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Ultrasound Obstet Gynecol 2019; **54**: 740–745
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.20285

Crash sign: new first-trimester sonographic marker of spina bifida

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KEYWORDS: early diagnosis; fetal anomaly; first trimester; MMC; spina bifida; ultrasound

CONTRIBUTION

What are the novel findings of this work?
We describe a novel sonographic sign of spina bifida in the first trimester. The 'crash sign' is seen as posterior displacement and deformation of the mesencephalon against the occipital bone in the axial ultrasound view of the fetal head in fetuses with spina bifida.

What are the clinical implications of this work?
This marker can be used by sonographers and fetal medicine specialists when assessing fetuses in the first trimester. Presence of the crash sign may lead to earlier diagnosis and explanation of treatment options to patients.

ABSTRACT

Objectives *To describe a new first-trimester sonographic sign, the 'crash sign', associated with fetal open spina bifida, and to evaluate its clinical usefulness in the first-trimester diagnosis of spina bifida.*

Methods *This was a retrospective review of patients referred to three fetal medicine centers in the first trimester (11 + 0 to 13 + 6 weeks) with suspected spina bifida. Spina bifida was confirmed by direct visualization of the spinal defect on ultrasound by two experts and, when possible, by fetal postmortem examination. Ultrasound images were reviewed for the presence of the crash sign, which is the posterior displacement of the mesencephalon and deformation against the occipital bone in the axial view. The first-trimester ultrasound images of a mixed group of 10 cases and 40 control fetuses without spina bifida were assessed for the presence of the crash sign by two assessors blinded to the diagnosis.*

Results *The crash sign was present in 48 out of 53 confirmed cases of spina bifida. Of these, 27 had isolated spina bifida and 21 had an associated anomaly. Of the five cases without the crash sign, one had isolated spina bifida and four had an associated anomaly. The crash sign was not reported in any of the control fetuses.*

Conclusions *We have described a new first-trimester sonographic marker for the diagnosis of spina bifida. Our results suggest that the crash sign may be a useful tool in the first-trimester detection of spina bifida. Prospective evaluation of the crash sign would be beneficial, ideally in a routine clinical screening ultrasound setting. Copyright © 2019 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Open spina bifida (myelomeningocele) is usually detected in pregnancy on second-trimester ultrasound examination[1]. Closed spina bifida is rarely detected at this stage and will not be discussed further in this article. Diagnostic signs include a 'lemon-shaped' skull, a 'banana-shaped' cerebellum and visualization of the spinal lesion[2]. Detection of spina bifida at an earlier gestational age would be beneficial, as there is evidence that, in cases of significant abnormality, parents prefer to be informed as early as possible in the pregnancy[3]. Furthermore, termination of pregnancy, if decided on by the couple, is safer and more easily performed earlier in pregnancy[4,5]. Earlier diagnosis also allows time for detailed counseling and assessment at a specialist center if *in-utero* closure is being considered. Evidence from randomized controlled trials has shown that open fetal surgery to close spina bifida between 19 + 0 and 25 + 6 weeks improves motor outcome and reduces postnatal

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Accepted: 4 April 2019

ventriculoperitoneal shunt rate compared with postnatal repair[6], and is now performed in a number of centers worldwide[7].

A number of sonographic signs have been described in the last decade to aid early detection of spina bifida, although they have yet to become well established in clinical practice. Most evidence has been derived from retrospective reviews; prospective evaluation of first-trimester signs of spina bifida, particularly in low-risk populations undergoing routine ultrasound examination, is lacking. The most extensively researched first-trimester sonographic signs of spina bifida are intracranial translucency, brainstem diameter, brainstem–occipital bone distance, aqueduct of Sylvius-to-occiput distance and frontomaxillary facial angle[8–12]. As opposed to pattern recognition, these markers all involve taking measurements, which may add significant time to the examination.

We describe a new first-trimester ultrasound sign of open spina bifida – the 'crash sign' (Figure 1) – and evaluate it in a cohort of pregnant women whose fetus was suspected to have spina bifida at 11 + 0 to 13 + 6 weeks'

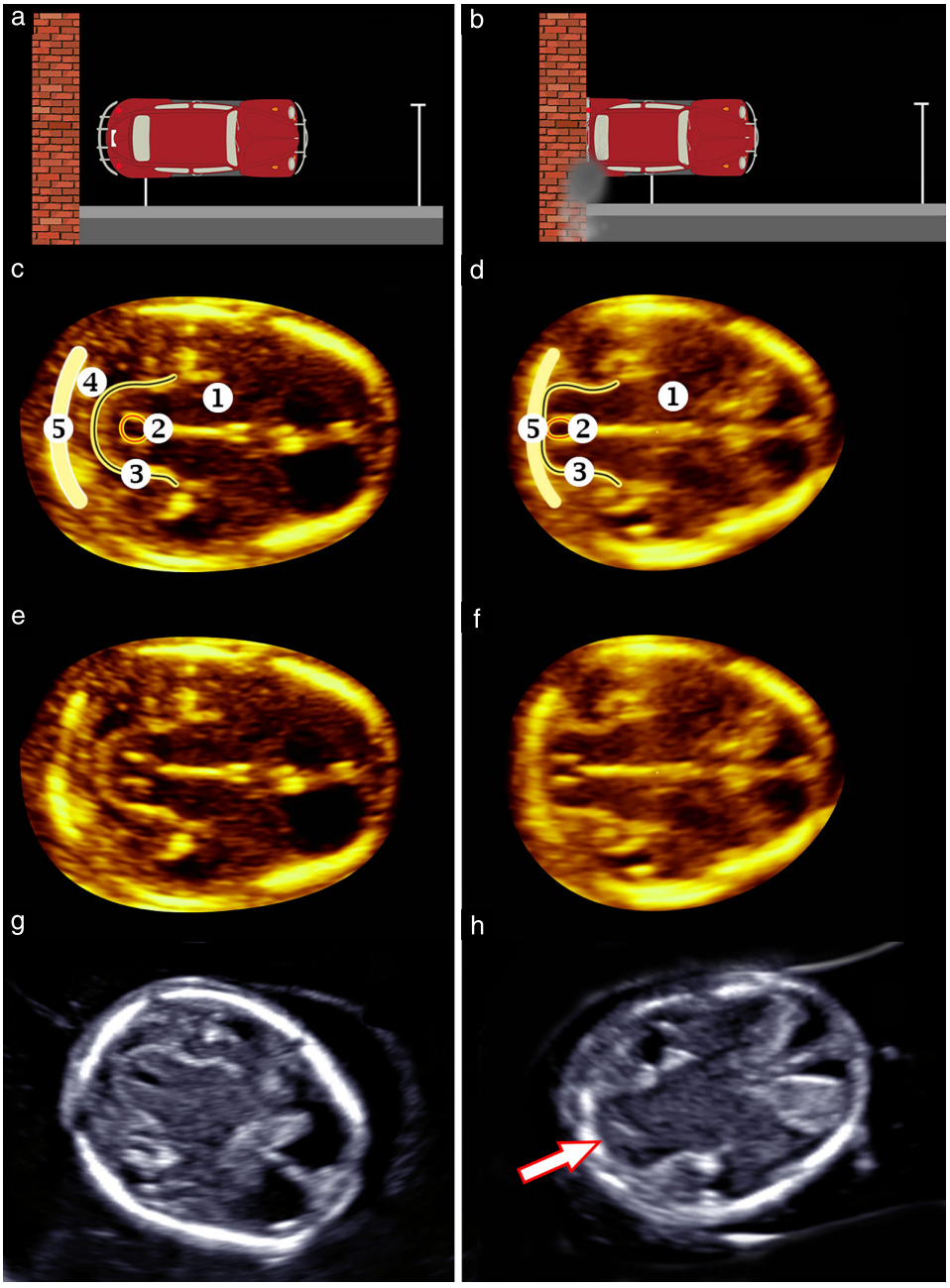

Figure 1 Schematic diagrams showing car stationed away from wall, representing mesencephalon (car) and occipital bone (wall) in normal fetuses (a), and reversed into wall, representing posterior displacement of mesencephalon and deformation against occipital bone ('crash sign') in fetuses with open spina bifida (b). (c–h) Ultrasound images in axial view at 12–13 weeks' gestation, showing mesencephalon in normal fetuses (c,e,g) and crash sign in fetuses with open spina bifida (d,f,h). (c–f) Three-dimensional reconstructed images of two sets of monochorionic twins discordant for spina bifida. (g,h) Images of singleton fetuses without (g) and with (h) crash sign (arrow). 1, thalamus; 2, aqueduct; 3, mesencephalon; 4, arachnoid space; 5, occipital bone.

gestation, and who were referred to a fetal medicine specialist for evaluation. The crash sign is based entirely on pattern recognition rather than measurements, and therefore has the potential to be easily assessed and adopted during a first-trimester scan.

METHODS

Study participants

This was a retrospective observational study conducted at three large fetal medicine referral centers (University College London Hospital (UCLH), London, UK; Moscow Regions Research Institute of Obstetrics and Gynecology, Moscow, Russia; and Emergency University Hospital of Craiova, Romania). Women who were referred in the first trimester (11 + 0 to 13 + 6 weeks' gestation) for an ultrasound examination between January 2012 and December 2015 owing to suspicion of fetal spina bifida were included. In these centers, a detailed anatomical examination of the fetus was performed routinely at 11 + 2 to 14 + 1 weeks' gestation according to last menstrual period or crown–rump length if there was a discrepancy of more than 5 days between the dates. The scan assessed viability, gestational age, multiple pregnancy and nuchal translucency. The protocol included examining the fetal brain in axial and sagittal views, as well as obtaining axial and longitudinal vertebral views of the spine with assessment of the overlying skin. The transvaginal approach was used in cases in which the transabdominal route was unable to produce an image of adequate quality or was not possible owing to fetal position. Of note, patients were referred to the fetal medicine units following suspicion of spina bifida for any reason (e.g. brain changes, spinal appearance) and not necessarily because the primary operator detected the crash sign.

Experienced fetal medicine specialists performed all examinations using 730, E8 and E10 Voluson Ultrasound machines (GE Healthcare, Zipf, Austria). Patients underwent ultrasound examination of the brain and spine by one of the authors, including three-dimensional (3D) neurosonography in the majority of cases. All findings were video archived. A prenatal diagnosis of spina bifida was made by visualization of the myelomeningocele and spinal defect on ultrasound by at least two independent fetal medicine experts; if findings were inconclusive, a repeat ultrasound examination was scheduled for 10–14 days later. All women with a diagnosis of spina bifida were offered chorionic villus sampling to check for chromosomal abnormality. In cases in which the pregnancy was terminated or natural pregnancy loss occurred, postmortem examination was offered to confirm the ultrasound findings.

Cases of spina bifida suspected in the first trimester were collated and images were reviewed retrospectively for the presence of a new first-trimester ultrasound sign, the 'crash sign', by one author at each institution (F.U., E.A. and S.T.).

Crash sign

The crash sign described here was first detected by one of the authors (F.U.) following review of stored first-trimester brain 3D ultrasound volumes from fetuses with spina bifida. It is the posterior displacement of the mesencephalon and deformation against the occipital bone in the axial view (Figure 1). It is so named as it resembles the back of a car that has crashed into a wall. Additionally, the moving image of a car reversing into a wall is a good aide memoire for hindbrain herniation that occurs in spina bifida[13], making the sign easily memorable.

In order to assess the presence of the crash sign, the standard axial view of the head in the first trimester (11 + 0 to 13 + 6 weeks' gestation) is obtained at the level of the mesencephalon[14]. In the normally developed fetus, the mesencephalon is visualized as a semicircular structure in the posterior brain and appears as a continuation of the thalami. It contains a round echolucent structure centrally, which represents the cerebral aqueduct of Sylvius. The mesencephalon is surrounded by the fluid-filled arachnoid space, which separates it from the occipital bone. In fetuses with open spina bifida, the arachnoid space is no longer fluid filled and the mesencephalon sits directly against the occipital bone. Narrowing of the aqueduct of Sylvius may also occur, and in some cases it may no longer be visible. The crash sign can be readily recognized on axial sonographic views by using either a transabdominal or transvaginal approach.

Control group

In order to confirm that the crash sign cannot be seen in pregnancies unaffected by spina bifida, we created a control group by using a random-number generator to select 55 records from the population of all women attending one of the institutions (UCLH) for a first-trimester examination performed during the same time period. One author (A.S.) checked that the patients selected randomly as a control group had not been diagnosed with spina bifida or any other abnormality during the pregnancy. A mixed group of controls ($n = 40$) and cases ($n = 10$) were then assessed separately by one author (F.U.) and one independent fetal medicine specialist (not an author) blinded to the outcomes.

RESULTS

During the 4-year study period, there were 62 suspected cases of spina bifida at 11 + 0 to 13 + 6 weeks, based on the appearance of the brain and spine on ultrasound. Figure 2 gives details of the study participants and their outcome. Nine cases were excluded from the analysis as the patients were lost to follow-up and the diagnosis of spina bifida could not be confirmed. Figure 3 shows ultrasound images from 15 consecutive cases of spina bifida from one hospital (UCLH).

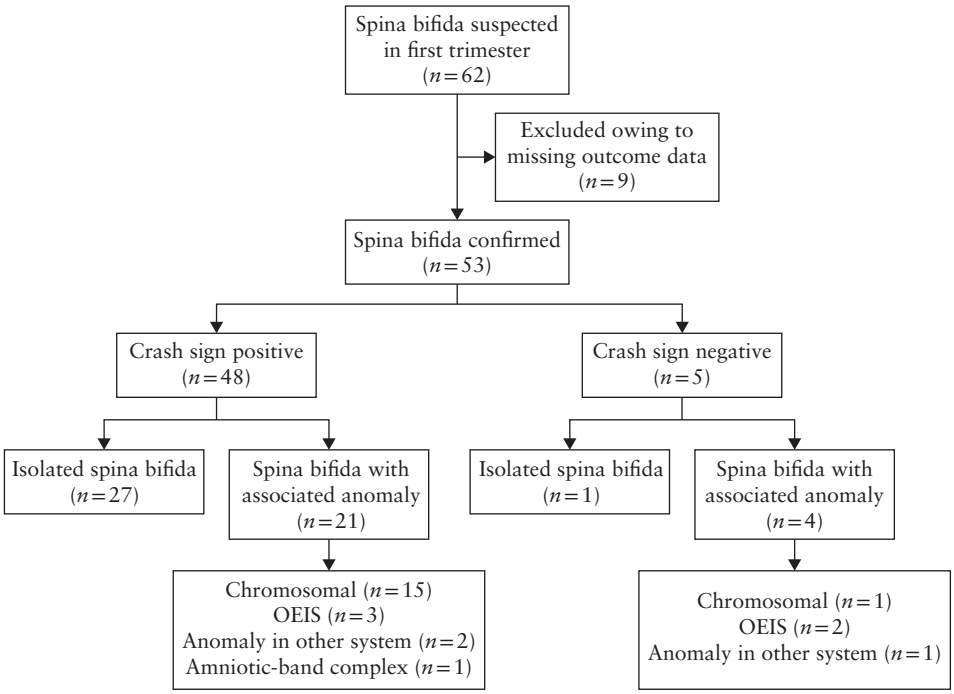

Figure 2 Flowchart summarizing inclusion of fetuses with open spina bifida and outcome according to presence of crash sign. OEIS, omphalocele–exstrophy–imperforate anus–spinal complex.

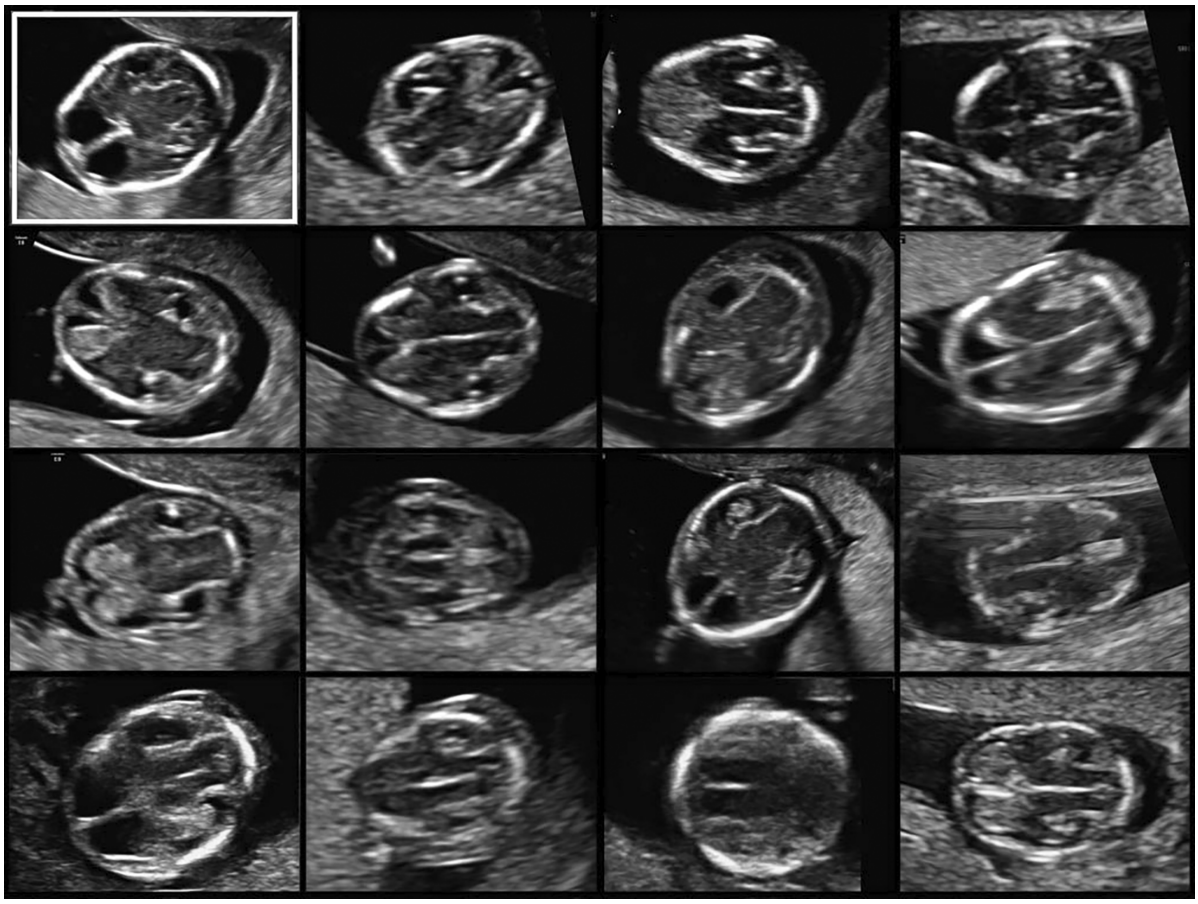

Figure 3 Ultrasound images of fetal brain in axial view, showing crash sign in 15 consecutive cases of spina bifida from one hospital (University College London Hospital) and, for comparison, normal case without crash sign (white box).

Among the 53 cases with known outcome, all screening was performed between 11 + 2 and 14 + 1 weeks' gestation, with a mean gestational age of 12 weeks and 3.6 days. Fifty cases were singleton pregnancies and three were multiple. Maternal age ranged from 19 to 44 years, with a mean of 32.1 years. Maternal body mass index was not recorded for all patients (available in 29/53 cases) but in those recorded it ranged from 18.9 to 35.0 kg/m^2, with a mean of 25.6 kg/m^2.

All included cases were confirmed to have spina bifida. Forty-eight of these were confirmed by ultrasound only and five were also subsequently confirmed by fetal postmortem examination (Figure 4). There were 37 cases of myelomeningocele and 16 cases of rachischisis.

Of the 53 cases of spina bifida, 48 showed the crash sign and five did not (Figure 2). Of the 48 patients with spina bifida that were positive for the crash sign, 27 (56.3%) had isolated spina bifida, while 21 (43.8%) had an associated anomaly. Of the five fetuses with spina bifida that were negative for the crash sign, one (20.0%) had isolated spina bifida and four (80.0%) had an associated anomaly. Associated anomalies were as follows: trisomy 18 ($n = 10$), trisomy 13 ($n = 2$), triploidy ($n = 4$), omphalocele–exstrophy–imperforate anus–spinal complex ($n = 5$), structural anomalies in other organ systems ($n = 3$) and amniotic-band complex ($n = 1$).

The mixed group of cases ($n = 10$) and controls ($n = 40$) were identified correctly by two assessors blinded to the diagnosis, with no reports of the crash sign present in patients without spina bifida (i.e. no false positives).

DISCUSSION

In this study, we describe the crash sign, a new sonographic marker of spina bifida for use in the first trimester. We evaluated retrospectively its presence in cases of spina bifida detected at 11 + 0 to 13 + 6 weeks' gestation, and found that 90.6% (48/53) of confirmed cases displayed this sign on retrospective review. The crash sign is based on the changes that develop in the mesencephalon as a result of the reduced intracranial pressure associated with spina bifida. In normal early development, the fetal skull is soft owing to incomplete ossification, and the shape of the head is therefore a function of the intracranial pressure, which is created by cerebrospinal fluid (CSF) production within the large choroid plexuses in the lateral, third and fourth ventricles. In the normal fetus, there is constant CSF flow in the caudal direction of the spinal cord within a closed system. However, in cases with an open spinal defect, CSF leaks out with consequent reduction in intracranial pressure. This in turn causes collapse of the skull with the appearance of reduced fluid or a 'shriveled' brain. In human fetuses, this process would explain the reduction in frontomaxillary facial angle[12] as well as the findings of reduced biparietal diameter and the ventricular system changes seen in the first trimester in fetuses with spina bifida[15].

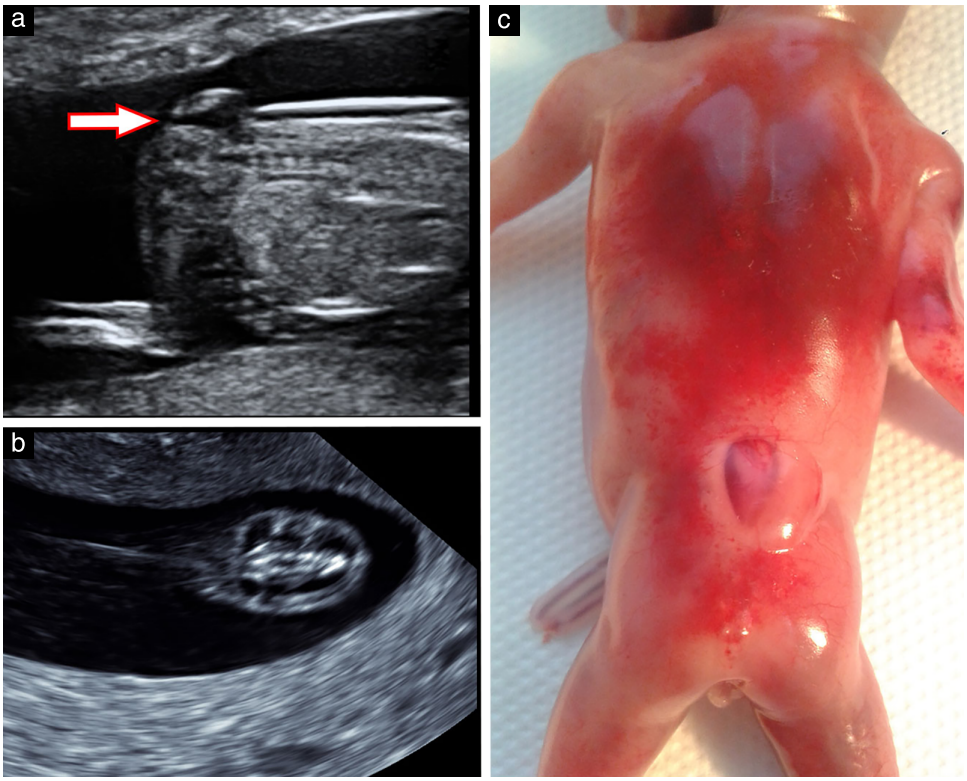

Figure 4 Sagittal (a) and coronal (b) ultrasound images and postmortem examination (c) of three fetuses with myelomeningocele at 11–13 weeks' gestation. Arrow indicates myelomeningocele sac.

Unidirectional leakage of the fluid towards the open spinal defect results from a pressure gradient between the 'high-pressure' CSF-filled choroid ventricles and the 'low-pressure' spinal cord, which produces posterior and caudal displacement of the mesencephalon. During this process, the mesencephalon meets the only firm cranial structure on its way, the occipital bone, and is compressed against it. The resulting deformation of the mesencephalon represents the crash sign, which we evaluated in the current study.

The strength of this study is that it was multicenter, meaning that the findings are likely to be generalizable. However, the study was conducted by retrospective review of images and by fetal medicine specialists experienced in neurosonography. Therefore, there may be bias in the diagnostic ability of the crash sign to detect spina bifida prospectively. In addition, not all fetuses with confirmed spina bifida were positive for the crash sign. All scans were performed by sonographers with considerable expertise and experience in first-trimester anomaly scanning, and transvaginal ultrasound was available if necessary. However, the thalamic plane is advisable as a good practice point for head biometry in the first trimester[14], and it should be possible for all practitioners performing ultrasound examinations at $11+0$ to $13+6$ weeks to evaluate the posterior fossa for the crash sign. Certainly, in situations in which a first-trimester anomaly scan is being performed for suspected fetal abnormality, we believe that proper evaluation of the fetal mesencephalon is important. Posterior displacement and deformation of the mesencephalon against the occipital bone in the axial view of the brain should prompt the specialist to examine carefully the spine for a defect.

This was a retrospective study describing a new marker, and the next stage should be prospective validation of this sign, with comparison with other widely researched signs. In particular, aqueduct of Sylvius-to-occiput distance quantitatively assesses caudal displacement of the mesencephalon, although it does not assess qualitative deformation of this structure, and it would be interesting to compare these two markers to see if either is superior.

In conclusion, we have described the use of a new sonographic marker, the crash sign, for diagnosing spina bifida in the first trimester. Our results show that first-trimester detection of spina bifida is possible using this sign. Further prospective evaluation by multiple blinded operators is needed to determine the value of the crash sign in a clinical setting, and to compare it with other established first-trimester markers.

ACKNOWLEDGMENTS

We are very grateful to Ruchi Bhutani for blindly assessing our mixed case/control group. A.L.D. is supported by the NIHR University College London Hospitals Biomedical Research Centre.

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