Clinical Practice Guideline Prenatal Screening Tests
Department Women's Health

Target Audience

Clinical Staff in Women's Health

Purpose

To guide clinicians regarding the available options for screening in pregnancy. To ensure women are receiving consistent information regarding the options available to them allowing informed decision making regarding prenatal screening.

Guideline

The most common chromosomal cause of intellectual disability in children and adults remains Down Syndrome (trisomy 21). It occurs at a frequency of about 1 in 800 and the majority of cases are sporadic. Maternal age remains an important risk factor for this and other chromosomal anomalies including Edwards syndrome (trisomy 18) and Patau syndrome (trisomy 13). These conditions are associated with variable disability, pregnancy loss or death in the newborn.

Prenatal screening tests help to identify pregnancies at increased risk of chromosomal aneuploidies, such as trisomy 18 and 21, and other abnormalities including neural tube defects (NTD). All pregnant women should be offered screening tests as early as possible in pregnancy. This allows for adequate time to consider testing options as well as to provide timely results in case of the need for invasive testing or termination of pregnancy as timing constraints exist for availability of these management options.

Patients should be informed that participation in any testing is voluntary and that pregnancy management will not change if screening options are not undertaken, nor does undertaking screening imply that the detection of a high risk result means further action must be taken.

In discussing screening tests, it is important to explain;

- the chromosomal abnormalities for which screening is available
- where and how tests can be accessed and the cost involved
- the importance of timing the tests against an accurate assessment of gestational age
- that screening tests indicate risk but are not diagnostic of any condition
- that a low risk result does not exclude all risk to the pregnancy

Other considerations in screening for fetal abnormalities include;

- the sensitivity and specificity of the test and the risk score obtained
- options for women who receive a high-risk result, including NIPT or invasive testing
- that a fetus with normal chromosomes and a high risk result may indicate the presence of other fetal anomalies (diaphragmatic hernia, cardiac anomaly, IUGR)
- a discussion around the options for management of a pregnancy with an abnormal result including pregnancy termination

Women should also be made aware of the availability of diagnostic testing but due to the risk of miscarriage should not be offered this as first line screening. After individualised counselling however some women may choose a diagnostic rather than a screening test.

Screening decision making tools such as the on line tool offered by the Murdoch Children's Research Institute may be helpful.

SCREENING TESTS AVAILABLE

Combined First Trimester Screening

Provides a risk assessment for trisomy 21, trisomy 18 and trisomy 13. Combines maternal age, serum PAPP-A and free bHCG together with ultrasound findings of NT, CRL and if performed by an accredited sonographer nasal bone length.

- Maternal blood collected between 9+0 and 13+6 weeks (best around 10 weeks)
- Ultrasound performed between 11+1 and 13+6 weeks (CRL = 45 to 84mm)
- The detection rate of trisomy 21 is 85-93%, adjusted for a false positive rate of 5%
- Testing is medicare rebated and out of pocket cost is approximately $100 plus any associated ultrasound cost

Second Trimester Maternal Serum Screening

Provides a risk assessment for trisomy 21, trisomy 18 and trisomy 13 and neural tube defects by analyzing maternal serum levels of alpha-fetoprotein, free bHCG, unconjugated oestriol and inhibin A.

- Maternal blood collected between 14+0 and 20+6 weeks
- Accurate request from maternal age and pregnancy specific data
- The detection rate for trisomy 21 is 85%, adjusted for a false positive rate of 7%
- No risk of NTD reported if blood collected prior to 15 weeks
- Fully funded for public patients

Non-invasive prenatal testing (NIPT)

Cell Free DNA (cfDNA) from the placenta is present in the maternal circulation and can be assessed to provide a risk of trisomy 21, trisomy 18, trisomy 13 and sex chromosome aneuploidies. It is currently the most accurate screening test available.

- Maternal serum collected anytime from 10 weeks gestation
- There is a test failure rate of up to 4% and higher with an elevated BMI. Most test failures will yield a result with repeat testing
- Ultrasound to exclude structural fetal abnormalities is still very important; nuchal translucency and morphology ultrasounds are recommended
- NIPT can also test for fetal sex and some sex chromosome abnormalities.
- The sensitivity for trisomy 21 is 99.5 and for trisomy 18 is 99%. It is less accurate for the detection of trisomy 13, sensitivity 79–92%

- False positive rates are very low at 0.2%
    - If confined placental mosaicism exists a false positive may occur
    - Maternal chromosomal abnormalities may rarely cause false positive results
    - Termination of pregnancy should never be performed on the basis of NIPT result alone
- The cost varies by provider between $395-450. No medicare rebate is available

Ultrasound

11+1 – 13+6 week ultrasound

- Measurement of nuchal translucency and nasal bone
- Early assessment of fetal anatomy
- Recommended to be combined with first trimester serum screening for increased detection rate of chromosomal aneuploidies
- Should still be recommended for any woman choosing NIPT as primary screening modality to assess anatomy and nuchal thickness but does not alter risk assessment
- May overlap with assessment of gestational age

18-22 week ultrasound

- Should be offered to all women in addition to other forms of screening
- Can detect markers associated with an increased risk of aneuploidy
- Detects approximately 50% of T21 cases and most T18 and T13 cases
- Can detect other anatomical abnormalities that may alter pregnancy management

The out of pocket cost for all pregnancy ultrasounds varies by provider

INTERPRETATION OF RESULTS

Patients should be informed of their result as soon as possible. A woman with a low risk result from any test can be reassured but must be aware that that low risk does not equal no risk and a small risk of aneuploidy or other abnormality remains.

Combined first trimester

A high risk result is defined as a risk of at least:

- 1:300 for trisomy 21
- 1:175 for trisomy 18
- 1:100 for trisomy 13

This reflects the background prevalence of these disorders. In addition to aneuploidy risk attention must be given to isolated findings within the report.

Low PAPP-A in an otherwise low risk screen; PAPP-A <0.45MoM

Low first trimester PAPP-A is associated with an increased risk of poor pregnancy outcomes including IUGR, preeclampsia, preterm birth and pregnancy loss <20 weeks. The relationship between PAPP-A and these outcomes is inverse, the lower the PAPP-A the higher the risk. Women with a low PAPP-A on first trimester screening bloods should be managed in an obstetric clinic or by an obstetrician and should have third trimester ultrasounds for surveillance of fetal growth and wellbeing. RCOG Guidelines recommend 4 weekly growth scans from 28/40 if the PAPP-A is <0.4 MOM.

Increased nuchal translucency in an otherwise low risk screen, NT >3.5mm

An elevated nuchal translucency is associated with an increased risk of poor pregnancy outcomes including chromosomal abnormalities, miscarriage, FDIU, structural abnormalities, genetic syndromes and microdeletions of clinical significance. Women with a thickened nuchal translucency between 11+1 and 13+6 weeks gestation should be referred to a fetal diagnostic unit for specialist ultrasound and counseling regarding consideration of invasive testing for molecular karyotyping.

Second trimester

A high risk result is defined as a risk of at least:

- 1:250 for trisomy 21
- 1:200 for trisomy 18
- 1:100 for trisomy 13

In addition to aneuploidy risk attention must be given to isolated findings within the report.

Elevated AFP in an otherwise low risk screen; AFP >2.0MoM

A high AFP is a marker of a high risk for neural tube defect, detection rate of 93% and a false positive rate of 3%. Women with a high AFP should be referred for a fetal diagnostic unit ultrasound and counseling

Non Invasive Prenatal Testing

Reported without numerical values. High risk or low risk only. High risk results should never be acted on without diagnostic testing for confirmation as false positives can occur. Referral for fetal diagnostic ultrasound and invasive testing is recommended.

High Risk Results

A screen positive or high risk result means further testing is recommended. Many women with a high risk screening test will go on to have a negative diagnostic test and a healthy baby

All patients returning a high risk screening test should be reviewed in obstetric clinic or by an obstetrician for further counseling about management options which will vary depending on the primary screening tool used and the condition screened for.

Women returning a high risk result for chromosomal aneuploidy with maternal serum screening or combined first trimester screening should be offered NIPT prior to referral for invasive testing. A subsequent low risk NIPT result is considered more sensitive and specific than the prior modality and will exclude the need for diagnostic testing in the absence of any structural anomalies. No rebate currently exists regardless of the indication for NIPT.

Patients with low risk screening but other anomalies detected including a structural anomaly, thickened nuchal or high aFP should have a scan supervised by a COGU certified sonologist (Fetal Diagnostic Service at Peninsula Health, FDU at Monash or tertiary private provider) and counseling regarding invasive diagnostic testing

DIAGNOSTIC TESTS

- Chorionic villus sampling (CVS) is performed from 11+4 weeks onwards (no upper limit) and carries a procedure- related risk of miscarriage of approximately 1 in 400.
- Amniocentesis can be performed from 15+5 weeks onwards and carries a procedure related risk of miscarriage of approximately 1 in 800.
- The risks associated with these procedures may be modified by the performing obstetrician/ clinician depending on individual patient factors.
- Rhesus negative women having invasive testing performed should be administered prophylactic anti D
- If the woman has a blood borne virus, consideration should be given to modality of testing. Amniocentesis is the preferred option if there are concerns about feto-maternal spill posing a risk of infection. Hepatitis B and C carrier state is not a contraindication to diagnostic testing. Women with HIV should have viral load testing prior and consideration should be given to delaying a diagnostic procedure until the viral load is undetectable post treatment. This should be decided in liaison with an infectious disease specialist.

MULTIPLE PREGNANCIES

Screening in multiple pregnancies occurs in the same time frames as for singletons. For all testing multiple pregnancy and chorionicity should be noted on the request form.

Nuchal translucency can be used alone.

CFTS can be used for twins and the risk reported is given for the whole pregnancy, not the individual fetus

- If monochorionic, the risk is for both fetuses having Down syndrome.
- If dichorionic, the risk is for one, or the other, or both fetuses, having Down syndrome.

NIPT can detect trisomies in twin pregnancies but this is limited by zygosity. It is not currently recommended that NIPT/CfDNA be used as the sole screening method in multiple pregnancies.

Serum screening should not be recommended in higher order multiples.

OTHER SCREENING TESTS

PreEclampsia

Some private ultrasound departments (Monash Ultrasound for Women, Peninsula Imaging) are offering preeclampsia risk estimations using the Fetal Medicine Foundation Algorithm. This is performed at the time of nuchal translucency assessment and combines:

- Maternal demographic characteristics obtained by clinical history;
- Serum biochemical markers of PAPP-A and placental growth factor
- Mean arterial blood pressure performed between 11+2 and 13+6
- Maternal uterine artery Doppler performed between 11+2 and 13+6

Recent studies show that first trimester screening for preeclampsia identifies 75% of the cases of preeclampsia that require birth before 37 weeks and more than 90% of the cases requiring birth before 32 weeks. This level of detection is achievable with a false positive rate of 10%.

For high risk women (suggested cut-off 1:100), low dose aspirin (150 mg) initiated before 16 weeks reduces by more than 60% the incidence of preterm preeclampsia and by more than80% the risk of early-onset disease. It is also prudent to observe these women more closely, especially beyond 20 weeks.

Inheritable genetic disorders

VCGS offer pre-pregnancy or prenatal screening for low risk individuals and couples for a number of conditions with moderate carrier prevalence. Screening of the biological mother is recommended first and the father tested only if she positive. The conditions able to be tested for are:

- Cystic Fibrosis
- Spinal Muscular Atrophy
- Fragile X Syndrome

Testing will identify about 90% of people who are carriers of CF, 95% of people who are carriers of SMA and over 99% of people who are carriers of FXS. The prevalence of carriers within the population are CF 1:25, SMA 1:40 and FXS 1:150. Testing is performed on blood or saliva specimens and costs $385. No rebate is available. Request forms and patient information are available at vcgs.org.au

Appendix 1: Summary of Antenatal Screening Options

Test	Type of Test	Conditions	Blood Test	Ultrasound	Results	Cost / Availability
Combined First Trimester Screening	Non Invasive MA, Free B-HCG, PAPP-A, Fetal NT	Trisomy 21 Trisomy 18 Detection rate for Trisomy 21 is 85-93% False positive 5%.	Week 10 (9 to 13^6)	Week 12 (11^1 to 13^6) NT and Nasal Bone	Week 13 Increased risk: T21 ≥1:300; T18 ≥1:175 Raised NT exclude cardiac & genetic defects	Private opt ion Out of pocket expense for US
Fetal Nuchal Translucency and Fetal Nasal Bone	Screening Non Invasive Factors in maternal age	Raised NT measurement Exclude cardiac & genetic defects		Week 12 (11^1 to 13^6)	Week 12 11^1 to 13^6 Sensitivity NT 70-80%, NT & NB 90%	Private
NIPT Non Invasive Prenatal Testing	Screening Non Invasive Uses cell free fetal DNA (cfDNA) found in maternal blood. Fetal sex is always reported. Clinician to disclose to patient on request.	Identifies most common aneuploidies eg Trisomy 21, Edwards syndrome(T18) and Patau syndrome (T13).	Week 10 onwards	Week 10 onwards To confirm at least 10 weeks gestation and viable singleton pregnancy	3-5 days Sensitivites; T21 ≥99.5% (false-positive rate 0.2%). T18 99%. T13 79-92%	Private VCGS (percept™). Dorevitch (Generation Screening™) Melbourne Pathology (Harmony™) Australian Clinical Labs (Harmony™)

Test	Type of Test	Conditions	Blood Test	Ultrasound	Results	Cost / Availability
Maternal Serum Screening: Second Trimester Screening	Screening Non Invasive MA, AFP, Unconjugated Oestriol, Free B-HCG, Inhibin A	Trisomy 21 Trisomy 18 Neural Tube Defects	Wk 14-20 (14 to 20^{6})		Week 14-20 High risk T21 ≥ 1:250 T18 1:200 NTD MS-AFP cut off: 2.5 MoM	Bulk billed
Chorionic Villous Sampling	Diagnostic Invasive			Week 11-13 Safer before 14 weeks	Risk of miscarriage 1:400	Monash/ Private providers
Amniocentesis	Diagnostic Invasive			Week 15 or later	Risk of miscarriage 1:800	Monash/ Private providers
Diagnostic Ultrasound Morphology	Screening Non Invasive	Diagnoses structural abnormalities		Week 18-22 20-21 weeks for high BMI		Monash/ Private providers

References

Joint HGSA/RANZCOG Statement: Prenatal screening and diagnosis of chromosomal and genetic conditions in the fetus in pregnancy C-Obs 59, May 2016, Royal Australiana and New Zealand College of Obstetricians and Gynaecologists

Joint HGSA/RANZCOG Statement: Prenatal assessment of fetal structural abnormalities C-Obs 60 May 2016, Royal Australiana and New Zealand College of Obstetricians and Gynaecologists

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