Evaluation of the lemon and banana signs in one hundred thirty fetuses with open spina bifida

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The incidence and diagnostic accuracy of the lemon and cerebellar ultrasonographic markers, as well as head size and ventriculomegaly, were evaluated in a study of 1561 patients at high risk for fetal neural tube defects. In the 130 fetuses with open spina bifida there was a relationship between gestational age and the presence of each of these markers. The lemon sign was present in 98% of fetuses at ≤24 weeks' gestation but in only 13% of those at >24 weeks' gestation. Cerebellar abnormalities were present in 95% of fetuses irrespective of gestation; however, the cerebellar abnormality at ≤24 weeks' gestation was predominantly the banana sign (72%) whereas at gestations >24 weeks it was cerebellar "absence" (81%). Both growth regardation and cerebral ventriculomegaly significantly worsened with gestation while the head circumference remained disproportionately small throughout gestation. On the basis of these data, a new approach is proposed for the investigation of patients at high risk for fetal open spina bifida.
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The ultrasonographic diagnosis of fetal open spina bifida has been greatly enhanced by the recognition of associated abnormalities in the skull and brain. These abnormalities include cerebral ventriculomegaly, microcephaly, frontal bone scalloping (lemon sign), and obliteration of the cisterna magna with either an "absent" cerebellum or an abnormal anterior curvature of the cerebellar hemispheres (banana sign). In a retrospective study of 70 fetuses with open spina bifida at 16 to 24 weeks' gestation the lemon sign was present in each instance while in those cases in which the posterior fossa could be evaluated, 95% had either an "absent" or a banana-shaped cerebellum.[1] Similarly, Furness et al.[2] have reported the presence of the lemon sign in each of the 13 fetuses with open spina bifida that they diagnosed at 14 to 22 weeks' gestation while Pilu et al.[3] noted posterior fossa and cerebellar abnormalities in all 19 of their cases. Subsequently, the lemon and cerebellar ultrasonographic signs were prospectively studied at 16 to 24 weeks' gestation from 903 patients whose fetuses were at high risk for open spina bifida. Of the 62 cases with open spina bifida, 61 had a lemon-shaped skull and 59 an absent or banana-shaped cerebellum; the false-positive rates for the lemon and abnormal cerebellar signs were 1% and 0%, respectively.[4]

Recently, Nyberg et al.[5] suggested that the presence of a lemon sign is related to gestational age. Among their 50 cases with open spina bifida, they noted a lemon sign in 89% of the 27 fetuses examined before 24 weeks, in 50% of the 16 fetuses examined between 24 and 34 weeks, and in none of the seven fetuses examined after 35 weeks. Similarly, Penso et al.[6] observed the lemon sign in all 13 cases of open spina bifida diagnosed at 15 to 22 weeks' gestation but in only three of the 11 cases that were examined at 27 to 40 weeks' gestation.

This study evaluates the incidence and diagnostic accuracy of the lemon and cerebellar signs, as well as head size and ventriculomegaly, in the investigation of 1561 patients at high risk for fetal neural tube defects and examines the relationship between gestational age and the presence of each of these markers.

Patients and methods

During a 3-year period (1986 to 1988), 1561 patients at high risk for fetal neural tube defects were referred to our unit for a detailed ultrasonographic examination. The specific indications were a personal or family history of neural tube defects (n = 396), ingestion of antifolate drugs (n = 14), raised maternal serum α-fetoprotein (n = 796), and suspected fetal neural tube defect from an initial routine ultrasonographic scan (n = 355). Gestational age was calculated from menstrual data and confirmed by ultrasonographic measurement of fetal femur length. Follow-up information

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Table I. Indications for referral and numbers of fetuses with proved open spina bifida

Indication	*Referrals (n = 1561)*	*Affected fetuses (n = 130)*	
		No.	*%*
History of neural tube defect	396	4	1%
Raised maternal serum α-fetoprotein	796	43	5%
Drugs	14	2	14%
Suspicious ultrasonographic findings			
Lemon-shaped skull	19	9	47%
Brain-spinal defect	336	72	21%

was obtained through postmortem examinations and review of delivery records.

In our unit each patient was scanned (Hitachi EUB360 or Aloka SSD-650) by an obstetrician, radiographer, or midwife experienced in fetal anomaly scanning. The ultrasonographers were instructed to examine the fetal head before examining the spine and to record the presence or absence of the lemon and cerebellar signs. The shape of the fetal skull was evaluated from the section that is used routinely in this center for measuring the biparietal diameter. This is a transverse plane of the brain that shows a central midline echo broken in its anterior third by the cavum septum pellucidum and in which both the anterior and posterior horns of the lateral ventricles can be visualized. For examination of the posterior fossa a suboccipital bregmatic view was used.[7] The biparietal diameter, head circumference, hemisphere, anterior and posterior cerebral ventricles, abdominal circumference, and femur length were measured and values were compared to nomograms produced and routinely used in our unit. A detailed anatomic survey was then performed, including a complete longitudinal view of the fetal spine followed by sequential transverse scans of each neural arch. All anomalies were recorded, and whenever open spinal defects were diagnosed, their location and extent were noted.

In five fetuses with open spina bifida diagnosed at ≤24 weeks' gestation, the parents elected to continue the pregnancy, and serial ultrasonographic examinations with biometric measurements were done.

Statistical analysis was performed with the Statistics Package for Personal Computers (P. Royston, Timberlake Clarke Ltd., 40B Royal Hill, London, UK SE 10). In normal fetuses with biparietal diameter, head circumference, abdominal circumference, and femur length increase with gestation while the ratios anterior ventricle/hemisphere and posterior ventricle/hemisphere decrease. In the fetuses with spina bifida, Δ-values, representing the degree of departure from the normal mean in SD units, were calculated for each of the above parameters. Regression analysis was then used to examine any correlation between Δ-values and gestation, while the χ^2 test was used to determine the significance of observed differences in the incidence of ultrasonographic markers between the ≤24-week and >24-week groups.

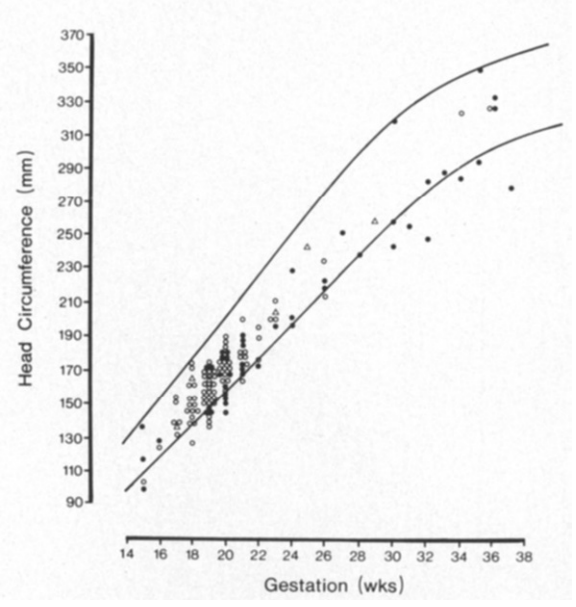

Fig. 1. Ultrasonographically determined head circumference of 130 fetuses with open spina bifida plotted on the reference range (95% confidence intervals) for gestation; cerebellar abnormalities are indicated by an *open triangle* if "absent" and an *open circle* if banana-shaped.

Results

Open spina bifida was diagnosed in 130 of the 1561 fetuses assessed (Table I) and was confirmed in all cases by postmortem or postnatal examinations; there were no cases in which the diagnosis was missed. The site of the spinal lesion was sacral (n = 30), lumbar (n = 8), thoracic (n = 1), cervical (n = 2), lumbosacral (n = 75), thoracolumbosacral (n = 5), or thoracolumbar (n = 9).

Of the 1431 fetuses without spina bifida, 1325 were anatomically normal, 64 had other central nervous system defects, and 42 had malformations of other systems. The central nervous system anomalies included anencephaly (n = 18), encephalocele (n = 25), isolated hydrocephalus (n = 15), iniencephaly (n = 3), holoprosencephaly (n = 1), Dandy-Walker malformation (n = 1), and absent cerebellar vermis (n = 1). The malformations of other systems were: abdominal wall defects (n = 15), renal malformations (n = 11), sacrococcygeal teratomas (n = 4), isolated kyphoscoliosis

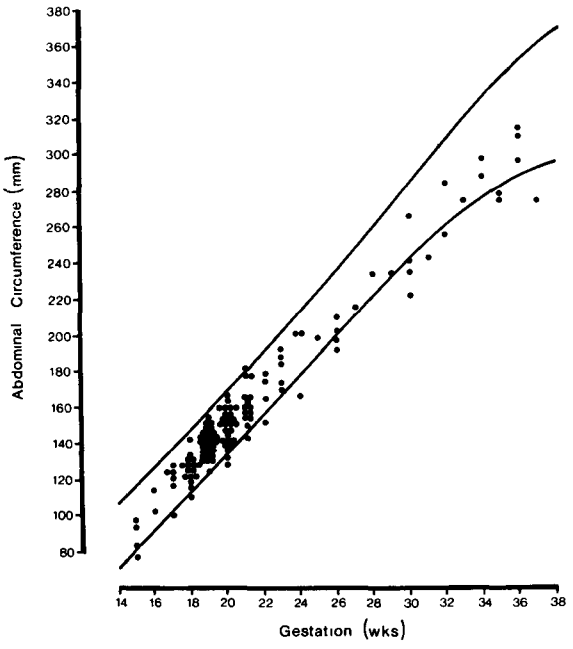

Fig. 2. Ultrasonographically determined abdominal circumference of 130 fetuses with open spina bifida plotted on the reference range (95% confidence intervals) for gestation.

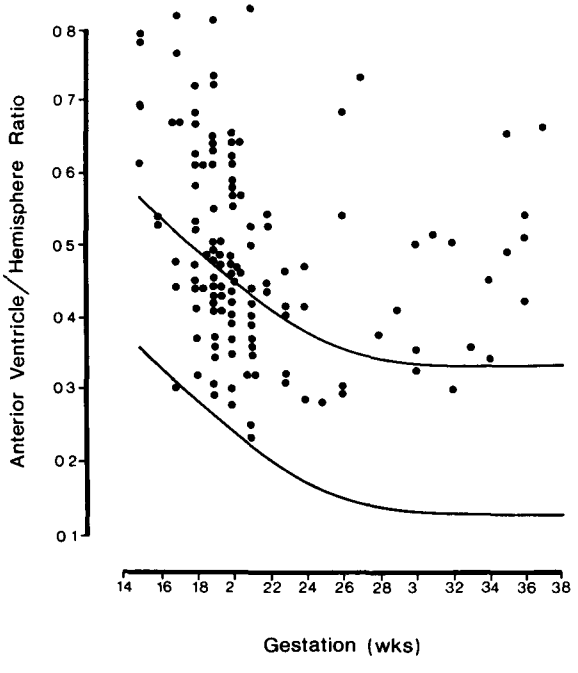

Fig. 3. Ultrasonographically determined anterior cerebral ventricle to hemisphere ratio for 130 fetuses with open spina bifida plotted on the reference range (95% confidence intervals) for gestation.

(n = 5), cystic hygromas (n = 4), congenital heart deformities (n = 2), and VATER syndrome (vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia) (n = 1).

The head and abdominal cicumferences and the

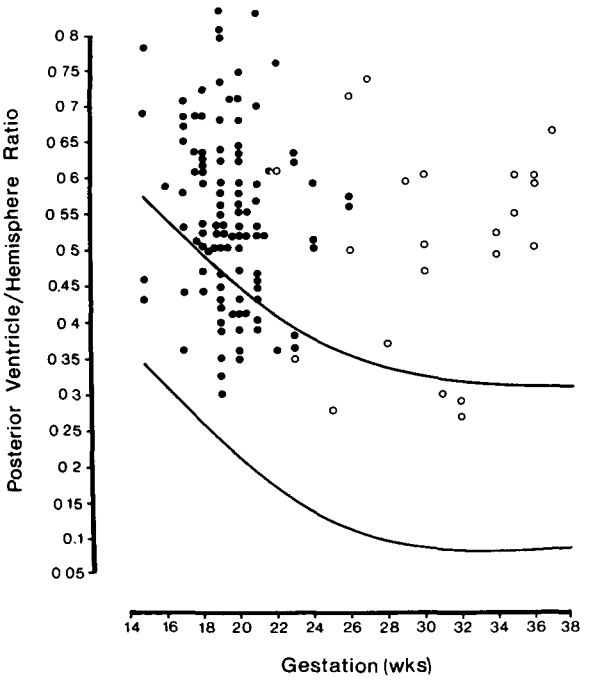

Fig. 4. Ultrasonographically determined posterior cerebral ventricle to hemisphere ratio for 130 fetuses with open spina bifida plotted on the reference range (95% confidence intervals) for gestation; a positive lemon configuration of the skull is indicated by a *solid circle.*

anterior ventricle/hemisphere and posterior ventricle/hemisphere ratios of the 130 fetuses with open spina bifida are plotted on our reference ranges with gestation in Figs. 1 to 4. The presence or absence of the cerebellar and lemon signs is illustrated in Figs. 1 and 4, respectively. The incidence of these signs, as well as the incidence of abnormal measurements (outside 95% confidence intervals of normal ranges), is shown in Table II. The head circumference and abdominal circumference measurements were <2.5th percentile in 30 (23%) and 17 (13%) cases, respectively (Figs. 1 and 2). There were no fetuses with macrocephaly or macrosomia (Δ-head circumference or Δ-abdominal circumference >97.5th percentile). Regression analysis demonstrated that the Δ-abdominal circumference fell significantly with gestation (n = 130, $r = -0.371$, $p < 0.0001$, constant = 0.906, slope = −0.077), while an analogous decrease in Δ-head circumference did not reach statistical significance (n = 130), $r = -0.135$). The anterior ventricle/hemisphere and posterior ventricle/hemisphere ratios were >97.5th percentile in 79 (61%) and 98 (75%) cases and the Δ-values of both parameters increased significantly with gestation (n = 130, $r = 0.209$, $p < 0.05$, constant = 0.662, slope = 0.108 and n = 130, $r = 0.340$, $p < 0.001$, constant = 0.475, slope = 0.155, respectively).

Of the 130 fetuses with open spina bifida, only one

Table II. Ultrasonographic findings in 130 fetuses with open spina bifida in relation to gestational age

Feature	Gestation		Statistics
	≤ 24 wk (n = 107)	> 24 wk (n = 23)	
Positive lemon sign	105	3	$p < 0.001$
Abnormal cerebellum	103	21	NS
Positive banana sign	74	4	$p < 0.001$
"Absent" cerebellum	29	17	
Anterior ventricle/hemisphere ratio			
> 50th Percentile	94	23	NS
> 97.5th Percentile	61	18	NS
Posterior ventricle/hemisphere ratio			
> 50th Percentile	101	23	NS
> 97.5th Percentile	79	19	NS
Head circumference			
< 50th Percentile	87	18	NS
< 2.5th Percentile	20	10	$p < 0.05$
Abdominal circumference			
< 50th Percentile	76	22	$p < 0.05$
< 2.5th Percentile	8	9	$p < 0.001$

Table III. Sensitivity, specificity, and predictive values for the detection of open spina bifida in fetuses at ≤ and > 24 weeks' gestation by means of lemon and cerebellar signs

	Sensitivity (%)	Specificity (%)	Predictive value	
			Positive (%)	Negative (%)
≤ 24 wk				
Lemon sign	98	99	92	99.8
Cerebellar sign*	96	100	100	99.7
> 24 wk				
Lemon sign	13	100	100	67
Cerebellar sign*	91	100	100	96

*Banana sign or "absent" cerebellum.

had no abnormalities of the skull or brain; this was a fetus at 25 weeks' gestation with an extensive lumbar lesion. In the remaining 129, there was a significant relationship between the incidence of the various markers and gestation (Table II). Thus, among the 107 fetuses with open spina bifida diagnosed at ≤24 weeks' gestation, 105 (98%) cases had a positive lemon sign and 103 (96%) had abnormal cerebellar findings. The cerebellar abnormalities included presence of a banana sign in 74 fetuses and "absence" of the cerebellum in the remaining 29. In contrast, among the 23 patients diagnosed at >24 weeks' gestation three (13%) showed a lemon sign and 21 (91%) fetuses had cerebellar abnormalities (four with a banana sign and 17 with an "absent" cerebellum). In the 1367 cases with no central nervous system defects, nine had a lemon sign (false = positive rate = 0.01) and none had abnormal cerebellar signs. The ability of the lemon and cerebellar signs to predict open spina bifida at ≤ and >24 weeks' gestation was evaluated by measuring the sensitivity and specificity, as well as the predictive value of a positive and negative test (Table III). These figures are for a referral group and cannot be extrapolated to the unselected population with a much lower prevalence of positive findings.

In each of the five patients with fetal open spina bifida at ≤24 weeks' gestation where the pregnancy was not electively aborted, there was a lemon sign on initial ultrasonographic examination but this disappeared with advancing gestation (Table IV). In three cases the fetus was found to have a banana-shaped cerebellum on the initial examination; this was subsequently "absent" in two, while in the third the banana-shaped cerebellum was still present during the final scan at 29 weeks' gestation. In the remaining two cases the cerebellum was "absent" at both the initial and subsequent scans.

Comment

In the vast majority of fetuses with open spina bifida, there are associated abnormalities of the skull and brain, and this study has demonstrated that these ab-

Table IV. Evolution of cranial and cerebellar signs with gestation in five cases of open spina bifida

Case No.	Gestational age (wk)	Site*	Lemon	Cerebellum	Δ-Value (SD from mean)		
					Head circumference	Anterior ventricle/hemisphere ratio	Posterior ventricle/hemisphere ratio
1	18	S	+	Banana	−2.0	2.7	4.4
	36		−	Absent	−0.4	3.7	6.6
2	19	S	+	Banana	−2.8	2.2	0.0
	25		−	Banana	−2.6	2.1	1.4
	29		−	Absent	−3.1	3.2	6.3
	34		−	Absent	−2.9	2.1	5.0
3	19	LS	+	Absent	−0.6	3.2	4.6
	30		−	Absent	−3.4	0.3	0.5
4	19	S	+	Banana	−2.0	−0.6	1.1
	23		+	Banana	−0.9	2.1	1.3
	29		−	Banana	−2.0	3.0	1.9
5	20	TLS	+	Absent	−2.4	−1.3	1.0
	24		+	Absent	−2.0	2.3	2.9
	27		−	Absent	−1.9	0.6	2.2

*S, Sacral; *LS*, lumbosacral; *TLS*, thoracolumbosacral.

normalities evolve with gestation. Thus the lemon sign was present in 98% of fetuses at ≤24 weeks' gestation but in only 13% of those at >24 weeks' gestation. Cerebellar abnormalities were present in 95% of fetuses irrespective of gestation; however, the cerebellar abnormality at ≤24 weeks' gestation was predominantly the banana sign (72%) whereas at gestations >24 weeks it was cerebellar "absence" (81%). The validity of the hypothesis, that these skull and brain signs follow a systematic change in conjunction with fetal development, is reinforced by the finding that, in those fetuses studied longitudinally, the pattern of evolution for ultrasonographic markers was similar to that found in fetuses studied cross-sectionally.

Images of these easily recognizable alterations in skull and brain morphologic features are often more readily attainable than detailed spinal views. Indeed, in several of our cases with very obvious cranial and cerebellar signs, ultrasonographic demonstration of the spinal lesion was possible only after a prolonged and diligent search by experienced operators. In a postmortem study of aborted fetuses with open spina bifida, Bell et al.[8] reported that isolated sacral defects were not associated either with ventriculomegaly or with the Arnold-Chiari malformation. However, in the present study it was especially reassuring that all sacral tip lesions were consistently accompanied by these ultrasonographic markers. In contrast, the only case with a totally normal skull and brain was one with an extensive lumbar defect that was readily visible on spinal views. Interestingly, in the study of Nyberg et al.,[5] the three cases of open spina bifida with a normal-shaped skull at <24 weeks' gestation also had lumbar lesions.

The cerebellar signs of open spina bifida are a consequence of the Arnold-Chiari malformation.[9, 10] These may be attributed to a coning phenomenon that is secondary to decreased intraspinal pressure[11] and/or a tethering of the spinal cord at the site of the lesion, with downward displacement of the brain as the fetus grows.[12] The lemon sign may then be the result of decreased intracranial pressure and collapse of the normal frontal contour. Although with advancing gestation there is further herniation of the brain through the cisterna magna, with a consequent increase in the incidence of an "absent" cerebellum, the lemon sign disappears. The loss of the lemon sign may be due to decreased deformability of the skull or alternatively to the cerebral ventriculomegaly, which may compensate for the loss of brain mass through the cisterna magna. Supportive evidence for the latter may be provided from the finding of progressive ventriculomegaly with advancing gestation; however, a substantial proportion of fetuses with open spina bifida and a positive lemon sign at ≤24 weeks' gestation had ventriculomegaly of a degree comparable to that of fetuses from later gestations where the lemon sign was absent (Fig. 4). Thus, in agreement with both Penso et al.[6] and Nyberg et al.,[5] we favor the hypothesis that the ultimate loss of the lemon sign in fetuses with open spina bifida results from maturation and strengthening of the fetal skull.[5, 6]

Cerebral ventriculomegaly is common in fetuses with open spina bifida, and both the anterior and posterior horns of the lateral ventricles enlarge progressively with advancing gestation (Figs. 3 and 4). Despite this progressive ventriculomegaly, the head circumference

remains disproportionately small throughout gestation. Wald et al.,[13] who reported that biparietal diameters were significantly smaller in fetuses with spina bifida, attributed this reduced head size to fetal growth retardation. Roberts and Campbell[14] subsequently confirmed the reduction in biparietal diameter; however, they suggested that this was not due to fetal growth retardation because in their 15 fetuses with spina bifida at <24 weeks' gestation the abdominal circumference was well within normal limits.[14] The findings of the present study indicate that in fetuses with open spina bifida the abdominal circumference is reduced and the degree of growth retardation increases with advancing gestation. However, it is unlikely that the observed reduction in head size is due to overall fetal growth retardation as this relative microcephaly is present in early gestations when abdominal circumference measurements are still within normal limits.

In routine ultrasonographic scanning of pregnant women, demonstration of fetal cranial and cerebellar markers identifies a group at high risk of open spina bifida. Even for gestations >24 weeks, when the lemon sign is no longer useful, cerebellar signs, cerebral ventriculomegaly, and relative microcephaly are often present. Patients with suspected fetal cranial and cerebellar signs, as well as those with raised maternal serum α-fetoprotein levels, antifolate medications, or a history of neural tube defects, should be referred to experienced ultrasonographers where a confident diagnosis of open spina bifida can be made by a diligent examination of the fetal spine. Present data indicate that in such patients, if results of an ultrasonographic examination of the fetal spine, cranium, and cerebellum appear to be normal, the chance of an undetected spinal lesion must be extremely low and therefore amniocentesis, with a procedure-related risk of up to 1%, is unnecessary.[15] In contrast, amniocentesis should be considered for those patients in whom definitive spinal defects cannot be demonstrated despite suggestive cranial and cerebellar signs.

REFERENCES

1. Nicolaides K, Campbell S, Gabbe S, Guidetti R. Ultrasound screening for spinal bifida: cranial and cerebellar signs. Lancet 1986;2:71-4.
2. Furness M, Barbary J, Verco P. Fetal head shape in spina bifida in the second trimester. JCU 1987;15:451-3.
3. Pilu G, Romero R, Reece A, Goldstein I, Hobbins J, Bovicelli L. Subnormal cerebellum in fetuses with spina bifida. Am J Obstet Gynecol 1988;158:1052-6.
4. Campbell J, Gibert W, Nicolaides K, Campbell S. Ultrasound screening for spina bifida: cranial and cerebellar signs in a high risk population. Obstet Gynecol 1987; 70:247-50.
5. Nyberg D, Mack L, Hirsh J, Mahony B. Abnormalities of fetal cranial contour in sonographic detection of spina bifida: evaluation of the "lemon" sign. Radiology 1988; 167:387-92.
6. Penso C, Redline R, Benacerraf B. A sonographic sign which predicts which fetuses with hydrocephalus have an associated neural tube defect. J Ultrasound Med 1987;6: 307-11.
7. Smith P, Johansson D, Tzannatos C, Campbell S. Prenatal measurement of the fetal cerebellum and cisterna cerebellar medularis by ultrasound. Prenat Diagn 1986;6:133-42.
8. Bell J, Gordon A, Maloney A. The association of hydrocephalus and Arnold-Chiari malformation with spina bifida in the fetus. Neuropathol Appl Neurobiol 1980;6:29-39.
9. Chiari H. Uber Veranderungen des Kleinhirns infolge von Hydrocephalie des Grosshirns. Dtsch Med Wochenschr 1891;17:1172-5.
10. Schwalbe E, Gredig M. Uber Entwicklungsstorungen des Kleinhirns, Hirnstamms und Halsmarks bei Spina Bifida. Beitr Patol Anat 1907;40:132-94.
11. Williams B. Cerebral spinal fluid pressure gradients in spina bifida cystica with special reference to the Arnold-Chiari malformation and aqueductal stenosis. Dev Med Child Neurol 1975;17(suppl 35):138-50.
12. Ingraham F, Scott H. Spina bifida and cranium bifida. V. The Arnold-Chiari malformation: a review of twenty cases. N Engl J Med 1943;229:108-14.
13. Wald N, Cuckle H, Boreham J, Stirrat G. Small biparietal diameter of fetuses with spina bifida: implications for antenatal screening. Br J Obstet Gynaecol 1980;87:219-21.
14. Roberts A, Campbell S. Fetal head measurements in spina bifida. Br J Obstet Gynaecol 1980;87:927-8.
15. Tabor A, Philip J, Madsen M, Bang J, Obel E, Norgaard-Pedersen B. Randomised controlled trial of genetic amniocentesis in 4606 low-risk women. Lancet 1986;1:1287-93.