PRENATAL DIAGNOSIS
*Prenat Diagn* 2009; **29**: 402–411.
Published online 19 March 2009 in Wiley InterScience
(www.interscience.wiley.com) **DOI:** 10.1002/pd.2250

**REVIEW**

# Prenatal screening and diagnosis of neural tube defects

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This review article discusses prenatal screening and diagnosis of neural tube defects (NTD). High detection rates occur in countries operating ultrasound screening programmes because classical two-dimensional ultrasound cranial signs (lemon shaped head, banana cerebellum, ventriculomegaly) are important diagnostic clues to the presence of spina bifida. Careful evaluation of both the spine and a search for other abnormalities is warranted. Important prognostic information for spina bifida relates to the lesion level, with a "watershed" between L3 and L4 marking a very high chance of being wheelchair bound with the higher lesions. Three-dimensional ultrasound using multiplanar views can achieve diagnostic accuracy within one vertebral body in around 80% of patients. There are high rates of pregnancy termination for spina bifida in many European countries, but the use of new imagining techniques allow better prediction of outcome, and consequently a refinement of prenatal counselling. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS: prenatal screening; 3D ultrasound; 4D ultrasound; Neural tube defects; spina bifida; meningocele; myelomeningocele; anencephaly; encephalocele

## INTRODUCTION

Neural tube defects (NTD) range from the lethal (anencephaly) to the potentially asymptomatic (some closed spina bifida). Spina bifida outcomes appear to be highly variable and difficult to predict. This is in part not only due to the genuine heterogenicity of the condition but also due to image interpretation and a lack of prospective outcome data (Boyd *et al*., 2008). We review prenatal screening options for NTD, and the role of two-dimensional (2D) and three-dimensional (3D) ultrasound techniques in achieving diagnosis with prognostic prediction.

## PRENATAL SCREENING FOR NTD

### Risk assessment prior to biochemical and/or ultrasonic screening

The average incidence of NTD is 1 : 1000 births, but this masks a marked geographical variation between countries with the highest rates of NTD (e.g. UK and USA), and the lowest (e.g. Japan) (Davis and Young, 1991; Ehara *et al*., 1998; Pilu, 2008). Risks increase to 2 to 3% if one pregnancy has been affected, to 10% if two pregnancies have been affected. Other independent risk factors are valproic acid, folic acid antagonists (methotrexate and aminopterin), vitamin A, maternal diabetes, maternal obesity, hyperthermia and folate deficiency (Padmanabhan 2006; Shaer *et al*., 2007; Rasmussen *et al*., 2008). However, 90% of children with NTD are born to women with no identifiable risk factors.

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Two approaches have been used for NTD screening in low-risk populations: biochemical testing of maternal blood for alpha-fetoprotein (AFP) or the use of traditional 2D ultrasound. Some screening programmes combine the two techniques.

### Biochemical screening

For over 30 years, maternal serum AFP has been used as a screening test for open NTD. AFP is a glycoprotein, secreted by the fetal yolk sac and liver. Fetal serum concentrations are 150 to 200 times that of amniotic fluid (Habib, 1977). Amniotic fluid levels of AFP and acetylcholinesterase were historically used to diagnose NTDs, but have been superseded by fetal ultrasound. Open NTD increase AFP in both amniotic fluid and maternal blood. As closed NTD (10% of lesions) do not increase AFP, biochemical screening is not effective. The maternal serum level of AFP varies with gestation, so needs to be expressed as multiples of the median (MoM). Using 2.5 MoM as screen positive in singleton pregnancies, the detection rate for anencephaly is expected to be >95% and for open NTD between 65 and 80%. False-positive rates should lie between 1 and 3% (Bradley *et al*., 2005). A raised serum AFP is not diagnostic for open NTD as it can be associated with other abnormalities including gastroschisis, omphalocele, congenital nephrosis and fetal demise. Many now question the benefit of amniotic fluid biochemical markers where there is access to high-quality ultrasound (Kooper *et al*., 2007).

### Ultrasound screening

Traditional 2D ultrasound has largely superseded maternal AFP as a screening tool. Boyd *et al*. (2008) recently

*Received: 25 July 2008*
*Revised: 2 February 2009*
*Accepted: 2 February 2009*
*Published online: 19 March 2009*

surveyed the national screening policies current in 2004 for 18 European countries. There was a formal national ultrasound screening policy for structural anomalies in 14 of the 18 European countries, with 3 of 18 having no official policy but regularly performing an 18- to 22-week anomaly scan. The overall prenatal detection rate for NTD was 88%, (range 25–94%). Detection rates were highest in those countries with standards determined by a national screening policy.

Gestational age and type of NTD greatly influences detection rates. First trimester studies typically quote detection rates of >90% for anencephaly and encephalocele (80%), but lower rates for spina bifida (44%) (Whitlow *et al*., 1999; Taipale *et al*., 2003). Second trimester scanning improves the detection of spina bifida, typically to 92–95% (Grandjean *et al*., 1999; Smith and Hau, 1999). An important principle is that, in diagnosing an NTD a careful evaluation of the whole fetus should be performed because associated malformations are found in around 20% (Stoll *et al*., 2007).

## IMAGING TECHNIQUES FOR DIAGNOSING NTD

### 2D ultrasound

#### *Anencephaly*

Failure of closure of the rostral neuropore causes failed cranial vault development and the condition of exencephaly, the precursor of anencephaly. Ossification of the skull vault is not always apparent until 12 weeks' gestation and anencephaly should not be diagnosed before this time (Russell *et al*., 2007). This should be an easy diagnosis to make. First trimester ultrasound findings include absent calvarium, reduced crown-rump length, exposed neural tissue with a lobulated appearance (exencephaly), or absent neural tissue, and a loss of the normal head contour with the orbits marking the upper limit of the fetal face in the coronal plane (Figure 1). By the second or third trimester there may be associated polyhydramnios from impaired fetal swallowing.

#### *Cephalocele*

To confirm the diagnosis, it is necessary to visualize the bony skull defect through which the meningeal sac alone (meningocele) or sac plus cerebral tissue (encephalocele) herniated (Figure 2). This communication between external mass and intracranial cavity differentiates cephaloceles from other lesions such as lipomas or teratomas. Seventy-five percent arise from a defect in the occipital bone, with remainder roughly equal between parietal and frontal bones. Associated findings including cerebral ventriculomegaly, microcephaly, Dandy–Walker malformation, agenesis of the corpus callosum, facial clefts and cardiac defects.

#### *Spina bifida*

Detection rates by routine ultrasound screening should approach 100% for open spina bifida due to the presence of the easily recognizable cranial signs; the "lemon" and "banana" signs (Nicolaides *et al*., 1986) (Figures 3 and 4).

The lemon sign describes the shape of the skull in transverse plane caused by the concavity of the parietal bones. It is gestation dependent; has been described as early as 13 weeks (Blaas *et al*., 2000), and in 98% before 24 weeks but in only 13% after 24 weeks (Van den Hof *et al*., 1990). Its resolution is thought to be due to further ossification and strengthening of the bony calvarium, increasing intracranial pressure or both. The lemon sign is not specific for open NTD (Ball *et al*., 1993) with up to 1% of normal fetuses displaying a mild concavity of

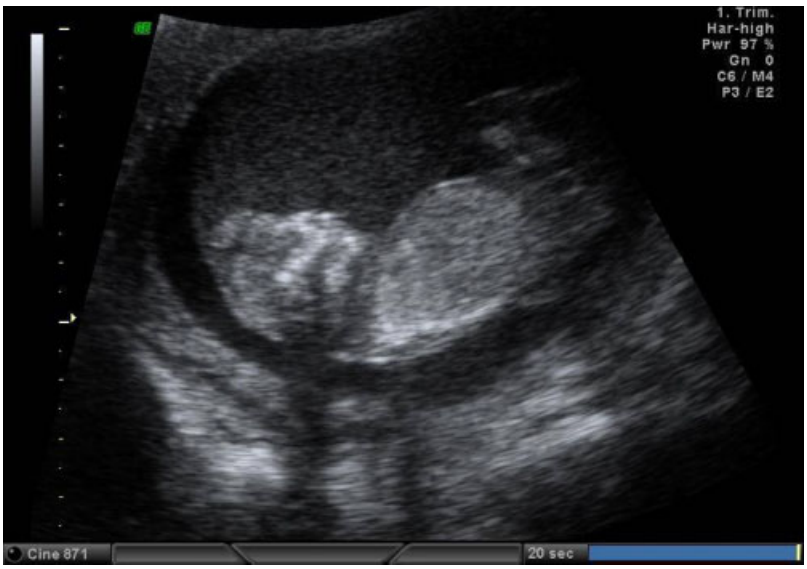


Figure 1—Two-dimensional Ultrasound of anencephaly



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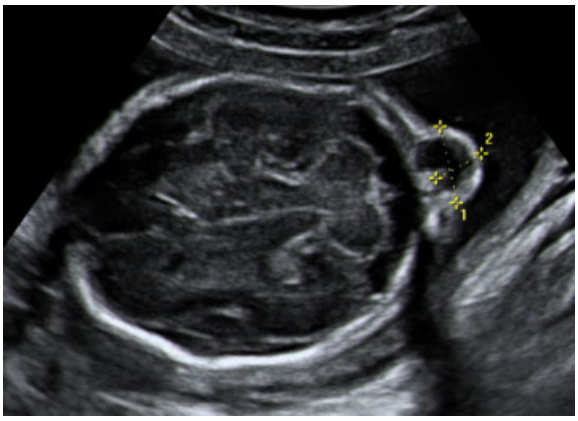

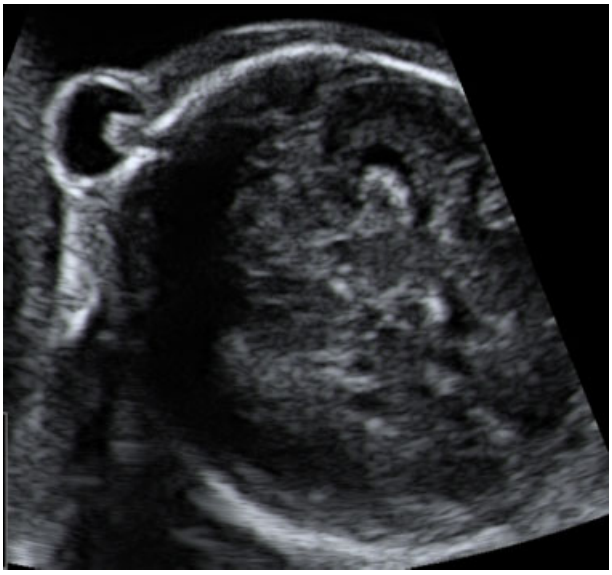

Figure 2—Occipital encephalocele

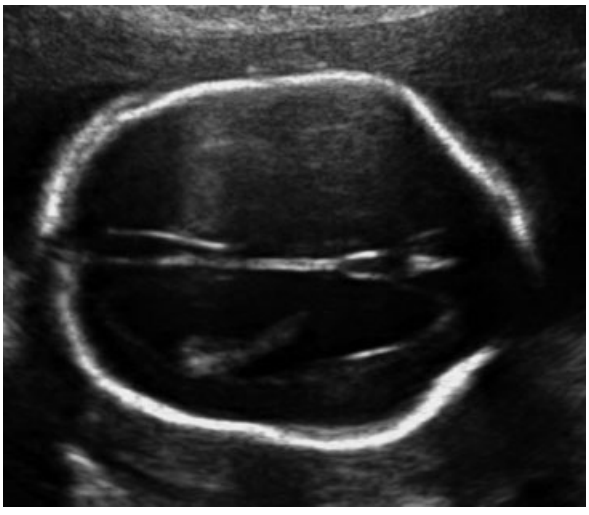

Figure 3—Classical lemon shaped head with ventriculomegaly seen in a fetus with spinabifida

the frontal bones (Campbell *et al*. 1987; Nyberg *et al*., 1988).

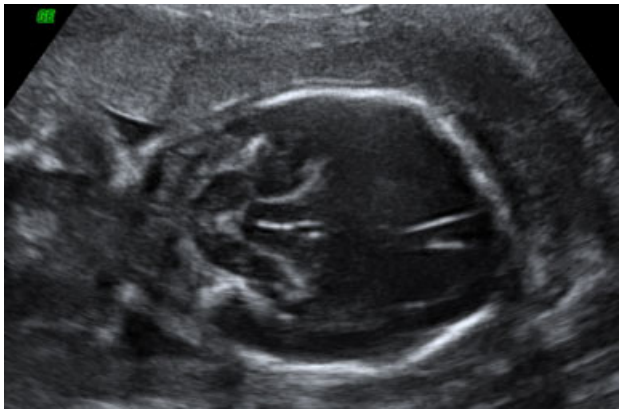

Figure 4—Banana cerebellum associated with spina bifida

The banana sign refers to the shape of the cerebellum, which is distorted as part of the Chiari type II malformation. The cerebellum may also be absent as part of the Chiari type II malformation which is seen in 95% of open NTD and does not resolve as the pregnancy advances.

Pooled data from 234 fetuses with spina bifida showed that 99% had at least one cranial finding at less than 24 weeks (Watson *et al*., 1991). Lemon and banana (or absent cerebellum) signs were both seen in 97% of fetuses, with ventriculomegaly seen in 75%, cisterna magna obliteration in 68% and small biparietal diameter in 61%. An Italian study recently reported on 49 fetuses with spina bifida and assessed six sonographic signs in prenatal diagnosis (D'Addario *et al*. 2008). They found a small cerebellum in 96% of cases, an effaced cisterna magna in 93% and a small posterior fossa in 96%. Less consistent cranial signs were ventriculomegaly (81%) and "lemon" sign (53%).

Subtle supratentorial signs are seen with the Chiari type II malformation. Fujisawa *et al*. (2006) described late pregnancy changes in the shape of the enlarged posterior horn of the lateral ventricle in the coronal view, and Callen and Filly described a lateral ventricle with a pointed shape in axial view although this was more common prior to 24 weeks and in ventricles of normal size (Callen and Filly 2008).

Ghi *et al*. (2006) reported that while all 53 cases of open spina bifida had alterations in cranial anatomy (including the "banana" and "lemon" signs), with closed spina bifida (7% of their population) cranial signs do not develop. They conclude that the "the differentiation between open and closed spina bifida is best shown by the sonographic demonstration of abnormal or normal cranial anatomy."

To accurately identify the type and extent of the lesion sagittal, coronal and axial spinal views are all required (Figure 5). The bony defect is identified by splaying of the posterior lamina ossification centers in the coronal and axial plane (Figure 6). The bony defect may lie at or cranial to, the level at which there is protrusion of the meninges (meningocele) or meninges plus neural tissue (myelomeningocele).

All lesions arise from a dysraphism (defect of closure) and are classified as open or closed depending on



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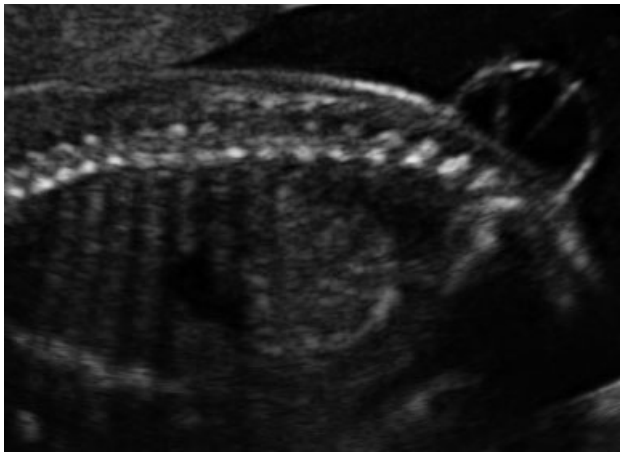

Figure 5—Sagittal plane demonstrating a meningocele

whether the overlying skin is breached. Closed lesions have a more favorable prognosis and include lipomas, teratomas, haemartoma, and myelocystocele (a closed, ependyma-lined cystic lesion, communicating with the central canal of the spinal cord) (Meyer *et al*., 1998).

## 3D Ultrasound for NTD

Three-dimensional ultrasound can provide excellent views of a spinal lesion (Figures 7 and 8). The American Institute of Ultrasound in Medicine, reporting on the diagnostic benefits of obstetric 3D ultrasound, endorsed defining the upper level of the lesion and identifying vertebral anomalies as examples of its practical clinical application (Benacerraf *et al*., 2005). An in depth review, commissioned to raise awareness of the specific benefits of 3D ultrasound included examination of the fetal brain and spine (Goncalves *et al*., 2005). For the diagnosis of NTD, 3D offers:

1. 3D visualization of the entire spine, allowing examination of structures in planes of section other than the original acquisition planes.
2. Ability to review and manipulate volume data after the patient has left the ultrasound room.
3. A range of rendering algorithms that allows visualization of different characteristics of the same structure. Maximum or skeletal modes will highlight bony structures and surface mode will render the sac or overlying skin integrity.
4. Facilitation of orientation by display of multiple planes displayed at one time.
5. The ability to transmit data over networks for consultation in other centers.
6. The potential to use off-line software programs as interactive educational tools.

## 3D ultrasound technique for NTD assessment

Views are best obtained with the fetal spine uppermost and seen in sagittal section. The initial region of interest is selected to include the maximum spinal length possible, whilst the sweep angle can be reduced to 35° to 40° improving lateral resolution and acquisition time. Before starting the acquisition, attention should

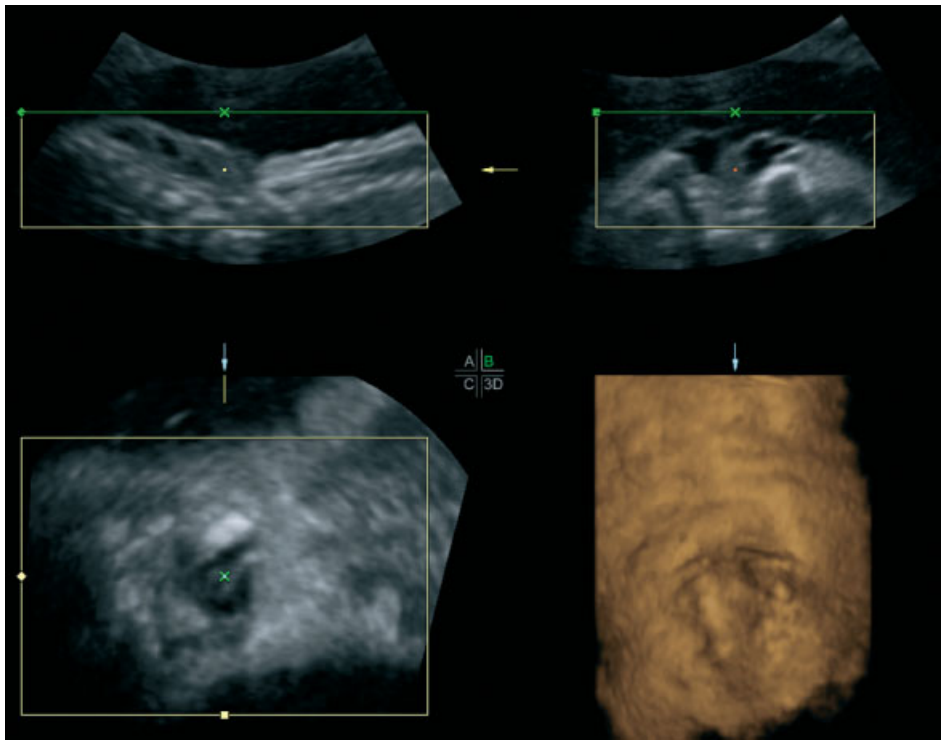


Figure 6—Three-dimensional multiplanar view showing splaying of the posterior lamina ossification centers in the B-plane axial view (top right)



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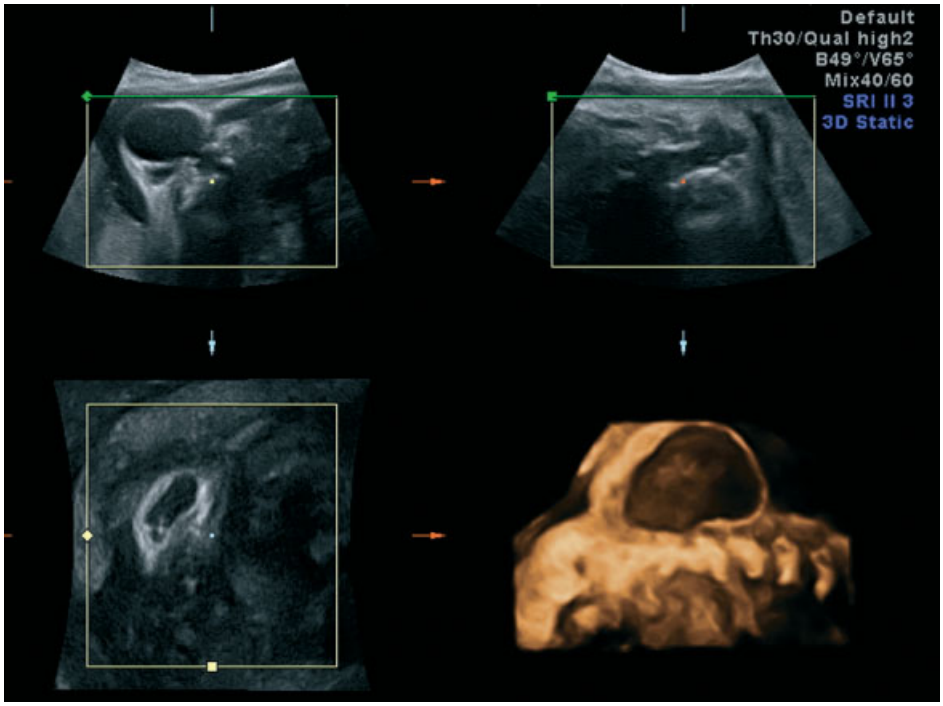


Figure 7—Multiplanar 3D ultrasound of meningocele. B-plane image (top left) shows continuation with spinal canal, A-plane image (top right) shows empty sac as does the surface rendered image (bottom right)

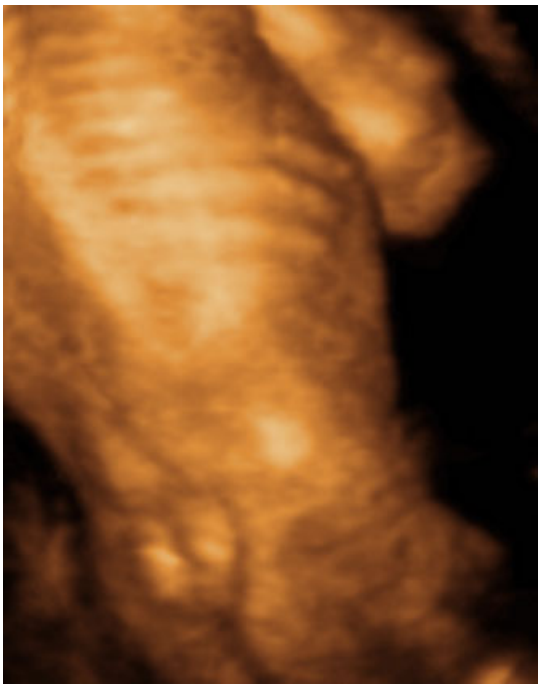

Figure 8—Surface rendering of a low lumbosacral spina bifida. Although useful to demonstrate the lesion to the parents, the view provides little additional clinical information to the 3D multiplanar view

be paid to the 2D image, optimising the gain, focal depth, and magnification settings. Unfortunately the best 2D setting for surface rendering are quite different from those for skeletal examination and it is unlikely that a single volume will be optimal for both. For surface rendering, set the gain so that the liquor is as dark as possible without losing detail from the surface reflections. Surface rendering requires a window of amniotic fluid, but this is unnecessary for examination of the bony defect. Although, an acquired image taken using the surface rendering mode may later be converted into skeletal mode, the original gain setting may be too low for the full extent of the ossification centers to be seen. It is preferable to make a separate acquisition using the skeletal mode from the outset. The fetus should be lying still at the time to avoid movement artifact. Whilst a static 3D sweep will always provide greater detail than a 4D volume, as moving structures are not being examined the difference in image quality is minor. Using 4D skeletal mode has the advantage of allowing real-time adjustments to the image settings, especially fine-tuning the gain, threshold and angle of acquisition, the latter to avoid shadow artefact from the fetal limbs or pelvic bone.

Once the volume has been stored, it is displayed in multiplanar mode. This allows simultaneous visualization of the sagittal (A-plane), axial (B-plane), and coronal (C-plane) views (Figure 9). The upper left image corresponds to the acquisition plane in accordance with the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) consensus statement on standardization of 3D images (Merz *et al*., 2007). From these planes, a rendered volume is derived and displayed as a virtual reconstruction of the spine seen in the coronal plane. Once the volume is acquired, place the B-plane reference dot within the vertebral body or canal and rotate around this axis until the vertebral ossification centers are clearly seen in perfect cross-section. The



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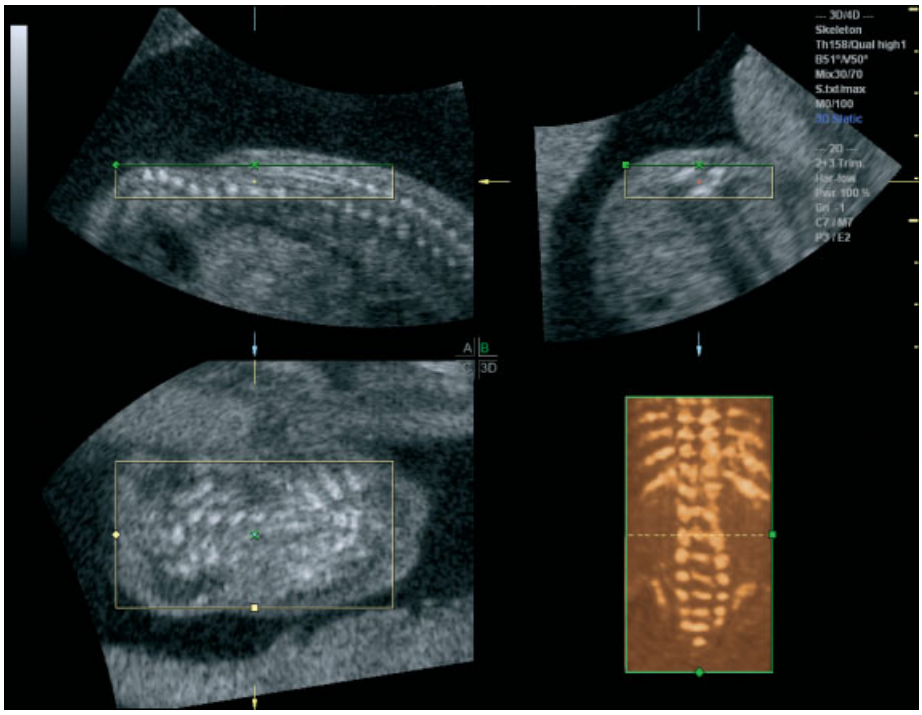


Figure 9—Skeletal or 'maximum' mode rendering. The L3 vertebra is seen in the axial or 'B-plane' (upper right image). The three ossification centers are clearly seen with intact overlying skin. The rendered coronal view identifies the B-plane segment with a dotted green line. T12 is seen and counting caudally from this confirms that the vertebral level is L3

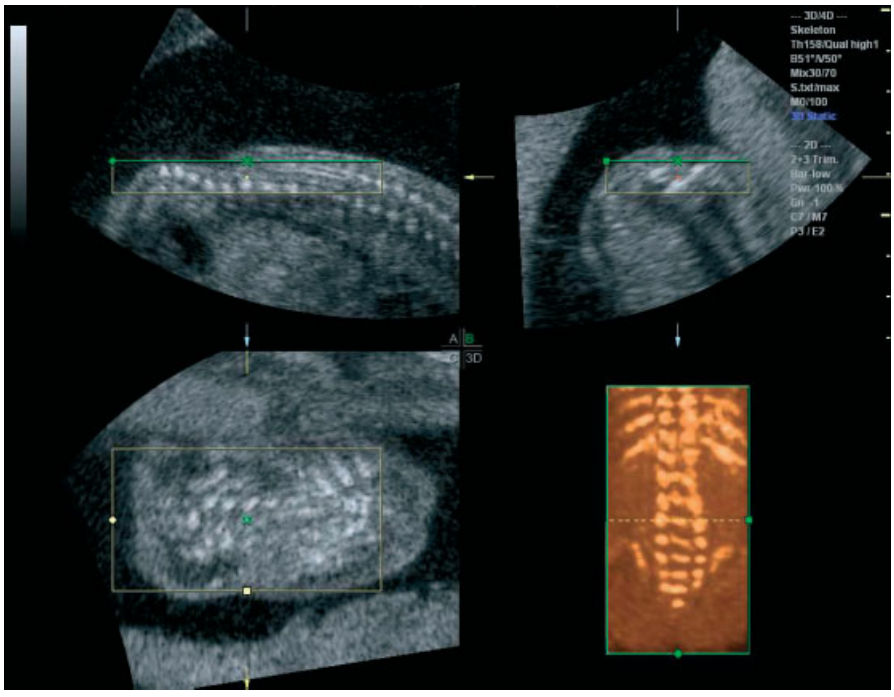


Figure 10—Skeletal or maximum mode rendering of the lower spine. Moving caudally in the B-plane L4 is now shown, showing widening of the posterior ossification centers. This widening can also be seen in the rendered coronal view but it less obvious

A-plane and C-plane automatically update to provide sagittal and coronal views of the spine, respectively. This reference dot corresponds to the level of the green line in the rendered view. In the B-plane, adjust the magnification and the size of the render box so that it includes the skin surface and a depth which includes the vertebral body. Move the image plane cranially and caudally, through each vertebra using the green line on the rendered image to determine the vertebra level (Figures 9 and 10).



DOI: 10.1002/pd

The lowest rib identifies T12, and the lumbosacral spine can be counted caudally from there. This is a very useful landmark, but in around 6% of fetuses there is abnormal number of ribs (Hershkovitz, 2008). Most (4.6%), however, have either an additional or absent rib on one side alerting sonographers to the variation from normal. Alternatively, some authors describe the superior aspect of the iliac crest as L5, and therefore lesion level can be identified by counting cephalically (Bruner *et al*., 2004). Note, that whilst in the adult the iliac crest corresponds to the body of L4, in the fetus it is the iliac ossification center that is seen and its upper border is lower, closer to L5 or even S1, (Figure 9) (Budorick *et al*., 1991). The lowest ossification center is S3 during the second trimester and S4 during the third trimester. The upper edge of the kidney lies at T11, but this is not a stable landmark as the renal position alters with fetal breathing.

Apart from orientation, the rendered coronal image may be misleading, widening of the posterior ossification centers is often subtle and the normal curvature of the spine may give this impression. The B-plane image is most helpful as it shows an axial view of each vertebra and this will allow assessment of all three ossification centers as well as the integrity of the overlying skin.

Volume contrast imaging [(VCI); GE Medical Systems Kretztechnik, Zipf, Austria] is a volume acquisition technique that displays a large surface area, but with a narrow predefined thickness. Such views may be derived from 3D volumes but VCI can also be used from the outset, scanning in real time (in the A-plane or a derived C-plane) with only a slight reduction in frame rate. A smoother image is created with improved contrast coupled with a reduction in signal noise. We have found it particularly useful for hemivertebra (Figure 11), or when the fetal spine is close to the uterine wall.

Further accounts are given for the normal spine and thorax (Riccabona *et al*., 1996), spina bifida lesion level (Lee *et al*., 2002), cranium and spine (Mueller *et al*., 1996) and central nervous system (CNS) anomalies (Pilu *et al*., 2007).

## Using ultrasound to prognosticate in spina bifida: the level of the lesion

What do we mean by the level of the lesion? For prenatal sonographers, it refers to the upper most vertebra showing widening of the posterior ossification centers. After delivery, the gold standard is the upper level of the bony defect seen on plain x-ray, or increasingly on magnetic resonance imaging (MRI) (Bruner *et al*., 2004), or it may refer to the neurological level at which there is sensory or motor impairment; which may be different from the level of the bony lesion.

Before being too critical of prenatal ultrasound, it is worth remembering that postnatal radiology does not always correlate exactly with functional level. Although two small series found a close correlation (finding an exact match in 10/11 and 12/15, respectively) (Kollias *et al*., 1992; Coniglio *et al*., 1996), a larger series only found agreement in 74% of 189 cases when grouped as thoracic, lumbar, or sacral (Rintoul *et al*., 2002). This agreement fell to 39% for an exact level match with radiology tending to underestimate the degree of functional impairment by an average of two segments in nearly half of all cases.

Such a variable correlation with dysraphism and functional levels can appear disheartening when faced with the challenge of prenatal counselling for spina bifida. Indeed, Bruner *et al*. argue that prospective parents often initially meet obstetricians who counsel pessimistically with regard to disability, and encourage consideration for pregnancy interruption (Bruner and Tulipan, 2004). They argue that although spina bifida results in a disability spectrum to have any opportunity to counsel appropriately, one needs to predict accurately the upper lesion level. Of 171 community examinations, the upper level of the lesion was only specified in 29% of cases (Bruner

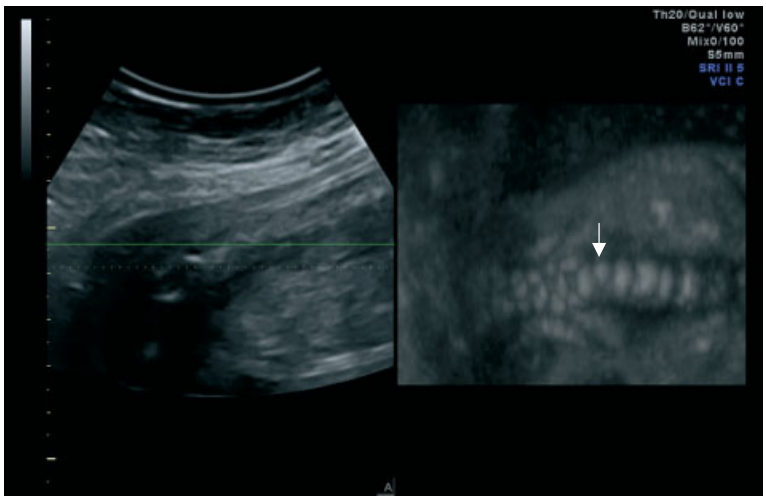


Figure 11—Two-dimensional (2D) scan image (left) and C-Plane Volume contrast imaging (on right), depth of slice 5.0 mm. VCI enables the vertebral body ossification centers to be clearly seen with a single abnormal hemivertebra demonstrated (arrow). The spine lies close to the uterine wall making a traditional 2D coronal view difficult, VCI overcomes this with no degradation of the image



DOI: 10.1002/pd

*et al*., 2004). They went on to ascribe a level to all fetuses referred to their tertiary unit. The tertiary center was significantly more accurate at assigning the lesion level with complete agreement between prenatal US and postnatal MRI in 38%, agreement within one level in 78% and within two levels in 96%.

Even accepting that the prenatal determination of the level of the lesion is not perfect, and many other factors will come into play after birth, there does appear to be a significant functional watershed at L4 with the majority of children who are ambulatory having lesions at or below this level. Consequently, efforts to classify whether a lesion is at L3, L4 or L5 are important in determining prognosis. Table 1 summarizes ambulatory status based on lesion level. Although numbers are small and comparisons between studies are difficult, all authors report decreasing mobility as lesion level rises. There is clearly a need for further studies exploring the link between prenatal findings and outcome to inform more accurate prenatal counselling.

## Chromosomal and syndromic diagnoses

Most NTD occur sporadically and are multifactorial in origin; should karyotyping be offered? For anencephaly, a uniformly lethal condition (Forrester and Merz, 2003), chromosomal anomaly rates are between 0.6 and 5.5% (Chen, 2007), however, karyotyping is unlikely to alter prenatal counselling. Combining four cases series ($n = 217$) the karyotype abnormality rate for cephaloceles was 6.5% (Chen, 2007). For cephalocele, however, other structural anomalies are often present (23–37.5%) (Simpson *et al*., 1991; Stoll *et al*., 2007) and underlying syndromic causes should be considered, especially the autosomal recessive Meckel–Gruber syndrome. Combining nine series reporting 547 cases of spina bifida there were 53 chromosomal abnormalities (9.7%) (Chen, 2007). Trisomy 18, trisomy 13, and triploidy are the most common chromosomal abnormalities. Chromosomal anomaly rates approach 25% if there are additional structural anomalies (Hume *et al*., 1996; Kennedy *et al*., 1998).

Without concurrent structural anomalies, chromosomal anomaly rates are significantly lower (anencephaly 1.3%, cephalocele 9.1%, and meningomyelocele 2.6%) (Kennedy *et al*., 1998). It is our opinion that, for potentially non-lethal NTD it is appropriate to offer fetal karyotyping. Whether a unit wishes to quote lower rates than these will depend upon their confidence at excluding even subtle structural anomalies.

## Prenatal counselling and management of NTD

Prenatal management of NTD requires parental decisions about fetal karyotyping and whether to continue or terminate the pregnancy. Counselling is important and influenced by several factors including prognosis for the type of NTD, extent of the lesion, and associated anomalies.

Countries operate within differing legal frameworks dictating the availability of termination of pregnancy (ToP) for fetal anomaly. A systematic review found higher termination rates for anencephaly (84%) than for spina bifida (64%) (Mansfield *et al*., 1999). A recent analysis of 12 countries of the European Surveillance of Congenital Anomalies (EUROCAT) registries found overall NTD termination rates of 88%, but rates varied widely (Boyd *et al*., 2008). Dery *et al*. (2008) explored attitudes toward the acceptability of pregnancy termination due to fetal abnormalities and concluded that

Table 1—Ambulatory status and its relationship in myelomeningoceles to the upper level of the lesion

| Imaging modality (Total case numbers) | Upper lesion level | | | | |
|---|---|---|---|---|---|
| | Thoracic | L1-L3 | L4 | L5 | Sacral |
| Postnatal MRI (n = 268) (Fletcher *et al*. 2005) | (82) 1% independent, 9% ambulatory with aid, 90% non-ambulatory | (186) 1% normal, 26% independent, 40% ambulatory with aid, 33% non-ambulatory | | | |
| Postnatal radiology and clinical assessment (n = 71) (Bowman *et al*., 2001) | L3 or above, all non-ambulatory majority of the time | | 57% ambulatory | (11) 91% majority of the time ambulatory majority of the time | (15) 93% independent |
| Prenatal ultrasound (n = 33) (Biggio *et al*., 2001) | (11) All non-ambulatory | (12) 50% ambulatory | (10) L4 or below, all ambulatory | | |
| Prenatal ultrasound and/or postnatal MRI (n = 17)(Appasamy *et al*., 2006) | (7) L3 or above, 2 non-ambulatory, 5 ambulatory with aid | | (10) L4 or below, 1 independent, 4 ambulatory with aid, 5 non-ambulatory | | |



DOI: 10.1002/pd

care providers were significantly more supportive of ToP than women. Bruner and Tulipan argue convincingly that "while spina bifida results in a spectrum of disabilities, with comprehensive medical care most affected children will grow into young adults with normal intelligence, walking, and with social continence of both bladder and bowel" (Bruner and Tulipan, 2004). Consequently in helping parents decide whether to terminate or continue with a pregnancy affected by spina bifida, accurate information must be given. This may require a multidisciplinary approach, including counselling from a pediatric neurosurgeon if possible.

For women considering continuing with the lethal condition anencephaly, they must understand they expose themselves to pregnancy complications including preeclampsia, polyhydramnios and antepartum hemorrhage. In 211 women, choosing conservative management a third delivered before 37 weeks, while 10% progressed beyond 42 weeks (Jaquier *et al*., 2006). Twenty-six percent required cesarean delivery, although the authors were unable to explore the reasons for this. Fetuses liveborn were 72%. A third survived beyond 24 h, 4% up to 10 days, but none survived beyond 28 days. With this in mind, a clear postnatal plan needs to be agreed between parents, obstetricians and neonatologists about care for these babies.

Parents may enquire about the possibility of organ donation. This is a complex issue and the practicalities are discussed elsewhere (Department of Health Working Group, 1998; DHSS, 1988; Paediatric Child Health, 2005). The Canadian Paediatric Society recommend that organ donation in these circumstances should not be undertaken (Paediatric Child Health, 2005). In the United Kingdom, the heart or heart valves are considered to be the only tissue suitable for donation (UK Transplant, 2003).

For spina bifida three key issues need exploring: mobility or ambulation, intelligence and mental capacity, and continence (urinary and faecal). Mobility has been discussed in relation to the lesion level. The postnatal outcome of spina bifida is covered elsewhere within the journal (Thompson, 2009, in this issue). In our experience, parents continuing with a fetus with spina bifida often have preconceived ideals about mode of delivery; particularly that caesarean delivery is "safer" for the baby's spine. Luthy *et al*. (1991) suggest that motor deficit is increased following vaginal delivery. However, Merrill *et al*. (1998) found no differences in short- or long-term outcome for 60 cases and Rintoul *et al*. (2002) found no differences in functional level for 40 cesarean births compared with 40 vaginal deliveries. Vaginal delivery for spina bifida should be judged on a case-by-case basis.

## CONCLUSIONS

The diagnosis of spina bifida with accurate assessment of lesion level represents a significant challenge to the sonographer, but it is only with this information that accurate prognostic information can be relayed to the pregnant woman. Three- dimensional sonography offers advantages over routine 2D ultrasound that are helpful when predicting lesion level. MRI is a scarce resource within many health services, and it has not been shown to be superior to ultrasound. We believe that trained sonographers should use 2D and 3D ultrasound to distinguish between open and closed spina bifida, delineate the lesion level, and perform a comprehensive search for other structural anomalies. This information is vital when informing prospective parents about the likely outcome for their child.

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