The Effects of Improved Serum Screening on Prenatal Invasive Testing

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Abstract

Objective: One goal of new technologies for prenatal screening is to decrease loss of healthy fetuses attributable to invasive testing. Our objective was to determine the impact of new screening technologies on invasive diagnostic testing by chorionic villous sampling (CVS) or amniocentesis.

Methods: Genetics and ultrasound databases were searched for singleton pregnancies undergoing invasive procedures and/or prenatal screening. Rates of CVS and amniocentesis were compared across three cohorts (November-October): T1- 2004-05, immediately prior to first trimester screening; T2- 2010-11, first trimester screening well established; and T3- 2012-13, following implementation of cell-free fetal DNA noninvasive prenatal tests.

Results: Invasive testing decreased significantly by 33% from T1 to T2 and another 46% from T2 to T3. In T1, 136 patients tested; in T2, 94 tested [136/3530 (3.9%) vs. 94/3646 (2.6%), $p = .0002$]. In T3, 51 tested [51/3713 (1.4%), $p < .0001$]. The indications for seeking specific invasive tests were significantly impacted over the three periods of genetic screening: Amniocentesis $p = .027$; CVS $p = .003$. The percent of invasive tests resulting in abnormal karyotype increased ($p = .007$).

Conclusions: Over time, we did less invasive testing of our high risk patients but identified more abnormalities; thus we have put fewer healthy fetuses in our region at risk.

Key Words: Invasive prenatal testing; Noninvasive prenatal screening test; Prenatal genetic screening

Introduction

According to the American College of Obstetricians and Gynecologists (ACOG), all pregnant women should be offered screening for fetal chromosomal abnormalities (aneuploidies) regardless of the mother's age.[1] The technology of prenatal genetic screening has evolved considerably over the past several decades, and there are a variety of screening tests now available. ACOG has recommended that obstetricians determine which screening tests to offer based on the evidence regarding accuracy and geographic availability of each screening test.[1] The newer screening tests have been made available to women in western North Carolina as resources have allowed.

There are several options for screening for women in the first and second trimester of their pregnancies; these include screens that utilize serum hormone assessment, ultrasound, or a combination of these to assess for risk of trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), and open neural tube defects.[2-4] The options for women who are first seen during the second trimester of pregnancy (13-25 weeks gestation) are limited to the quadruple screen (a serum screen known as the "quad screen" most often done at 16-18 weeks gestation)[5] and ultrasound examination. Traditionally, women who present past 23 weeks gestation do not have the option for serum screening, and ultrasound is our only way of assessment past that point in a pregnancy. The sensitivity of serum screening and combined serum/ultrasound screening ranges from 80-90% depending on the test used. Ultrasound alone has a lower sensitivity for aneuploidy detection, around 50%.[1]

Women who are seen in the first trimester (conception-12 weeks gestation) have more options that provide earlier information and a higher detection rate. First trimester screening with nuchal

translucency plus serum analytes can be used between 11 and 14 weeks gestation and has been validated in both low- and high-risk populations. Cell-free fetal DNA screening is the newest, noninvasive prenatal screening test (NIPT) that indicates if a woman is at increased risk of having a fetus with trisomies 21, 18, or 13.[2-3,6] The test can be performed any time after 10 weeks gestation, and it measures the relative amount of free fetal DNA in the mother's blood.[7] NIPT offers a much better detection rate for these aneuploidies than any other screening test currently available. This method is thought to detect greater than 99% of all Down syndrome pregnancies and greater than 96% of all trisomy 18 pregnancies. It detects about 91% of all trisomy 13 pregnancies.[8-9] Owing to its decreased invasiveness and higher detection rate, NIPT is recommended for use with women at increased risk for aneuploidy by professional organizations including ACOG, the Society for Maternal-Fetal Medicine, the International Society for Prenatal Diagnosis, the American College of Medical Genetics and Genomics, and the National Society of Genetic Counselors.[7,10-13]

Regardless of chosen screening method, including no screening at all, women have the option to undergo invasive, confirmatory, prenatal testing using either amniocentesis or chorionic villus sampling (CVS).[14-16] However, there is an increased risk of miscarriage associated with these procedures.[17] Previous research suggests the number of women who opt for invasive prenatal testing has declined following the introduction of first trimester screening at various institutions.[18-23] Likewise, with the uptake of NIPT, patients' desire to undergo invasive testing has declined considerably, although considerable variation still exists in overall rates, test-specific rates, and population-specific rates of invasive testing.[24]

Due to the limited obstetric resources in western North Carolina, first trimester screening options and invasive testing *without* prenatal screening have been restricted to patients at high risk for aneuploidy, such as those women with advanced maternal age (AMA) or a prior aneuploid fetus. Thus, the rate of change and overall rate of invasive testing in our region may not mirror that which has been reported from larger urban areas with more ample resources or from geographic regions outside Appalachia.

The objective of this paper is to compare the western North Carolina rates of invasive testing, amniocentesis and CVS, in three cohorts of women at high-risk for aneuploidy: (1) Prior to the local introduction of first trimester screening; (2) Post-implementation of first trimester screening; and (3) Post local implementation of cell-free fetal DNA NIPT.

Methods

This was a retrospective cohort study spanning three time spans of prenatal screening technologies available in the region's referral center for high risk obstetric care. MAHEC OB/GYN Specialists serves the 16-county region of western North Carolina; our Department of Maternal-Fetal Medicine performs virtually all invasive procedures for prenatal diagnosis in the region. We have three out-posted genetic counselors that rotate days of patient care in our office. This project was approved by the Mission Hospital Institutional Review Board.

We included all pregnant women undergoing early screening for aneuploidy within three selected 1-year periods reflecting availability of screening options within our clinic:

1. Time 1, immediately prior to the introduction of first trimester screening (T1: Pre NT/MSS), ran from November 2004 through October 2005;
2. Time 2, first trimester screening, nuchal translucency and maternal serum screening, was well established; however, NIPT was not yet available (T2: NT/MSS), ran from November 2010 through October 2011.
3. Time 3, when NIPT was fully available (T3: NIPT), ran from November 2012 through October 2013.

Genetics and ultrasound databases were searched for singleton pregnancies undergoing invasive procedures and/or nuchal translucency with maternal serum screening or cell free fetal DNA NIPT for the indications of AMA, previous child with chromosomal/genetic abnormality for which prenatal testing is available, abnormal US (aneuploidy marker or major structural difference), abnormal serum screen (NT + serum, NIPT, quad screen). Patient names during the three time periods were extracted electronically from the prenatal testing laboratory and provided by the testing company to the genetic counselor co-investigator. We reviewed the MAHEC OB/GYN Specialists medical records of these patients and manually extracted the research data via paper and pencil. Data were entered and analyzed using SPSS 18.0.1 (SPSS, Inc. Chicago, IL; 2009).

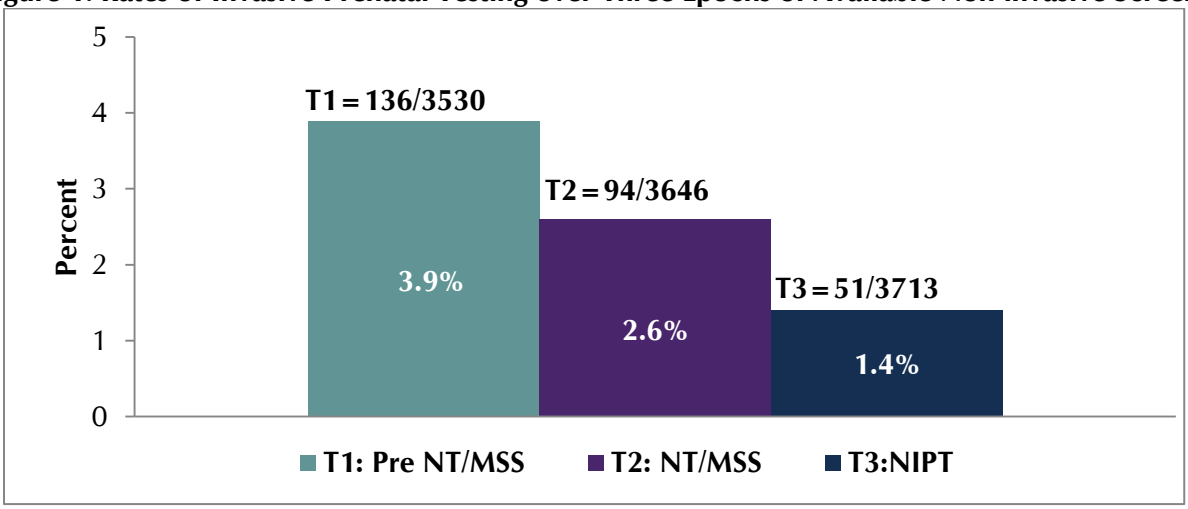
Descriptive statistics were used to summarize the rates and indications for invasive testing. Ages of patients at the time of testing were compared using Kruskal-Wallis tests over the three periods of time, and using Mann-Whitney for comparison between types of invasive tests. Rates of invasive confirmatory testing over time were compared using Chi square analysis. As percentage of multiple gestations, referral patterns, and patient volumes have remained stable over the last decade, denominators for the Chi square analyses equaled 95.2% of total the births for each of the respective 1-year periods, in our regional hospital.

Results

The rate of invasive testing decreased significantly by 33% from T1 to T2 ($p = 0.001$), and another 46% from T2 to T3 ($p = 0.001$). Overall, invasive testing decreased from 3.85% (95%CI 3.21 - 4.49) to 2.58% (95%CI 2.06 – 3.10) to 1.37% [(95%CI 0.99 – 1.75); $p = 0.001$; see Figure 1].

The rates of decline of amniocentesis and CVS did not follow a similar pattern (see Table1). Amniocentesis dropped 14.3% between T1 and T2 and then 56.9% between T2 and T3 for an overall decline of 63.1%. For CVS, the decline between T1 and T2 was 57.7% and between T2 and T3 was 9.1% for an overall decline of 61.5%.

Figure 1. Rates of Invasive Prenatal Testing over Three Epochs of Available Non-invasive Screens



The percentages of each type of invasive testing changed significantly over time to an increased percentage of amniocentesis during T2 but dropped back again in T3 ($p = 0.040$; (Amniocentesis T1 = 61.8%, T2 = 76.6%, T3 = 60.1%; CVS T1 = 38.2%, T2 = 23.4%, T3 = 30.1%). There was no change in ages of women choosing invasive testing across the three time periods (amniocentesis $p = 0.856$; CVS $p = 0.060$; see Table 1). Overall, however, women choosing amniocentesis were younger than those choosing CVS [34.4 years (17-45.9) vs. 38.1 years (20.3-45.2), respectively; $p = 0.001$)].

Table 1. Patient Age and Indication for Invasive Prenatal Testing

	Amniocentesis			CVS		
	T1 n=84	T2 n=72	T3 n=31	T1 n=52	T2 n=22	T3 n=20
Ages Median (min-max)	32.2 (16-45)	32.7 (18-44)	32.8 (18-43)	38.7 (34-45)	38.5 (25-43)	38 (20-43)
Indication n(%)						
Abnl screen	20 (24)	12 (17)	5 (16)	0	0	0
Abnl scrn & AMA	8 (10)	15 (21)	2 (7)	0	0	2 (10)
Abnl US	18 (21)	24 (33)	10 (32)	0	0	3 (15)
Abnl US & AMA	7 (8)	5 (7)	3 (10)	3 (6)	0	3 (15)
Previous child w/abnormality	1 (1)	2 (3)	2 (7)	1 (2)	3 (14)	1 (5)
Previous child w/abnormality & AMA	0	0	1 (3)	1 (2)	1 (5)	0
AMA only	30 (36)	14 (19)	5 (16)	46 (90)	18 (82)	11 (55)

The indications for invasive tests were significantly impacted over the three time spans of genetic screening (amniocentesis p=0.027; CVS p=0.003; see Table 1). Invasive testing by amniocentesis occurred more commonly for abnormal ultrasound findings or serum screens (any kind) than for AMA alone or in combination with these other factors. Even CVS, despite the earlier gestational age at testing, showed a shift in indication; AMA alone declined and AMA plus abnormal screen or US increased dramatically.

The number of invasive tests resulting in abnormal karyotype increased from 2.9% to 6.4% to 15.7% (p=.007). The increased positive detection rate per invasive test was most pronounced for CVS which increased from 1.9% to 20%. The type of abnormality identified is shown in Table 2. Additionally, the abnormal karyotypes diagnosed via invasive testing shifted away from predominately trisomy 18 and to trisomy 21.

Table 2. Abnormal Results of Invasive Testing

	Amniocentesis			CVS		
Time Period Screened	**T1** n=84	**T2** n=72	**T3** n=31	**T1** n=52	**T2** n=22	**T3** n=20
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Positive Test Results	3 (3.6)	5 (6.9)	4 (12.9)	1 (1.9)	1 (4.5)	4 (20)
Karyotypes	46XY,T18 47XY,T21 47XY,T21	47XY,T18 47XY,T18 47XX,T18 47XX,T18 47XY, T21	47XY, T13 47XY, T13 47XX,T21 47XY,T21	47XY,T21	47XX,T21	45XO 47XX,T21 47XX,T21 47XY,T21

Discussion

In our practice, the successive introduction of improved, early screening tests for aneuploidy in a high risk population has led to a significant decline in the total number of patients seeking invasive testing by amniocentesis or CVS. Overall, the rates were very low. The initial rate of 3.9% was reduced by 33% with the introduction of first trimester screening, and another 46% following the introduction of

NIPT. Patients were more likely to pursue invasive testing when an abnormal finding (ultrasound or serum screen) accompanied by advanced maternal age. Further, the detection of abnormal karyotypes per invasive test was increased; thus, we have decreased risks of invasive testing to healthy fetuses in our region.

We found one other report that traced changes in the rates of invasive testing over the three periods of prenatal screening technologies. Larion, et al. found a steady decline in the number of amniocentesis performed annually in the Norfolk, VA area: 755 before the combined first trimester screen to an average of 300 afterwards, and then 160 in the first year following the introduction of NIPT. Declines were reported as 60.3% and another 46.7%, respectively, for an overall decline of 78.8%.[25] CVS rates, however, spiked sharply with an increase of 81.8% after the combined first trimester screen. The rate then dropped precipitously after the introduction of NIPT – down 78% - for annual numbers of procedures equal to 55 then 100 and then 22, respectively. We traced our decline in annual amniocentesis to be somewhat small after the introduction of the first trimester screen (14.3%) but higher than Larion, et al. after the introduction of NIPT (56.9%). Our CVS decline pattern was quite different than Larion, et al. as we witnessed a substantial decline after the introduction of the first trimester screen (57.7%) followed by a smaller reduction of 9.1% post NIPT.

Changes with the Introduction of First Trimester Screening (T1: Pre NT/MSS to T2: NT/MSS)

Our decrease in invasive testing rates with the introduction of first trimester screening, whether nuchal translucency and/or serum screening with the quad screen (33% reduction to 2.6%), are consistent with most literature that focused solely on before versus after first trimester screenings. Zoppi, et al. focused specifically on the introduction of nuchal translucency in Cagliari, Italy and reported a 10.3% decrease in invasive testing among women of advanced maternal age.[18] Chasen, et al. found women in Ithaca, NY were less likely to undergo CVS following nuchal translucency screening compared to women without the screening: 1.9% versus 7.1% respectively.[20]

Benn, et al. focused on the rate of invasive testing after the introduction of serum screening and second trimester ultrasounds in Connecticut, and reported an overall reduction of 50% in invasive tests.[19] Comas, et al. reported a dramatic reduction of 75.5% in invasive testing among women in Barcelona, Spain.[22] Meng, et al. reported a 57.2% decline between 2000 and 2012, prior to the introduction of NIPT, in New Haven County, Connecticut.[24] Conversely, Blumenfeld, et al. from Stanford, CA, reported no change in monthly invasive testing rates in the first 12 months following the introduction of state-sponsored first trimester screening.[26] And while Larion, et al. reported a decline in amniocentesis, they reported a dramatic uptick of 81.8% in CVS.[25] Nakata, et al. reported a 61% decrease in the rate of CVS among women in Los Angeles, CA, (from 36% to 14%; an average 3% decline per year in 2001-2007), but a sharp rebound in 2008 to 24%. Likewise, they noted a 45% reduction in amniocentesis (from 56% to 31%; an average decline of 4% per year) with a sharp rebound in 2008 back to 36%.[21] Thus, changes in the rate of invasive testing while generally declining, were nevertheless population and test-specific.

Some researchers noted shifts in the type of invasive test as the overall rates declined. Zoppi, et al. reported a slight reduction (-2% to 29%) in proportion of CVS versus amniocentesis;[18] Comas, et al., however, found an increase (+10% to 13%).[22] Larion, et al. reported a substantial increase in the proportion of CVS relative to amniocentesis.[25] We found the proportion of CVS to amniocentesis declined 28% from 33.3% to 23.4% between T1 and T2.

We also found an increase in the proportion of abnormal karyotypes per invasive testing - from one abnormal karyotype in 34 tests (2.9%) up to one in 15.7 tests (6.4%). This was consistent with Benn, et al. who reported similar changes from one abnormal karyotype in 43 tests (2.3%) to one in 14 tests (7.0%), and with Meng, et al. who reported the diagnostic yield increased from 7.2% to 13.4%.[19,24] This was, however, inconsistent with Zoppi, et al. who reported no change (2.75% vs. 2.18%).[18]

Changes with the Introduction of Noninvasive Prenatal Testing (NIPT) (T2: NT/MSS to T3: NIPT)

NIPT similarly impacted the rate of invasive testing among our patients – down 46% from 2.6% to 1.4%. This post NIPT decline in invasive testing is consistent with the hypothetical model predictions (from 50% to 95%) and the studies of high-risk women's prenatal genetic testing choices reviewed by Warsof, et al. in their 2015 systematic review.[23] Actual decreases in invasive testing in the United States were cited as ranging between 17% and 72%; Warsof, et al. conclude the considerable variability is a result of varied populations of patients studied (e.g., AMA only, positive prenatal screen only, all comers for genetic counseling, etc.), variability in rates of testing (e.g., percentages in single digits through 40% of patients opting for invasive testing), and differences in change patterns between types of tests. Decreases in CVS rates ranged from 14% to 77%, while decreases in rates of amniocentesis ranged from 23% to 53%.

Despite this considerable variability, declines were reported from virtually all studies. Platt, et al. concluded that the declines they observed over multiple sites were probably a national trend rather than regional findings. Close inspection, however, revealed Platt, et al.'s work over multiple sites were primarily urban areas in California, Nevada, Connecticut, Virginia, and Minneapolis.[27] The studies conducted in the United States reviewed by Warsof, et al. were likewise conducted in cities in California, Virginia, Texas, and Maine.[23]

In our predominantly rural region of western North Carolina, we have found similar overall reductions in invasive testing after our introduction of NIPT. The rate of CVS, however, decreased minimally – less than any reported - while the rate of amniocentesis dropped by more than half.

Of note, the rate of and specific karyotypes identified also changed after the introduction of NIPT. Our rate of detection increased from 6.4% to 15.7%.Before NIPT, two of six abnormalities were T21 while the other four were T18. Post NIPT, the majority of the abnormal karyotypes were T21 (five of eight) and none were T18. Norton, et al. reviewed almost 3000 abnormal karyotypes identified from invasive testing in California; they reported a detection rate of 11.5% with 53.2% being T21. It is possible that our patients with T18 aneuploidies detected by NIPT chose not to have invasive testing whereas women screened positive for T21 and T13 chose confirmatory testing; it is also possible that this is a random finding due to our small prevalence of abnormal karyotypes.

Another limitation of our results stems from not following cases from positive screening through testing, other than reporting indications for genetic counseling associated with invasive testing. Further, we did not examine our results by gestational age at screening nor did we include the rate of fetal loss from invasive testing procedures, miscarriage or termination. Additionally, our results are specific to our region and one high-risk maternity care program, and thus, not generalizable to other sites in Appalachia or other mostly rural regions in the United States.

Conclusion

Studies that have examined rates of invasive testing with the introduction of first trimester screening *or* the introduction of NIPT generally report decreases in population-specific and test-specific prevalence of invasive testing in urban centers around the United States. Ours is only the second report to examine longitudinal change over three epochs of evolving screening technologies, and it is the only one we found that focused on a population of pregnant women seeking genetic counseling in a regional referral center in the southern Appalachians.

In the setting of this patient-driven testing scheme, our rate of invasive testing declined while the proportion of abnormal results of invasive testing is higher. Thus, we may put fewer healthy fetuses at risk.

References

1. ACOG Committee on Practice Bulletins. ACOG Practice Bulletin No. 77: screening for fetal chromosomal abnormalities. Obstet Gynecol. 2007 Jan;109(1):217-27. PubMed PMID: 17197615.
2. Mayo Clinic [Internet]. Rochester: Mayo Clinic; c. 1998-2016 [updated 2015; cited February 4, 2016]. Available from: http://www.mayoclinic.org/tests-procedures/quad-screen/basics/definition/prc-20013408.
3. U.S. National Library of Medicine [Internet]. Washington, DC: U.S. National Library of Medicine; c. 1993-2016 [updated 2012; cited February 3, 2016].Available from: http://ghr.nlm.nih.gov/condition/down-syndrome.
4. U.S. National Library of Medicine [Internet]. Washington, DC: U.S. National Library of Medicine; c. 1993-2016 [updated 2012; cited February 3, 2016]. Available from: http://ghr.nlm.nih.gov/condition/trisomy-18.
5. March of Dimes [Internet]. Washington, DC: March of Dimes; c. 2016 [updated 2012; cited February 3, 2016].Available from: http://www.marchofdimes.org/complications/neural-tube-defects.aspx.
6. U.S. National Library of Medicine [Internet]. Washington, DC: U.S. National Library of Medicine; c. 1993-2016 [updated 2013; cited February 1, 2016]. Available from: http://ghr.nlm.nih.gov/condition/trisomy-13.
7. Committee Opinion No. 640: Cell-Free DNA Screening For Fetal Aneuploidy. Obstet Gynecol. 2015 Sep;126(3):e31-7. doi: 10.1097/AOG.0000000000001051. Review. PubMed PMID: 26287791.
8. Gil MM, Quezada MS, Revello R, Akolekar R, Nicolaides KH. Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol. 2015 Mar;45(3):249-66. doi: 10.1002/uog.14791. Epub 2015 Feb 1. Review. PubMed PMID: 25639627.
9. Verweij EJ, van den Oever JM, de Boer MA, Boon EM, Oepkes D. Diagnostic accuracy of noninvasive detection of fetal trisomy 21 in maternal blood: a systematic review. Fetal Diagn Ther. 2012;31(2):81-6. doi: 10.1159/000333060. Epub 2011 Nov 17. Review. PubMed PMID: 22094923.
10. Society for Maternal-Fetal Medicine [Internet]. Washington, DC: Society for Maternal-Fetal Medicine; c. 2000-2016 [updated 2015; cited August 18, 2015]. Available from: https://www.smfm.org/publications/157-%20SMFM-statement-maternal-serum-cell-free-dna-screening-in-low-risk-women%202000-2015.
11. Benn P, Borell A, Chiu R, Cuckle H, Dugoff L, Faas B, Gross S, Johnson J, Maymon R, Norton M, Odibo A, Schielen P, Spencer K, Huang T, Wright D, Yaron Y. Position statement from the Aneuploidy Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis. Prenat Diagn. 2013 Jul;33(7):622-9. doi: 10.1002/pd.4139. Epub 2013 May 21. PubMed PMID: 23616385.
12. Gregg AR, Gross SJ, Best RG, Monaghan KG, Bajaj K, Skotko BG, Thompson BH, Watson MS. ACMG statement on noninvasive prenatal screening for fetal aneuploidy. Genet Med. 2013 May;15(5):395-8. doi: 10.1038/gim.2013.29. Epub 2013 Apr 4. PubMed PMID: 23558255.
13. Devers PL, Cronister A, Ormond KE, Facio F, Brasington CK, Flodman P. Noninvasive prenatal testing/noninvasive prenatal diagnosis: the position of the National Society of Genetic Counselors. J Genet Couns. 2013 Jun;22(3):291-5. doi: 10.1007/s10897-012-9564-0. Epub 2013 Jan 22. PubMed PMID: 23334531.
14. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 88, December 2007. Invasive prenatal testing for aneuploidy. Obstet Gynecol. 2007 Dec;110(6):1459-67. PubMed PMID: 18055749.

15. Mayo Clinic [Internet]. Rochester: Mayo Clinic; c. 1998-2016 [updated 2015; cited February 4, 2016]. Available from: http://www.mayoclinic.org/tests-procedures/amniocentesis/basics/definition/prc-20014529.
16. Mayo Clinic [Internet]. Rochester: Mayo Clinic; c. 1998-2016 [updated 2015; cited February 4, 2016]. Available from: http://www.mayoclinic.org/tests-procedures/chorionic-villus-sampling/basics/definition/prc-20013566.
17. Ogilvie C, Akolekar R. Pregnancy Loss Following Amniocentesis or CVS Sampling-Time for a Reassessment of Risk. J Clin Med. 2014 Jul 8;3(3):741-6. doi: 10.3390/jcm3030741. PubMed PMID: 26237475; PubMed Central PMCID: PMC4449654.
18. Zoppi MA, Ibba RM, Putzolu M, Floris M, Monni G. Nuchal translucency and the acceptance of invasive prenatal chromosomal diagnosis in women aged 35 and older. Obstet Gynecol. 2001 Jun;97(6):916-20. PubMed PMID: 11384696.
19. Benn PA, Egan JF, Fang M, Smith-Bindman R. Changes in the utilization of prenatal diagnosis. Obstet Gynecol. 2004 Jun;103(6):1255-60. PubMed PMID: 15172861.
20. Chasen ST, McCullough LB, Chervenak FA. Is nuchal translucency screening associated with different rates of invasive testing in an older obstetric population? Am J Obstet Gynecol. 2004 Mar;190(3):769-74. PubMed PMID: 15042012.
21. Nakata N, Wang Y, Bhatt S. Trends in prenatal screening and diagnostic testing among women referred for advanced maternal age. Prenat Diagn. 2010 Mar;30(3):198-206. doi: 10.1002/pd.2434. PubMed PMID: 20063323.
22. Comas C, Echevarria M, Rodríguez I, Serra B, Cirigliano V. Prenatal invasive testing: a 13-year single institution experience. J Matern Fetal Neonatal Med. 2014 Aug;27(12):1209-12. doi: 10.3109/14767058.2013.855893. Epub 2013 Nov 8. PubMed PMID: 24131234.
23. Warsof SL, Larion S, Abuhamad AZ. Overview of the impact of noninvasive prenatal testing on diagnostic procedures. Prenat Diagn. 2015 Oct;35(10):972-9. doi: 10.1002/pd.4601. Epub 2015 May 21. Review. PubMed PMID: 25868782.
24. Meng J, Matarese C, Crivello J, Wilcox K, Wang D, DiAdamo A, Xu F, Li P. Changes in and Efficacies of Indications for Invasive Prenatal Diagnosis of Cytogenomic Abnormalities: 13 Years of Experience in a Single Center. Med Sci Monit. 2015 Jul 5;21:1942-8. doi: 10.12659/MSM.893870. PubMed PMID: 26143093; PubMed Central PMCID: PMC4497468.
25. Larion S, Warsof SL, Romary L, Mlynarczyk M, Peleg D, Abuhamad AZ. Association of combined first-trimester screen and noninvasive prenatal testing on diagnostic procedures. Obstet Gynecol. 2014 Jun;123(6):1303-10. doi: 10.1097/AOG.0000000000000275. PubMed PMID: 24807333.
26. Blumenfeld YJ, Taylor J, Lee HC, Hudgins L, Sung JF, El-Sayed YY. Utilization of available prenatal screening and diagnosis: effects of the California screen program. J Perinatol. 2012 Dec;32(12):907-12. doi: 10.1038/jp.2012.8. Epub 2012 Mar 8. PubMed PMID: 22402484.
27. Platt LD, Janicki MB, Prosen T, Goldberg JD, Adashek J, Figueroa R, Rodis J, Liao W, Sehnert AJ, Snyder HL, Warsof SL. Impact of noninvasive prenatal testing in regionally dispersed medical centers in the United States. Am J Obstet Gynecol. 2014 Oct;211(4):368.e1-7. doi: 10.1016/j.ajog.2014.03.065. Epub 2014 Apr 3. PubMed PMID: 24705127.
28. Norton ME, Jelliffe-Pawlowski LL, Currier RJ. Chromosome abnormalities detected by current prenatal screening and noninvasive prenatal testing. Obstet Gynecol. 2014 Nov;124(5):979-86. doi: 10.1097/AOG.0000000000000452. PubMed PMID: 25437727.

Disclosure: None of the authors have any conflicts of interest to disclose.
Funding: No external funding supported this project.
Authors' Contributions:

Carol C. Coulson, MD, Maternal-Fetal Medicine Specialists and Faculty Mentor: Project conceptualization and design, interpretation, critical revision, and approval of the final manuscript
Shelley L. Galvin, MA, Director of Research: Data analysis and interpretation, manuscript drafts and critiques, final approval of the manuscript
Shearon F. Roberts, MS, CGC, Genetic Counselor: Obtained data, interpretation, critical revision, and final approval of the manuscript
Rick Loftis, MD, MAHEC OB/GYN Resident: Interpretation, and prior presentation
Jennifer E. Warren, MD, Maternal-Fetal Medicine Specialists and Faculty Mentor: critical revision and final approval of manuscript

Previous Presentation:

Coulson CC, Galvin SL, Roberts SF, Loftis RM, Warren JE. Prenatal testing five years after the start of nuchal translucency/first trimester serum screening. Poster session presented at: American College of Medical Genetics Annual Clinical Genetics Meeting; 2013 March 22; Phoenix, AZ.

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