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Enlarged Intracranial Translucency, as a Potential Marker for Diagnosis of Joubert Syndrome during First-Trimester Screening: A Case Report

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Abstract

Joubert syndrome (JS) is a rare autosomal recessive neurodevelopmental disorder that is usually diagnosed late in pregnancy or postnatally based on a pathognomonic midbrain–hindbrain malformation seen on magnetic resonance imaging brain, which consists of the hypoplasia of the cerebellar vermis, thickened superior cerebellar peduncles, and a deepened interpeduncular fossa described as molar tooth sign. The recurrence rate of JS in the same family is high (25%). In the era of first-trimester anomaly scan, early diagnosis of fetal anomaly is of utmost importance. First-trimester screening or first-trimester scan that is performed from 11 to 13 weeks, 6 days plays an important role in early diagnosis of posterior fossa abnormalities like Blake's pouch cyst, Vermian hypoplasia, Dandy-Walker malformation, and JS and related disorders based on increased intracranial translucency thickness. Our case also shows that early diagnosis of JS can be done by an enlarged intracranial translucency.

Keywords
- enlarged intracranial translucency
- fetal anomaly
- first-trimester screening
- intracranial translucency
- Joubert syndrome

Introduction

Joubert syndrome (JS) is a rare, typically autosomal recessive ciliopathy. Till date, pathogenic variants in 34 genes are known to cause JS, out of which 33 are inherited as autosomal recessive and one as X-linked. Except for X-linked inheritance, the high recurrence rate in the same family is approximately 25%. The most characteristic brain image of JS is the molar tooth sign (MTS) in the axial plane, which reflects thickened superior cerebellar peduncles, cerebellar vermis hypoplasia, a deepened interpeduncular fossa first described by Maria et al.[1] In recent years, it has been reported that JS is part of a spectrum of diseases characterized by the MTS with overlapping features and standing for distinct syndromes. Finally, the term Joubert syndrome and related disorders (JSRD) has been defined as all disorders showing the MTS on brain imaging studies. According to the different organs involved, Brancati et al[2] divided JSRD into six clinical subtypes, including pure JS, JS with ocular defects, JS with renal defects, JS with oculorenal defects, JS with hepatic defects, and JS with orofacial digital defects. Each subtype of JS

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is associated with various genotypes and one special gene mutation can cause various subtypes. Classical Jourbert's manifests with intermittent dyspnea, developmental delay, ataxia, muscle tone loss, oculomotor apraxia, and other abnormalities of the nervous system, but not retinal, renal, liver, or other organ disorders in a new born. Prenatal diagnosis is rare. Molecular genetics research contributes to disease prediction and genetic counseling. Chaoui et al introduced intracranial translucency (IT) as an open spina bifida marker in first-trimester scan.[3,4] IT represents the future fourth ventricle and its obliteration or reduction of its thickness is present in fetuses affected by open spina bifida. Other recent publications confirm this observation. Recently Chaoui et al[5] reported enlarged IT in a fetus with Blake's pouch cyst (BPC). Garcia-Posada et al[6] reported two cases of BPC, and they described the cisterna magna that was enlarged. Numerous studies highlight the alteration of IT in various posterior fossa pathologies. Nizard et al[7] reported four cases of fetuses with Dandy-Walker syndrome, with posterior fossa changes starting from first trimester and demonstrating enlarged IT. Early diagnosis of JSRD has been described previously for which the diagnosis was suspected only from an abnormal fetal posterior fossa in pregnancies at high risk of JSRD recurrence. In such cases, the abnormality of the posterior fossa was described as cystic, without detailed anatomical elaboration. Quarello et al[8,9] also reported a case of JSRD with high recurrence rate (25%) based on enlarged IT and MTS in the first trimester as features of JSRD. Our case also adds to the growing list of posterior fossa abnormalities (encephalocele, Dandy-Walker malformation, vermian hypoplasia, BPC) which can be diagnosed early in pregnancy during first-trimester screening (FTS) by the assessment of IT.

Case Report

A 24-year-old woman, gravida 2 para 1 living issue 1, presented with a history of homozygous mutation in *INPP5E* gene in previous child for first-trimester ultrasound at gaestational age (GA) of 10 weeks, 3 days by her last menstrual period (LMP). On ultrasound examination crown rump length (CRL) was 39.7 mm (corresponding to GA of 10 weeks 3, days (►**Fig. 1A**). The uterine artery mean pulsatility index (1.355) was normal. Both parents are carriers for mutation in the *INPP5E* gene, which is responsible for JS recurrence rate of JS in our case is 25%. FTS was done at a GA of 13 weeks, 2 days by her LMP. On FTS, CRL was 71.7 mm (►**Fig. 1B**) corresponding to 13 weeks, 3 days. Fetal aneuploidy screening was normal (►**Fig. 2A–D**). Fetal anatomy showed head, neck, spine, face, thorax, heart, abdomen, KUB, and extremities as normal condition. Midsagitta view showed normal nuchal translucency thickness and an increased IT = 4 mm (►**Fig. 3A, B**). Normal maxillary triangle showed two nasal and a normal mandible (►**Fig. 4**). On the basis of enlarged IT = 4 mm (►**Fig. 5**) and presence of homozygous mutation for JS in previous child high possibility of JS in current pregnancy was suspected. Chorionic villus sampling was done. This showed a homozygous variation in exon 2 of the *INPP5E* gene by Sanger sequencing. This variation is responsible for JS; hence, fetus is affected with the JS. The couple opted for termination of pregnancy.

Discussion

We report a case of JS diagnosed prenatally during FTS on the basis of an enlarged IT. Our case indicated that enlarged IT during FTS is a reliable marker for diagnosis of JS especially in cases with high recurrence rate. In normal fetuses, the three spaces are usually recognized on the transaxial plane of fetal head that includes (from anterior to posterior) the brain stem (BS), the developing fourth ventricle, that is, IT, and the future cisterna magna (►**Fig. 6**). These three spaces are divided by four echogenic lines. The IT is marked anteriorly by the echogenic posterior wall of

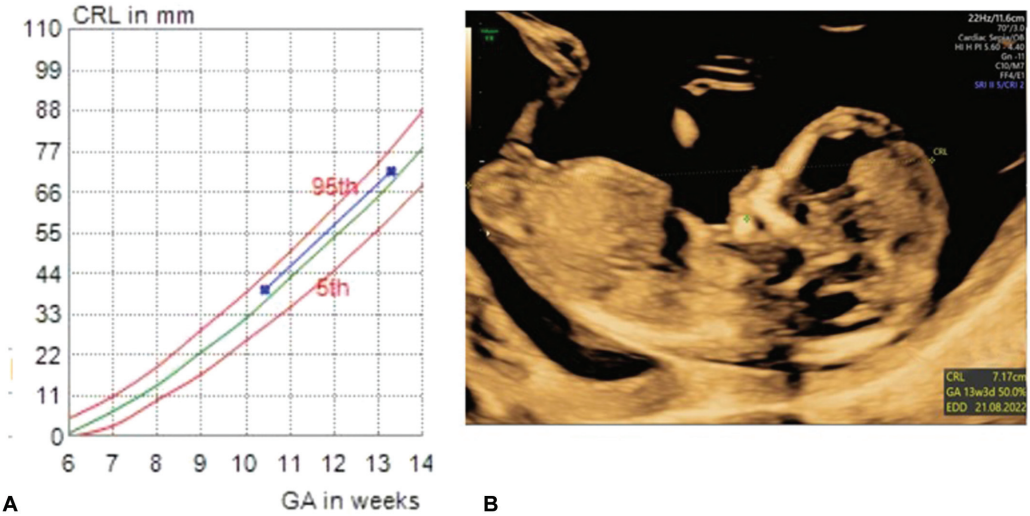

Fig. 1 (**A**) Linear growth of crown rump length (CRL) from 39.3 mm (10 weeks, 3 days) to 71.7 mm (13 weeks, 3 days). (**B**) Showing CRL = 71.7 mm (13 weeks, 3 days corresponding to gestational age (GA) by last menstrual period).

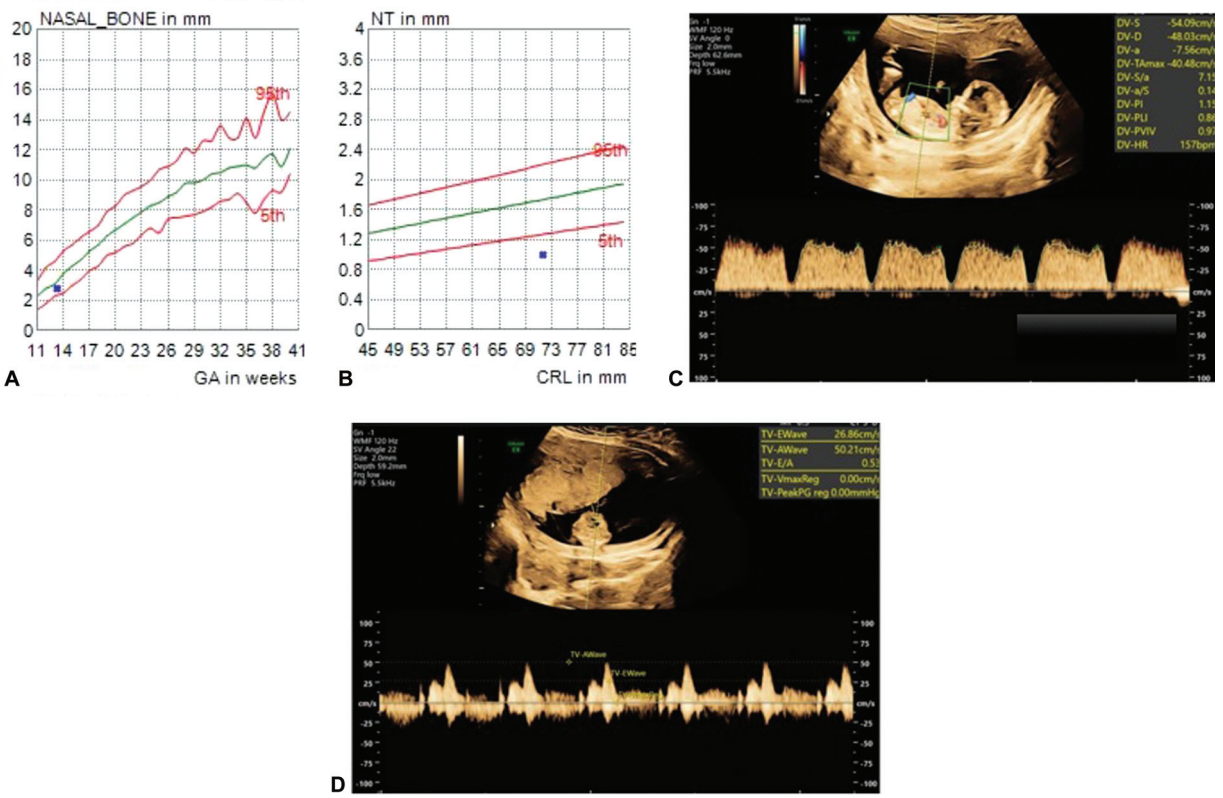

Fig. 2 (**A**) Nasal bone length = 2.8 mm seen (26%). (**B**) nucal translecency = 1 mm (1%). (**C**) Ductus venosus showing normal flow. (**D**) Tricuspid valve doppler wave form normal.

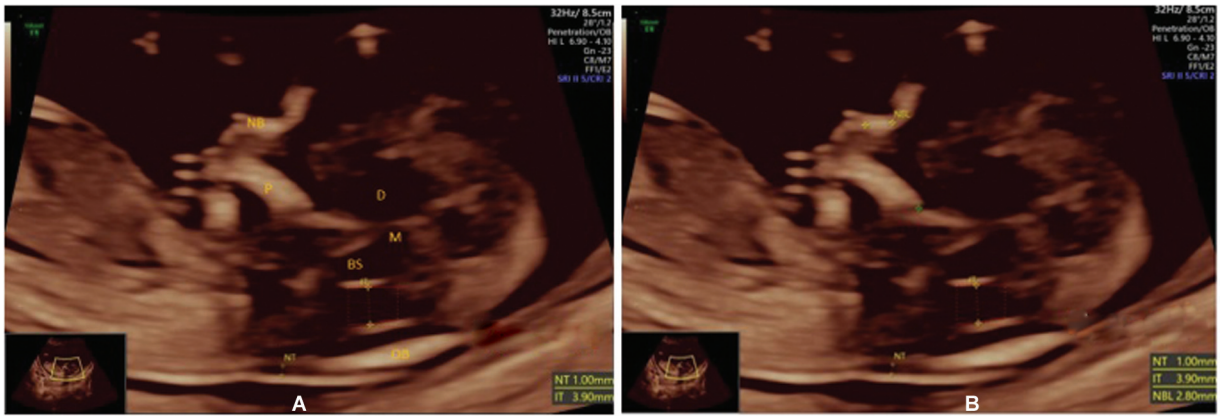

Fig. 3 (**A**, **B**) = Mid saggital view showing enlarged intracranial translucency (IT) = 3.90 mm, nuchal translucency (NT) = 1.00 mm, nasal bone length (NB) = 2.8 mm, palate (P), diencephalon (**D**), midbrain (M), brainstem (BS), occipital bone (OB). IT is lined anteriorly by echogenic posterior border of brain stem and posteriorly by choroid plexus of 4th ventricle.

the BS and posteriorly by the choroid plexus of the fourth ventricle. In normal fetuses, the IT thickness increased from 1.5 mm at a CRL of 45 mm to 2.5 mm at CRL of 84 mm.[4] FTS is usually done to assess the risk of aneuploidy based on nuchal translucency thickness and nasal bone length. Measurement of these three spaces is usually taken during FTS. The measurement of these spaces remains within the range for a particular GA; any enlargement in the IT indicates posterior fossa abnormalities (Dandy-Walker malformation, BPC, vermis hypoplasia, JS) and reduction indicates open spina bifida.[10] Enlarged IT with decreased brain stem/brain stem to occipital bone (BS/BSOB) ratio is seen in cystic malformation of the posterior fossa like in Dandy-Walker malformation, BPC, and vermis hypoplasia.[6,7] Obliterated IT with increased BS/BSOB ratio is seen in usually seen in open spina bifida.[4,5] In our case, enlarged IT was associated with

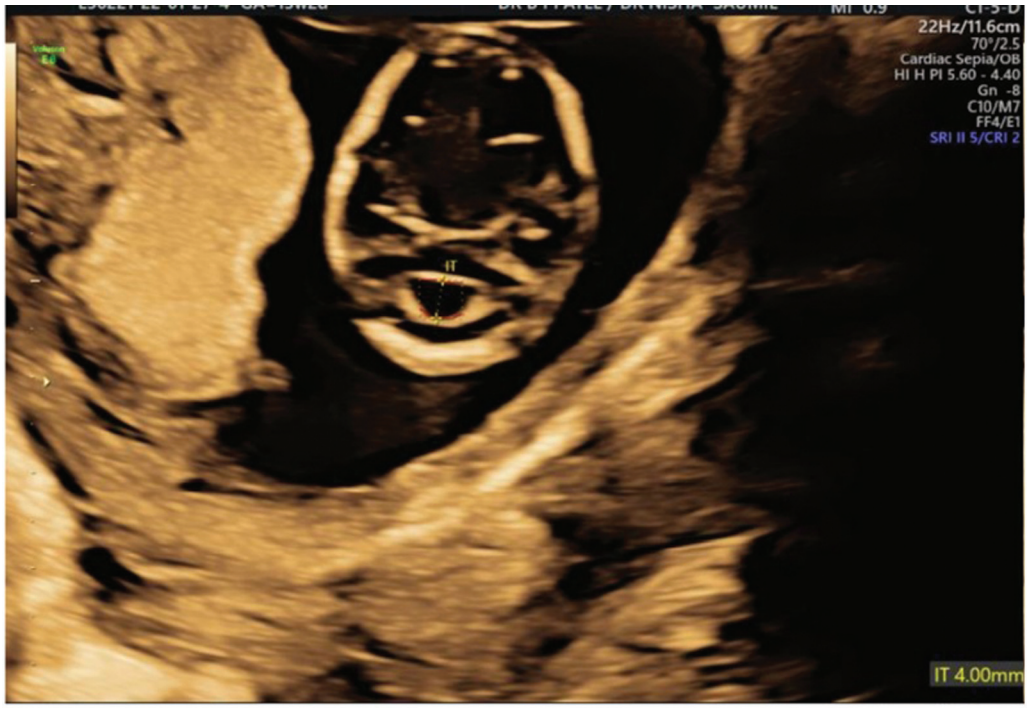

Fig. 4 Maxillary triangle, two nasal bones and two mandibular bones.

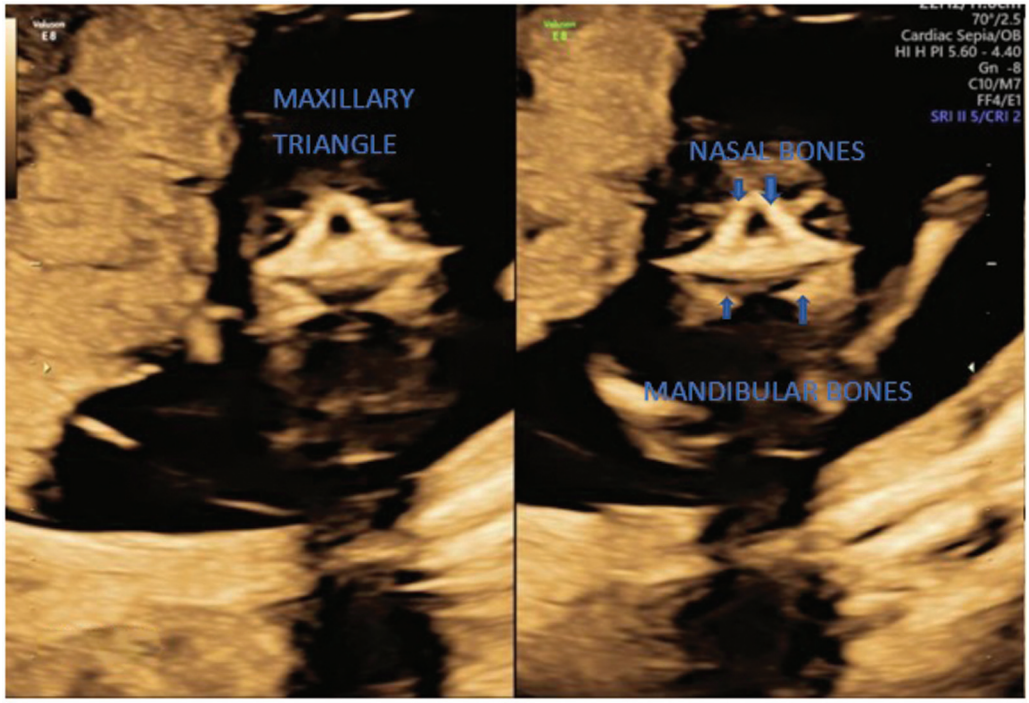

Fig. 5 Transaxial view of fetal head showing enlarged intracranial translucency (IT) = 4 mm,with clearly visible four echogenic lines and three spaces. IT is lined anteriorly by echogenic posterior border of brain stem and posteriorly by choroid plexux of fourth ventricle.

normal BS/BSOB ratio and the three spaces were clearly visible (►**Figs. 7** and **8**). In cystic malformations of the posterior fossa there is a usually enlargement of the cisterna magna and usually two spaces are seen instead of three spaces[6,7] and in open spina bifida IT is usually obliterated: two spaces are visible, that is, enlarged BS and cisterna magna.[4,5] Literature shows that an IT more than 2.5 mm should always be assessed for posterior fossa abnormalities

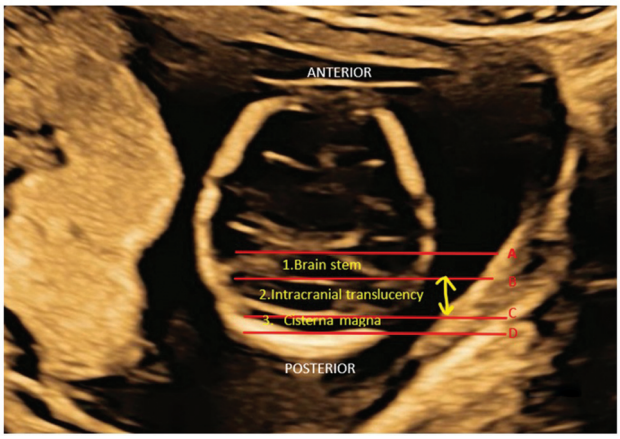

Fig. 6 Transaxial view of fetal head showing three spaces of brain stem, intracranial translucency and future cisterna magna (from anterior to posterior) divided by four (**A**, **B**, **C**, and **D**) echogenic lines.

and the BS/BSOB ratio helps in differentiating JS from other cystic malformations of the posterior fossa. Previously diagnosis of JS was usually made in the second trimester (►**Fig. 9A, B**).

Conclusion

An enlarged IT during FTS ultrasound is associated with JS. This can be evaluated in the mid-sagittal view which is routinely performed for first-trimester aneuploidy screening. Early diagnosis of JS is of great value as JS has poor postnatal outcome. Early diagnosis allows the option of termination of pregnancy in the first trimester.

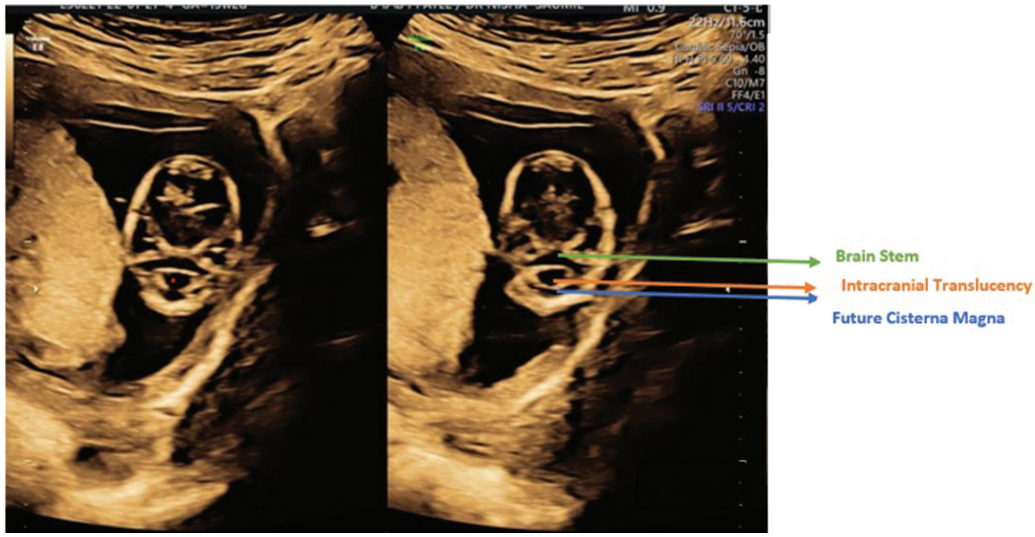

Fig. 7 Transaxial view of fetal head showing enlarged intracranial translucency (IT).

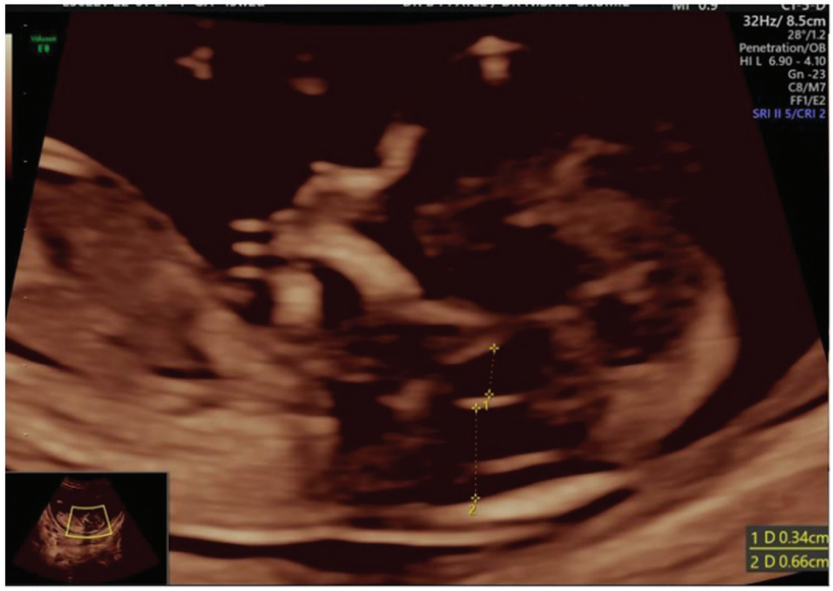

Fig. 8 Mid saggital view showing brain stem (BS) diameter = 0.34 cm, brain stem to occipital bone (BSOB) diameter = 0.66 cm, BS/BSOB ratio= 0.51(<1) normal. In open spina bifida BS/BSOB ratio is >1 as brain stem diameter is increased and BSOB is decreased.

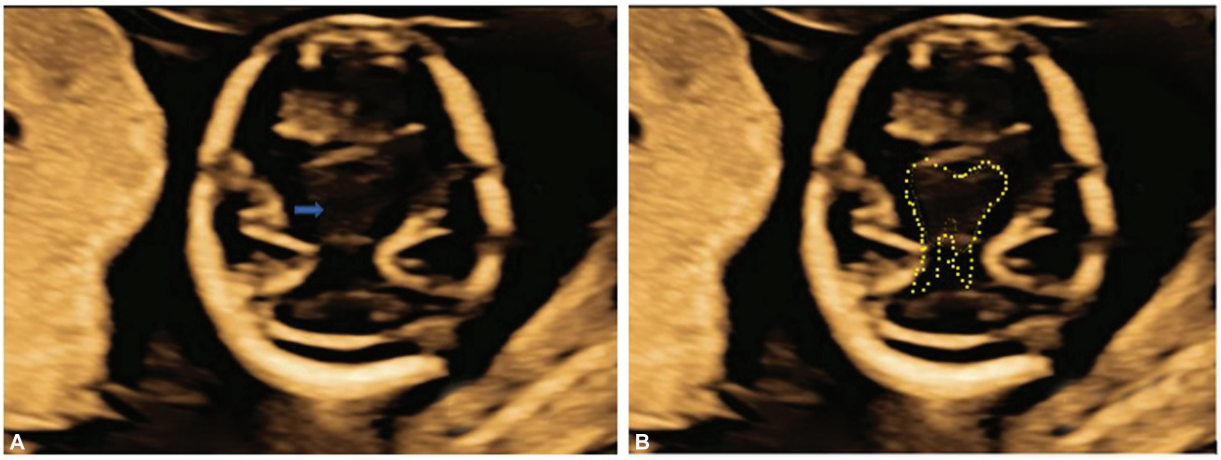

Fig. 9 (**A**) Blue arrow indicates the site of appearance of MTS. (**B**) Dotted line indicates MTS. MTS, molar tooth sign.

Competing Interest

Authors are required to disclose financial or nonfinancial interests that are directly or indirectly related to the work submitted for publication

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