Referee Commentary

Re: First-trimester screening based on ultrasound and cell-free DNA *vs* first-trimester combined screening: a randomized controlled trial. K. O. Kagan, R. Sroka, J. Sonek, H. Abele, K. Lüthgens, M. Schmid, P. Wagner, S. Brucker, D. Wallwiener and M. Hoopmann. *Ultrasound Obstet Gynecol* 2018; **51**: xxx–xxx.

In this issue of the Journal, Kagan and colleagues report the results of a prospective single-center study comparing two first-trimester screening protocols for Down syndrome. In this study, 1518 pregnant women underwent detailed ultrasound examination at 11–13 weeks' gestation. Those with normal ultrasound findings were offered randomization to either (i) serum analysis for first-trimester combined screening (FTCS), or (ii) cell-free DNA (cfDNA)-based screening for whole-chromosome aneuploidies of 21, 18, 13, X and Y. Serum samples were stored for the cfDNA group in case of cfDNA test failure, in which case, 'reflex' FTCS was performed. Outcomes were assessed via newborn examination or prenatal or postnatal genetic testing.

The primary outcome of the study was the false-positive rate for each screening group. A positive screen for both FTCS and cfDNA testing was defined as trisomy 21 risk > 1 in 100. The authors found that the group that were randomized to FTCS had a higher rate of false-positive screening results (17/688, 2.5%) compared with the cfDNA group (0/688, 0%). Ten (1.4%) women in the group randomized to cfDNA did not receive a result and thus required reflex FTCS. These women all had low-risk results on FTCS.

The finding that the false-positive rate was higher with FTCS compared with cfDNA is not at all surprising given that it has already been well established that non-invasive prenatal testing has the highest specificity of any screening test for Down syndrome[1]. This study was underpowered to compare any other substantive performance measures, such as sensitivity for Down syndrome or atypical chromosomal abnormalities.

Nevertheless, there are valuable observations to be made from this prospective study, as the use of randomization removes many of the selection biases associated with prenatal testing choices. One of the strengths is the use of a structured, detailed first-trimester ultrasound examination as the entry point for their patients, which allowed women with ultrasound indications for diagnostic testing to be excluded prior to randomization. Thus, all seven fetuses with Down syndrome were removed from the study population, having been identified by nuchal translucency thickness (NT) ≥ 3.5mm or structural abnormality. Overall, 2.0% of the initial cohort were offered diagnostic testing directly, on the basis of ultrasound abnormality, highlighting the advantages of performing detailed a 11–13-week scan prior to

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blood sample-based aneuploidy screening. Performing cfDNA screening later (12–13 weeks) rather than earlier (10–11 weeks) in the first trimester also has the advantage of avoiding unnecessary cfDNA testing on pregnancies that are destined to miscarry; 1.6% of asymptomatic women with a sonographically confirmed live fetus miscarry in the first trimester[2], and the miscarriage rate is higher for a fetus with Down syndrome, estimated at 6% between 10 and 12 weeks[3].

Following the protocol for first-trimester fetal assessment recommended by ISUOG, the investigators also detected, in fetuses with normal NT, a range of structural abnormalities, including phocomelia, Roberts syndrome, thoracic cyst, mesenteric cyst, diaphragmatic hernia, retrognathia, cardiac abnormalities and spinal defects. Early detection of major structural abnormalities, while not necessarily improving perinatal outcome compared with later detection, nevertheless maximizes management options, and is usually preferred by women.

The authors conclude their paper by proposing that universal cfDNA screening after detailed first-trimester ultrasound obviates the need for biochemical markers. Yet, 1.4% of women did not get a result on cfDNA; it is unclear what clinical pathway the authors would have offered if serum markers for FTCS had not been collected. The study was also unable to assess the yield of FTCS for atypical chromosomal abnormalities not detectable on cfDNA[4], as there were only a few atypical cases in this cohort. What this randomized trial does demonstrate, in addition to confirming the low false-positive rate of cfDNA, is the value of a high-quality first-trimester ultrasound examination prior to any blood sample-based screening for aneuploidy.

L. Hui
University of Melbourne,
Department of Perinatal Medicine,
Mercy Hospital for Women,
Melbourne, Australia
(e-mail: lisahui77@gmail.com)

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