The aqueduct of Sylvius: a sonographic landmark for neural tube defects in the first trimester

M. FINN, D. SUTTON, S. ATKINSON, K. RANSOME, P. SUJENTHIRAN, V. DITCHAM, P. WAKEFIELD and S. MEAGHER
Monash Ultrasound for Women, Melbourne, Australia

KEYWORDS: aqueduct of Sylvius; first-trimester ultrasound; midbrain; neural tube defect; prenatal diagnosis

ABSTRACT

Objectives To describe a new first-trimester sonographic landmark, posterior displacement of the midbrain and aqueduct of Sylvius, which may be useful in early screening for neural tube defects.

Methods This was a prospective study of 457 normal fetuses at 11 + 0 to 13 + 6 weeks' gestation. We measured the distance from the posterior border of the aqueduct of Sylvius to the anterior border of the occiput (AOS-to-occiput distance) in the axial plane and created a reference range. In the nine fetuses with abnormal midbrain position identified in the first trimester and with neural tube defect subsequently confirmed, we analyzed ultrasound images to determine the position of the aqueduct of Sylvius.

Results The lower limit of normal AOS-to-occiput distance (mean minus 2 SD) ranged from 1.7 mm at a crown-rump length (CRL) of 43 mm to 3.7 mm at a CRL of 84 mm. In the nine cases with abnormal position of the midbrain and confirmed neural tube defect, juxtaosition of the midbrain to the occiput was the clue to diagnosis of the spinal abnormality. In all nine cases, the AOS-to-occiput distance was below the established normal range.

Conclusions Examination of the midbrain in an axial plane may prove a reliable marker for the first-trimester diagnosis of neural tube defects. In contrast to recently reported subtle changes in the mid-sagittal view of the posterior cranial fossa, axial imaging of the midbrain reveals striking displacement of this structure, with virtual juxtaosition to the occiput, in fetuses with confirmed open spina bifida. This anatomical distortion of the midbrain can be quantified by measurement of the AOS-to-occiput distance. Copyright © 2011 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

The diagnosis of neural tube defect is generally made at the mid-trimester fetal morphology scan, prompted by the identification of cranial signs. The lemon sign has been reported in 98% of spina bifida fetuses examined before 24 weeks and in 13% of cases in the third trimester, and the banana sign has been reported in 72% and 81% of these cases, respectively. These features, however, are rarely present in the first trimester. Furthermore, those fetal spinal abnormalities which are diagnosed in the first trimester are usually severe and frequently associated with other major defects, and the diagnosis of isolated defects is difficult. Thus, the early diagnosis of spina bifida is challenging and a second-trimester scan is still regarded as necessary to detect most cases.

In an attempt to address this diagnostic difficulty, Chaoui et al. recently described the ‘intracranial translucency’, the anteroposterior dimension of the fourth ventricle in the sagittal plane, as a new first-trimester sonographic marker for open spina bifida. Another marker, decreased frontomaxillary facial angle, has also been proposed. The brainstem diameter and brainstem-to-occipital bone distance (BSOB) have also been described in fetuses with open spina bifida at this gestation. More recently, the first-trimester transcerebellar and cisterna magna diameters in the axial plane have been described as potentially valuable signs. The search continues for a first-trimester sonographic landmark that is comparable to the easily recognisable and highly predictive mid-trimester ‘banana shaped’ cerebellum.

The aims of this study were to define quantitatively the position of the first-trimester fetal midbrain by establishing a normal range for the distance between the aqueduct of Sylvius and the occiput (AOS-to-occiput distance) and to determine whether this distance is reduced in fetuses with open spina bifida, which could suggest its...
potential as a marker for the early detection of neural tube defects.

METHODS

Monash Ultrasound for Women is a dedicated obstetric and gynecologic practice and center for fetal diagnosis which provides first- and second-trimester sonographic screening by highly skilled sonographers for chromosomal and structural defects in low- and high-risk pregnancies. We follow The Fetal Medicine Foundation guidelines for first-trimester ultrasound examinations, which are performed routinely by both transvaginal and transabdominal approaches in each patient; the higher transducer frequency of the former approach facilitates optimal evaluation of the fetal structure, while the latter permits a wider range of angles of insonation to achieve the desired planes. Since early 2010, the fetal midbrain has been examined and the AOS-to-occiput measurement performed routinely at our center during the first-trimester scan, following our recognition of its characteristic sonographic appearance due to posterior displacement in four fetuses with confirmed neural tube defects.

In this prospective study, we examined consecutive fetuses presenting for first-trimester screening during a 9-month period from July 2010. Ultrasound examinations were performed using Voluson E8 and Voluson 730 (GE Healthcare Ultrasound, Zipf, Austria) machines, equipped with a 3D 4–8-MHz probe for transabdominal and a 5–9-MHz probe for transvaginal examinations.

The desired axial image plane was acquired during the routine cranial sweep in the axial plane used to identify the choroid plexus, confirm brain symmetry and measure head size. The midbrain was visualized immediately caudal to the plane in which the biparietal diameter is measured. The aqueduct of Sylvius, which is narrower and more difficult to visualize in the second trimester, is easily identified at this gestational age as a prominent echogenic ‘box’ traversing the midbrain. A superoinferior oblique plane of insonation was avoided by exclusion of the choroid plexus in the lateral ventricles and by ensuring that the aqueduct of Sylvius was ‘square’ in appearance rather than elongated. A lateral oblique plane was avoided by ensuring symmetry of the right and left halves of the brain. The calipers were placed on the posterior border of the aqueduct of Sylvius and the anterior border of the occiput (Figure 1). Care was avoided to distinguish the occipital cortex from the bony occiput. The images were obtained either transvaginally or transabdominally at the discretion of the sonographer, depending on which provided the better insonation plane for optimal visualization of the midbrain.

A scoring system was employed retrospectively to identify high-quality images in fetuses which subsequently had a normal neural sonogram at 19–20 weeks’ gestation. This scoring system allocated 1 point for optimal magnification of the image (fetal cranium at least 60% of the size of the image), 1 point for identification of the correct axial plane, 1 point for clear demarcation of the aqueduct of Sylvius and 2 points for correct placement of the calipers. Only those images with a total score of 5 points were included for subsequent analysis in this study to establish the normal range.

Once the normal range had been established, inter- and intraobserver variation was evaluated for three of the sonographers (authors; Operators A, B and C) in a separate study of a further 22 fetuses between 11 and 14 weeks’ gestation. Each operator acquired and measured an axial midbrain image on two separate occasions during the ultrasound examination. Images were acquired either transabdominally or transvaginally according to operator preference. Operators A and B each performed the complete fetal morphology study in 11 patients. Operator C was the second observer for both, performing the examination in all 22 patients. Each operator was unaware of prior measurements, the images being stored for later analysis. When more than two images were recorded, the two of highest quality were selected for analysis.

The AOS-to-occiput distance was also measured in nine fetuses with confirmed neural tube defect. In seven of these fetuses, the abnormal midbrain position was identified in the first trimester, leading to early diagnosis of spina bifida; in the other two fetuses, in whom spina bifida was diagnosed at the mid-trimester morphology examination,
the abnormal midbrain position was identified in retrospect on evaluation of the earlier first-trimester ultrasound study.

The DVD recording of the ultrasound examination of each patient was reviewed in iMovie (2009, Apple Inc., ●Cupertino, CA, USA) and relevant frames were isolated. An average of two to four AOS-to-occupit measurements for each fetus was determined after importation to OsiriX imaging software. ●Data were analyzed using Numbers '09 spreadsheet (iWork 2009, Apple Inc.). Statistical analysis was performed using Predictive Analytics SoftWare (PASW, SPSS Inc., Chicago, IL, USA).

Approval to perform this study was obtained from Monash Surgical Private Hospital Human Research Ethics Committee.

RESULTS

Follow-up was unavailable for 15 patients, who had moved interstate or overseas. Using the strict scoring system, 457 images of 50 kg and 94 kg, respectively. The mean (SD) for the Gaussian distribution of gestational age at examination was 89 (3) days and of crown–rump length (CRL) was 67 (7.6) mm.

We observed a positive linear correlation between AOS-to-occupit distance and gestational age and a stronger correlation between AOS-to-occupit distance and CRL (Figure 2). The linear regression of AOS-to-occupit distance (in mm) as a function of CRL (in mm) was:

\[ \text{AOS-to-occupit distance} = 0.095 \times \text{CRL} - 2.1 \]

Analysis of variance revealed that the model was statistically significant (Pearson’s correlation coefficient \( R = 0.698 \), \( P < 0.001 \)).

A Gaussian distribution was identified for the AOS-to-occupit distance for CRL intervals of 5 mm. The normal ranges (mean and 2 SD, Table 1) were constructed based on parametric data analysis. As our practice encourages referral of patients after 12 weeks’ gestation to view the fetal anatomy optimally, the majority of fetuses in our study had CRL > 55 mm. The lower limit of normal ranged from 1.7 mm at a CRL of 45–49 mm to 3.7 mm at a CRL of 80–84 mm.

In the separate study of 22 fetuses, low intraobserver variation in measurements was found. The intraclass correlation coefficient (ICC) and 95% confidence limits for Observer A was 0.86 (0.58–0.96), for Observer B was 0.95 (0.86–0.98) and for Observer C was 0.97 (0.89–0.99). The variation between Observers A and C and Observers B and C was similarly low, with ICCs of 0.89 (0.8–0.97) and 0.96 (0.88–0.99), respectively.

Table 1: Aqueduct of Sylvius (AOS)-to-occupit distance according to crown–rump length (CRL)

<table>
<thead>
<tr>
<th>CRL (mm)</th>
<th>n</th>
<th>Mean – 2 SD</th>
<th>Mean</th>
<th>Mean + 2 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>45–49</td>
<td>8</td>
<td>1.7</td>
<td>2.3</td>
<td>2.6</td>
</tr>
<tr>
<td>50–54</td>
<td>20</td>
<td>2.0</td>
<td>2.8</td>
<td>3.6</td>
</tr>
<tr>
<td>55–59</td>
<td>55</td>
<td>2.1</td>
<td>3.5</td>
<td>4.9</td>
</tr>
<tr>
<td>60–64</td>
<td>77</td>
<td>2.3</td>
<td>3.9</td>
<td>5.3</td>
</tr>
<tr>
<td>65–69</td>
<td>118</td>
<td>2.6</td>
<td>4.2</td>
<td>5.8</td>
</tr>
<tr>
<td>70–74</td>
<td>110</td>
<td>3.1</td>
<td>4.7</td>
<td>6.3</td>
</tr>
<tr>
<td>75–79</td>
<td>49</td>
<td>3.6</td>
<td>5.2</td>
<td>6.8</td>
</tr>
<tr>
<td>80–84</td>
<td>20</td>
<td>3.7</td>
<td>5.7</td>
<td>7.7</td>
</tr>
</tbody>
</table>

These fetuses were representative of those in the main study, the CRL ranging from 53 to 83 (mean, 65) mm.

Among the nine abnormal cases, the sonographic observation of an unusual midbrain appearance in one at 12 weeks’ gestation flagged it as being high risk, and it was subsequently recognized as having a spinal defect at the mid-trimester ultrasound examination (Case 1, Table 2). Subsequent recognition of a similar first-trimester midbrain appearance in five fetuses led to diagnosis of a neural tube defect within 2 weeks. In the seventh fetus, although the midbrain abnormality was identified in the first trimester, the patient chose not to return for review until 20 weeks, when the spinal lesion was diagnosed. In a further two fetuses, in which the spinal defect was diagnosed at mid-trimester, the abnormal midbrain appearance was detected retrospectively, on review of the first-trimester ultrasound study. The relevant clinical information for all nine fetuses with confirmed neural tube defect is outlined in Table 2. In all nine...
Table 2 Findings at first-trimester ultrasound examination and follow-up in nine cases of spina bifida associated with first-trimester posterior displacement of the fetal midbrain

<table>
<thead>
<tr>
<th>Case</th>
<th>GA (weeks)</th>
<th>CRL (mm)</th>
<th>MW (kg)</th>
<th>AOS (mm)</th>
<th>Ultrasound findings</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12 + 5</td>
<td>61</td>
<td>64</td>
<td>1.2</td>
<td>Sonographer’s impression of abnormal midbrain, ultrasound report: no structural abnormality</td>
<td>Sacral NTD identified at 20 weeks’ gestation, 15-mm sacral meningocoele, features of Arnold–Chiari malformation</td>
</tr>
<tr>
<td>2</td>
<td>12 + 3</td>
<td>57</td>
<td>74</td>
<td>1.0</td>
<td>Posterior displacement of midbrain, small fourth ventricle seen on axial view, sagittal posterior fossa obscured by shadowing, lumbosacral spine appeared intact</td>
<td>NTD identified at 15 + 4 weeks, 4-mm lumbosacral meningocoele, ventriculomegaly and banana-shaped cerebellum, TOP before 16 weeks</td>
</tr>
<tr>
<td>3</td>
<td>12 + 6</td>
<td>70</td>
<td>95</td>
<td>1.4</td>
<td>Midbrain juxtaposed to occiput, fourth ventricle identified on 3D imaging, sagittal posterior fossa difficult to interpret, 11-mm lumbosacral meningocoele identified</td>
<td>TOP before 14 weeks</td>
</tr>
<tr>
<td>4</td>
<td>12 + 3</td>
<td>52</td>
<td>92</td>
<td>0.9</td>
<td>Midbrain juxtaposed to occiput, Obliteration of intracranial translucency, 5-mm lumbosacral meningocoele</td>
<td>TOP before 14 weeks</td>
</tr>
<tr>
<td>5</td>
<td>13 + 0</td>
<td>68</td>
<td>111</td>
<td>1.5</td>
<td>Midbrain juxtaposed to occiput, obliteration of cisterna magna, five-segment thoracolumbar spinal rachischis</td>
<td>TOP before 14 weeks</td>
</tr>
<tr>
<td>6</td>
<td>12 + 6</td>
<td>63</td>
<td>61</td>
<td>1.3</td>
<td>Midbrain juxtaposed to occiput, sagittal posterior fossa obscured by shadowing, NTD not identified, recommended review in 5 days</td>
<td>Rachischisis confirmed at 13 + 4 weeks, TOP before 14 weeks</td>
</tr>
<tr>
<td>7</td>
<td>12 + 5</td>
<td>69</td>
<td>63</td>
<td>1.7</td>
<td>Midbrain juxtaposed to occiput, sagittal profile difficult to interpret, NTD not identified, recommended review in 2 weeks</td>
<td>Returned for review at 20 weeks, large meningocoele (22 mm), Arnold–Chiari type 2, ventriculomegaly</td>
</tr>
<tr>
<td>8</td>
<td>13 + 1</td>
<td>72</td>
<td>57</td>
<td>2.1</td>
<td>Dichorionic diamniotic twin gestation, ultrasound report: no structural abnormality, sagittal profile difficult to interpret</td>
<td>Spina bifida diagnosed at mid-trimester, Retrospective identification of first-trimester midbrain juxtaposed to occiput</td>
</tr>
<tr>
<td>9</td>
<td>12 + 4</td>
<td>63</td>
<td>75</td>
<td>1.4</td>
<td>Ultrasound report: no structural abnormality, sagittal profile difficult to interpret</td>
<td>Lumbosacral NTD seen at mid-trimester, Arnold–Chiari type II, Ventriculomegaly, retrospective identification of first-trimester midbrain juxtaposed to occiput</td>
</tr>
</tbody>
</table>

3D, three-dimensional; AOS, aqueduct of Sylvius-to-occiput distance; CRL, crown rump length; GA, gestational age; MW, maternal weight; NTD, neural tube defect; TOP, termination of pregnancy.

DISCUSSION

There are several contenders for sonographic markers for early diagnosis of neural tube defects, all based on the pathophysiology of inferior displacement of the brain secondary to cerebrospinal fluid leakage into the amniotic cavity in open spinal lesions.

In 1993, Blumenfield et al.9 identified the cranial signs of lemon-shaped head and banana-shaped cerebellum in three of four 14–16-week singleton fetuses with spina bifida, as well as the evolution in a 12-week fetus of anterior curvature of the cerebellum to the definitive banana shape 3 weeks later.

A landmark paper by Buisson et al. in 200210 led the way to discovery of first-trimester cranial signs as markers for open spina bifida. In a retrospective evaluation of two cases at 12 weeks’ gestation, the authors described ‘acorn-shaped’ narrowing of the frontal bones and a parallelism of the cerebral peduncles in the axial plane. They observed a flat occiput and a straighter than normal metencephalon in the sagittal view, consistent with displacement of the brain towards the foramen magnum.

The intracranial translucency seen in the midsagittal plane has gained widespread recognition since the first description of its absence in four cases of open spina bifida, drawn from a database of fetal anomalies3. This absence was attributed to compression of the fourth ventricle.
In stored images of 18 of 20 fetuses with open spina bifida, the mean frontomaxillary facial angle was found to be almost $10^\circ$ lower than that in controls and was below the $5^{th}$ percentile. This flattening of the frontal bones is equivalent to the lemon-shaped frontal bone scalloping in the second trimester.

In a study investigating the BSOB in stored images of 30 fetuses with open spina bifida, the brainstem diameter was $>95^{th}$ percentile of the control group in 29 cases, the BSOB was $<5^{th}$ percentile in 26 cases and the brainstem diameter : BSOB ratio was $>95^{th}$ percentile in all cases. More recently, a reduced transcerebellar diameter, as measured in the axial fronto-occipital plane, was described in one case of confirmed open spina bifida.

However, there have recently been reports of cases of open spina bifida without obliteration of the fourth ventricle. Difficulties with image interpretation in the midsagittal plane have included non-visualization of the fourth ventricle due to posterior acoustic shadowing from

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the frontal bone, poor contrast discrimination between
the hypoechoic brainstem and the fourth ventricle and
misidentification of the cisterna magna and the midbrain
as the fourth ventricle. 

In theory, the BSOB measurement should prove
more sensitive than is measurement of the intracranial
translucency, as it includes compression of both cisterna
magna and the fourth ventricle. A similar marker,
however, described as the posterior fossa translucency,
which also includes the fourth ventricle and cisterna
magna, was not observed in 11/880 (1.25%) normal
fetuses and was observed falsely in 7/16 (43.7%) of spina
bifida cases.

In our nine cases of open spina bifida, the mid-sagittal
view was not easy to interpret, with variable identification
of reduced or absent cisterna magna and/or fourth
ventricle. Yet, all nine cases shared a common positive
ultrasound feature: an elongated and ‘pushed back’
midbrain, to the point of virtual juxtaposition with the
occiput. While this presented a striking visual diagnostic
clue, we further sought to identify a sonographic
marker with which to quantify this finding. A suitable
objective assessment of posterior midbrain displacement
was determined to be the distance between the posterior
border of the sharply defined aqueduct of Sylvius, which
traverses the midbrain, and the anterior border of the
occiput. In our series, the lower limit of the established
normal range (mean minus 2 SD) ranged from 1.7 mm
at a CRL of 45 mm to 3.7 mm at CRL of 84 mm, while
in all nine cases of confirmed neural tube defect, the
AOS-to-occiput distance was below the normal range for
gestational age. This observation of virtual juxtaposition
of the midbrain to the occiput, supported by objective
AOS-to-occiput distance measurements, is much easier,
in our opinion, than interpretation of linear hypoechoic
regions in the mid-sagittal image.

In practice, it must be remembered that the cut-off
level for each CRL interval is not diagnostic of
spina bifida, but serves as a guide below which one
should consider the possibility of neural tube defect. The
diagnosis of neural tube defect is based on the finding
of interrupted neural arches in three orthogonal scanning
planes. The first-trimester diagnostic ultrasound findings
present similarly to those in the second trimester but
may be difficult to visualize because of their relatively
smaller size. Visualization of the flat lesion of rachischisis,
as seen in two of our cases, is a particularly difficult
challenge. Indeed, in these cases it was the strong belief
in the midbrain sign (i.e. its juxtaposition to the occiput,)
that led the operator to persist and eventually identify
the spinal lesion. In the cases of spina bifida described
in our study, when the spinal defect was believed to
be present at the initial first-trimester examination, the
patient was requested to return for review within 14 days
to confirm the diagnosis. A confident diagnosis of the
spinal abnormality afforded the patient the option of
early termination of pregnancy.

The subtle changes in echogenicity of structures and
the multiple parallel echogenic lines in the midsagittal
view of the posterior fetal brain have the potential to
confuse. The strength of our proposed new marker for
first-trimester neural tube defects lies in the ease of
acquisition of the appropriate ultrasound plane during
a routine cranial sweep in the axial plane (Videoclip S1)
using the transabdominal or transvaginal approach,
the readily recognizable abnormal midbrain position seen
in this cranial sweep (Videoclips S2–4) and the ease
of measurement of the distance between the aqueduct
of Sylvius and the occipital bone in both normal and
abnormal fetuses. Just as the banana-shaped cerebellum
is a striking feature in the axial plane at mid-trimester, so
too is the midbrain position in the first trimester.

ACKNOWLEDGMENTS

We would like to thank Shirley Sanderson, Joan Steen and
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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

- **Videoclip S1** Videoclip of normal cranial sweep, showing level of choroid plexus, midbrain, the aqueduct of Sylvius ‘box’ and brainstem (transvaginal approach).
- **Videoclip S2** Videoclip of abnormal cranial sweep, showing level of choroid plexus, ‘pushed back’ midbrain, the aqueduct of Sylvius ‘box’ and brainstem in fetus with confirmed neural tube defect (transvaginal approach) (Case 2).
- **Videoclip S3** Videoclip showing cranial and spinal images of fetus with open spina bifida (Case 3).
- **Videoclip S4** Videoclip showing cranial and spinal images of fetus with rachischisis (Case 5).
QUERIES TO BE ANSWERED BY AUTHOR & EDITOR

IMPORTANT NOTE: Please list all query corrections in an e-mail and send to the production contact as detailed in the covering e-mail, or mark all corrections directly on the proofs and send the scanned copy via e-mail. Please do not send corrections by annotated PDF file and do NOT mark your corrections on this query sheet.

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AQ1 Is the short title ok: “Aqueduct of Sylvius and early NTD screening”

AQ2 Please check that all affiliations are correct and complete.

AQ3 The affiliations of each author are normally presented briefly (as you said in your reply), but the Correspondence address at the bottom of the first page is normally the full postal address for one person – the author. Would you prefer to leave it as it is or add the full details of your postal address?

AQ4 SORRY – I meant anomaly not anatomy – but morphology is fine if you prefer.

AQ5 I’ve defined BSOB here at first mention and used the abbreviation elsewhere – OK?

AQ6 ‘and the AOS-to-occiput measurement performed’ added here in response to your reply in the next section – OK?

AQ7 ‘due to posterior displacement’ added – OK?

AQ8 Rather than ‘a subtle structure’, how about ‘narrower and more difficult to visualize’? I can’t think of one word to use instead here – we can ask Sarah H at proof stage if she has any suggestions.

AQ9 Please could you clarify ‘Care was avoided to distinguish’ – has something been cut from here by mistake? Do you mean care was taken? Or care was taken to avoid – what exactly?

AQ10 I’ve reworded here in response to your reply – have I represented what you meant appropriately? “at the discretion of the sonographer, depending on which provided the better insonation plane for optimal visualization of the midbrain”

AQ11 Figure 1 - I’ve added ‘double-headed arrow and calipers’ at the end - OK?

AQ12 Do you want to specify their initials? Did all authors participate in the main study (and any other sonographers also?)

AQ13 I’ve changed ‘Each operator acquired and measured two axial midbrain images at varying intervals during the ultrasound examination.’ To ‘Each operator acquired and measured an axial midbrain image on two separate occasions during the ultrasound examination.’ in response to your reply – is this ok?

AQ14 ‘Cupertino, CA, USA’ added – OK?

AQ15 ‘Data were analyzed...’ – I’ve moved these last two sentences to the end, assuming they apply to all fetuses – is this paragraph OK?

AQ16 Figs – I’ve left your wording as ‘95% of observations fall within the outer diagonal lines’ for now, as I’m not sure your new suggestion is much different – I think it’s fine as it is, now you’ve explained, but we can double check with Sarah H if you like? (There’s no recognized term for these lines, I gather?)

AQ17 So are the three mentions of BSOB here correct?

AQ18 I was wondering about the flow of these three paragraphs, which start with BSOB, move away from it, and then come back to it again. Let’s see how it reads in proof.

AQ19 ‘quantitative sonographic marker to represent this finding.’ Changed to ‘sonographic marker with which to quantify this finding’ – ok?

AQ20 Could you double check ref 000 please? I cannot find this edition online – are the date and title correct? Also, who were the authors?

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