VCGS
Leaders in Genetic Health

Victorian Clinical Genetics Services
Murdoch Childrens Research Institute
The Royal Children's Hospital
Flemington Road, Parkville VIC 3052
P (03) 8341 6201 W vcgs.org.au

Interpreting cFTS
with a low risk NIPT result or low PAPP-A

Introduction

When women choose to have both combined first trimester screening (cFTS) and non-invasive prenatal testing (NIPT), two separate test reports are issued. A low risk NIPT result provides very high confidence that the pregnancy is not affected by trisomy 21, trisomy 18, trisomy 13 or a sex chromosome condition. However, even when a patient has a low risk for these common abnormalities, cFTS may still provide useful information relevant to the management of the pregnancy.

Summary

NIPT is a high performance screen for the most common chromosome conditions. It is not a replacement for invasive prenatal diagnostic tests. When the cFTS risk is > 1 in 50 and/or the NT is ≥ 3.5 mm and/or there is very abnormal biochemistry, a CVS or amniocentesis should be considered. In addition, low PAPP-A may be associated with adverse obstetric outcomes.

1. Low PAPP-A (<0.45 MoM) and risk of pregnancy complications:

If a woman receives a low PAPP-A result (<0.45 MoM), a referral to a specialist O&G or specialist O&G service by 20 weeks gestation should be considered to allow for closer maternal and fetal surveillance.

A low pregnancy-associated plasma protein-A (PAPP-A) level, defined as a maternal serum PAPP-A value <0.45MoM (<5th centile), is associated with an increased frequency of adverse obstetric outcomes.1 Low PAPP-A may be indicative of poor early placentation resulting in complications such as intrauterine growth restriction (IUGR), fetal demise, preterm birth and pre-eclampsia in the third trimester.[2,3,4] The likelihood of an adverse pregnancy outcome increases as the PAPP-A level decreases as follows:

PAPP-A level	IUGR (birth weight <10th centile)	Delivery <34 weeks
<0.45 MoM (5th centile)	14% risk (odds ratio 2.7)	2.3% risk (odds ratio 2.3)
<0.29 MoM (1st centile)	24% risk (odds ratio 5.4)	2.5% risk (odds ratio 2.5)

2. Increased nuchal translucency measurement:

An invasive prenatal procedure (CVS or amniocentesis) and molecular karyotyping (microarray testing) should be offered in any pregnancy with increased NT ≥ 3.5mm +/- additional ultrasound findings.

An increased nuchal translucency (NT) measurement (≥ 3.5mm between 11+1 and 13+6 weeks gestation) is a strong marker for adverse pregnancy outcomes, even in the context of a low risk NIPT result. Fetuses with NT measurements ≥3.5mm (>99th centile) are at increased risk of a range of chromosomal abnormalities that are not detected by NIPT, especially when additional ultrasound abnormalities are present.

Even in the absence of a chromosome abnormality, increased NT can be associated with miscarriage, intrauterine death and other structural defects (e.g. cardiac, skeletal) as well as some genetic syndromes (e.g. Noonan syndrome).[5,6] Microarray testing will detect an additional 6.5-7.0% of clinically significant copy number changes in this high-risk setting when the conventional karyotype appears normal.[7]

3. Abnormal biochemistry and risk of chromosome abnormalities:

Very abnormal biochemistry levels alone may be considered as an indication for an invasive diagnostic test (CVS or amniocentesis) including the option of diagnostic prenatal microarray testing.

Abnormal levels of free β-human chorionic gonadotropin (<0.2 or ≥5.0 MoM) or very low PAPP-A levels (<0.2 MoM) have been shown to be associated with a range of chromosome abnormalities that can be detected by standard karyotype, but not by NIPT, as follows:[8]

Risk group	Risk of chromosome abnormality not detected by NIPT
PAPP-A <0.2 MoM	~4.0%
Free β-hCG <0.2 MoM	~7.0%
Free β-hCG ≥5.0 MoM	~0.5%

4. Increased cFTS risk and residual risk of atypical chromosome conditions:

When the cFTS risk is >1 in 50, an invasive procedure (CVS or amniocentesis) and molecular karyotyping (microarray testing) should be considered.

The known association between individual cFTS markers and chromosome abnormalities not detected by NIPT means women with an increased risk cFTS may also be at an increased risk of 'atypical' chromosome abnormalities (ie: not T21, T13, T18 or X/Y aneuploidy).

In a recent study, approximately 17% of women who underwent diagnostic testing following an increased risk cFTS result returned an abnormal fetal chromosome result that would not have been detected by NIPT.[9] Overall, a microscopically visible chromosome abnormality not detectable by NIPT was present in 2% of screen positive patients.

Of these abnormalities, approximately half (or 1% of all increased risk cFTS patients with low risk NIPT) would result in a viable live birth with an abnormal phenotype. These undetected atypical abnormalities may range from mild clinical outcomes to those associated with significant disability.

References

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