South Australian Perinatal Practice Guideline

Ultrasound Soft Markers of Aneuploidy

Note:

This guideline provides advice of a general nature. This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion.

Information in this statewide guideline is current at the time of publication.

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Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation.

If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom, and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for discussing care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes:

- The use of interpreter services where necessary,
- Advising consumers of their choice and ensuring informed consent is obtained,
- Providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct, and
- Documenting all care in accordance with mandatory and local requirements

Explanation of the aboriginal artwork:
The aboriginal artwork used symbolises the connection to country and the circle shape shows the strong relationships amongst families and the aboriginal culture. The horse shoe shape design shown in front of the generic statement symbolises a woman and those enclosing a smaller horse shoe shape depicts a pregnant woman. The smaller horse shoe shape in this instance represents the unborn child. The artwork shown before the specific statements within the document symbolises a footprint and demonstrates the need to move forward together in unison.

Australian Aboriginal Culture is the oldest living culture in the world yet Aboriginal people continue to experience the poorest health outcomes when compared to non-Aboriginal Australians. In South Australia, Aboriginal women are 2-5 times more likely to die in childbirth and their babies are 2-3 times more likely to be of low birth weight. The accumulative effects of stress, low socio economic status, exposure to violence, historical trauma, culturally unsafe and discriminatory health services and health systems are all major contributors to the disparities in Aboriginal maternal and birthing outcomes. Despite these unacceptable statistics the birth of an Aboriginal baby is a celebration of life and an important cultural event bringing family together in celebration, obligation and responsibility. The diversity between Aboriginal cultures, language and practices differ greatly and so it is imperative that Perinatal services prepare to respectively manage Aboriginal protocol and provide a culturally positive health care experience for Aboriginal people to ensure the best maternal, neonatal and child health outcomes.

Purpose and Scope of PPG

This PPG aims to assist clinicians to counsel and refer women and their families following identification of a soft marker for aneuploidy on morphology ultrasound scan. It includes likelihood ratios for individual isolated soft markers.

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Summary of Practice Recommendations

Effect of soft markers on risk of aneuploidy is always in relation to the individual woman's pre-existing/background risk of aneuploidy (i.e. their FTS or, if not available, their age-related risk).

There is nothing on the morphology scan that signifies that a baby DEFINITELY has an aneuploidy, but there are signs that significantly increase (or decrease) the risk of aneuploidy and that warrant offering further invasive, confirmatory testing.

Soft markers found on routine morphology scan need review and confirmation by an experienced clinician plus/minus a genetic sonogram (which specifically looks for all possible soft markers and is usually requested if there is some increased concern).

The likelihood ratios discussed below are intended for use in the absence of co-existing significant fetal structural anomalies or significant fetal growth restriction, as both of these would make a diagnosis of aneuploidy more likely: If either of these is present at the morphology ultrasound, referral and consultation with a tertiary Maternal Fetal Medicine Unit is recommended.

Always consider additive risk of multiple soft markers *and discuss these cases with tertiary referral centre/specialist.*

Abbreviations

CF	Cystic fibrosis
CMV	Cytomegalovirus
FGR	Fetal growth restriction
FTS	First trimester screen
LR	Likelihood ratio
MFM	Maternal Fetal Medicine
mm	millimetres
TORCH	Infection screen – toxoplasmosis, rubella, CMV, herpes simplex virus
T18	Trisomy 18
T21	Trisomy 21
>	Greater than
<	Less than
≥	Greater than or equal to

Likelihood Ratios[1]

ISOLATED soft marker	LR T21	Recommendation
Aberrant right subclavian artery	3.9	Recalculate risk of T21 and refer for counselling and further testing
Absent or hypoplastic nasal bone	6.6	Recalculate risk of T21, and refer for counselling and further testing
Echogenic bowel	1.7	Recalculate risk of T21 and consider testing for CF and CMV; recommend uterine artery Dopplers and follow-up growth ultrasound 28 and 32 weeks
Increased nuchal fold ≥ 6mm	3.8	Recalculate risk of T21, and refer for counselling and further testing
Ventriculomegaly	3.8	Recalculate risk of T21 and refer for counselling and further testing
Choroid plexus cyst (CPC)	No increase	If CPC ≥ 5mm and hands are not seen to open, recalculate risk for T18 with likelihood ratio of 5.6 and refer for counselling and further testing
Intracardiac echogenic focus	No increase	Reassure
Mild hydronephrosis	No increase	Repeat ultrasound third trimester for worsening hydronephrosis
Shortened humerus	No increase	If less than 2.5th percentile, check all long bones and consider referral to tertiary MFM unit (possible skeletal dysplasia)
Shortened femur	No increase	If less than 2.5th percentile, check all long bones and consider referral to tertiary MFM unit (possible skeletal dysplasia)
Single umbilical artery	No increase	Recommend uterine artery Dopplers and third trimester ultrasound for growth as associated with FGR

Ultrasound Soft Marker

Aberrant right subclavian artery

Can be determined on ultrasound using colour flow Doppler.

The subclavian artery is seen just above the level of the “three-vessel view” of the pulmonary artery, aorta, and superior vena cava. It is normally placed when it is in front of the trachea and aberrant when behind the trachea.

This finding, in isolation, is associated with a likelihood ratio of 3.9 for T21, therefore recalculation of risk of T21 and referral for further counseling and testing is recommended.

Absent or hypoplastic nasal bone

The nasal bone is assessed on a sagittal view of a fetus, with the head in a neutral position and the ultrasound probe at a 45-degree angle to the nasal bone. The nasal bone is seen parallel to the skin line, but just below it, and is more echogenic than skin. The length of the nasal bone should be measured and plotted on a gestational age-specific chart and is considered hypoplastic if <2.5th percentile for gestational age [2].

An absent or hypoplastic nasal bone is associated with a likelihood ratio of 6.6 for a diagnosis of T21, therefore recalculation of risk of T21 and referral for counseling and further testing is recommended.

Echogenic bowel

Defined as bowel that has equal echogenicity to that of bone.

In isolation, likelihood ratio of T21 is 1.7, so recalculation of risk is recommended, with referral for counseling and further testing if now considered high risk (>1 in 250) for aneuploidy.

Also associated with cystic fibrosis and congenital infections such as CMV, therefore parental testing for CF gene mutations and TORCH screen is recommended.

Most commonly seen as a result of fetal swallowing of blood, therefore, history of maternal bleeding should be elicited.

Increased nuchal fold thickness

Defined as nuchal fold thickness of 6mm or more at time of morphology ultrasound.

As an isolated finding, associated with likelihood ratio of T21 of 3.8, therefore risk should be recalculated and referral for counseling and further testing is recommended.

Intracardiac echogenic focus

As an isolated finding, unlikely to be a marker for trisomy 21.

Isolated finding has likelihood ratio of 0.95, thus, in an otherwise low risk pregnancy (i.e. <1 in 250 risk from FTS) can be reassured as normal variant and nil further testing is required.

Mild hydronephrosis

Defined as minimum anteroposterior diameter of the renal pelvis of 4mm or greater.

As an isolated finding, unlikely to be a marker for trisomy 21.

Isolated finding has likelihood ratio of 1.08, thus, in an otherwise low risk pregnancy (i.e. <1 in 250 risk from FTS) can be reassured and nil further testing for aneuploidy required.

Recommend repeat ultrasound in third trimester/early neonatal review to assess for progression to hydronephrosis.

Short femur

Defined as femur length <2.5th percentile from standardized gestational age-specific charts.

Unlikely associated with T21 as an isolated finding.

However, review of lengths and appearances of other long bones, as well as other markers of skeletal dysplasia, is required and consideration of referral to a tertiary MFM unit.

Shortened humerus

Defined as humerus length <2.5th percentile.

However, review of lengths and appearances of other long bones, as well as other markers of skeletal dysplasia, is required and consideration of referral to a tertiary MFM unit.

Increased nuchal fold thickness

Defined as nuchal fold thickness of 6mm or more at time of morphology ultrasound.

As an isolated finding, associated with likelihood ratio of T21 of 3.8, therefore risk should be recalculated and referral for counseling and further testing is recommended.

Ventriculomegaly

Ventriculomegaly is defined as the diameter of the lateral cerebral ventricle of 10mm or more.

In isolation, associated with likelihood ratio of 3.8 for T21, therefore recalculation of risk and referral for counseling and further testing is recommended.

Presence of multiple soft markers at a routine morphology ultrasound

Presence of multiple soft markers at routine morphology ultrasound has a greater than additive effect on risk of aneuploidy

Presence of multiple soft markers for aneuploidy should always prompt referral to a tertiary Maternal Fetal Medicine Unit for further imaging and testing

An online calculator for recalculating risk of T21, in the presence of multiple soft markers can be found at this site (see ‘Supporting Information’ section). Please note that this does not provide confidence intervals for estimates of combined likelihood ratios:

https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1002/uog.12364

References

1. Agathokleous M, Chaveeva P, Poon LCY, Kosinski, P & Nicolaides KH. Meta-analysis of second-trimester markers for trisomy 21. Ultrasound in Obstetrics & Gynecology. 2013, 41(3): 247-261 available at: https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/uog.12364
2. Mogra R, Schluter P, Ogle R, Walter M, Borg M & Hyett J. Normal ranges for fetal nasal bone length determined by ultrasound at 18-20 weeks of gestation in a multiethnic Australian population. Australian & New Zealand Journal of Obstetrics & Gynaecology. 201; 51: 347-352.

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