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Acrania-exencephaly-anencephaly sequence phenotypic characterization using two- and three-dimensional ultrasound between 11 and 13 weeks and 6 days of gestation

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Abstract

The study presents a pictorial essay of acrania-exencephaly-anencephaly sequence using two- (2D) and three-dimensional (3D) ultrasonography, documenting the different phenotypic characterization of this rare disease. Normal and abnormal fetuses were evaluated during the first trimester scan. The International Society of Ultrasound in Obstetrics and Gynecology practice guidelines were adopted to standardize first trimester anatomical ultrasound screening. The guidelines outline the importance of systematic fetal head and brain examination including the formation of cranial bones, choroid-plexus and ventricles. Acrania-exencephaly-anencephaly sequence and/or other neural tube defects, such as meningoencephalocele, may be identified during a routine 11–14 week scan. Early first trimester detection of acrania-exencephaly-anencephaly sequence with the characterization of different related phenotypes, 2D and 3D ultrasound imaging as well as differential diagnosis are also presented in this pictorial essay. The main diagnostic ultrasound features of the disease may be characterized by findings of acrania with increased amniotic fluid echogenicity; “Mickey-Mouse” bi-lobular face, cystic, elongated, irregular and overhanging head morphology. Lightening techniques have also been added to 3D ultrasound to enhance anatomical details. Moreover, discordant amniotic fluid echotexture in the setting of twin pregnancies may be the first sign of acrania-exencephaly-anencephaly sequence. Extracranial malformations, aneuploidy and genetic syndromes associated with acrania-exencephaly-anencephaly sequence are also reported and described. First trimester neuroscan by an expert sonographer with appropriate training together with the application of standardized protocol are essential for a high detection rate of this rare type of neural tube defect malformation during a scan performed at 11 and 13 weeks and 6 days.

Introduction

First trimester scan, which is routinely performed between 11 and 13 weeks and 6 days gestation, is a well-established study for routine aneuploidy screening, but it also facilitates anatomical assessment allowing early diagnosis of structural anomalies⁽¹⁾. ISUOG (International Society of Ultrasound in Obstetrics and Gynecology) practice guidelines for first trimester scan require identification of the fetal head, appropriate development of cranial bones, and identification of choroid-plexus and cerebral ventricles⁽²⁾. Cranial ossification should be visible from the 11th week onwards.

Acrania-exencephaly-anecephaly sequence is a rare malformation with an estimated incidence ranging between 3.68 to 5.4 for 10,000 live births⁽³⁾. A Danish group⁽³⁾ dem-

onstrated that two-dimensional (2D) ultrasound detection rate of acrania-exencephaly-anecephaly sequence improves with training and when performed by a maternal-fetal medicine (MFM) operators, it ranges from 69% to 86% (mean detection rate of 58.5% during basic scan) with many undiagnosed cases when gestational age is less than 11 weeks⁽³⁾. In contrast, higher detection rates (100%) were achieved by another research group⁽⁴⁾.

The introduction of the transvaginal approach has enabled detection of acrania-exencephaly-anecephaly sequence at an early stage of fetal development, with the earliest diagnosis at 9 weeks and 3 days and 10 weeks onwards^(5–10). In addition, an increased echogenicity of the amniotic fluid at 11–14 weeks by 2D ultrasound is a useful sonographic marker of cases of acrania-anecephaly sequence that may be seen in 89% of cases⁽¹¹⁾.



Fig. 1. Acrania detected by 3D ultrasound at 8 weeks and 6 days of gestation using multiplanar mode (A) and HDlive™ rendering mode: note the increased echogenicity of the amniotic fluid (B)



Fig. 2. 2D transabdominal ultrasound performed at 11 weeks and 3 days. A "Mickey-Mouse" bi-lobular face" appearance is clearly evident



Fig. 3. 2D transvaginal ultrasound showing "cystic" acrania at 10 weeks and 5 days of gestation

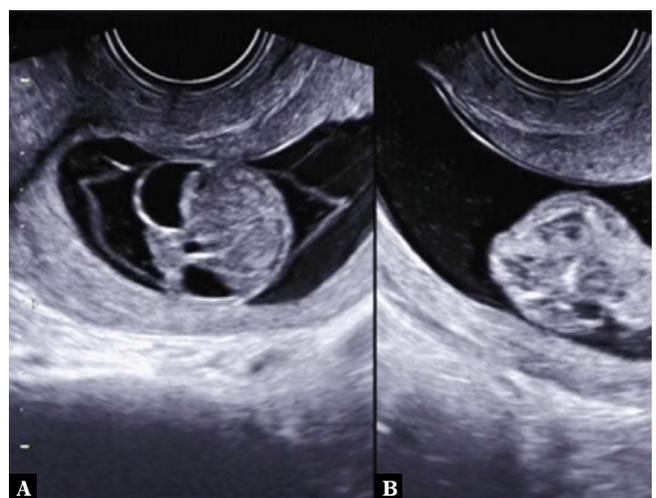


Fig. 4. A variant of cystic acrania (A) phenotype with associated exomphalos (B) detected at 10 weeks and 2 days of gestation



Fig. 5. Fore shortened phenotype of acrania diagnosed at 11 weeks and 1 day of gestation by 3D ultrasound with HDlive™ rendering mode



Fig. 6. Elongated phenotype of acrania by 2D ultrasound at 11 weeks and 1 day of gestation

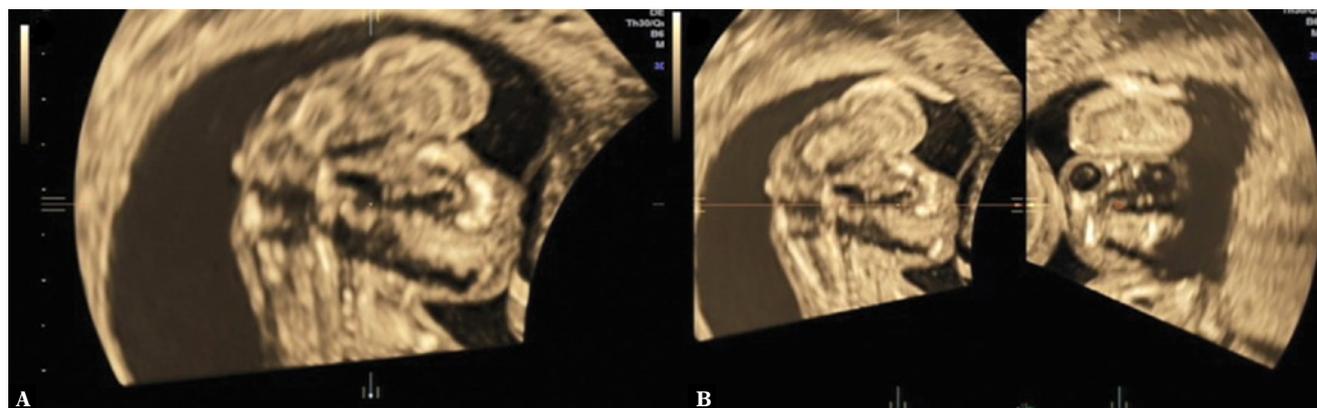


Fig. 7. 3D ultrasound in multiplanar mode in sagittal (A, detail) and sagittal and coronal planes (B): the “overhanging” phenotype is well depicted

The aim of this pictorial essay is to show the different phenotypic appearance at 2D- and 3D-ultrasound in fetuses with acrania-exencephaly-anecephaly sequence diagnosed at first trimester scan.

Materials and methods

Voluson E8/E10 (GE Medical Systems, Milwaukee, WI) ultrasound systems equipped with real-time high frequency 4–8.5 MHz transabdominal/transvaginal 2D and 3D/4D volumetric probes (RIC 5–9W and RAB 4–8L) were used. For the purpose of standardization, ultrasound was performed according to the ISUOG guidelines for first trimester scan. In some cases, acrania was detected at an early stage (8 weeks); in these instances, transvaginal approach was employed. Two and three-dimensional volume datasets were digitally acquired during fetal rest period and analyzed in the ultrasound system during the examination. The embryos and fetuses were insonated preferentially in the coronal and sagittal plane with a sweep time of 8–15 s for volume acquisition. Multiplanar mode with surface



Fig. 8. Discordant amniotic fluid echotexture in the setting of monozygotic diamniotic twin pregnancy may be the first sign of acrania-exencephaly-anecephaly sequence

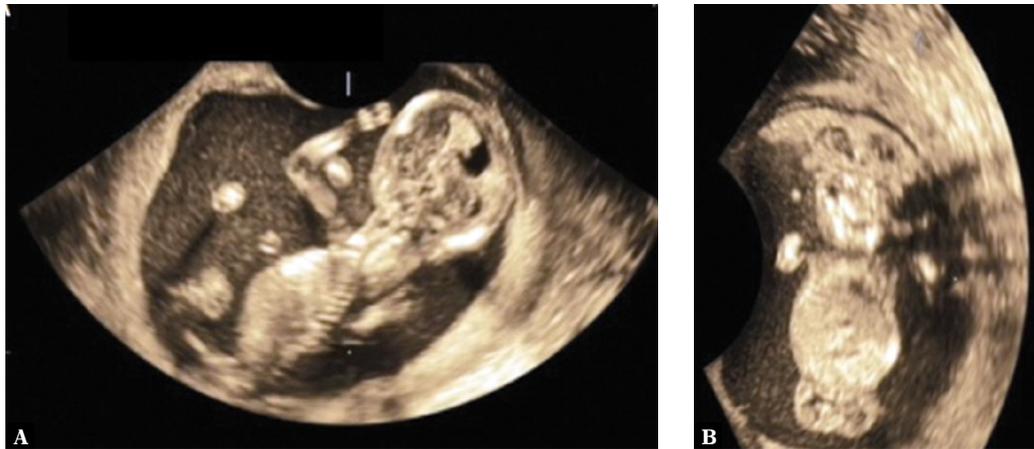


Fig. 9. 3D ultrasound volume contrast imaging (VCI) enhancement in sagittal (A) and coronal (B) plane in monochorionic-monoamniotic (MCMA) twin pregnancy: note the increased echogenicity of the amniotic fluid

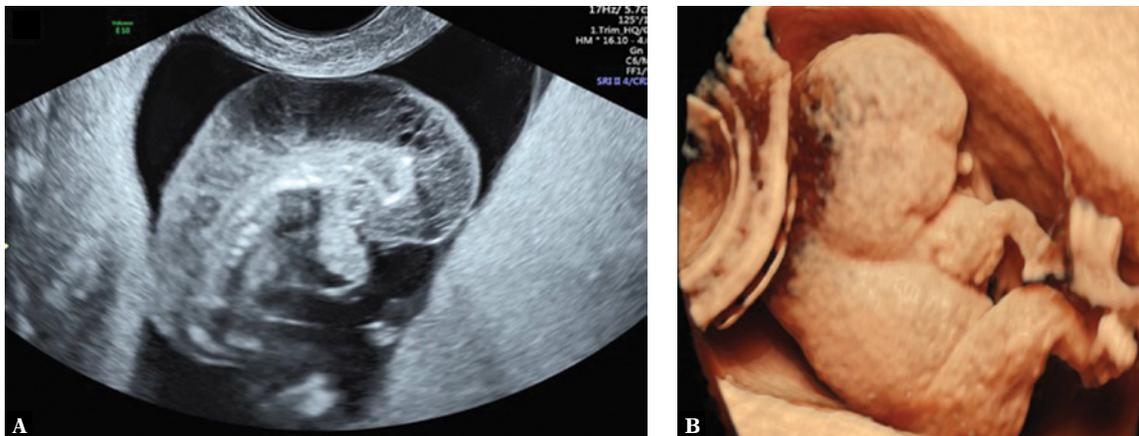


Fig. 10. 2D transvaginal ultrasound: TRAP (twin reversed arterial perfusion) sequence in a co-twin is documented in a monochorionic/monoamniotic (MCMA) twin pregnancy (A). 3D ultrasound in HDlive™ rendering mode (B)

rendering was used as standard 3D ultrasound visualization. Lightening technique (HDlive™) was also applied to enhance image rendering. Written informed consent signed by each participant was obtained during exams at the Monash Ultrasound for Women, Clayton, Victoria, Australia.

Results

Two-dimensional ultrasound was routinely used for normal and pathological cases. In the latter ones, 3D ultrasound was applied as a complementary diagnostic tool. An ultrasound perspective of different phenotypic appearance of acrania-exencephaly-anencephaly sequences is described (acrania with increased amniotic fluid echogenicity; “Mickey-Mouse” bi-lobular face, cystic, elongated, and irregular head shape) and shown in Fig. 1, Fig. 2, Fig. 3, Fig. 4, Fig. 5, Fig. 6, Fig. 7.

Notwithstanding, discordant amniotic fluid echotexture in the setting of twin pregnancies may be the first sign of acrania-exencephaly-anencephaly sequence (Fig. 8, Fig. 9). Furthermore, a very rare malformation was observed at

13 weeks and 6 days, when acrania-exencephaly was seen in both monochorionic/monoamniotic (MCMA) twins. In this case, TRAP (twin reversed arterial perfusion) sequence was the underlying cause of acrania and acardia in the co-twin (Fig. 10). Finally, acrania-exencephaly-anencephaly sequence may be present in only one fetus of dichorionic twin pregnancies (Fig. 11).

Exencephaly can be greatly visualized by using 3D ultrasound especially at an early stage of embryonic development (8 weeks and 2 days) or to document associated facial dysmorphism such as low set ears at later stage (Fig. 12). This defect can be clearly displayed at necropsy (Fig. 13).

Although it may be challenging, precise antenatal differentiation between acrania-exencephaly-anencephaly sequence and other types of NTDs such as meningo-encephalocele is fundamental for appropriate genetic counseling and pregnancy management (Fig. 14). The additional use of 3D ultrasound enables patients to better understand brain malformations, which is of value in certain situations when a patient is doubtful about the diagnosis, particularly if folate prophylaxis was implemented.

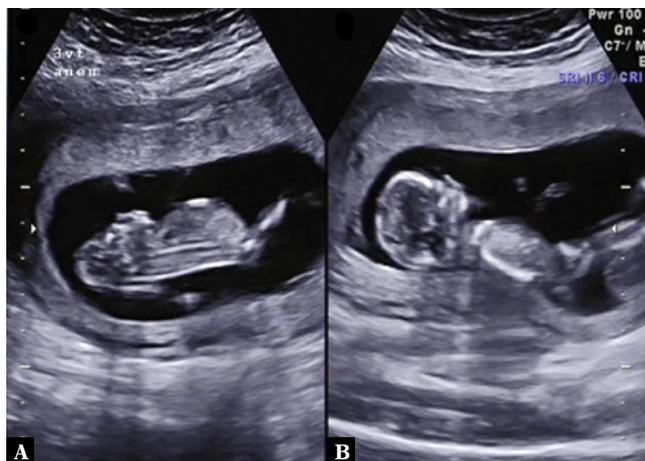


Fig. 11. Dichorionic diamniotic (DCDA) twin pregnancies showing one fetus with acrania-exencephaly-anencephaly sequence (A, B)

Another differential diagnosis which may be considered is craniopagus parasiticus (Fig. 15), an extremely rare form of conjoined twins which occurs in approximately 5 per 10 million births and presents with a parasitic head attached to the normal head in the developed twin.

Discussion

First trimester scan is a well-established examination during routine obstetric practice. The examination has the potential to identify embryo-fetal defects in pregnant women who are at increased risk of congenital anomalies.

The use of a standardized protocol in the ultrasonographic assessment of the embryo-fetal anatomy is fundamental for the early prenatal diagnosis of fetal abnormalities. If

the ultrasound examination is performed by a maternal-fetal medicine operator using high frequency real-time 2D/3D ultrasound equipment, the sensitivity of the detection of major congenital anomalies overall can be assessed to be around 60% in high-risk pregnancy populations, while a detection rate of nearly 100% can be reported for acrania⁽¹⁾.

Combining abdominal and transvaginal ultrasonography can be extremely helpful in improving the diagnostic accuracy. In the case of a retroverted uterus, elevated body mass index, and myomata, the transvaginal approach is beneficial in most cases. Limitation in the movements of the transvaginal probe and patient's acceptance are conditions which may limit the value of transvaginal ultrasonography^(12,13).

Acrania represents the first stage of this maldevelopment sequence that takes place 18–20 days post-fertilization⁽¹⁴⁾ and the progression from exencephaly to anencephaly was first described by Wilkings *et al.*⁽¹⁵⁾. When acrania is seen at an early stage, disorganized brain tissue (vasculo-membranous area) is detectable above the orbits, a process called exencephaly⁽¹⁶⁾. Anencephaly evolves as a result of failed closure of the midbrain and forebrain, but with normal fusion at the level of the hindbrain and the cervical cord region⁽¹⁷⁾. It has been demonstrated that about 12–25% of these cases have other associated structural anomalies, with 1–5% being aneuploidy^(3,18,19).

Tonni *et al.*⁽²⁰⁾ reported early 3D ultrasound diagnosis of acrania/exencephaly sequence in a fetus with a diagnosis of tetraploidy by coelocentesis. These authors concluded that 3D ultrasound using the transvaginal approach aided early prenatal diagnosis of acrania/exencephaly sequence and was useful in excluding different disorders, such as iniencephaly and/or alobar holoprosencephaly⁽²⁰⁾. Three-dimen-

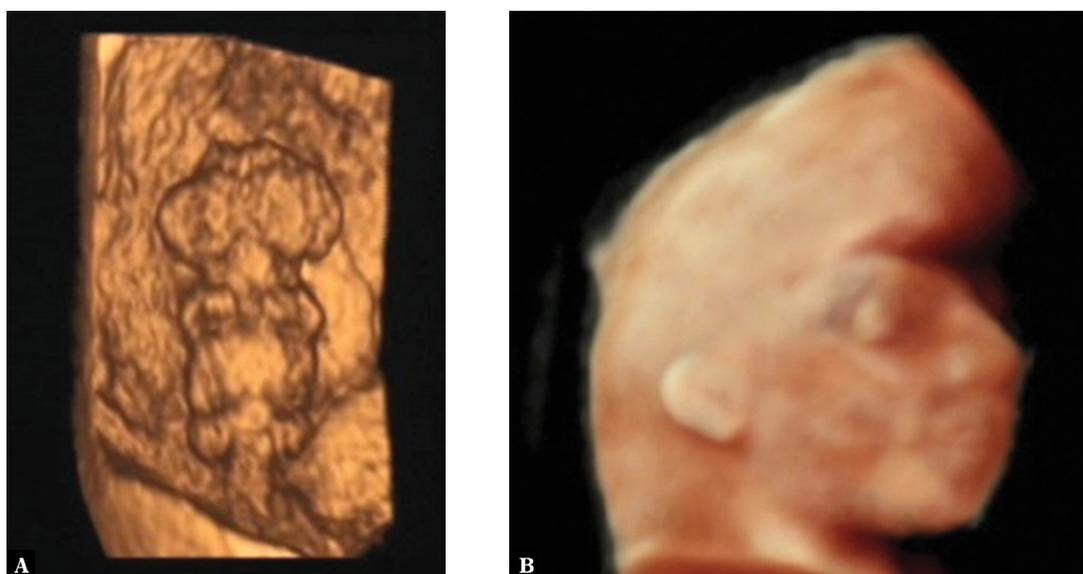


Fig. 12. Exencephaly can be visualized by using 3D ultrasound in the rendering mode, especially at an early stage of embryonic development (A, 8 weeks and 2 days of gestation) or to demonstrate associated facial dysmorphism, such as low set ears at a later stage (B, 13 weeks of gestation)



Fig. 13. Exencephaly: note the developing brain located completely outside the fetal skull



Fig. 14. Encephalocele (arrow) is another type of neural tube defect (NTD) that may be differentiated from acrania-exencephaly-anecephaly sequence



Fig. 15. Case of acrania in craniopagus parasiticus conjoined twins: 2D ultrasound (A) and 3D ultrasound (B) with HDlive™ rendering mode are reported at 9 weeks and 3 days of gestation

sional ultrasound, especially during the first trimester scan and the use of the transvaginal approach to display the coronal or sagittal planes may be particularly useful in this regard. It is known for instance that the coronal plane may be difficult to achieve using conventional 2D ultrasound⁽²¹⁻²⁴⁾.

A training program for the detection and definition of the diverse types of NTDs as well as precise knowledge of embryologic development according to the Carnegie Classification⁽²⁵⁾ are important in understanding the pathogenesis and achieving accurate diagnoses in clinical practice^(26,27).

The diagnosis of the acrania-exencephaly-anecephaly sequence is particularly difficult at lower gestational ages, and many cases still remain undetected at this stage of pregnancy^(4,28).

Conflict of interest

Authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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