# Crash Sign: A New First Trimester Sonographic Marker of Spina Bifida

Short running title: Crash Sign in Spina Bifida

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**Key words:** spina bifida, MMC, fetal anomaly, ultrasound, first trimester, early diagnosis

## Acknowledgments

We gratefully thank Ruchi Bhutani for blindly assessing our mixed case/control group. ALD is supported by the NIHR University College London Hospitals Biomedical Research Centre

## Conflict of Interest statement:

The authors report no conflicts of interest

Abstract

*Objectives*

To describe a new first trimester sonographic sign associated with open fetal spina bifida ("crash sign") where there is posterior displacement and deformation of the mesencephalon against the occipital bone in the axial view, 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 centres in the first trimester (11-13+6 weeks) with suspected spina bifida. Spina bifida was confirmed by direct visualisation of the spinal defect by two experts and, where possible, examined at fetal post-mortem. Images were reviewed for the presence of the crash sign. A control group of 55 first trimester scans not affected by spina bifida was created and reviewed by two assessors blinded to the pregnancy diagnosis.

*Results*

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

*Conclusions*

We have described the use of 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.

Plain language summary

“Crash sign” is a new way to try to diagnose spina bifida at the first pregnancy ultrasound scan.

## Introduction

Open spina bifida (myelomeningocele, MMC) is usually detected in pregnancy by second trimester ultrasound scan[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 visualisation of the spinal lesion. Detection of spina bifida at an earlier gestation would be beneficial as there is evidence that in cases of significant abnormalities, parents prefer to be informed as early as possible in the pregnancy[2] and also that termination of pregnancy, if the ultimate choice of the couple, is safer and more easily performed at earlier gestations[3 4]. Earlier diagnosis allows time for detailed counselling and assessment in a specialist centre if in-utero closure is being considered. Randomised controlled trial evidence has found that open fetal surgery to close spina bifida between 19+0 to 25+6 weeks improves motor outcomes and reduces postnatal ventriculoperitoneal shunt rates compared to postnatal repair[5] and this is now available in a number of centres worldwide[6].

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 a low risk population routinely scanned by sonographers, is lacking. The most extensively researched first trimester sonographic signs of spina bifida are the intracranial translucency[7], brainstem diameter[8], brainstem-occipital bone (BSOB) distance[9], aqueduct of Sylvius (AOS) to occiput distance[10] and frontomaxillary facial angle[11]. Rather than pattern

recognition, these markers all involve taking measurements, which may add significant time to the scan.

We describe here a new first trimester ultrasound sign – the “crash sign” – and its evaluation in a cohort of pregnant women whose fetus was suspected to have spina bifida at 11-13+6 weeks of gestation, and who were referred to a fetal medicine specialist for evaluation. The crash sign is based entirely on pattern recognition and not measurements, and therefore has the potential to be easily performed and adopted during a first trimester scan.

## Methods

### Crash sign

The “crash sign” described here was first detected by one of the authors (FU) following reviews of stored first trimester brain 3D ultrasound volumes from fetuses with spina bifida. It is the posterior displacement and deformation of the mesencephalon against the occipital bone in the axial view (Figure 1). It is so named as it resembles the back of a car which has crashed into a wall; additionally, the moving image of a car reversing into a wall is a good aide memoir for the hindbrain herniation which occurs in spina bifida[12], making the sign easily memorable.

In order to assess for crash sign, the standard axial view of the head in the first trimester[13] (11-13+6 weeks of gestation) is taken at the level of the mesencephalon. In the normally developed fetus, the mesencephalon is visualised as a semi-circular 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 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 recognised on axial sonographic views by using both transabdominal and transvaginal approaches.

Study participants

This was a retrospective observational study from three large fetal medicine referral centres (University College London Hospital, London; Moscow Regions Research Institute of Obstetrics and Gynaecology; and Emergency University Hospital of Craiova, Romania). Women who were referred for a fetal medicine ultrasound scan between January 2012 and December 2015 due to concerns regarding fetal spina bifida were included. In these centres, a detailed anatomical examination of the fetus was routinely performed 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 where the transabdominal route was unable to produce an image of adequate quality or was impossible due to fetal position. Of note, patients were referred to the fetal medicine units following a 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 on the following models of Voluson Ultrasound Scanners: 730, E8 and E10 (GE Healthcare, United States). The patient underwent ultrasound examination of the brain and spine by one of the authors, including 3D neurosonography in the majority of cases. All findings were video archived. A prenatal diagnosis of spina bifida was made by visualisation of the myelomeningocoele and spinal defect by at least two independent fetal medicine

experts; if findings were inconclusive a repeat ultrasound scan was scheduled for 10-14 days later. All women with a diagnosis of spina bifida were offered chorionic villus sampling (CVS) to check for chromosomal abnormalities. In cases where the pregnancy was terminated or natural pregnancy loss occurred, post-mortem examination was offered to confirm the ultrasound findings.

Cases of spina bifida suspected in the first trimester were collated and images retrospectively reviewed by one author in each institution (FU, EA and ST) for the presence of crash sign.

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 our institutions (UCLH) for first trimester scans over the same time period. One author (AS) checked that the patients randomly selected as a control group had not been diagnosed with spina bifida or any other abnormality during the pregnancy. A mixed group of controls (40) and cases (10) were then separately assessed by one author (FU) and one independent fetal medicine specialist (not an author) blinded to the outcome.

## Results

During the four-year period of this study there were 62 suspected cases of spina bifida at 11 to 13 weeks, based on the appearance of the brain and spine. Figure 2 outlines the study participants and their outcomes. Nine cases were excluded from our analyses as the patients were lost to follow up and the diagnosis of spina bifida could not be confirmed. Figure 3 represents images of 15 consecutive cases of spina bifida from one hospital (UCLH).

Of 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 3.6 days. Fifty cases were singleton pregnancies and three were multiple. Maternal age ranged from 19 years to 44 years, with a mean age of 32.1 years. Maternal body mass index (BMI) was not recorded for all patients (29/53 available) but when recorded ranged from 18.9 to 35 with a mean BMI of 25.6.

All included cases were confirmed to have spina bifida present. Forty-eight of these were confirmed by sonography only as described above and five were also subsequently confirmed by fetal post-mortem (Figure 4). There were 37 cases of myelomeningocele and 16 cases of rachischisis.

In the 53 cases of spina bifida, 48 had crash sign present and five did not (Figure 2). Of the 48 patients with spina bifida and positive crash sign, 27 (56.3%) had isolated spina bifida whereas 21 (43.7%) had other associated anomalies. Of the five patients with spina bifida who were crash sign negative, one (20.0%) had isolated spina bifida

and four (80.0%) had other associated anomalies. Associated anomalies were as follows: trisomy 18 (10), trisomy 13 (2), triploidy (4), omphalocele-exstrophy-imperforate anus-spinal (OEIS) complex (5) and structural anomalies in other organ systems (4).

The mixed group of cases (10) and controls (40) were correctly identified by two blinded assessors, with no reports of 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 have retrospectively evaluated its presence in cases of spina bifida detected at 11-13+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 due to incomplete ossification, and the shape of the head is therefore a function of the intracranial pressure. Intracranial pressure 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. In the case of an open spinal defect however, 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 “shrivelled” brain. In human fetuses this process would explain the reduction in frontomaxillary facial angle[11] as well as the findings of reduced biparietal diameter and the ventricular system changes seen in the first trimester fetuses with spina bifida[14].

Unidirectional leakage of the fluid towards the open spinal defect results from a pressure gradient between the ‘high’ pressure choroid filled ventricles and the ‘low’ pressure spinal cord. This 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 have evaluated in our study.

The strength of our study is that it was multicentre, meaning that the findings are likely to be generalisable. However, this study was conducted by retrospective review of images and by fetal medicine specialists experienced in neurosonography. Therefore there may be a bias in the diagnostic ability of the crash sign to prospectively detect spina bifida. In addition, not all fetuses with confirmed spina bifida were crash sign positive. All scans were performed by sonographers with considerable expertise and experience in first trimester anomaly scanning where transvaginal ultrasound was available if necessary. However, the thalamic plane is advisable as a good practice point for head biometry in the first trimester[13], and it would could be possible for all practitioners performing ultrasound scans at 11-13+6 weeks to evaluate the posterior fossa for the crash sign. Certainly in situations where a first trimester anomaly scan is being performed for suspected fetal abnormalities, 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 carefully examine the spine for a defect.

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

## Conclusions

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 with multiple blinded operators is needed to determine the value of crash sign in a clinical setting, and to compare it to other established first trimester markers.

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