SMFM White Paper – Aneuploidy Screening in Twin Pregnancies

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The Problem

Over the last four decades, twin pregnancies have increased from 18.9 per 1,000 births in 1980 to 32.6 per 1,000 births in 2018. [1] With this increase in incidence and advances in genetic technology, MFM practitioners are more frequently faced with new challenges in the selection of testing for appropriate aneuploidy screening. Theoretically, the risk of aneuploidy in a dizygotic twin gestation is twice that of a singleton gestation. However, large-scale studies have shown that the observed risk of aneuploidy in a dizygotic twin pregnancy may be lower than expected in clinical practice. [2] In monozygotic twin pregnancies, the genetic makeup of each twin is almost always identical, although case reports exist that describe discordant genotypes in this setting. [3] Unfortunately, no form of serum-based genetic screening in twins is as accurate as in singletons, which can present clinical dilemmas for patients and providers alike.

Aneuploidy Screening Options in Twin Pregnancies

The currently available aneuploidy screening options in twin pregnancies include first-trimester nuchal translucency screening, second-trimester quad marker screening, and cell-free DNA screening.

Historically, comprehensive first-trimester aneuploidy screening consisted of a sonographically assessed nuchal translucency measurement and serum testing of beta hCG and PAPP-A. Prats et al. performed a systematic review of the literature to determine the performance of comprehensive first-trimester screening for Trisomy 21 in twin pregnancies. Their analysis determined that the pooled sensitivity of the test was 89.3%, with a pooled specificity of 94.6% for the detection of Trisomy 21. [4] The performance of comprehensive first-trimester genetic screening in twin gestations for Trisomy 13 and Trisomy 18 has not been well described in the literature, presumably due to the low number of affected fetuses. With the recent closure of a large first-trimester PAPP-A and free beta hCG screening laboratory, some practices now face challenges in offering first-trimester aneuploidy screening. Nonetheless, nuchal translucency measurement alone is still a screening option for twin pregnancies. While the sensitivity for Trisomy 21 screening in this setting is similar to the sensitivity in singletons (70 to 80%), there is a greater false positive rate, which some authors attribute to an inherent nuchal translucency discordance in monochorionic twin gestations. [5] This increased false positive rate may lead to an increase in invasive procedures.

Second–trimester quad marker screening, which consists of the serum measurement of AFP, unconjugated estriol, inhibin A, and hCG, presents another option for aneuploidy screening in twin pregnancies. In singleton pregnancies, the quad screen has an overall detection rate for Trisomy 21 of 81 percent, with a screen positive rate of 5 percent. [6] In twin pregnancies, various detection rates have been reported for quad marker screening for Trisomy 21. One European meta-analysis reported the Trisomy 21 detection rate to be as low as 47 percent. [7] As is the case with all forms of serum-based screening in twins, concern exists with quad

marker screening that abnormal analytes related to an affected twin may be masked by the presence of normal screening analytes in the unaffected cotwin. [8]

The analysis of cell-free DNA is currently the most accurate aneuploidy screening test available in singleton pregnancies, with pooled detection rates of 99.2%, 96.3%, 91%, 90.3%, and 93%, and false positive rates of 0.09%, 0.13%, 0.13%, 0.23%, and 0.14% for Trisomy 21, Trisomy 18, Trisomy 13, Monosomy X, and all other sex chromosomal aneuploidies respectively. [9] In October 2020, the American College of Obstetricians and Gynecologists supported offering all prenatal genetic screening options, including cell–free DNA screening, to all pregnant women regardless of their a priori risk. [10] When examining the performance of cell-free DNA screening in twin pregnancies, the existing data demonstrates that it has the highest sensitivity, specificity, and accuracy of all serum screening tests for Trisomy 21. Utilizing data from The Fetal Medicine Foundation, Judah et al. performed a large cohort study and meta-analysis to assess the performance of cell-free DNA screening for the detection of Trisomy 21, Trisomy 18, and Trisomy 13 in twin pregnancies. In their analysis, the pooled detection rates were 99.0%, 92.8%, and 94.7%, with pooled false positive rates of 0.02%, 0.01%, and 0.10% for Trisomy 21, Trisomy 18, and Trisomy 13, respectively. The authors concluded that cell-free DNA screening for Trisomy 21 in twin pregnancies is highly accurate, with a slightly lower detection rate and an equivalent false positive rate compared to singletons. The authors also reported that while cell-free DNA performance for Trisomy 13 and Trisomy 18 in twin pregnancies is promising, conclusive statements were limited by the small number of affected cases. [11]

Payor Policy Implications

Insurance coverage for cell-free DNA screening differs across various insurance plans and is frequently denied by many insurers, creating an undue financial burden on patients. [12] Within twin gestations, denial of cell-free DNA screening coverage while simultaneously covering less accurate genetic screening tests exacerbates substantial financial burden while possibly increasing psychological stress upon these patients. Assessment of insurance coverage of cell–free DNA screening in twin pregnancies showed that only three of the nine major national private health plans (UnitedHealthcare, Anthem, Aetna, Cigna Health and Life Company, Centene Corporation, TRICARE, BCBS Federal Employee Health, Molina Healthcare, and Humana) provide coverage of cell-free DNA screening in twins.[13] The proprietary information of one major health plan states that “the evidence base is limited in quantity and quality” and that there are a “lack of prospective studies” and an “inability to determine which twin was affected.”[14] On the contrary, many of the same health plans that deny cell–free DNA coverage often provide coverage for quad screening, which has many of the same limitations for aneuploidy screening in twins, including the inability to determine which twin is affected and poorer performance when compared to singletons. Hence, the decision by some plans to restrict payment for NIPT screening in twins appears incongruent with decisions made for other genetic screening tests in this population.

When patients with twin gestations cannot obtain the most accurate aneuploidy screening test available, some patients may opt to proceed initially with diagnostic testing via either a chorionic villus sampling or an amniocentesis. Problematically, the pregnancy loss rate following diagnostic testing for twin pregnancies is higher than for singletons. However, this is confounded by the fact that the overall baseline spontaneous loss rate is higher in multiple gestations than in singletons.[15,16,17]

Patients with twins should be offered the option of cell-free DNA genetic screening, as do patients with singletons, with payors contributing to financial coverage. Having this knowledge deduced as early as 9 – 10 weeks of gestation via cell-free DNA screening not only provides valuable information for patients with twins

to allow decision-making about invasive/diagnostic procedures but may potentially allow earlier access to reproductive health options in states with more restrictive laws and may allow safer reproductive options. Collaborative discussion between maternal-fetal medicine specialists and insurance payers will hopefully raise more awareness of the implications and importance of this issue and hopefully assist in providing payor coverage for cell-free DNA screening to patients with twin pregnancies. All currently accepted blood screening tests for aneuploidy have been shown to have decreased accuracy in twin gestations yet are still covered by payers for usage in this population. Screening for twin pregnancies should follow the logic of typical genetic screening pathways used for other screening tests and for singleton gestations. As cell-free DNA screening appears to possess at least equivalent detection of aneuploidy (if not superior) to the other currently available non-invasive payer-covered screening options in twin pregnancies, payers should cover this option.

In addition to the information provided here, further information can be found at the SMFM Coding Committee website list of white papers, where you can find the White Paper 'Billing Scenarios for imaging and aneuploidy screening in the First Trimester' discussing clinical scenarios and appropriate coding and billing.[18]

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