Prenatal Screening

1. INTRODUCTION

Prenatal screening tests help to identify pregnancies at increased risk of chromosomal anomalies such as trisomy 18, trisomy 21 and neural tube defect (NTD). All pregnant women should be offered screening tests as early as possible in pregnancy after proper counselling. Counselling should cover the details of the nature, purpose, limitations and consequences of this test. The patients should be informed that participation in this test is voluntary and that the pregnancy management will not change if the decision made is not to have any screening.[1] Results and management need to be followed up, communicated and documented.

2. DISCUSSING SCREENING

It is recommended that GPs counsel women about prenatal screening as early as possible in the pregnancy and use Victorian Clinical Genetics Services (VCGS) resources. VCGS resources include a pathology form with attached patient information as well as resources in different languages.[2]

In discussing screening tests, it is important to explain;

- the chromosomal abnormalities for which screening is available;
- the screening pathway, the decisions that need to be made at each point and their consequence
- the importance of timing the tests against an accurate assessment of gestational age;
- that a screening test alone indicates a risk but does not give a diagnosis of any abnormalities;

Other considerations in screening for fetal chromosomal abnormalities;

- the **sensitivity and specificity of the test** and a full explanation of the risk score obtained (eg high risk /low risk, 1:300 for combined first trimester screening for trisomy 21);
- the **options for women who receive a high risk result,** including information about follow up for NIPT, chorionic villus sampling and amniocentesis;
- a high risk screen in a fetus with normal chromosomes may indicate the presence of **other fetal anomalies** (diaphragmatic hernia, cardiac anomaly, IUGR);
- factors that increase the risk of some fetal chromosomal abnormalities (advanced maternal age, family history of chromosomal abnormalities);
- where and how tests can be accessed if the woman chooses to have them;
- situations in which first-trimester screening may be difficult or impossible (eg high BMI, fetal positioning, multiple pregnancy);
- situations in which the testing may be modified to exclude serum testing (multiple pregnancy);
- the costs involved for the woman and the timeframe for receiving results

3. RECOMMENDED SCREENING TESTS

(i) FIRST TRIMESTER COMBINED MATERNAL SERUM SCREEN for Trisomy 21 & 18[1]

STEP ONE - Maternal blood collected around 10 weeks gestation (9-13^{6} weeks)

- A request form can be downloaded from VCGS MSS Referral Form - VCGS
- Measures PAPP-A and Free B-HCG

STEP TWO - Nuchal Translucency measurement 11^{1} - 13^{6} weeks gestation (CRL = 45 to 84mm).

- The above results should be sent to the Victorian Cytogenetic Service, Melbourne as soon as possible for the calculation of risk.
- In case of twin pregnancy, VCGS should be notified of the chorionicity for the appropriate correction of biochemical values. Additional factors that modify risk include previous pregnancy with trisomy, assisted reproduction and maternal weight. VCGS should also be informed of these, if present.
- An increased risk for Trisomy 21 is a risk of 1:300 or greater at the time of screening
- The test detection rates for Trisomy 21 is 85-93%, with a false positive rate of 5%.

(ii) SECOND TRIMESTER MATERNAL SERUM SCREEN (Quadruple test) for Trisomy 21 & 18 & Neural Tube Defect (NTD)

STEP ONE - The pathology request form

- A request form can be downloaded from VCGS MSS Referral Form - VCGS
  This form accurately records
  - Patient identity
  - Date of birth, weight and gestation (LMP or EDD).
  - Current weight in kilograms
  - Previous pregnancy information
  - Pregnancy affected by Down syndrome or Neural Tube Defect
  - Current Pregnancy Information
  - Threatened Miscarriage
  - IVF pregnancy (the age of the egg used to achieve pregnancy will affect risk).
  - Diabetes
  - Multiple Pregnancy (chorionicity)
  - Ultrasound if performed – document date of scan, BPD and CRL

STEP TWO - The serum screening blood test 14-20[6] weeks

- The blood test measures four analytes: alpha feto-protein (AFP), unconjugated oestriol, free beta human chorionic gonadotrophin (free beta-HCG) and inhibin A.
- This is used with the pathology request form information to give final result of risk for Trisomy 21, Trisomy 18 and NTD.
- Increased risk is defined as Trisomy 21 1:250 / Trisomy 18 1:200 / NTD 2.5 MoM

(iii) NIPT- NON INVASIVE PRENATAL TESTING

While this testing has now become locally available in Australia, it is still costly and, as per the latest evidence and Guidelines from RANZCOG, RACGP and other bodies, has not reached a stage to offer distinct benefits over and replace the First Trimester Combined Screening as first line testing. [4,5]

A request form can be downloaded from VCGS (Percept™ test): NIPT Referral Form - VCGS
NIPT can also be requested through other pathology providers. See individual websites for Dorevitch (Generation Screening™), Melbourne Pathology (Harmony™) or Australian Clinical Labs (Harmony™)

Important counselling points[5]

- The test is very accurate for detection of Down syndrome (sensitivity 99.5%) and Edward syndrome (99%). It is less accurate for the detection of Patau syndrome (79–92%).
- It is unlikely to give a false-positive result (0.2%) but all positive results need to be confirmed by an invasive test (amniocentesis or chorionic villus sampling)
- The cost is significant.
- There is a test failure rate of up to 4% (this is higher as body mass index increases: the test failure rate is likely to be 50% at a maternal weight of 160 kg).
- 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 blood test can be taken from 10 weeks gestation.

Possible NIPT Clinical Pathways

1. First or Second Trimester Screen → High Risk → NIPT → High Risk → Diagnostic Testing
   → Diagnostic Testing
2. NIPT → High Risk → Diagnostic Testing

4. TIMING OF ULTRASOUND

- The timeframe for ultrasound assessment of gestational age (preferably 10-12 weeks) overlaps with that for assessment of nuchal translucency thickness as part of screening for fetal chromosomal abnormalities (11 weeks to 13 weeks 6 days) , which may enable some women to have both tests from results of a single scan. This should only occur if women have been provided with an explanation of both tests and have given their consent to them both[2].
- Ultrasound for NIPT can be done from 10 weeks gestation onwards.
- Women choosing the NIPT s**hould still be advised to have a scan for fetal anomalies and nuchal translucency** at **11 to 13**[6] weeks if an ultrasound (for dating, viability) has been done before 11 weeks.

5. RESULTS including INCREASED RISK RESULTS

Low risk or "screen negative" results mean that a woman is very unlikely to have an affected pregnancy but a few women still may.

An increased risk or "screen positive" result means that further test should be considered to see if the pregnancy is affected. Most women with a positive result will still have a negative diagnostic test and a healthy baby.

Clinical Considerations[1]

- **GPs should refer women with an increased risk result immediately to Frankston Hospital Obstetric Clinic or private obstetrician for counselling and discussion regarding further investigations.** GP to contact Women's Services Manager on 9784 2647 to arrange Obstetric Clinic appointment
- Women with increased risk should be fully counselled face-to-face regarding their options and offered further testing. For women having either first trimester screening or maternal serum screening, the follow up testing could involve the NIPT, which has a higher sensitivity, but if this is also positive, invasive testing such as an amniocentesis or chorionic villus sampling will be needed to confirm diagnosis.
- Women with an increased risk should be offered counselling and diagnostic testing as soon as possible and be seen within 72 hours of the practitioner receiving result.
- Victorian Clinical Genetic Service also offer post-test counselling for women with a result indicating increased risk.
- Only diagnostic testing can confirm whether a pregnancy is affected.
- CVS is safer before 14 weeks and amniocentesis is safer after 15 weeks[7].
- If the maternal screening test indicates increased risk of neural tube defect (spina bifida, anencephaly) the woman should be offered specialist obstetric ultrasound.
- Women with a high-risk first trimester screening test result but negative diagnostic test should be referred for further specialist assessment because of an increased risk of other fetal abnormalities such as diaphragmatic hernia, cardiac anomaly[2].

Test	Type of Test	Conditions	Blood Test	Ultrasound	Results	Cost/ Availability
Maternal Serum Screening - Combined First Trimester Screening	**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} wks	**Week 12** 11^{1} to 13^{6} wks Nuchal translucency and Nasal Bone	**Week 13** Increased risk: - Trisomy 21 ≥1:300; - Trisomy 18 risk ≥1:175 - Raised NT exclude cardiac & genetic defects	Private opt in 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} wks	Week 12 11^{1} to 13^{6} wks 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; Trisomy 21 ≥99.5% (false-positive rate 0.2%). Trisomy18 99%. Trisomy 13 79-92 %	**Private** -percept™ (VCGS). -Dorevitch (Generation Screening™), -Melbourne Pathology (Harmony™) -Australian Clinical Labs (Harmony™)
Maternal Serum Screening - Second Trimester Screening	**Screening Non Invasive** -MA -AFP -Unconjugated oestrogen -Free B-HCG -Inhibin A	Trisomy 21 Trisomy 18 Neural Tube Defects	Week 14-20 14 to 20^{6} wks		Week 14-20 High risk ;Trisomy 21 1:250 Trisomy 18 1:200 NTD MS-AFP cut off: 2.5 MoM	State funded
Chorionic Villous Sampling	**Diagnostic Invasive**			Week 11-13 Safer before 14 weeks	Risk of miscarriage 1:100	Monash/ Private providers
Amnio centesis	**Diagnostic Invasive**			Week 15 or later	Risk of miscarriage 1:100	Monash/ Private providers
Diagnostic Ultrasound Morphology	**Screening Non Invasive**	Diagnoses structural abnormalities		**Week 18-20** 20-21 weeks for high BMI		Monash/ Private providers

Appendix 1

- Maternal Serum Screening VCGS
- Prenatal Testing VCGS – Summary of tests including ultrasound, maternal serum screening, chorionic villous sampling, amniocentesis
- Reproductive Genetic Testing VCGS - percept™ NIPT, prepair™ carrier screen, Maternal Serum Screening, Prenatal Diagnosis and Pregnancy Loss

- **VCGS Referral Forms** include patient information
  - MSS Referral Form -VCGS
  - NIPT Referral Form - VCGS

References

1. CLINICAL PRACTICE GUIDELINE **PRENATAL SCREENING TESTS** PROMPT doc no: **18126941** Version: **1.0** First created: **10/07/2015** Page 1 of 4 Last reviewed: Version changed: **10/07/2015**

2. VCGS Maternal Serum Screening
http://www.vcgs.org.au

3. Prenatal screening and diagnosis of chromosomal and genetic abnormalities in the fetus in pregnancy RANZCOG March 2015

4. https://www.ranzcog.edu.au/womens-health/college-communiques/1357-dna-based-noninvasive-prenatal-testing-for-fetal-aneuploidy.html

5. http://www.racgp.org.au/afp/2014/july/noninvasive-prenatal-testing/

6. https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/pregnancy-tests-maternal-serum-screening

7. Akolekar. R et al 2015. Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. Ultrasound Obstet Gynecol, 45:16.