnant patient. Knowledge of the benefits, limitations, and drawbacks of each screening test is an integral part of appropriate genetic counseling.

.

References

•American College of Obstetrics and Gynecologists Committee on Genetics, Society for Maternal-Fetal Medicine. (2015). Committee Opinion Number 640: Cell-free DNA Screening for Fetal Aneuploidy. *Obstetrics & Gynecology, 125*(6), 1544-1547. doi:10.1097/01.AOG.0000466370.86393.d2

•American College of Obstetrics and Gynecologists, Society for Maternal-Fetal Medicine. (2016). Practice Bulletin Number 163: Screening for Fetal Aneuploidy. *Obstetrics and Gynecology, 127*(5), 979-981. doi:10.1097/AOG.0000000000001439 [doi]

•Bianchi, D. W., Parker, R. L., Wentworth, J., Madankumar, R., Saffer, C., Das, A. F., . . . Sehnert, A. J. (2014). DNA sequencing versus standard prenatal aneuploidy screening. *New England Journal of Medicine, 370*(9), 799-808. Doi:10.1056/NEJMoa1311037

•Brewer, J., Demers, L., & Musci, T. (2016). Survey of US obstetrician opinions regarding NIPT use in general practice: Implementation and barriers. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, , 1-4. doi:10.1080/14767058.2016.1225035 [doi]

•Gregg, A. R., Skotko, B. G., Benkendorf, J. L., Monaghan, K. G., Bajaj, K., Best, R. G., . . . Watson, M. S. (2016). Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. *Genetics in Medicine,18*(10), 1056-1065. doi:10.1038/gim.2016.97

Acknowledgements

First and foremost I would like to thank my late father, **William Watson, MD**. His influence on my life has been and will always continue to be profound. I would also like to thank my advisor, Julie Solberg PA-C, for her support in my studies throughout the program. I would also like to thank my mother, Debbie Watson, for her encouragement and support. In addition, I would like to thank my husband, Travis Aukerman, for his support.