Chromosomal abnormality (aneuploidy) occurs in 0.1% to 0.2% of live births. Of these, trisomy 21 (Down syndrome) is the most clinically significant as it is more often associated with impaired survival. Aside from intellectual impairment, newborn babies affected by Down syndrome are at high risk of associated structural defects including congenital heart disease and gastrointestinal abnormalities.

Many of the structural defects associated with trisomy 21 and other chromosomal abnormalities may be recognised at the 18-20 week ultrasound. Some structural defects are considered ‘hard signs’ of aneuploidy, and include major cardiac defects (see Fig. 1) cystic hygroma, exomphalos, cerebral ventriculomegaly and duodenal atresia. One or more may be seen in 25-33% of fetuses with aneuploidy and are considered clear indications for offering fetal karyotyping.

Many of the structural defects associated with trisomy 21 and other chromosomal abnormalities may be recognised at the 18-20 week ultrasound.

Several less prominent sonographic markers – or ‘soft signs’ – have also been reported to be associated with Down syndrome. In contrast with the ‘hard signs’ the ‘soft signs’ are not indicative of a local structural defect in themselves but they have been reported to increase the likelihood that Down syndrome affects a fetus. These ‘soft signs’ are also known as ‘weak markers for aneuploidy’ and include findings such as a thickened nuchal fold, echogenic bowel (see Fig. 2), shorter than expected humeri and/or femora, echogenic intracardiac foci and renal pyelectasis, to mention but a few. Even more weakly associated with aneuploidy are ‘soft signs’ such as increased iliac wing angles, an increased gap between the first and second toes, and hypoplasia of the 5th middle metacarpal bone. Choroid plexus cysts are generally accepted as not being a marker for Down syndrome but have been reported to be (weakly) associated with trisomy 18 (Edwards Syndrome), and then are probably only of importance when other features of the disorder are present. Of the ‘soft signs’, the thickened nuchal fold is the only one that has repeatedly stood up to scientific scrutiny as an independent marker of Down syndrome and has been attributed with an up to 18-fold increase in risk when detected in a fetus.

Most of the groups reporting detection of ‘soft markers’ were performing morphology scans on ‘high risk’ patients presenting for amniocentesis on the basis of either advanced maternal age or a positive triple test. Some used these markers to develop an ‘aneuploidy score’. Of these the Benacerraf Score and Nyberg Age-Adjusted Ultrasound Risk Assessment (AAURA) are the best known. In their author’s hands, these screening strategies had detection rates for Down syndrome of up to 80%. Unfortunately these detection rates were both operator dependant and were inflated by the relatively high background incidence of aneuploidy in the high-risk population screened. In ‘low risk’ or general populations, detection rates are seen to drop to well below 50%.
Whereas ‘hard signs’ are relatively uncommon ultrasound findings at the 18-20 week scan, ‘soft signs’ are commonly seen, with up to 10% of normal fetuses having one or more of these markers. The difficulty then becomes one of how to factor the presence of a soft marker in to an individual patient’s risk of Down syndrome.

The situation is made even more complex when a patient has been screened for Down syndrome earlier in the pregnancy by nuchal translucency and first trimester serology, or by the Triple Test. First trimester screening with nuchal translucency and serology can already detect up to 80-90% of fetuses with Down syndrome. Second trimester serum screening can also detect up to 75% of Down syndrome. It therefore needs to be appreciated that when ‘soft signs’ are found at 18-20 weeks in a fetus previously screened, that the positive predictive value of the ‘soft signs’ will be markedly reduced, as 75-90% of the aneuploid fetuses would already have been detected by that stage. The relevance of ‘soft markers’ in a previously screened population consequently needs careful interpretation.

To help estimate the risk of aneuploidy when a soft sign is seen in a patient in whom earlier screening has been performed (ie. NT–plus or triple test) it is SUFW policy to modify the NT–plus or Triple Test risk based on likelihood ratios assigned to these soft markers by Nyberg (AAURA – see Table 1). Although this is not ideal, in the absence of an evidence-based alternative strategy it would appear to be a more logical approach than ignoring the previous screening in determining the ‘a priori risk’. It is also SUFW policy to only report the presence of soft markers when the final calculated risk of aneuploidy exceeds a threshold of 1 in 300, which roughly approximates the risk of Down Syndrome at 35 years of age. When calculated risks are lower, amniocentesis is not clearly indicated, and ‘soft signs’ are generally not reported as they are often interpreted by patients not as markers but as genuine fetal abnormalities, and become an unnecessary source of parental anxiety.

Indeed, the issue of parental anxiety should not be ignored. Many studies have shown that the detection of any abnormality on an antenatal ultrasound creates emotional disturbance for a mother and her partner. This can result in various feelings such as anxiety, depression and loneliness in the mother.

A major challenge facing obstetrical ultrasound today is how to gauge the importance of soft markers in individual patients and decide whom to inform and whom not to inform so as to minimise the negative impact of these findings.

### Table 1: Age-Adjusted Ultrasound Risk Assessment

<table>
<thead>
<tr>
<th>Marker</th>
<th>Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural Defect</td>
<td>25</td>
</tr>
<tr>
<td>(e.g. cardiac, hygroma, ventriculomegaly)</td>
<td></td>
</tr>
<tr>
<td>Nuchal Thickening (&lt;5 mm)</td>
<td>18</td>
</tr>
<tr>
<td>Echogenic Bowel (grades 203)</td>
<td>5.5</td>
</tr>
<tr>
<td>Short Humerus</td>
<td>2.5</td>
</tr>
<tr>
<td>Short Femur</td>
<td>2.2</td>
</tr>
<tr>
<td>Echogenic Intra-cardiac Focus</td>
<td>2</td>
</tr>
<tr>
<td>Renal Pyelectasis (&gt;3 mm)</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Professor Roy Filley from the University of California, San Francisco, develops this argument in his editorial in the Journal of Ultrasound in Medicine titled ‘Obstetrical Sonography: The Best Way to Terrify a Pregnant Woman’. He describes the dilemma of finding a ‘soft marker’ in a low risk patient who is being scanned for reassurance and the perceived need to share such findings with the patient, despite the likelihood of their importance being small. He rightly points out that the main reason that this approach has developed in the USA is the threat of litigation, which is also now particularly relevant in Australia. Indeed, a major challenge facing obstetrical ultrasound today is how to gauge the importance of soft markers in an individual patient and decide whom to inform and whom not to inform about the presence of these weak indicators, which we know will be seen in 10% of normal pregnancies.

### References

4. SUFW, unpublished observations
5. SUFW, unpublished data

To be added to or removed from the distribution list for Sound Advice or to follow through on any issue featured in this newsletter, please contact Raquel Smeel on 9553 8512 or smeel@sufw.com.au
A 66 year old woman was referred for pelvic ultrasound after two episodes of light postmenopausal bleeding. She was not using hormone replacement therapy but was on Warfarin because of an artificial heart valve. INR’s (clotting studies) were within the therapeutic range. Transvaginal pelvic ultrasound revealed an endometrium with a thickness at the fundus of 4 mm (Fig. 1a). No focal endometrial, ovarian or myometrial pathology was evident.

Saline infusion sonohysterography was subsequently performed, which revealed asymmetric, irregular thickening of the posterior endometrium to 4 mm, not extending to the cervix, and with no sonographic evidence of gross myometrial invasion. The anterior and fundal wall endometrium appeared atrophic (< 1 mm) (Fig. 1b). As the features were considered sinister, an aspiration biopsy was performed. The histopathology was ‘Grade 1 endometrioid carcinoma’. Subsequent hysterectomy confirmed a Stage 1 Grade 1 endometrioid carcinoma of the uterus.

COMMENT

The risk of finding endometrial pathology increases with increasing endometrial thickness, which can be measured accurately by transvaginal ultrasound. Up to 80% of women not on HRT with postmenopausal bleeding and an endometrial thickness > 5 mm will have endometrial pathology (eg. hyperplasia, polyp, malignancy). Of these, 5-15% of women will have endometrial carcinoma, but less than 1% will have endometrial malignancy when the endometrial thickness is 4 mm or less on transvaginal ultrasound.

Transvaginal ultrasound assessment of the uterus and ovaries, with measurement of the endometrial thickness, is therefore a useful first line investigation of postmenopausal bleeding. When endometrial thickness is clearly increased, pelvic ultrasound can provide additional information as to whether there is focal thickening (suggestive of polyp formation), global thickening (suggestive of hyperplasia), or gross myometrial involvement (as may be seen with malignancy). It should also reveal whether there is indication of a recent unexpected ovulation, or evidence of ovarian cysts.

Transvaginal ultrasound assessment of the uterus and ovaries, with measurement of the endometrial thickness, is a useful first line investigation of postmenopausal bleeding.

In the setting of an otherwise healthy postmenopausal woman with vaginal bleeding and abnormally thickened endometrium, the most appropriate next step in management is referral for hysteroscopy, curettage and histological assessment of the endometrial curettings. In this clinical setting, saline infusion sonohysterography is best reserved as a second-tier investigative tool – for those patients where lack of local resources or concurrent medical disease makes sonohysterography and endometrial sampling preferable to curettage under general anaesthetic.

However, in the postmenopausal woman who has an episode of vaginal bleeding, the pelvic ultrasound has not suggested any endometrial or ovarian abnormality, the endometrial thickness is less than 5 mm, and the likelihood of endometrial malignancy is considered low, then saline infusion sonohysterography (+/- endometrial sampling) is a valid alternative to curettage.

Saline infusion sonohysterography will add information about endometrial contour, symmetry and thickness, which is of a quality superior to unenhanced transvaginal sonography. It also provides an opportunity for endometrial sampling by aspiration. Occasionally, significant pathology will be detected, as seen in this report, but when the results are all negative, there is an added level of reassurance to both the patient and the referring doctor in continuing with a conservative management plan.

Case Report: PMB and Saline Sonohysterography

A 66 year old woman was referred for pelvic ultrasound after two episodes of light postmenopausal bleeding. She was not using hormone replacement therapy but was on Warfarin because of an artificial heart valve. INR’s (clotting studies) were within the therapeutic range. Transvaginal pelvic ultrasound revealed an endometrium with a thickness at the fundus of 4 mm (Fig. 1a). No focal endometrial, ovarian or myometrial pathology was evident.

Saline infusion sonohysterography was subsequently performed, which revealed asymmetric, irregular thickening of the posterior endometrium to 4 mm, not extending to the cervix, and with no sonographic evidence of gross myometrial invasion. The anterior and fundal wall endometrium appeared atrophic (< 1 mm) (Fig. 1b). As the features were considered sinister, an aspiration biopsy was performed. The histopathology was ‘Grade 1 endometrioid carcinoma’. Subsequent hysterectomy confirmed a Stage 1 Grade 1 endometrioid carcinoma of the uterus.
The RADIUS study showed that in comparison with general ultrasound facilities, obstetric imaging facilities with highly qualified staff experienced higher detection rates for fetal abnormality, to the degree that the average radiology practice was not considered a cost-effective way of screening for fetal malformation. There is also less chance of an incorrect diagnosis taking place at a specialised obstetric imaging facility, such as SUFW, than at a radiology clinic; the importance of which is underlined by the current litigious medical environment.

Innovations in obstetric screening procedures, such as nuchal translucency screening and first trimester serology were introduced into Australian clinical practice by SUFW. Audited detection rates in SUFW’s practice are high (90% plus) and are set to improve again by including the presence or absence of the nasal bone to the other parameters already in use. A detection rate of around 97% has been recorded in a large UK study duplicated in SUFW’s practices.

With the state of the art digital technology used by SUFW, clarity is generally very good, although sometimes the position of the fetus or the mother’s build may mean that a repeat examination will be necessary to obtain all the views required during this examination. Often the sex of the fetus can be identified at the 18-20 week ultrasound examination as well.

The 18-20 week ultrasound cannot accurately diagnose chromosome abnormalities such as Down syndrome in itself. However, changes may be identified that indicate a higher likelihood of a chromosome abnormality being present, prompting further investigation by amniocentesis. This issue is further discussed in the leading article of this Sound Advice.

You can see the range of brochures SUFW produce at www.sufw.com.au Free copies of the brochures can be ordered by contacting Raquel Smeet at smee@sufw.com.au or on 9553 6512.

Free 18 Week Ultrasound Brochures

Sydney Ultrasound for Women (SUFW) has a range of free, informative and easy to understand brochures that both doctors and patients should find useful. They discuss various obstetric and gynaecological ultrasound procedures such as the 18-20 week obstetric ultrasound examination (or morphology scan).

The purpose of this examination is to assess:
- The number of fetuses present.
- The size and gestational age of the fetus.
- Fetal development and the presence of fetal abnormality.
- The position of the placenta.
- The amount of amniotic fluid present.
- The cervix.

The examination takes place between 18 and 20 weeks because good detail can usually be obtained at this time, allowing a thorough physical assessment of the fetus.

SUFW Locations

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