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Newsletter

Update On The Quadruple Test

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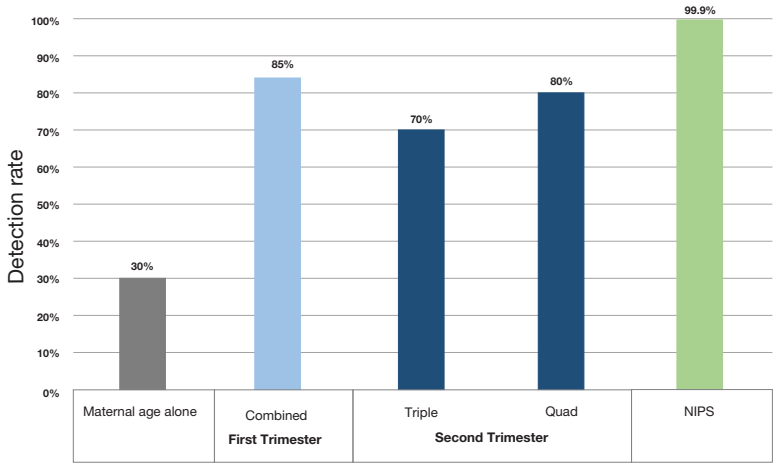
The quadruple test, using alpha-foetoprotein (AFP), uncongugated oestriol (uE3), human chorionic gonadotropin (HCG) and Inhibin-A as biochemical markers, has been available at Lancet Laboratories as a screening test in the second trimester for almost a year. There has been positive feedback from obstetricians using the test.

Figure 1. Performance of maternal age and screening options for Down syndrome



The bar graphs describe approximate detection rates attained at a fixed 5% false-positive rate for each of the screening tests.
A combined test refers to a first trimester test based on ultrasound and maternal serum measurements: Nuchal translucency (NT), free beta HCG and PAPP-A, together with maternal age.

Whilst the quadruple test is primarily used as a screening tool for Down syndrome, trisomy 18 and neural tube defects, there are additional clinical scenarios where the test may provide useful information.

1. Pre-eclampsia (PE):

This complication affects 2 – 8% of pregnancies and is an important cause of maternal and perinatal morbidity. The pathogenesis of early-onset (before 34 weeks gestation) and late-onset PE differs. In early-onset PE, there are compromised terminal villi volume and surface area resulting in smaller placentas with higher infarction rates. The aetiology of late-onset PE is likely due to an imbalance between cardiovascular supply and the metabolic demands of the foetus and placenta.

Inhibin-A is a hormone initially produced by the corpus luteum and later by the placenta. It regulates embryo implantation and differentiation, affects permeability and integrity of maternal blood vessels, reduces placental blood flow and may aggravate placental ischaemia and metabolic disorders. Studies have reported an association between pre-eclampsia and a high Inhibin-A level.

Cuckle et al. demonstrated that an elevated Inhibin-A level was predictive of pre-eclampsia, whilst Aquilina et al. improved screening efficacy by adding uterine artery Doppler to this marker at 20 weeks. In a nested case control study, Wald et al. noted that Inhibin-A and HCG values were significantly raised, uE3 values significantly lowered, and AFP levels not significantly different for patients who developed pre-eclampsia.

In a recent study, Bunyapipat et al. evaluated 31 of 55 women with late onset pre-eclampsia in a cohort of 200 women at a hospital in Thailand. A logistic regression model demonstrated that a combination of maternal risk factors (maternal age, history of pre-eclampsia, history of infertility, cardiac disease, chronic hypertension, and thyroid disease) and inhibin-A levels from the quadruple test had good predictive ability for late-onset PE.

This predictive model would benefit these patients by closer monitoring, particularly in developing countries where many pregnant women are unable to access antenatal care until the second trimester.

2. Small for gestational age (SGA) Foetuses'-:

SGA is defined as a birth weight of less than the 10th percentile for gestational age. These high-risk pregnancies may result in higher perinatal morbidity and mortality, and abnormal foetal neurodevelopment. There may be poor maternal outcomes such as higher rates of caesarean section, maternal depression, and increased cost of antenatal and postnatal care. Early detection of SGA is useful to provide effective antenatal care, thereby ensuring the prevention of unexpected adverse outcomes.

A preliminary population-based study in a cohort of 10 155 women in Thailand by Boonpiam et al. showed:

- Foetuses with growth restriction had significantly higher AFP, HCG and Inhibin-A, reported as multiples of the median (MoM), with lower uE3 MoMs.
- Whilst AFP had the strongest association, all analytes had significant predictive value for SGA.
- The combined model yielded the best prediction.

If the combined model is integrated into the built-in software of the machine (this study used the DELFIA Xpress system, USA for analysis of the quadruple test analytes), the risks of SGA and Down syndrome could be simultaneously estimated and reported without extra cost. More research is ongoing in this area.

3. Adverse pregnancy outcomes:

In addition to chromosomal abnormalities and pregnancies affected by neural tube or abdominal wall defects like omphalocele and gastroschisis, there is a growing body of evidence that abnormal results from quadruple screen serum markers may indicate greater risk for adverse pregnancy outcomes like placental abruption, intrauterine growth restriction (IUGR), foetal death and preterm birth. The link between these pregnancy outcomes and abnormalities in these markers likely stems from placental malfunction.

Information from the quadruple screening test may be valuable in further antenatal surveillance. Abnormal levels of both AFP and Inhibin-A have been associated with an increased risk of stillbirth. One study found that AFP levels greater than 2.5 MoM demonstrated a relative risk of spontaneous abortion of 12.5 [95% CI: 9.7-16.1] compared to AFP levels of 0.75 - 1.24 MoM, but this association did not persist when adjusted for low birth weight. However, rates of stillbirth with Inhibin-A values greater than 2.0 MoM on second trimester serum analyte screening were as high as 9.4 per 1 000, despite adjusting for low birth weight. This prompted an update to the committee opinion published by the American College of Obstetricians and Gynaecologists and the Society for Maternal Foetal Medicine to recommend that providers consider weekly foetal surveillance starting at 36 weeks gestation for these pregnancies.

Additionally, the Society of Obstetricians and Gynaecologists of Canada (SOCG) recommends that an unexplained increased AFP in the setting of placenta praevia warrants additional imaging and altered delivery planning due to the high association with an invasive placental pathology (ex. placenta accreta).

4. The Quadruple test in Assisted Reproductive Treatments (ART):

Guducu et al. investigated differences in quadruple test parameters between pregnancies achieved by ART and spontaneous conception. The study retrospectively evaluated levels of AFP, uE3, HCG and Inhibin-A as well as screen positive test results. Levels of all quadruple test parameters were statistically significantly increased in ART pregnancies when compared to spontaneous pregnancies. Overall, screen positive tests nearly doubled.

Obstetricians should be aware that there are increased quadruple screen positive test results and serum levels of all four biomarkers in ART. Many of the ART subgroup achieve pregnancy after long-standing infertility and treatment, therefore avoiding unnecessary amniocentesis is important in this subgroup of patients. Screening with cell-free foetal DNA in maternal serum, i.e. non-invasive prenatal screening (NIPS) would be a better option in this patient cohort.

The NIPS is now performed at Lancet Laboratories with an improved turnaround time. We continue to advocate with medical aid providers to increase or offer more funding for this test when there are clinical indications for request. There is also a payment plan option whereby the laboratory offers patients who are not covered by their medical aid a four-month payment plan option.

Please contact your Lancet marketing officer, client services or laboratory nursing staff who will provide the clinician and patient with the payment options.

If genetic counselling is required, please e-mail genetics@lancet.co.za for an appointment with the clinical geneticist.

References are available on request.

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