

# Trends in state/population-based Down syndrome screening and invasive prenatal testing with introduction of first trimester combined Down syndrome screening, South Australia 1995-2005

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Screening for Down syndrome historically consisted of simply determining a woman's age at delivery. If she was at least 35 years old, she had "screened positive" and was offered a second-trimester diagnostic amniocentesis. The late 1980s and early 1990s introduced population-based second-trimester maternal serum screening, initially with alpha-fetoprotein alone, subsequently in combination with  $\beta$ -human chorionic gonadotropin, unconjugated estriol, and inhibin-A. Improved ultrasound imaging and elucidation of prenatal sonographic features of trisomy 21 gave rise to the "genetic sonogram" in the mid 1990s. These screening tools increased Down syndrome detection while decreasing the amniocentesis rate.<sup>1,2</sup> These observations were even more remarkable because they coincided with a trend toward increasing maternal age at childbearing. Nonetheless, the sequence of screening and diagnosis did not begin until mid second trimester.

Further refinements in ultrasound evaluation, coupled with early prenatal diagnosis by chorionic villus sampling (CVS), enabled visionary investigators to explore the potential of first-trimester Down syndrome screening. Their efforts led to nuchal translucency screening, first as a stand-alone test and later as part of the combined screening that included maternal serum  $\beta$ -human chorionic gonadotropin and pregnancy-associated plasma protein A. The latter approach has been de rigueur in many European centers for the past decade, which proved effective in both high-risk and general obstetric populations.<sup>3</sup> However, until 2004, the American College of Obstetricians and Gynecologists maintained that "until further studies confirm the efficacy of first trimester nuchal translucency screening, with or without serum markers, this modality is not recommended for routine clinical use."<sup>4</sup>

Two large US multicenter investigations confirmed the efficacy of first-trimester combined screening, which suggested similar or improved trisomy 21 detection at lower screen-pos-

itive rates than did second-trimester multiple marker screening.<sup>5,6</sup> The American College of Obstetricians and Gynecologists subsequently noted "first-trimester screening for Down syndrome and trisomy 18 is an option" when specific criteria were met that included appropriate ultrasound training and ongoing quality monitoring, comprehensive patient counseling regarding available screening tests, and the availability of diagnostic testing for women with positive screening tests.<sup>7</sup>

Although combined screening performs consistently in clinical trials and the hands of experts where such prerequisites are ensured, the true performance of the method in population-based clinical practice was unknown. Muller et al demonstrate that combined screening may become widely accepted by clinicians and patients and may result in significantly fewer second-trimester serum screens. Moreover, after the implementation of the first-trimester program, significantly fewer women underwent invasive prenatal diagnosis, and fewer procedures were performed per aneuploidy detected. Yet, the overall trisomy 21 detection rate remained stable. These findings are notable especially because the obstetric population's age increased significantly over the study period.

The current investigation draws from several strengths that include a single heavily populated geographic region with centralized screening, data collection, and auditing. Nuchal translucency measurements were performed in 10 centers by trained sonographers who underwent continuous rigorous quality monitoring. The near-complete data ascertainment is notable, and trisomy 21 detection rates are consistent with previous reports.

However, the current report's design was subject potentially to the under ascertainment of Down syndrome cases, which led to the falsely increased detection rate. The authors, however, accounted for this possibility in a novel manner by additionally reporting detection rates that considered combined screen-positive fetuses that did not undergo prenatal diagnosis as affected. Of note, the screen-positive threshold for second-trimester serum screening shifted during the study period from 1 in 405 to 1 in 300 because of increasing screen-positive rates. Thus, the degree to which this change, rather than the introduction of combined screening, contributed to the declining use of invasive diagnostic procedures, remains unknown.

Two concerns commonly arise in first-trimester screening discussions. The first issue is the impact of broad-based combined screening on second-trimester serum screening validity. In addition to spontaneous losses, additional Down syndrome

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fetuses that are detected through combined screening will likely undergo pregnancy termination, which will reduce the pool of affected fetuses who are subjected to second-trimester screening. If second-trimester screen-positive thresholds remain unchanged after the introduction of combined screening, women who undergo second-trimester screening may experience higher screen-positive rates with lower positive predictive values and potentially more invasive procedures per detected aneuploidy fetus. Integrated screening may mitigate this concern. Although the current study did not seek to address the issue, the rapid acceptance of first-trimester screening at the expense of second-trimester serum testing suggests that the concern is clinically relevant and worthy of evaluation.

The second matter relates to the availability of prenatal diagnosis for combined screen-positive women. A benefit of first-trimester screening is first-trimester diagnosis by CVS. Somewhat surprisingly, Muller et al noted a stable CVS rate after instituting combined screening. Potential explanations for this unexpected finding include clinician bias in counseling for CVS-associated risks and limited availability of CVS services. Alternatively, the stable CVS rate simply may reflect the improved efficiency of combined screening in the authors' population, with fewer invasive procedures per detected aneuploidy. Because CVS availability is of concern in the United States, this observation warrants further study.

Arguably, we are witnessing the greatest paradigm shift in prenatal Down syndrome screening and diagnosis of the past 30 years. The practice of offering invasive prenatal diagnosis solely on the basis of maternal age, which has been a given for generations of obstetricians, now has been abandoned justifiably in favor of more efficient screening options.<sup>8</sup> The study by

Muller et al demonstrates that first-trimester screening is clinically practical and likely to find the same broad acceptance with the same well-recognized advantages of second-trimester serum screening. However, this practice shift is not without consequences for first-trimester diagnosis and second-trimester screening. These authors and others with centralized programs have the opportunity to answer these clinically important questions. ■

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