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Prognosis of Spina Bifida in the Era of Prenatal Diagnosis and Termination of Pregnancy

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Key Words
Spina bifida · Prenatal diagnosis · Prognosis

Abstract
Objective: To evaluate the current outcome of a selected prenatally diagnosed spina bifida group. ***Materials and Methods:*** We analyzed and followed up 74 cases of prenatally diagnosed spina bifida. ***Results:*** Termination of pregnancy was chosen in 72% of the cases and 28% were liveborn. Chromosomal defects were identified in 16%, although only 1.6% in isolated cases. Of the 21 live births, 3 died in the neonatal period. The other 18 (86%) were all alive after an average follow-up of 3 years and 6 months (range 5 months to 7 years and 4 months). From this group 11% are wheelchair-dependent, 87% of the patients older than 2 years of age are walking, 33% have had cerebral shunting and 72% have normal neurodevelopment. There was a better outcome in patients with closed defects; however, the rates of neuropathic bladder (50%) remain a concern. ***Conclusions:*** Even with prenatal diagnosis and a tendency towards apparently less severe defects in the cases in which the pregnancies continue, the prognosis in terms of morbidity needs to remain guarded.

Introduction

Neural tube defects are the most common congenital defects of the central nervous system. The reported incidence is about 1–2 per 1,000 births [1]. In contrast to anencephaly and the most severe encephaloceles which are almost invariably lethal, spina bifida has a survival rate of about 80% in the first year of life with high rates (88%) of associated lifelong disability [2, 3]. Spina bifida is a serious birth defect in which the dorsal vertebral arches fail to fuse together, thus allowing the meninges and/or spinal cord to protrude.

Today, with ultrasound screening for anomalies being part of routine prenatal care, prenatal detection of more than 90% of the cases is possible [4–7]. This enables a decision as to whether to continue with the pregnancy or to opt for termination of pregnancy (TOP). Moreover, the ultrasound screening can allow an assessment of which cases would have a worse outcome, and this information may be used to help parents make this difficult decision.

Therefore, prenatal selection of cases together with improvements in postnatal management and neurosurgical techniques may have contributed to outcomes in recent years, which were better than historically reported in the literature. We therefore reviewed our recent spina bifida cases and the decisions made in the hope that this may be useful for counseling future cases.

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Materials and Methods

We reviewed the notes of cases with a diagnosis of spina bifida identified from our fetal medicine database (Viewpoint; EuroKing, Addlestone, UK) between January 1999 and January 2007. We also reviewed the neonatal and pediatric/neurosurgical notes or postmortem examination reports when available. Patients were referred because of suspicious images at the ultrasound screening examination (62 cases), elevated levels of α-fetoprotein (AFP) in the biochemical screening test (11 cases) or because of a previous affected child (1 case).

The diagnosis of spina bifida was made by a fetal medicine specialist using 2-D ultrasound visualization of the cranial/cerebral features [8] (as described below) together with the spinal defect, including splaying of the posterior vertebral elements and protrusions or disruptions of the overlying fetal skin. Open spina bifida was diagnosed when the nervous tissue and/or meninges were exposed to amniotic fluid and a closed defect was diagnosed when the bone defect, herniated meninges and nervous tissue were covered by skin. In addition, acetylcholinesterase and AFP in amniotic fluid, were determined in some cases when amniocentesis was undertaken. Ventriculomegaly was diagnosed when the posterior horn of the lateral ventricle measurement was >10 mm in any of the ultrasound scans performed, and hydrocephaly was diagnosed when it was ≥15 mm. An Arnold-Chiari type II malformation was suspected when the cerebellum was found to be 'banana'-shaped or if the transverse cerebellar diameter was below the 5th centile for gestational age. Assessment was also made to determine the presence or absence of the classic abnormal head shape associated with spina bifida (the lemon sign) [8]. Talipes was diagnosed when a plantar view of the foot was seen in the same plane as the longitudinal view of the tibia/fibula.

The level of the lesion at 2-D ultrasound was established by determining the highest portion of spine affected and it was considered high lumbar between L1 and L2 and low lumbar between L3–L5.

The following were considered bad prognostic signs: lesions above L3 and severe ventriculomegaly or hydrocephalus (posterior horn of the lateral ventricle >15 mm).

Amniocentesis for karyotyping was offered to all the patients considering continuing the pregnancy, including quantification of amniotic fluid AFP and acetylcholinesterase. In some cases, when a closed spinal defect was suspected and both AFP and acetylcholinesterase in amniotic fluid were normal, a fetal MRI examination was offered.

When the ultrasound findings showed a spinal defect with cerebral signs, ventriculomegaly and upper lesions, the patients were counseled about possible postnatal events in accordance to published series [9–11]. The risks quoted were: 30% risk of moderate mental handicap, 30% risk of wheelchair-dependency, 70% risk of urinary incontinence, 30% risk of urinary and fecal incontinence, and 80–90% risk of cerebral shunting. For patients without cerebral changes and lower lesions, the counseling was more optimistic but with some uncertainty related to possible neurological impairment. All patients were offered the option to talk with the pediatric neurosurgical team about possible outcome, surgery and disabilities. TOP was offered as an option and, when accepted, postmortem examination was recommended.

Patients who continued the pregnancy were followed up by ultrasound examinations every 3–4 weeks. The place of birth was planned in discussion with neonatologists and neurosurgeons. Although reports of the scan findings varied through pregnancy, for this analysis we used the most severe ultrasound findings at any stage to compare with the first postnatal or postmortem assessments (MRI and/or X-ray).

Neonates were evaluated by the neurosurgical team on the first 1–2 days after birth, and open defects underwent surgical correction within the first 24–72 h of life. The patients were followed up by neurosurgeons, neonatologists/pediatricians, urologists, orthopedic surgeons and physiotherapists. Detailed neurological examinations were performed (including assessment of movement, strength and sensation in the lower limbs) together with general neurodevelopment, head measurements and bladder and bowel control.

Results

There were 74 cases of prenatally diagnosed singleton spina bifida cases during the period of the study. We excluded 4 twin pregnancies in which 1 fetus was affected and which resulted in selective feticide. The median gestational age at referral to our unit was 20+5 weeks (range 16+3 to 37+4). TOP was chosen in 53 cases (72%) and 21 were live-born (28%). Prenatal karyotyping was undertaken in 32 patients: 27 were normal and 5 were abnormal (16%: 2 cases of trisomy 18, 2 cases of trisomy 13, and 1 case with a pericentric inversion of chromosome 9). In the remaining 42 cases, no chromosomal abnormality was suspected and karyotyping was not undertaken (usually by parental choice). There were 11 spina bifida cases (15%) with associated abnormalities: 9 within the termination group and 2 in the live births (table 1); the other 63 were isolated. Four of the chromosomally abnormal karyotypes were not isolated defects, and only the case of the pericentric inversion of chromosome 9 (which could be a normal variant) was isolated.

The median gestational age at referral in the termination group was 20+1 weeks (range 16+3 to 37+4), 50 of 53 seen first before 24 weeks, versus 21+4 (range 17+5 to 36+6) weeks, 15 of 21 before 24 weeks, in the live-born group. There were no stillbirths in the continuing pregnancies. In the termination group, only 2 of 53 (4%) had a prenatal diagnosis of a closed defect. In the live-born cases, 7 of 21 had closed defects (33%), hence the total proportion of closed defects was 9 of 74 (12%). In all of the fetuses with closed defects, the fetal cranial anatomy appeared normal, and in the 6 in which acetylcholinesterase was measured, the results were all normal. Fetal MRI was performed in 3 of these cases but did not add additional findings to the diagnosis, although it did add support to the assessment of a closed defect. In the termination

Table 1. Additional abnormalities were found in 11 of 74 cases of prenatally diagnosed spina bifida

Associated abnormalities	Karyotype
Bilateral multicystic dysplastic kidneys	normal
VSD + doubled RV outlet	trisomy 18
Bilateral renal agenesis	normal
Encephalocele	declined
Bilateral hydronephrosis	normal
Bilateral pyelectasis	normal
VSD + diaphragmatic hernia + clenched hands	trisomy 18
VSD + 2 vessel cord	trisomy 13
Abdominal cyst	normal
Cloacal malformation, dysplastic kidneys, imperforated anus	normal
VSD + limb abnormalities + 2 vessel cord + renal pelvis dilatation	trisomy 13 (translocation)

The bottom 2 were live-born and the others had a TOP. The karyotype result when available is shown. VSD = Ventricle septal defect; RV = right ventricle.

Table 2. Comparison of prenatal ultrasound findings in cases which underwent TOP or were live-born

	TOP n = 53 (72%)	Live-born n = 21 (28%)	Total n = 74 (100%)
Mean gestational age at diagnosis, weeks	21+6	24	22+3
Type of defect			
Closed	2	7	9
Open	51	14	65
Lesion level			
Cervical	2	0	2
Thoracic	8	0	8
High lumbar	7	1	8
Low lumbar	15	8	23
Sacral	21	12	33
Talipes			
Bilateral	10	4	14
Unilateral	2		2
Arnold-Chiari	47 (89%)	9 (43%)	56 (76%)
Ventriculomegaly	42 (79%)	9 (43%)	51 (69%)

group, there were 17 lesions higher than L3, or 32.1% (CI 95%: 21.1–45.5%) of the cases, versus 1 in the live-born group, or 4.8% (CI 95%: 0.8–22.7%; Fisher $p < 0.01$). In addition, there were more Arnold-Chiari type II malformations and ventriculomegaly in the termination group than in the live-born group (89 vs. 43%, $p = 0.000$, and 79 vs. 43%, $p = 0.003$, respectively; table 2).

The median gestational age at birth was 38 weeks (range 27+3 to 41+2) with 13 cases delivered vaginally and 8 by cesarean section (38%). Most of the cesarean sections were performed for obstetric reasons (breech presentation, suspected fetal hypoxia, macrosomia); only in 1 case was it performed due to maternal request.

There were 21 live births, but 3 of these babies died in the neonatal period (14%). One of these babies was known prenatally to have trisomy 13, and a decision to continue the pregnancy was made. The 2nd neonatal death was seen in our unit at 16 weeks after premature rupture of the membranes, making the ultrasound difficult. This newborn had a closed lumbosacral defect, imperforated anus, dysplastic kidneys, cloacal malformation and hypoplastic lungs, and died 2 h after birth. The 3rd neonatal death occurred in a patient prenatally diagnosed as having a lumbosacral open defect with progressive ventriculomegaly (until 25 mm) who was delivered vaginally. In the end, the patient had a lumbar defect with breathing problems and paralysis of the vocal cords, and died 10 days after birth.

The other 18 (86%) were all alive after an average follow-up of 3 years and 6 months (range 5 months to 7 years and 4 months). The prenatal and postnatal assessments of the level of the spinal lesion agreed in 11 of 18 alive cases (61%); however, 4 cases which were diagnosed prenatally as sacral defects showed low lumbar defects in postnatal evaluation, 2 cases were prenatally diagnosed as low lumbar lesion but after birth were high lumbar, and 1 case was diagnosed as a low lumbar defect with postnatal evaluation showing a sacral defect. The prenatal assessment of the cranial changes (Arnold-Chiari type II and ventriculomegaly prenatally diagnosed vs. postnatal assessment) showed 88% agreement in the live-born group. In addition, 1 case of mild talipes was not identified prenatally (table 3). Postmortem examinations were available in 23 of 55 cases in which fetuses died from TOP (21) or neonatal death (2). As shown in table 4, the prenatal ultrasound findings were similar to postmortem findings; however, fewer cerebral and ventricular changes were found at the autopsy (although this may reflect postmortem changes).

At the last follow-up, 11 of 18 (61%) children were able to walk independently, 2 with support (1 with splints and the other with a walker/crutches), 2 were wheelchair-dependent (11%) and 3 were less than 2 years old but had good leg movement strength (table 5). Ten of 12 patients with open defects (83%), and 3 of 6 patients with closed defects had urinary incontinence (neuropathic bladder).

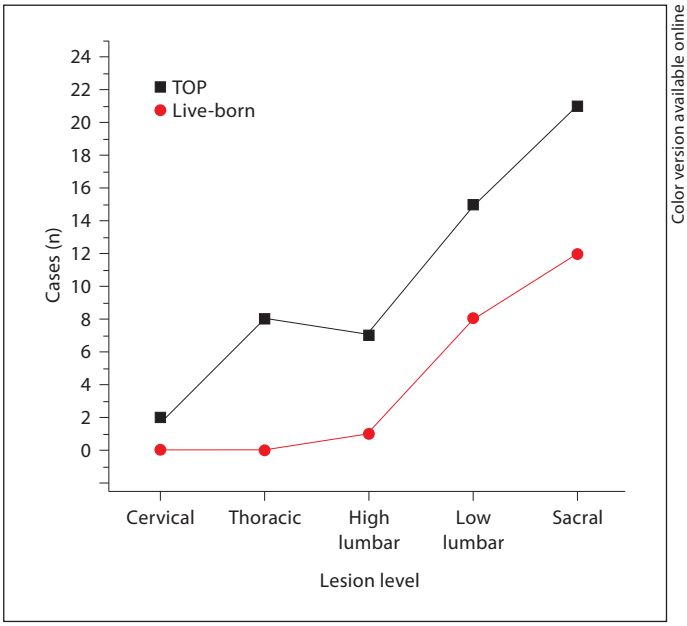

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Fig. 1. Comparison of lesion levels between TOP and live-born groups.

Table 3. Comparison of prenatal ultrasound findings and postnatal assessments in the live-born group (n = 21)

	Prenatal	Postnatal
Lesion level thoracic	0	0
High lumbar	1	4
Low lumbar	8	9
Sacral	12	8
Talipes bilateral	4	5
Arnold-Chiari	9	8
Ventriculomegaly	9	8

Table 4. Comparison of prenatal ultrasound findings and postmortem examinations in cases which died and in which a PM examination was undertaken[1]

	Prenatal	Postmortem
Lesion level thoracic	3	3
High lumbar	4	6
Low lumbar	7	9
Sacral	9	5
Talipes		
Bilateral	5	5
Unilateral	2	3
Arnold-Chiari	19	11
Ventriculomegaly	19	17

[1] n = 21 for TOP, n = 2 for neonatal deaths.

Only 6 of 18 patients (33%) had been shunted at the time of the study, but 11 of 18 had developed ventriculomegaly. All the patients with closed defects were operated on during the 1st year of life (7.2 months of age on average) because of neurological deterioration. Normal neurodevelopment appropriate to their age was found in 13 of 18 patients (72%) with 5 having developmental delay (mainly delay in language, mild in 2 of them and moderate in the other 3).

Discussion

Following careful case selection, the overall prognosis of a selected spina bifida group may be better than historical series suggest. Closed defects have a better prognosis; however, bladder dysfunction remains significant. Among the cases where the pregnancy was continued (which were largely of a milder ultrasound 'phenotype'), there were still some cases where the outcome was poor, this being largely unpredictable.

Accurate assessment and counseling of couples following the diagnosis of fetal spina bifida is essential. It is important to consider the association between spina bifida and other problems such as chromosomal abnormalities (16% in this study), especially when other abnormalities are found. When a spinal defect is isolated, the frequency of chromosomal abnormalities has been reported to be low: Sepulveda et al. [12] reported that all the patients with an abnormal karyotype in their study had associated anomalies, and Kennedy et al. [13] reported that 2.6% of the patients with isolated spina bifida had chromosomal abnormalities. In our study, 1 fetus with an apparently isolated spina bifida (out of 63) had a pericentric inversion of chromosome 9. In this case, the fetus developed severe hydrocephalus with intracranial signs at 37 weeks (the time of the referral to our unit and time when karyotyping was performed) and the couple opted for a late TOP.

It has been widely published that prenatal ultrasound usually has good agreement with the postnatal/postmortem findings in terms of the level of spinal defect, cranial changes and talipes [11, 14–18]. The importance of the spinal level and ventriculomegaly to predict outcome is

Table 5. Outcome data separated into open and closed lesions

	Open defects n = 12	Closed defects n = 6	Total n = 18
Average age of first surgery	2.1 days	7.2 months	2 months and 12 days
Shunted hydrocephalus	6 (55%)	0	6 (33%)
Ability to walk independently	5 (45%)	6 (100%)	11 (61%)
Wheelchair-dependent	2 (18%)	0	2 (11%)
Walking with support	2 (18%)	0	2 (11%)
Developmental delay	5 (45%)	0	5 (28%)
Neuropathic bladder	10 (83%)	3 (50%)	13 (72%)
Bowel dysfunction	3 (27%)	1 (17%)	4 (22%)

widely used. Lower spinal levels increase the chance that the child will be able to walk [10, 11], but this is also related to a higher incidence of neuropathic bladder [14, 19, 20]. The likely intellectual outcome tends to be worse when the degree of ventriculomegaly is more severe [9, 20, 21]. We found exactly the same spinal level prenatally versus postnatally in 61% of the cases, and the differences in the remaining cases were less than 2 spinal levels (similar to the published literature) [11, 14, 16, 17]. We also confirmed the previously published trend for prenatally diagnosed levels to be lower (1 or 2 levels) than the postnatal assessment [10, 11, 14, 16]. The prenatal/postnatal agreement in terms of ventriculomegaly and Arnold-Chiari type II malformation was also high (88% for each), as well as the agreement between prenatal/postmortem examinations (89% for ventriculomegaly and 58% for Arnold-Chiari). However, the reported cranial signs at postmortem examination were a little less than when assessed on fetal scanning. This likely reflects the difficulty of assessing the very soft fetal and neonatal brain which can be damaged during the course of an induced TOP and subsequent necropsy [22, 23]. In addition, the potassium chloride administration [23] used in some cases of late termination could be responsible for additional autolysis and maceration of the brain tissue; in some cases managed in this way, evaluation of the brain was not possible. Therefore, the prenatal ultrasound assessment may be the most reliable information available about the brain in some cases.

Unsurprisingly, the termination group had a higher proportion of cases assessed as being the most severe, and pregnancies were more often continued in the cases with better prognostic features. Closed spina bifida has been reported to be about 10–15% [24, 25] of prenatally diagnosed spinal defects, and a similar incidence was found in this study (12%). However, in the live-born group, 33% of the cases had closed defects. In addition, prenatal ultrasound evidence of ventriculomegaly and Arnold-Chiari type II malformation was found in less than 50% of the continuing cases. Furthermore, the majority of the prenatally diagnosed spinal defects were below L3. The results above demonstrate that the live-born cases are a selected group.

The survival rate of live-born cases after an average follow-up period of 3 years and 6 months was 86%, which compares favorably to the survival rate published in the literature of about 80% [26, 27] for the first year of life. The improvement in survival in our series may be even greater because the previous studies have looked at postnatal-diagnosed spina bifida cases before surgery, which would be expected to include only those with a better prognosis, excluding stillbirths and neonatal deaths (often due to concurrent pathologies, e.g. aneuploidy).

From this series, we conclude that for a select fetal spina bifida group with fewer cranial signs and low spinal defects (below L3), the outcome may be better than in the literature with 11% of patients wheelchair-dependent (vs. 30%), 87% of patients older than 2 years walking and 33% of patients having cerebral shunting (vs. 80–90% traditionally quoted). However, even after modern management, the incidence of a neuropathic bladder is high at 67% and continues to be a significant problem. We have also shown that in cases in which cerebral shunting is required, there is a higher incidence of developmental delay (4 of 5) compared to those who did not need this procedure (2 of 13).

In addition, if we consider that the preliminary results of prenatally repaired spina bifida have not shown significant improvement in neurological outcome [28], it is possible that postnatal repair will continue to be the only therapeutic tool for the moment.

The prenatal diagnosis of closed (skin covered) spina bifida has been previously reported [24], and the most valuable sonographic clue for differentiating these from open defects seems to be the absence of cranial changes. The finding of a cystic mass (usually anechoic) with a thin wall associated with spinal dysraphism has been described for open defects, and a complex appearance with echogenic components and thick wall has been described for closed defects [24–27, 29], but these findings are not always clear and sometimes impossible to distinguish. In our study, all the patients with closed defects had normal cranial anatomy, but the features of the spinal lesions varied and often did not have the so-called typical appearances described for closed defects. Fetal MRI and normal acetylcholinesterase were useful in order to support the previously suspected diagnosis, but it is noteworthy that no changes to the previous diagnosis were made by these investigations.

It is known that closed spinal defects usually have a good prognosis, but there are only a few reports in the literature [29, 30] about the prenatal diagnosis of these defects with corresponding follow-up. Our study results, although limited by small numbers (n = 6), show an excellent prognosis in terms of ability to walk independently (100%) and neurodevelopment (normal in 100% of the cases), but all of these children required spinal surgery during the first year of life and the development of neuropathic bladder during the follow-up period was considerable (3 of 6 cases).

After fetal medicine assessment and patient choice with modern multi-disciplinary management, the prognosis of the selected spina bifida group, while a little better in terms of survival rates, remains relatively poor in terms of morbidity, and the rates of neuropathic bladder problems in these children remain a concern.

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References

1 Botto L, Moore C, Khoury M, Erickson J: Neural tube defects. N Engl J Med 1999;341:1509–1519.
2 Date I, Yagyu I, Asari S, Ohmoto T: Long-term outcome in surgically treated spina bifida cystica. Surg Neurol 1993;40:471–475.
3 Zurmohle UM, Homman T, Schroeter C, Rothgerber H, Hommel G, Ermert JA: Psychosocial adjustment of children with spina bifida. J Child Neurol 1998;13:64–70.
4 Morris JK, Wald NJ: Prevalence of neural tube defect pregnancies in England and Wales from 1964–2004. J Med Screen 2007;14:55–59.
5 Stoll C, Alembik Y, Dott B, Roth MP: Impact of prenatal diagnosis on live birth prevalence of children with congenital abnormalities. Ann Genet 2002;45:115–121.
6 Chan A, Robertson EF, Haan EA, Ranieri E, Keane RJ: The sensitivity of ultrasound and serum alpha-fetoprotein in population-based antenatal screening for neural tube defects. South Australia 1986–1991. Br J Obstet Gynaecol 1995;102:370–376.
7 Vos JMI, Offringa M, Bilardo CM, Lijmer JG, Barth PG: Sensitive and specific screening for the detection of spina bifida by echography in the second trimester: systematic review and meta-analysis. Ned Tijdschr Geneeskd 2000;144:1736–1741.
8 Nicolaides KH, Campbell S, Gabbe SG, Guidetti R: Ultrasound screening for spina bifida: cranial and cerebellar signs. Lancet 1986;ii:72–74.
9 Olde Scholtenhuis MAG, Cohen-Overbeek TE, Offringa M, Barth PG, Stoutenbeek Ph, Gooskens RH, Wladimiroff JW, Bilardo CM: Audit of prenatal and postnatal diagnosis of isolated open spina bifida in three university hospitals in The Netherlands. Ultrasound Obstet Gynecol 2003;21:48–52.
10 Biggio JR, Owen J, Wenstrom KD, Oakes WJ: Can prenatal ultrasound findings predict ambulatory status in fetuses with open spina bifida? Am J Obstet Gynecol 2001;185:1017–1020.
11 Peralta CFA, Bunduki V, Plese JPP, Figueiredo EG, Miguelez J, Zugaib M: Association between prenatal sonographic findings and post-natal outcomes in 30 cases of isolated spina bifida aperta. Prenat Diagn 2003;23:311–314.
12 Sepulveda W, Corral E, Ayala C, Be C, Gutierrez J, Vasquez P: Chromosomal abnormalities in fetuses with open neural tube defects: prenatal identification with ultrasound. Ultrasound Obstet Gynecol 2004;23:352–356.
13 Kennedy D, Chitayat D, Winsor EJ, Silver M, Toi A: Prenatally diagnosed neural tube defects: ultrasound, chromosome, and autopsy or postnatal findings in 212 cases. Am J Med Genet 1998;77:317–321.
14 Appasamy M, Roberts D, Pilling D, Buxton N: Antenatal ultrasound and magnetic resonance imaging in localizing the level of lesion in spina bifida and correlation with postnatal outcome. Ultrasound Obstet Gynecol 2006;27:530–536.
15 Aaronson OS, Hernanz-Schulman M, Bruner JP, Reed GW, Tulipan NB: Myelomeningocele: prenatal evaluation – comparison between transabdominal US and MR imaging. Radiology 2003;227:839–843.
16 Kollias SS, Goldstein RB, Cogen PH, Filly RA: Prenatally detected myelomeningoceles: sonographic accuracy in estimation of the spinal level. Radiology 1992;185:109–112.
17 Isaksen CV, Eik-Nes SH, Blaas HG, Torp SH: Comparison of prenatal ultrasound and postmortem findings in fetuses and infants with central nervous system anomalies. Ultrasound Obstet Gynecol 1998;11:246–253.
18 Bruner JP, Tulipan N, Dabrowiak ME, Luker KS, Walters K, Burns P, Reed G: Upper level of the spina bifida defect: how good are we? Ultrasound Obstet Gynecol 2004;24:612–617.
19 Johnston LB, Borzyskowski M: Bladder dysfunction and neurological disability at presentation in closed spina bifida. Arch Dis Child 1998;79:33–38.

20 Mevorach RA, Bogaert GA, Baskin LS, Lazzaretti CC, Edwards MS, Kogan BA: Lower urinary tract function in ambulatory children with spina bifida. Br J Urol 1996;77:593–596.
21 Brumfield CG, Aronin PA, Cloud GA, Davis RO: Fetal myelomeningocele. Is antenatal ultrasound useful in predicting neonatal outcome? J Reprod Med 1995;40:26–30.
22 Knowles S, Parker S, Weckert RC, Furness ME: Gelating embedding and diagnostic ultrasound in the examination of the fetal and neonatal brain. Prenat Diagn 1989;9:73–75.
23 Carroll SGM, Porter H, Abdel-Fattah S, Kyle PM, Soothill PW: Correlation of prenatal ultrasound diagnosis and pathologic findings in fetal brain abnormalities. Ultrasound Obstet Gynecol 2000;16:149–153.
24 Ghi T, Pilu G, Falco P, Segata M, Carletti A, Cocchi G, Santini D, Bonasoni P, Tani G, Rizzo N: Prenatal diagnosis of open and closed spina bifida. Ultrasound Obstet Gynecol 2006;28:899–903.
25 Wingate EE, Hancock JA, Churchwell KE, Pipkins MJ: Spina bifida: a review of the importance of sonography's role in its detection. J Diagn Med Sonogr 2004;20:227.
26 Hunt GM, Oakeshott P: Lifestyle in adults aged 35 years who were born with open spina bifida: prospective cohort study. Cerebrospinal Fluid Res 2004;1:4.
27 Oakeshott P, Hunt GM: Long-term outcome in open spina bifida. Br J Gen Pract 2003;53:632–636.
28 Fichter MA, Dornseifer U, Henke J, Schneider KTM, Kovacs L, Biemer E, Bruner J, Adzick NS, Harrison MR, Papadopulos NA: Fetal spina bifida repair – current trends and prospects of intrauterine neurosurgery. Fetal Diagn Ther 2008;23:271–286.
29 Pierre-Kahn A, Sonigo P: Lumbosacral lipomas: in utero diagnosis and prognosis. Childs Nerv Syst 2003;19:551–554.
30 Thorne JA, Pierre-Kahn A, Sonigo P: Antenatal diagnosis of spinal lipomas. Childs Nerv Syst 2001;17:697–703.