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ORIGINAL ARTICLE

Beyond Open Neural Tube Defects: Sagittal Landmarks at 11–14 Weeks in the Prediction of Second Trimester Posterior Fossa Abnormalities

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Abstract

Background Objective assessment of posterior fossa landmarks such as the measurement of brain stem width or intracranial translucency have not been consistently shown to be predictive of future posterior fossa abnormalities, other than the Arnold–Chiari II malformation.

Objective To study the association between the objective and subjective assessments of the posterior fossa landmarks at the 11–14 weeks' scan and the posterior fossa abnormalities detected at the second-trimester anomaly scan.

Methods Design—Blinded retrospective case–control study. Setting—Tertiary level multioperator fetal medicine center. Cases-fetuses with one of the second trimester diagnoses of posterior fossa abnormalities (Blake's pouch cyst, mega cisterna magna, vermian agenesis, Dandy–Walker malformation, cerebellar hypoplasia) that had a 11–14 weeks' examination at our center; Controls-fetuses with normal second trimester anatomy that had a 11–14 weeks' examination at our center. Main outcome measures: measurements of the posterior fossa landmarks and subjective assessment of the landmarks.

Results Significant inter-rater agreement existed for three out of four measurements of posterior fossa landmarks. No significant difference was noted in the measurements between cases and controls, in fetuses with measurable landmarks. Abnormal landmarks were more in cases than controls (brainstem OR 4.2 (95% CI 1.5–11.8); intracranial translucency OR 3.7 (95% CI 1.3–10.1); any landmark OR 3.1 (95% CI 1.2–7.9).

Conclusion Abnormal posterior fossa landmarks at the 11–14 weeks' examination is associated with threefold risk of posterior fossa malformation.

Keywords Intracranial translucency · Posterior fossa · 11–14 weeks · First-trimester anatomy · Early pregnancy anomaly scan

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Introduction

The examination of the fetus at 11–14 weeks has greatly surpassed the initial objective of screening for Down syndrome by the nuchal translucency (NT) [1]. The examination is currently considered an 'early' window for targeted imaging for fetal anomalies that are apparent at this stage of gestation. Many studies have been published that have illustrated the diagnostic potential of this examination, culminating in the formulation of practice guidelines issued by the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) [2]. Fetal malformations can now be classified based on whether they can be diagnosed at the 11–14 weeks' scan as "always detectable", "sometimes detectable", and "not detectable". Abnormalities of the posterior fossa structures, by virtue of their completing development beyond the 18th gestational week, are not amenable to diagnosis at the 11–14 weeks' examination. Ever since the description of the landmarks of the posterior fossa in the screening for open neural tube defects (ONTD) [3], much attention has gone into the examination of the posterior fossa and its potential in predicting abnormalities other than ONTD

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[4, 5]. However, there is no consensus yet on the utility of the 11–14 weeks' posterior fossa landmarks in the prediction of malformations other than the Arnold–Chiari II malformation (ACM). Objective assessment of posterior fossa landmarks such as measurement of brainstem (BS) width or intracranial translucency (IT) has not been consistently shown to be predictive of future posterior fossa abnormalities, other than ACM. We aimed to study the association between the objective and subjective assessments of the posterior fossa landmarks at the 11–14 weeks' scan and the posterior fossa abnormalities detected at the second-trimester anomaly scan.

Materials and Methods

We designed a blinded retrospective case–control study to investigate the association between the landmarks at 11–14 weeks and the abnormalities at midtrimester target scan in the posterior fossa. Cases were defined as fetuses diagnosed at the midtrimester scan with posterior fossa abnormalities such as Blake's pouch cyst (BPC), vermian agenesis (VA), mega cisterna magna (MCM), Dandy–Walker malformation (DWM), or cerebellar hypoplasia (CH) that also had a first-trimester screening in our center. Controls were defined as fetuses with normal second-trimester anatomy that also had a first-trimester screening in our center. For every case, we randomly selected three controls during the same time period. Our center is a tertiary level fetal medicine center for the state of Tamilnadu and the surrounding districts of the neighboring states. The first-trimester screening department handles both routine and referred cases. All cases are screened in accordance with the 'rule of two' protocol (Table 1) that essentially covers all the aspects of first-trimester screening guidelines laid down by the ISUOG [2] with extended anatomy survey. The screening scans are performed by multiple operators, including fellows in fetal medicine, with different levels of experience and the images are subsequently audited by consultants. All data get entered into the fetal database, Sonocare^{TM} (Medialogic Solutions Private Limited, Chennai, India) immediately upon the completion of the examination. The database is equipped with image archiving, reviewing, querying, retrieving, and reprocessing capabilities and allows users to perform offline measurements on stored images.

Anonymized first-trimester sagittal head section images of the cases and controls during the study period from January 2010 through December 2015 were retrieved from the database and were given a study ID. Only one author (PG) had access to the code that revealed if the given image belonged to the case or control group. The images were randomly assigned to one of the two research coordinators (DG and JR) who was blinded to the case/control status of the fetus. The anonymized images were reviewed and reported on the preformatted data abstraction spreadsheet. Twenty images were reported by both and were used for inter-rater agreement analysis. The measurements of the

Table 1 The rule of two protocol followed in our centre at the 11–14 weeks fetal assessment

Category	Rule of two
Wellbeing	1. Cardiac activity
	2. Fetal movements
Biometry	1. Crown-rump length
	2. Biparietal diameter
Head	1. Calvarium
	2. Midline falx with lateral ventricles (butterfly sign)
Face	1. Orbits
	2. Premaxillary triangle
Spine	1. Intracranial translucency
	2. Vertebral column
Heart (color Doppler)	1. Inflows
	2. Arches
Abdomen	1. Stomach
	2. Bladder
Extremities	1. Upper limbs—2
	2. Lower limbs—2
Aneuploidy markers	1. Nuchal translucency
	2. Nasal bone
Others	1. Cord insertion
	2. Ductus venosus flow pattern

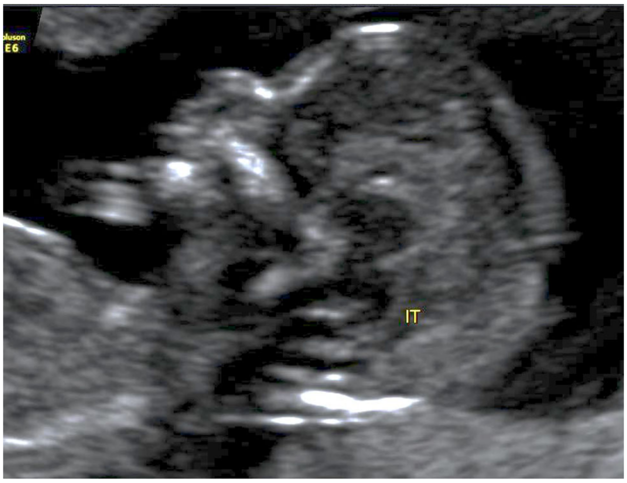

Fig. 1 Midsagittal section showing clear landmarks of the posterior fossa

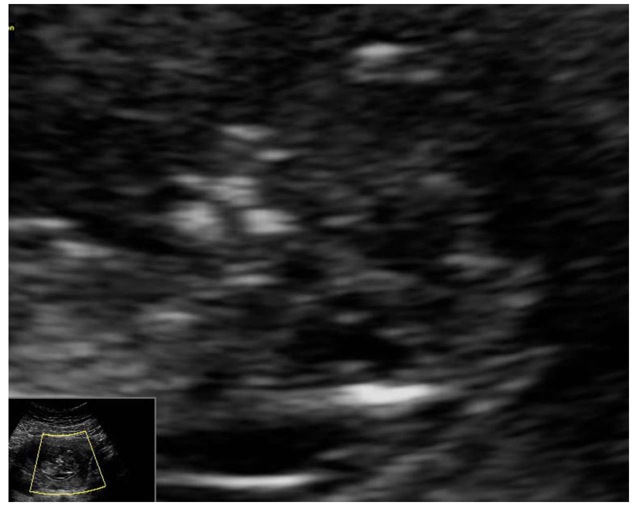

Fig. 2 Midsagittal section of fetal head showing abnormal posterior fossa landmarks

IT, BS width, cisterna magna (CM) width, and the brainstem–occipital bone (BSOB) distance were made as described previously [6]. The standard NT image was used for the assessment of the posterior fossa landmarks. However, unlike NT measurement, posterior fossa measurements need not be done on a strict midsagittal plane and hence images in sagittal planes that are off-midline slightly were also used, especially if the landmarks are well defined in these planes. The BS width was measured between the posterior surface of the sphenoid bone and the roof of the fourth ventricle; IT width was measured between the roof of the fourth ventricle and the echogenic tela choroidea of the fourth ventricle; the CM width was measured between the echogenic tela choroidea and the inner margin of the occipital bone; and the BSOB was measured from the posterior margin of the sphenoid bone to the inner margin of the occipital bone. The measurements were made with the caliper placement being 'on to on', similar to NT measurement (Fig. 1). Since the IT has been shown to have a linear relation with the crown-rump length (CRL) [7], these measurements were standardized by dividing with the corresponding CRL and multiplying by 100. The measurement was carried out only if the structure had well-defined landmarks; otherwise a comment 'not delineated' was given (Figs. 2, 3). Maternal and fetal baseline characteristics were retrieved from the database.

Statistical Methods

Inter-rater agreement was analyzed using intraclass correlation co-efficient for continuous measurements. The means between the groups were analyzed using the student *t* test; categorical variables were analyzed using Pearson's Chi-square test. The statistical analysis was done using SPSS version 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). A *p* value of less than or equal to 0.05 was set as statistically significant for the analyses.

Results

The database search for cases from January 2010 through December 2015 yielded 36 cases of posterior fossa abnormalities diagnosed in the midtrimester anomaly scan satisfying the inclusion criteria mentioned above. One hundred and eight fetuses with normal second-trimester anatomy were included as controls. The distribution of cases was as follows: 3 cases of BPC, 5 MCM, 3 VA, 8 DWM and 17 CH. The first-trimester sagittal images of the head of these fetuses were anonymized and assigned randomly to each of the two research coordinators, blinded to the final outcome. Each of the two research coordinators was assigned 82 fetuses such that 20 images were rated by both.

Table 2 describes the baseline characteristics of the mothers and fetuses among the controls and cases, and these were comparable between the groups. The inter-rater agreement for measurements of the posterior fossa structures was assessed by the intraclass correlation coefficient. Significant agreement existed for all measurements except the CM width as shown in Table 3.

As shown in Table 4, the measurements of the posterior fossa structures, standardized to the corresponding CRL did not differ significantly between the two groups. However, the distribution of the abnormal landmarks was

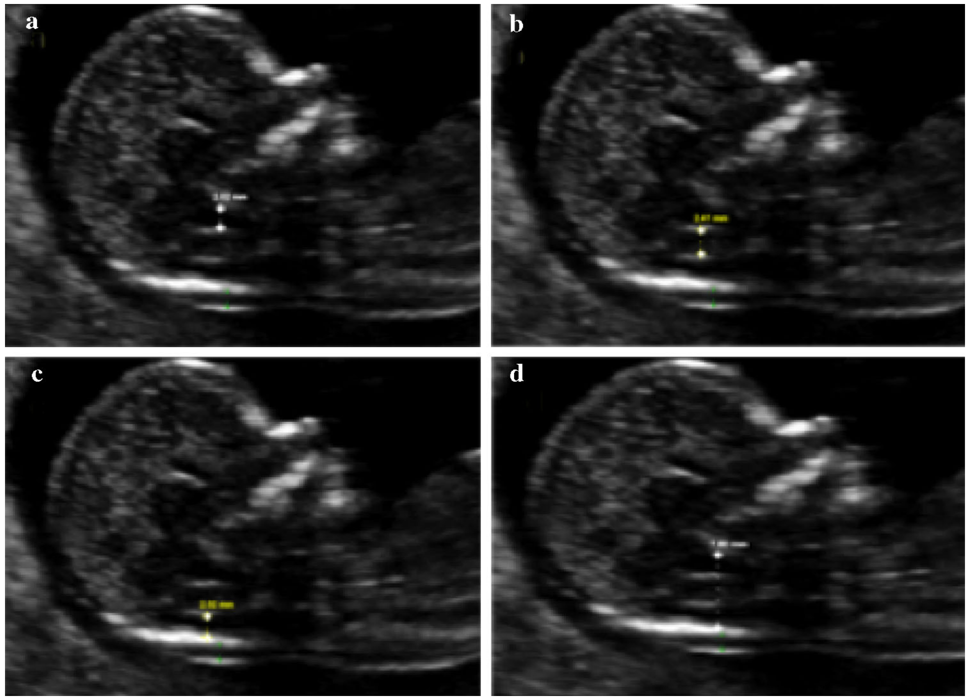

Fig. 3 Sagittal sections of fetal head showing measurements of posterior fossa landmarks: **a** brainstem, **b** intracranial translucency, **c** future cisterna magna, **d** brainstem occipital bone distance

Table 2 Baseline maternal-fetal characteristics

Baseline variables (mean, SD)	Cases n = 36	Controls n = 108	*p*
Maternal age	27 (4.6)	28 (4.5)	0.17
Maternal BMI	24.5 (4.8)	25.8 (4.8)	0.17
Gestational age	12 (0.6)	12 (0.6)	0.3
Crown-rump length	63 (10)	66 (7.9)	0.2
Nuchal translucency	1.9 (0.7)	1.7 (0.3)	0.09

Table 3 Inter-rater agreement for posterior fossa measurements

Variable	Operator 1, mean (SD)	Operator 2, mean (SD)	Intraclass correlation coefficient	*p*
BS width	2.2 (0.48)	1.9 (0.48)	0.6	0.02
IT width	1.9 (0.36)	1.6 (0.42)	0.7	0.007
CM width	1.4 (0.24)	1.3 (0.31)	0.5	0.11
BS-OB	5.2 (1.1)	4.8 (1.1)	0.8	<0.001

BS brainstem, *IT* intracranial translucency, *CM* cisterna magna, *BSOB* brainstem to occipital bone distance

significantly more in the cases compared to the controls, with the exception of future CM (Table 5).

Discussion

This case–control study has revealed an association between subjective assessment of the posterior fossa landmarks and the development of second-trimester abnormalities in the posterior fossa. Specifically, the risk is greatest when the brainstem (OR 4.2) or the IT (3.7) is not delineated well. The nondelineation of the CM was not significantly different between the control and cases group.

To our knowledge, the present study has the largest number of 'cases' of posterior fossa abnormalities analyzed by the first-trimester signs. Previous studies have looked at fetuses with abnormal posterior fossa landmarks and confirmed if they had developed abnormalities later in the course of pregnancy [4, 5]. We had analyzed from outcome

Table 4 Measurements of posterior fossa landmarks, standardized to crown-rump length

Landmark	Group	N	Mean	SD	*p*
BS	Case	27	2.8	0.8	0.1
	Control	100	3.1	0.8	
IT	Case	27	2.4	0.8	0.3
	Control	99	2.6	0.6	
CM	Case	29	2.1	0.7	0.9
	Control	97	2.1	0.4	
BSOB	Case	28	7.3	1.8	0.8
	Control	98	7.2	1.5	

BS brainstem, *IT* intracranial translucency, *CM* cisterna magna, *BSOB* brainstem to occipital bone distance

Table 5 Comparison of abnormal landmarks between cases and controls

Landmark abnormal	Case n = 36	Control n = 108	OR	95% CI
BS	9	8	4.2	1.5–11.8
IT	9	9	3.7	1.3–10.1
CM	7	11	2.1	0.8–6
Any	10	12	3.07	1.2–7.9

BS brainstem, *IT* intracranial translucency, *CM* cisterna magna

to exposure to determine the strength of association between the first-trimester abnormalities and later malformations. The retrospective nature of the study has both advantages and disadvantages. It eliminates the 'Hawthorne effect' and assesses the actual practical utility of the study of first-trimester posterior fossa landmarks in flagging up potential malformations to be detected later in gestation. In the setting of a multioperator environment, the element of variation in skill affecting the image quality is a potential pitfall. However, while designing the study, we argued that in actual communitywide practice, the skill levels would vary and therefore, this study would actually represent the 'effectiveness' rather than 'efficacy' of screening with first-trimester signs.

Another limitation of the study is the inclusion of a varied list of defects under the 'cases' group. However, from a clinical point of view, the purpose of a screening test is to be as sensitive as possible and let the diagnostic test be specific.

Most sonographers are well experienced with the axial anatomy of the posterior fossa due to extensive training and experience in the second-trimester targeted anatomy scan. Familiarity with the landmarks of the posterior fossa anatomy in the first-trimester midsagittal views is only recently being established. In the current study, the first-trimester protocol evolved from a restricted anatomical survey in the initial years (between 2010 through 2011) to an extended survey beginning from 2012. The midsagittal section of the fetal head was part of both protocols. However, we did not seek to study the impact of the familiarity of the posterior fossa landmarks on the outcomes, as the number of cases would be reduced. The third line in the 'four line' rule of the first trimester posterior fossa is the tela choroidea of the fourth ventricle, which in contrast to the other fixed landmarks, may be mobile. At present, this aspect has not yet been investigated and further research in this line might throw some light on the explanation for the false negative cases in the screening of ONTD as well as other malformations of the posterior fossa using first trimester landmarks.

In conclusion, lack of clear demarcation of the posterior fossa landmarks in the sagittal section should be used as a red flag for a careful assessment or expert examination of the posterior fossa in the second-trimester assessment. Further insights into the variation of the posterior fossa appearance with embryological and pathological correlation would improve the screening process.

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Compliance with Ethical Standards

Conflict of interest None.

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