Opinion

Screening for Down syndrome in the second trimester of pregnancy

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Antenatal screening for fetal anomalies has provided women and their partners with information to make reproductive choices based on the risk of serious chromosomal or structural defects since the 1990s. Alternative tests include first-trimester screening (combined ultrasound and maternal serum markers), second-trimester maternal serum markers and noninvasive cell-free DNA testing. The recent recommendations by the Royal Australian and New Zealand College of Obstetrics and Gynaecology and the Human Genetics Society of Australasia against second-trimester triple testing are based on unsound performance criteria, raise several contestable issues around access and equity and challenge the principles of governments providing affordable options.

Key words: antenatal screening, Down syndrome, triple test.

Background

Over the past 25 years, important improvements have occurred in antenatal screening for Down syndrome and other fetal structural and genetic anomalies. Beginning with maternal age as a primary screening tool, we have witnessed developments in maternal serum screening[1] and ultrasound[2] and newer genetic testing methods to refine risk estimates. Screening has been available to women in the second trimester of pregnancy – via maternal serum screening (the triple or quadruple test) – since the early 1990s, and in the first trimester – via combined first-trimester screening (cFTS) – since the early 2000s. More recently, noninvasive prenatal testing using cell-free DNA (cfDNA NIPT) has become available, offering those able to pay the opportunity to screen for Down syndrome, trisomies 13, 18 and sex-chromosomal anomalies.[3]

During the 1990s, the triple test was the dominant screening moiety in all Australian states[4,5] except for one laboratory in Victoria offering second-trimester quadruple screening tests.[6] Then, from around 2000, cFTS largely replaced second-trimester maternal serum screening as the preferred screening method, as it provided an earlier screening option with higher detection and lower false-positive rates for fetal Down syndrome and enabled the identification of additional structural abnormalities via ultrasound.[7–9] Nevertheless, laboratories have retained second-trimester maternal serum screening principally to provide a service to those women who cannot access NT ultrasound providers due to barriers such as cost and physical location, and for those who present for antenatal care after the first trimester. These are generally our most vulnerable pregnant women.

Recent guidelines issued by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) and the Human Genetics Society of Australasia (HGSA) no longer recommend the use of the triple test for second-trimester screening. Guideline 3.2 states women in the second trimester may be offered maternal serum screening with the quadruple test (15–20 weeks) or cfDNA testing (any gestation after 10 weeks) but advise against use of the triple test for trisomy 21 based on performance criteria (sensitivity <75%/specificity <95%) (http://www.ranzcog.edu.au/component/docman/doc_download/938-prenatal-screening-and-diagnosis-of-chromosomal-and-genetic-abnormalities-in-the-fetus-in-pregnancy-c-obs-59.html?Itemid=946).

This recommendation is based on limited evidence, is not supported by a Cochrane review and has implications for service providers, referral pathways and the provision of second-trimester screening to Australian women.

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Comparing the triple test to the quadruple test

The statistical evidence that quadruple tests are superior to triple tests is controversial.[10] In 2003, based on evidence from the Serum, Urine and Ultrasound Screening Study (SURUSS) multicentre evaluation of first- and second-trimester screening markers in more than 47 500 pregnancies, Wald *et al.* proposed that the evidence did not support continued use of the triple test.[11]

However, a more recent 2012 Cochrane review concluded that 'tests involving two or more markers in combination with maternal age are significantly more sensitive than those involving one marker' but that 'the value of combining four or more tests (including inhibin) has not been proven to show statistically significant improvement.[10] In a recent review of the performance of second-trimester screening protocols in the UK, Kevin Spencer reported the detection rate of triple test screening (67%) to be slightly lower than quadruple tests (72%).[12] Although the sample sizes are small, Australian data published by Jacques et al[13] on the Victorian quadruple test indicate detection rate of 72% (24/33) which is similar to the South Australian triple test 74% (50/67) data.[14] However, in both reports, the false-positive rates exceeded 7%. Clearly, detection rates can be improved by increasing the screen-positive rate, but at a conventional 5% false-positive rate, the performance will be less than reported above. Without a national audit to assess antenatal screening test characteristics, it is implausible that performance standards can be imposed without evidence that the standards can be achieved or maintained.

Despite the recommendation of the NHS Fetal Anomaly Screening Program in the UK that only quadruple tests be offered in the second trimester (http://www.fetalanomaly.screening.nhs.uk/publications), 64 of 137 laboratories (47%) participating in the NEQAS quality assurance program report triple test results in comparison with 34 of 137 (25%) reporting quadruple test results or a combination of AFP and hCG (25%). In the American College of Pathologists CAP survey, 27% of participating laboratories provide triple tests (44/118).[15]

Impact of new policy guidelines

Currently, the triple test is the only second-trimester maternal serum screening test available in Western Australia, South Australia, New South Wales, Queensland and the Northern Territory. The test may be provided to public patients through State funded health laboratories, or to private patients at private laboratories, with some private laboratories referring the tests to government laboratories. Public patient testing is funded by state governments, while private patients receive a Medicare rebate.

To comply with the new guidelines, laboratories that currently do the triple test would have to expand the screening panel to include inhibin A or no longer provide second-trimester screening. However, the 2012 Cochrane systematic review of second-trimester screening tests recommended against introducing quadruple tests into wider clinical practice without careful consideration of cost.[10] We estimate that adding inhibin A into the screening panel would increase the cost of maternal serum screening threefold. For public patients, the entire cost would be borne by the state government, whereas for private patients, a Medicare rebate would apply. However, the standard Medicare rebate is identical for both triple and quadruple tests. The additional cost to state governments (in the case of public patients) and private laboratories or women (in the case of private patients) is not justified by the potential marginal increase in detection.

If laboratories were to cease offering second-trimester screening, women presenting in the second trimester or unable to access FTS would have the option to have cfDNA NIPT, as referred to in the guidelines. Offering a much improved detection rate (>99% for Down syndrome) with a reduced number of invasive diagnostic tests,[16] cfDNA NIPT has been adopted enthusiastically by clinicians and pregnant women.[17–19] For private patients, in the absence of Medicare or private health funding for cfDNA NIPT, this would, for the first time in Australia, represent a shift into a user-pays model for second-trimester antenatal screening. With the exception of women in Victoria, it may be difficult for women to access affordable screening. Furthermore, within the state public system, the cost of providing cfDNA NIPT to patients would be disproportionate to that of providing the triple test and would initiate a publicly funded population NIPT program that would be difficult to manage in terms of demand access and equity. A further option to ensure access to second-trimester screening may be to have all second-trimester blood samples sent to the Victorian laboratory that provides quadruple tests. However, this would require agreement among public and private laboratories and is likely to increase costs for women and/or referring laboratories.

Conclusion

The stated aims of prenatal screening for fetal anomalies have always emphasised the provision of choice, specifically reproductive choice, over the detection and termination of fetuses with abnormalities such as Down syndrome. Choice is informed by the evidence about the performance of screening tests, the balance of risks involved with diagnostic invasive tests and the individual's personal decisions about having a child with a disability. There is also a public policy and health dimension that determines what resources should be invested in meeting public demands and expectations, and equality of access. A likely consequence of the current RANZCOG and the HGSA Guidelines against continued use of the triple test will be to increase health service inequality. These are complex issues and beyond the scope of this commentary, but they frame the current consensus about what are

reasonable screening tests to make available to pregnant women and their partners to inform their reproductive choices.

With these developments, it is reasonable to ask what antenatal screening options should be provided to pregnant women and their partners in Australia. Our health system provides a safe system that is accessible and equitable and generally meets the expectations of health consumers. In the absence of clear evidence as to the superiority of the quadruple test and a lack of robust evaluation of the triple and quadruple tests in Australia, the recommendation against the triple test is premature and threatens access to affordable second-trimester screening for women. The retention of both the triple and quadruple tests (in Victoria) appears warranted.

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