Anomalies of Ventral Induction: Holoprosencephaly

3

The prosencephalon (progenitor of the forebrain) is the most rostral of the three embryonic brain vesicles. It develops into the telencephalon (cerebral hemispheres and lateral ventricles) and the diencephalon (thalami and third ventricle). The prosencephalon cleaves (5–6 weeks gestational age) into right and left halves resulting in the two cerebral hemispheres and sets of basal ganglia on either side of the midline.

Failure of formation of prosencephalic vesicle and hence the prosencephalon is termed aprosencephaly. Failure of formation of telencephalon (cerebral hemispheres) with the presence of diencephalon (thalami) is termed atelencephaly. These are very rare disorders. Defective ventral induction results in total or subtotal failure of cleavage resulting in totally or partially uncleaved forebrain. This spectrum of disorders is termed holoprosencephaly (HPE).

Following is the DeMyer classification of HPE based on the severity (Fig. 3.1):

1. Alobar: This is the most severe form of HPE. Complete failure of cleavage of the prosencephalon results in absence of midline structures. The cerebrum is uncleaved and has a single ventricle called the primitive monoventricle. As there are no right and left hemispheres, the interhemispheric fissure and corpus callosum are absent. Failure of diencephalic cleavage leaves the thalamus without an interthalamic fissure (third ventricle). The tela choroidea of the roof of the primitive monoventricle may balloon out with CSF to form a dorsal sac or cyst. Depending on the shape of the cerebral mantle, three morphological types, namely, pancake, cup and ball forms,

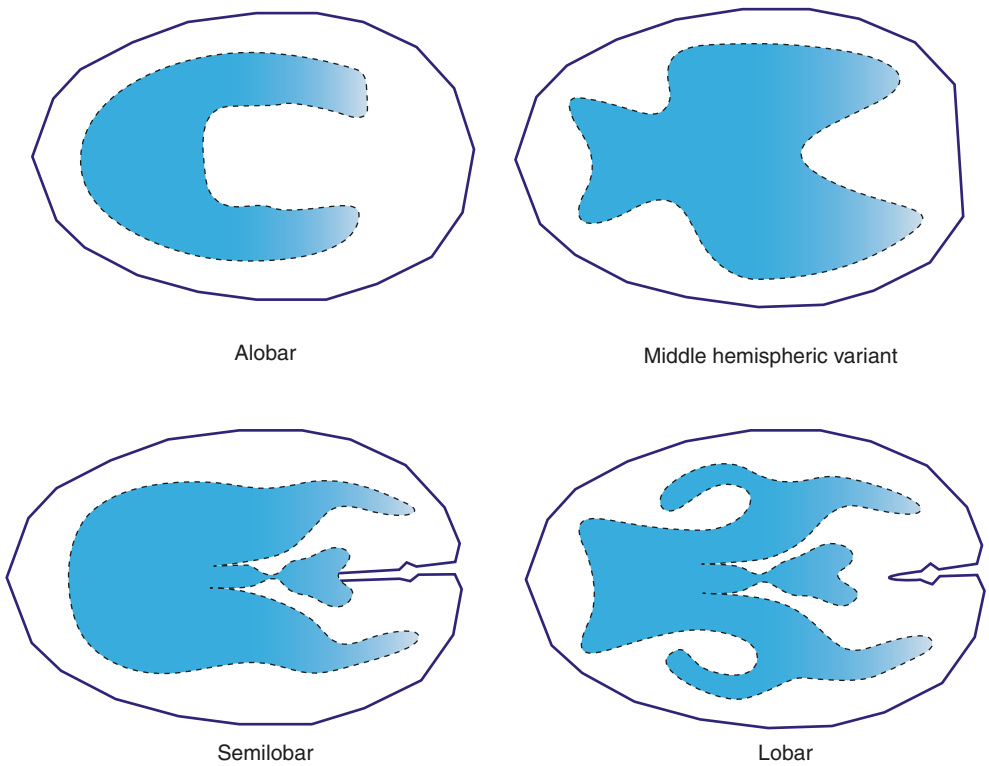


Fig. 3.1 Schematic diagram of the types of holoprosencephaly

B. S. Rama Murthy, *Imaging of Fetal Brain and Spine*, https://doi.org/10.1007/978-981-13-5844-9_3

have been described. The dorsal sac is present only in the pancake and cup forms. In the ball type the uncleaved cerebrum completely encloses the primitive monoventricle, and there is no dorsal sac. The cortical sulcation and operculation are often defective in alobar HPE.

2. Semilobar: Cleavage of the prosencephalon occurs only in the occipital region. The parietal and frontal regions of the cerebrum are uncleaved. Correspondingly, only the posterior horns of the lateral ventricles are cleaved. The bodies and the anterior horns are uncleaved and hence are continuous with each other across the midline. The IHF is present between the occipital lobes.
3. Lobar: The occipital and parietal lobes with the posterior horns and bodies of the lateral ventricles have cleaved. The frontal region (with the anterior horns) is not cleaved. The IHF is present between the occipital and parietal lobes but is absent anteriorly. The rostrum, genu and anterior body of the CC are deficient.
4. Middle hemispheric variant (syntelencephaly): In this type, cleavage occurs in the frontal and occipital regions. The parietal region alone is uncleaved. Correspondingly, the body of the lateral ventricle is uncleaved, and the anterior and posterior horns are cleaved (Fig. 3.1).

It should be noted that the word 'fused' has not been used to denote the lateral ventricular or thalamic status. The word 'fused' implies a previously cleaved state with 'fusion' occurring later on. In HPE, cleavage has not occurred to begin with and hence 'fusion' is not possible.

Midline facial defects are embryologically related to holoprosencephaly (polytopic field defect). They include cyclopia, hypotelorism, proboscis (ethmocephaly or cebocephaly), absent nose (arrhinia) and median cleft lip and palate.

3.1 Ultrasound Findings of HPE

Absent cavum septum pellucidum and abnormal anterior complex are the first clue to the presence of abnormality.

3.1.1 Alobar Holoprosencephaly

1. The CSP and CC are not seen (Figs. 3.2a, b, 3.3, 3.4 and 3.5).
2. The anterior complex is not seen. The IHF is completely absent.

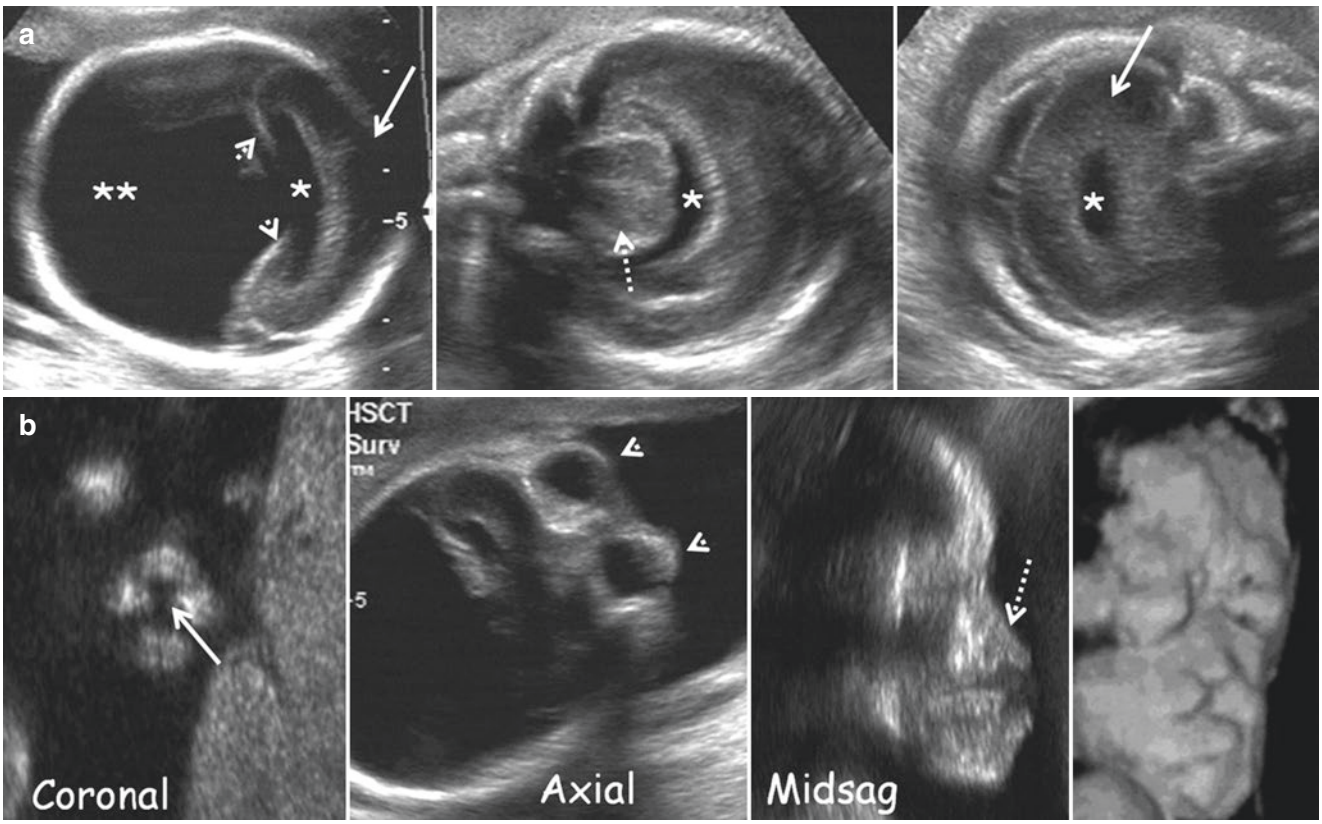


Fig. 3.2 (**a**) 25 weeks (TAS) *alobar holoprosencephaly* – axial, coronal transthalamic and transfrontal sections – absent interhemispheric fissure (IHF) and cavum septum pellucidum (CSP), primitive uncleaved ventricle (*), dorsal cyst (**), hippocampal ridges (arrowheads), cup-shaped cortical configuration with no sulcation (solid arrow), uncleaved thalamus (dotted arrow). (**b**) 25 weeks (TAS, 3D US) *alobar holoprosencephaly – facial findings*. Coronal section of face, axial section of orbits, midsagittal section of face, 3D surface rendering of fetal face – median cleft lip (solid arrow), protuberant eyes and hypotelorism (arrowheads), absent nose with flat facial profile (dotted arrow), 3D surface rendering of the face displaying all the findings in B mode images

3. A single primitive ventricle is seen and is often dilated.
4. Generalised paucity of the cerebral mantle is noted.
5. Dorsal cyst or sac is seen in the cup and pancake types and strongly correlates with an uncleaved thalamus.
6. Uncleaved thalamus is seen projecting into primitive monoventricle.
7. Third ventricle is absent.
8. The cranial size can be normal, small or large for gestational age.
9. The sulcation and operculation are abnormal.
10. Single or azygous anterior cerebral artery is seen.
11. The circle of Willis is abnormal.
12. Associated Dandy-Walker malformation may be seen.

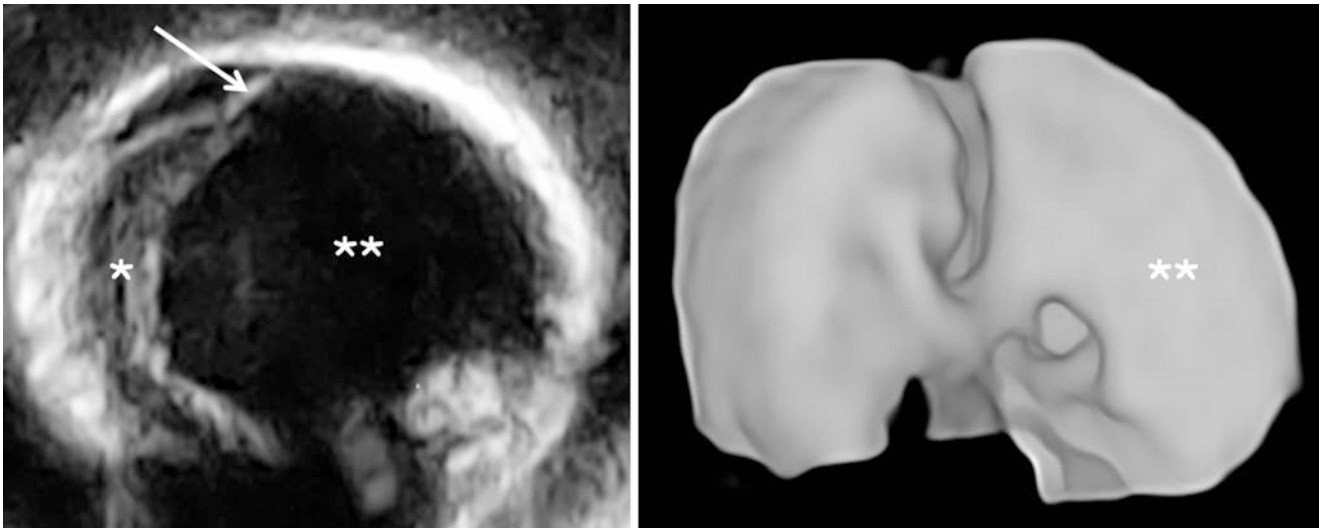


Fig. 3.3 23 weeks (TAS 3D US) *alobar holoprosencephaly* – multiplanar midsagittal section and 3D inversion – cup-shaped cortical configuration (*), dorsal cyst (**), membrane forming the ballooned dorsal cyst (solid arrow)

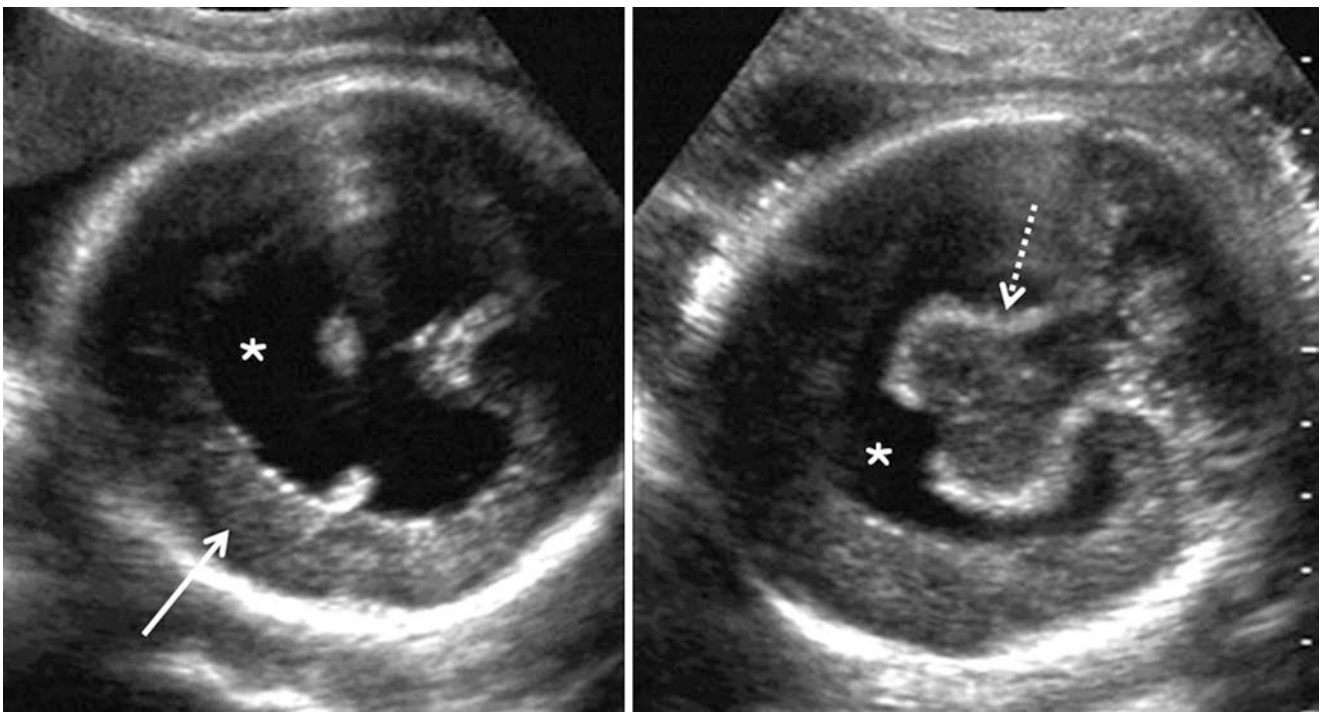


Fig. 3.4 26 weeks (TAS) *alobar holoprosencephaly* – axial transventricular and transcerebellar sections – absent interhemispheric fissure (IHF) and cavum septum pellucidum (CSP), primitive uncleaved ventricle with two choroid plexuses(*), no dorsal cyst, ball type of cortical configuration with no sulcation (solid arrow), uncleaved thalamus projecting into the uncleaved monoventricle (dotted arrow)

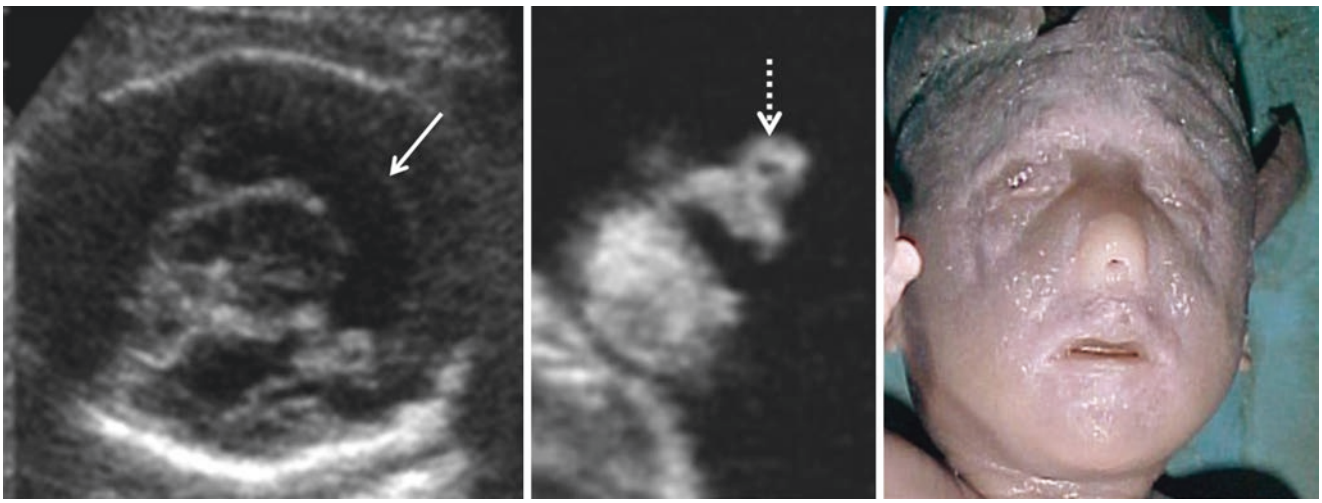


Fig. 3.5 20 weeks (TAS) *alobar holoprosencephaly with cebocephaly* – axial transthalamic section of cranium, coronal section of face, picture of abortus – primitive monoventricle (solid arrow), single nostril (dotted arrow)

Differential Diagnosis

1. Hydranencephaly: The absence of recognisable cerebral mantle, presence of falx (IHF) and normal face differentiate this from alobar HPE. The absence of intracranial arteries on color Doppler supports the diagnosis of hydranencephaly.
2. Hydrocephalus: The presence of falx (IHF), thin cerebral mantle and normal face differentiate hydrocephalus from alobar HPE.

Alobar HPE should be diagnosed in the first trimester (11–14 weeks) scan. Absence of the midline falx and choroid plexuses (butterfly sign) and presence of monoventricle with uncleaved thalamus confirm the diagnosis. Accelerated frontal bone ossification and premature closure of metopic suture may be seen (Fig. 3.6a–c).

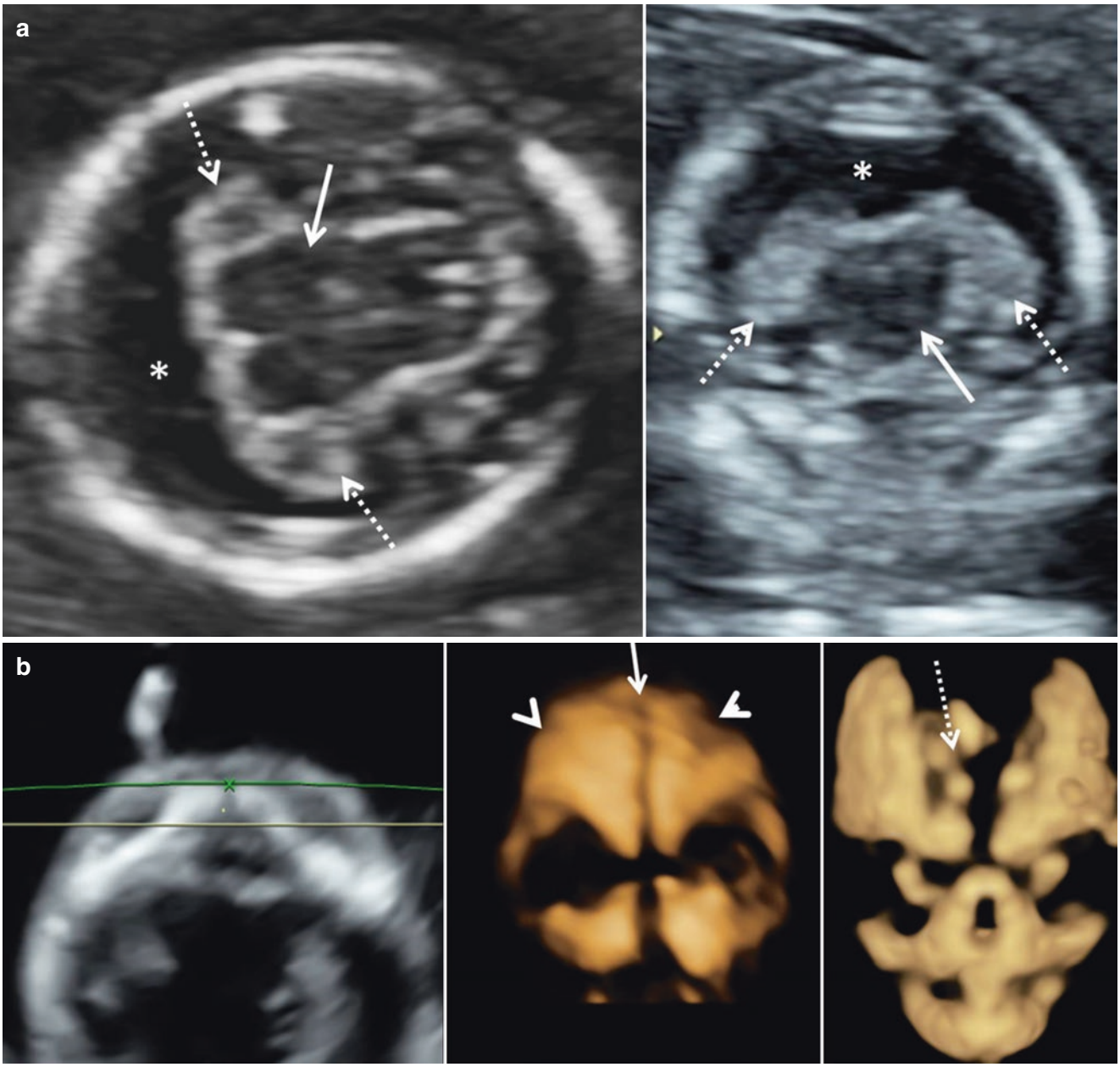


Fig. 3.6 (**a**) 13 weeks (TAS) *alobar holoprosencephaly* – axial and coronal sections – uncleaved thalamus (solid arrows), primitive monoventricle extending from side to side (*), choroid plexuses (dotted arrows). (**b**) 13 weeks (TVS 3D US) *alobar holoprosencephaly* – rendered image of the fetal face in maximum mode – accelerated frontal bone ossification (arrowheads) and premature metopic suture closure (solid arrow), normal metopic suture at 13 weeks in a normal fetus (dotted arrow). (**c**) 13 weeks (TVS, 3D US) *alobar holoprosencephaly* – midsagittal section of face, axial sections through orbits and upper lip, 3D surface rendering of the fetal face – flat facial profile (solid arrow), proptosis (arrowheads), median cleft lip (dotted arrow)

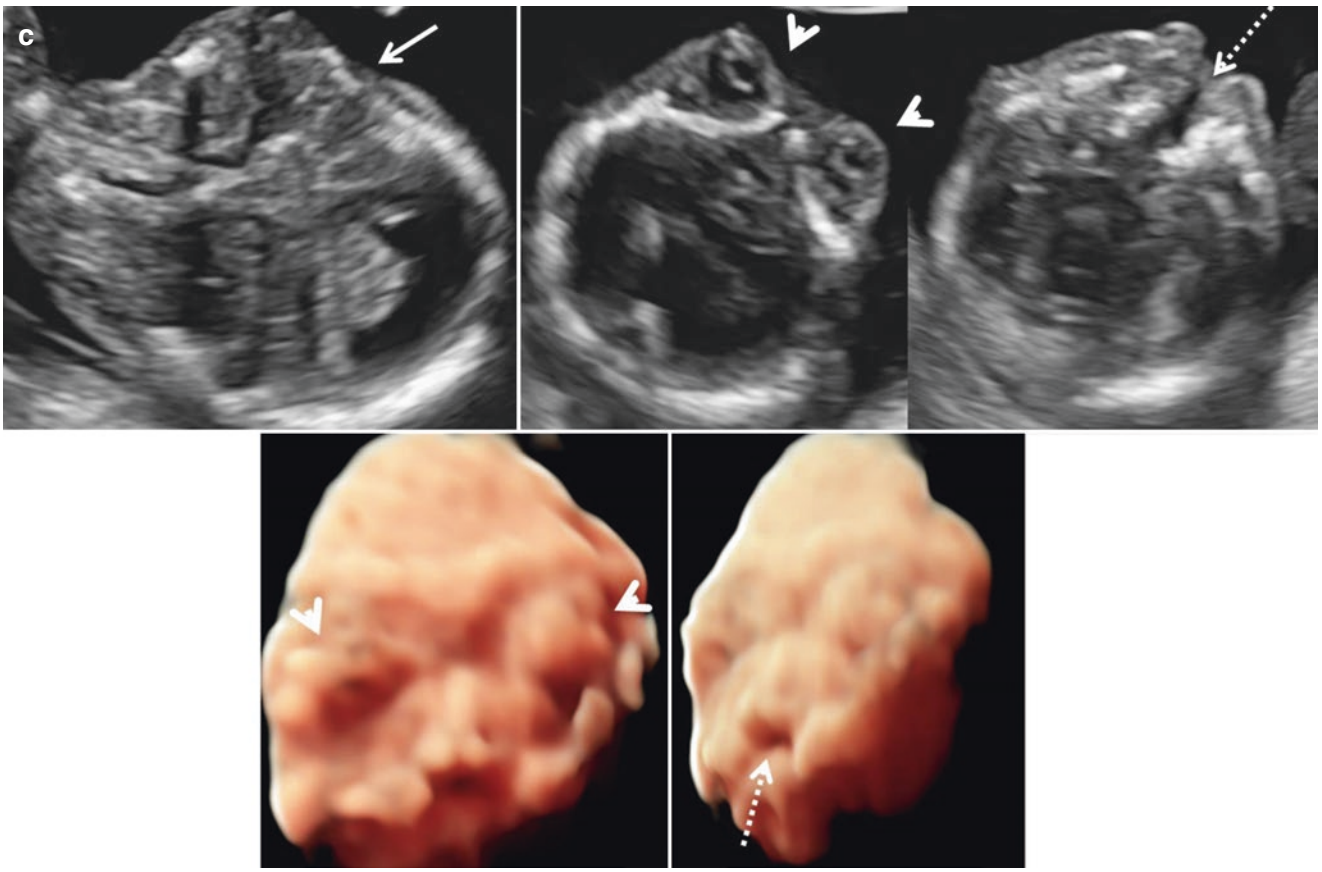


Fig. 3.6 (continued)

3.1.2 Semilobar Holoprosencephaly

1. The CSP is not seen.
2. The posterior horns are discrete and seen separately.
3. The body and anterior horns are continuous across the midline (Figs. 3.7a, b and 3.8a–c).
4. IHF is only seen between the occipital lobes.
5. The cerebral mantle is relatively better formed.
6. Frontoparietal side to side cortical continuity is seen.
7. The splenium and posterior part of body of CC are present. The rostrum, genu and anterior part of body are not seen.
8. Dorsal sac or cyst may be present.
9. Single or azygous anterior cerebral artery is seen on color Doppler.
10. The circle of Willis is abnormal.

Semilobar HPE can be diagnosed by TVS in the first trimester (11–14 weeks).

3.1.3 Lobar Holoprosencephaly

1. The CSP is not seen.
2. The body and posterior horns of the lateral ventricles are seen separately on either side.
3. The anterior horns of the lateral ventricles are continuous across the midline (Fig. 3.9).
4. The IHF is not seen anteriorly. The mid and posterior parts of the IHF are seen.
5. The frontal cortex is continuous across the midline.
6. Well-formed cerebral mantle is seen.
7. Posterior part of the body and the splenium of CC are seen.
8. Single or azygous anterior cerebral artery may be seen.

Detection of lobar HPE is difficult before 18 weeks.

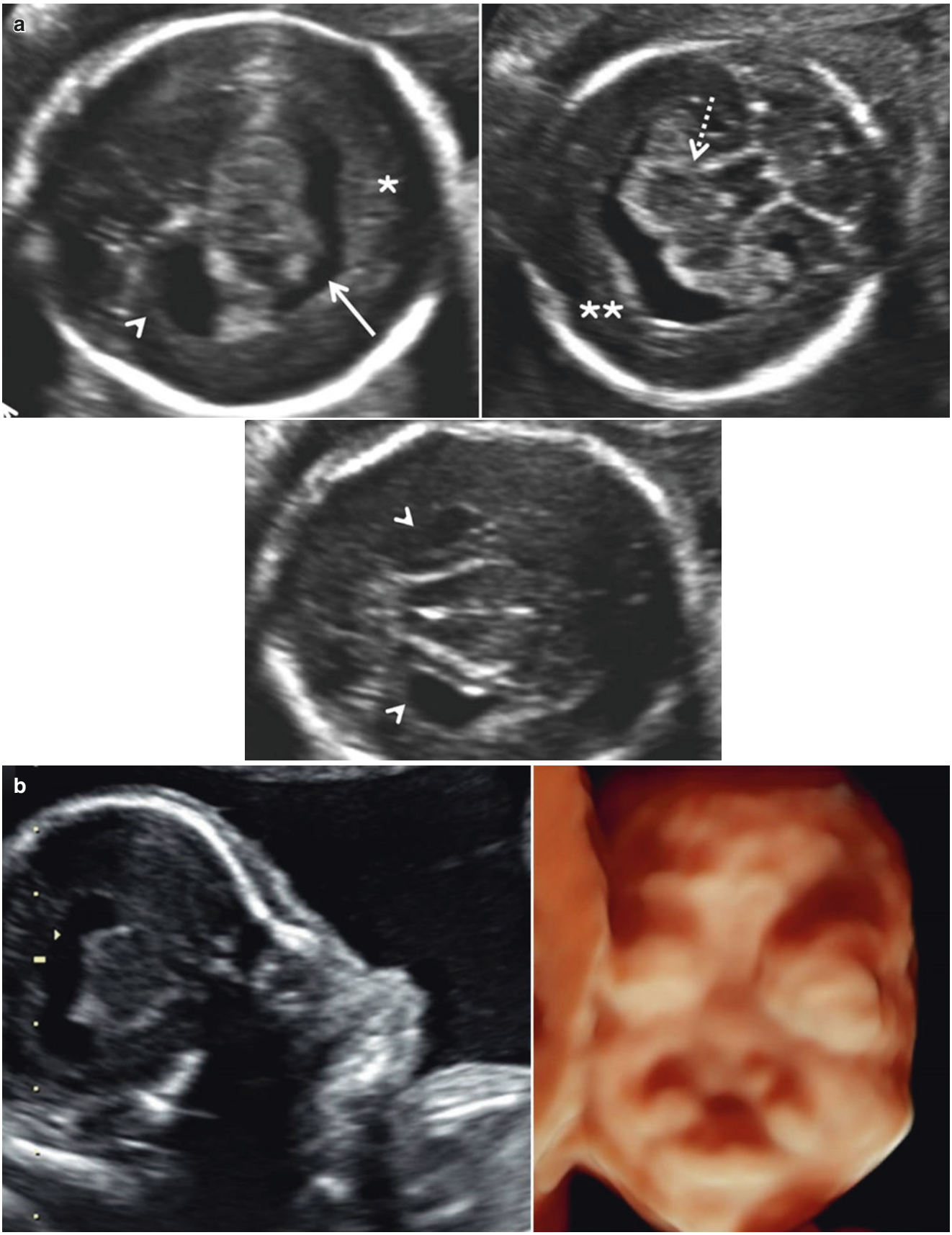
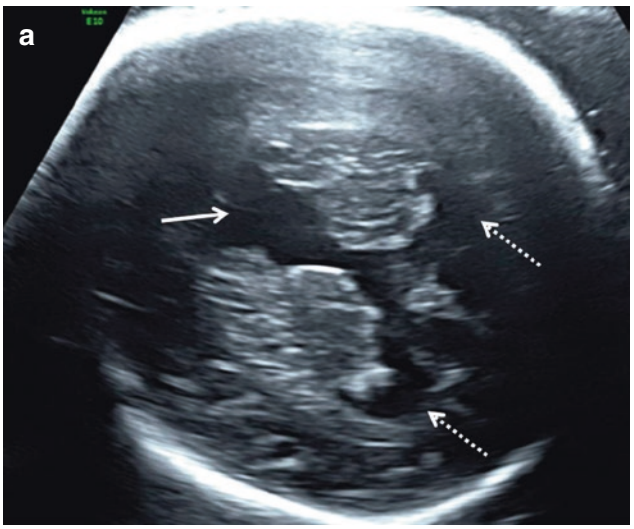


Fig. 3.7 (**a**) 24 weeks (TAS) *semilobar holoprosencephaly* – axial transventricular and transcerebellar sections – CSP and anterior IHF not seen with frontal cortical mantle continuous from side to side (*), uncleaved poorly formed anterior horns (solid arrow), posterior horns are cleaved (arrowheads), uncleaved thalami (dotted arrow), absent IHF, uncleaved parietal cortex (**). (**b**) 24 weeks (TAS, 3D US) *semilobar holoprosencephaly* – midsagittal section and 3D surface rendering of face – flat facial profile due to arrhinia, median cleft lip, flat nose and proptosis



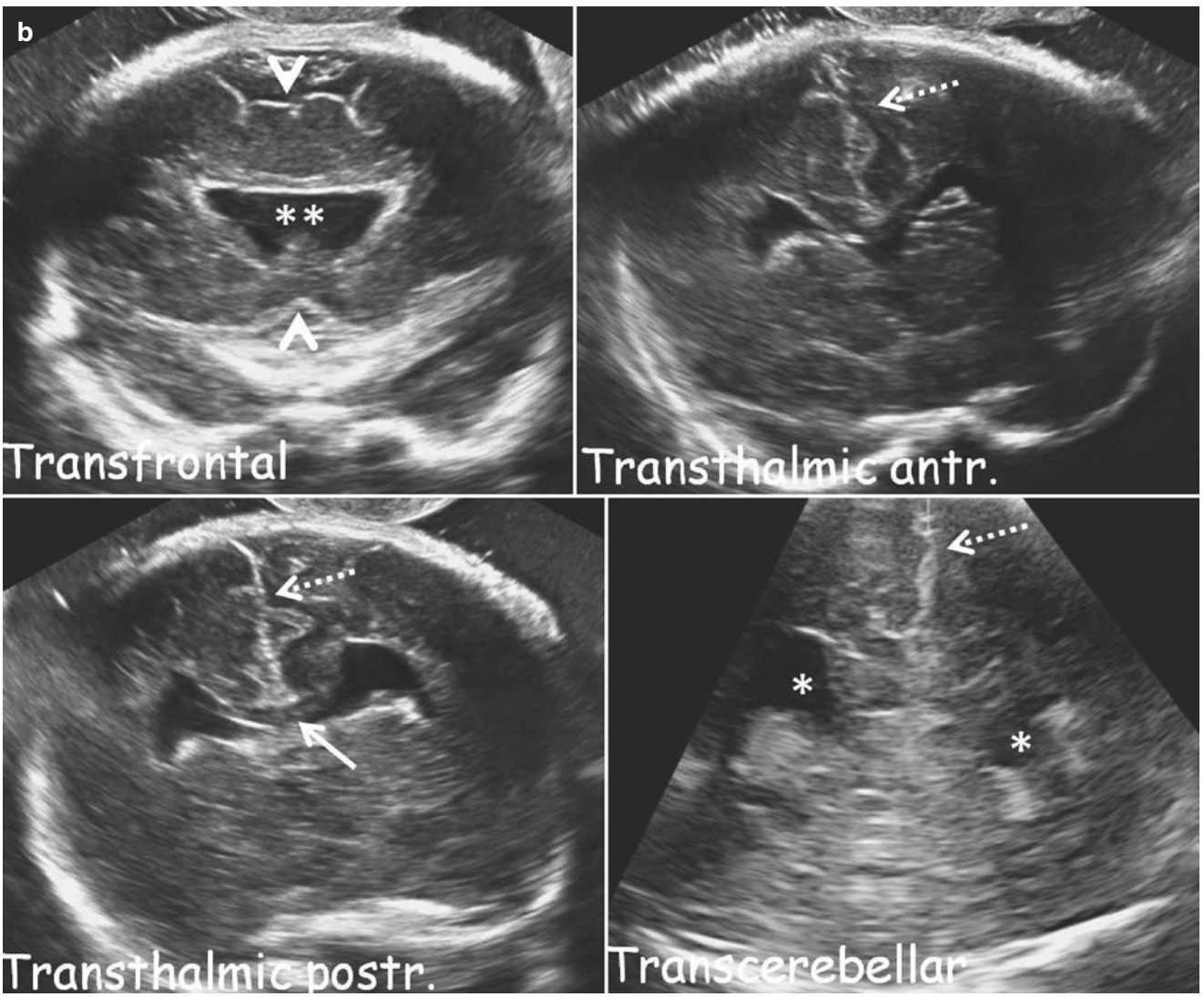
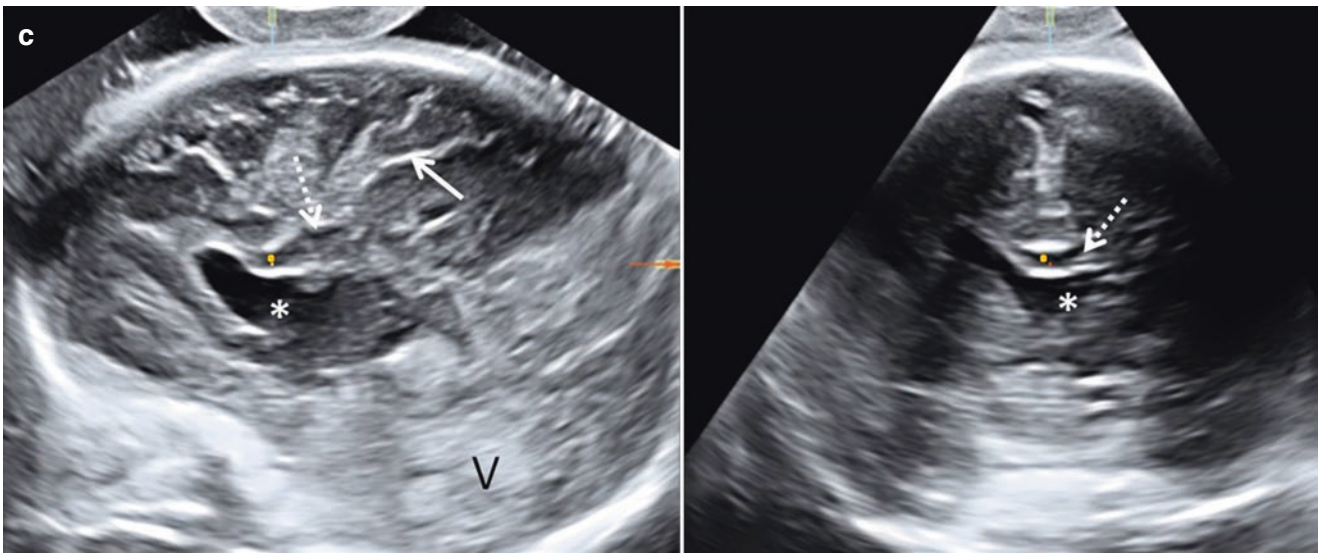


Fig. 3.8 (**a**) 38 weeks (TAS) *semilobar holoprosencephaly* – CSP is not seen, anterior horns are uncleaved (solid arrow), posterior horns are cleaved (dotted arrows). (**b**) 38 weeks (TVS) *semilobar holoprosencephaly* – coronal, transfrontal, anterior and posterior, transthalamic and transcerebellar sections – uncleaved anterior horns (**), uncleaved superior and inferior frontal cortex (arrowheads), no interhemispheric fissure (IHF) seen in transfrontal section, flat superior margin of uncleaved horns, olfactory sulci are absent, IHF is present in the transthalamic and transcerebellar sections (dotted arrows), the bodies of lateral ventricles are uncleaved and CC not seen in the anterior transthalamic section, bodies of lateral ventricles are cleaved and the CC is seen in the posterior transthalamic section, posterior horns are cleaved (*). (**c**) 38 weeks (TVS 3D US) *semilobar holoprosencephaly* – multiplanar midsagittal and coronal sections – uncleaved anterior horns and body of lateral ventricles (*), anterior segment of the body of CC seen (dotted arrows), rostrum, genu, posterior body and splenium of CC are absent, cingulate sulcus is absent, radiating medial sulci seen (solid arrow), vermis (v). Navigation dot is on CC



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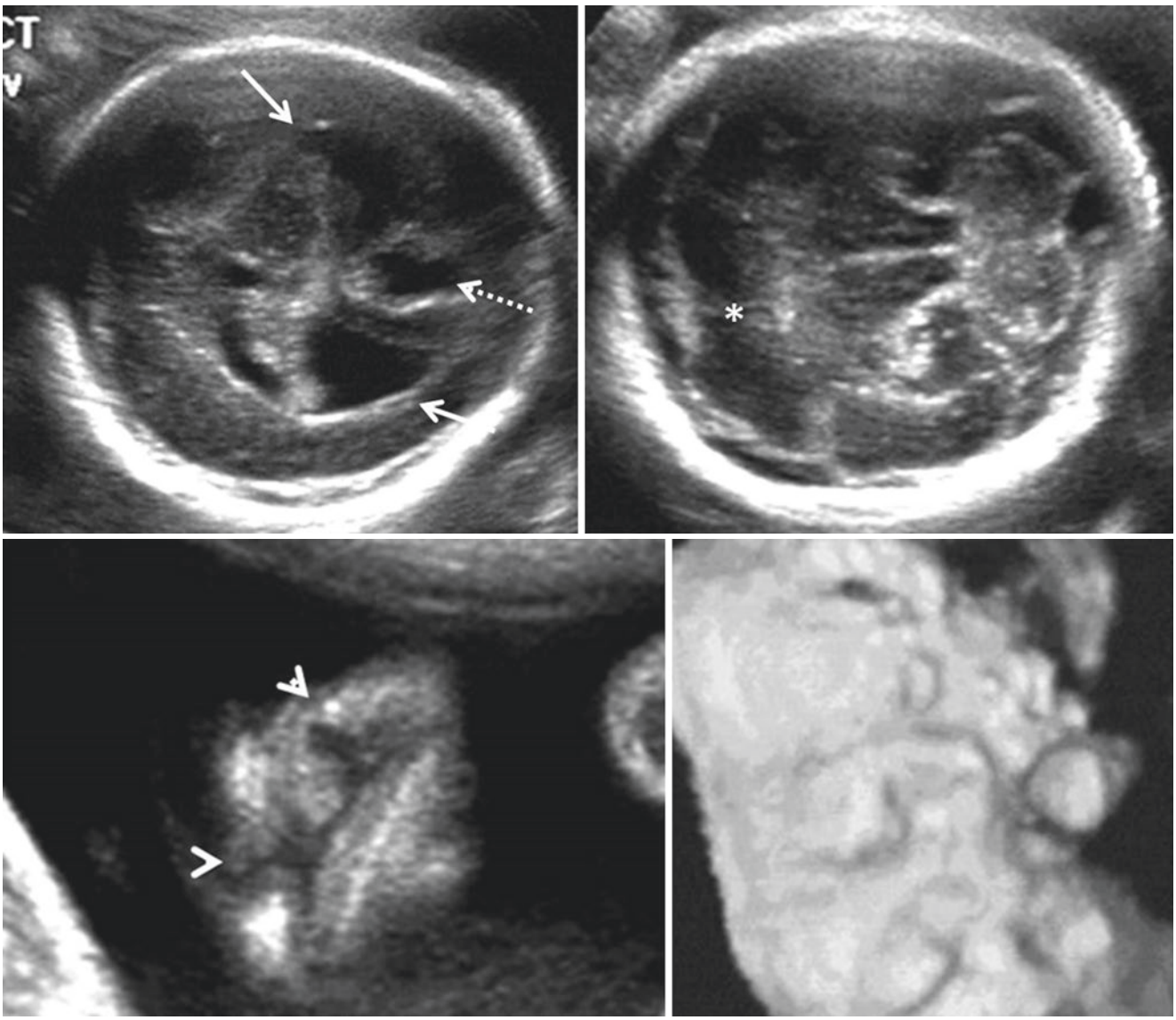


Fig. 3.9 23 weeks (TAS) *lobar holoprosencephaly* – axial transventricular and transcerebellar sections of the cranium, coronal section and 3D surface rendering of face – CSP and anterior IHF not seen, body and posterior horns are cleaved (solid arrows), posterior IHF (dotted arrow), frontal lobes are uncleaved continuous from side to side(*), anterior IHF not seen, bilateral paramedian cleft lip and cleft of primary palate (arrowheads)

Differential Diagnosis

1. Hydrocephalus: Barotraumatic destruction of the septum pellucidum may cause the lateral ventricles to be continuous with each other across the midline. However, the presence of the anterior falx (IHF) and well-formed anterior horns helps rule out lobar HPE.
2. Septal agenesis: The presence of well-formed anterior horns, IHF and normal CC helps to rule out lobar holoprosencephaly and confirm septal agenesis.

3.1.4 Middle Hemispheric Variant

1. The CSP is not seen.
2. The anterior and posterior horns are discrete. The body of lateral ventricles is continuous across the midline (Fig. 3.10a–e).
3. The IHF is absent in the posterior frontal and parietal regions.
4. The parietal cortex is continuous across the midline.

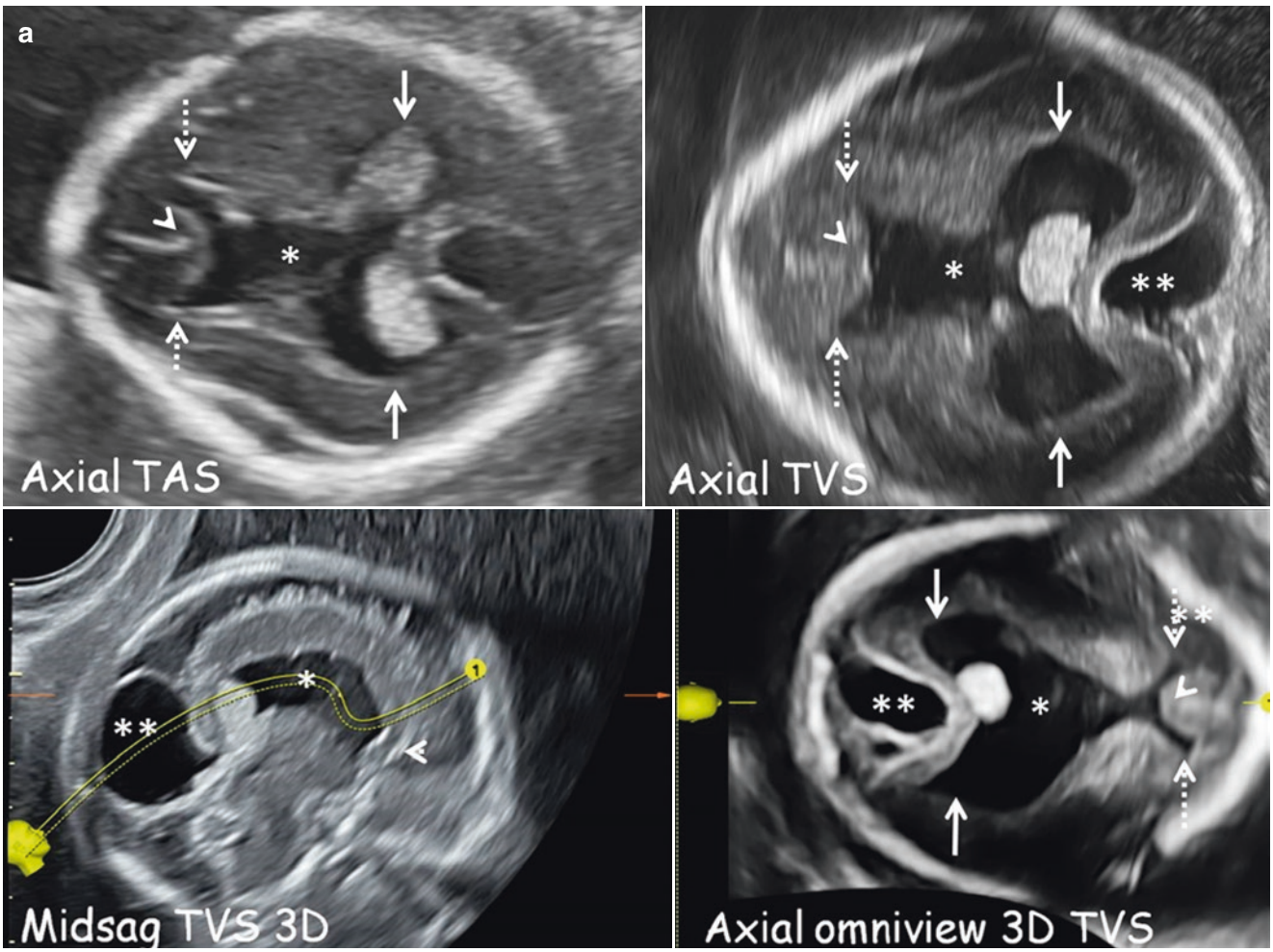
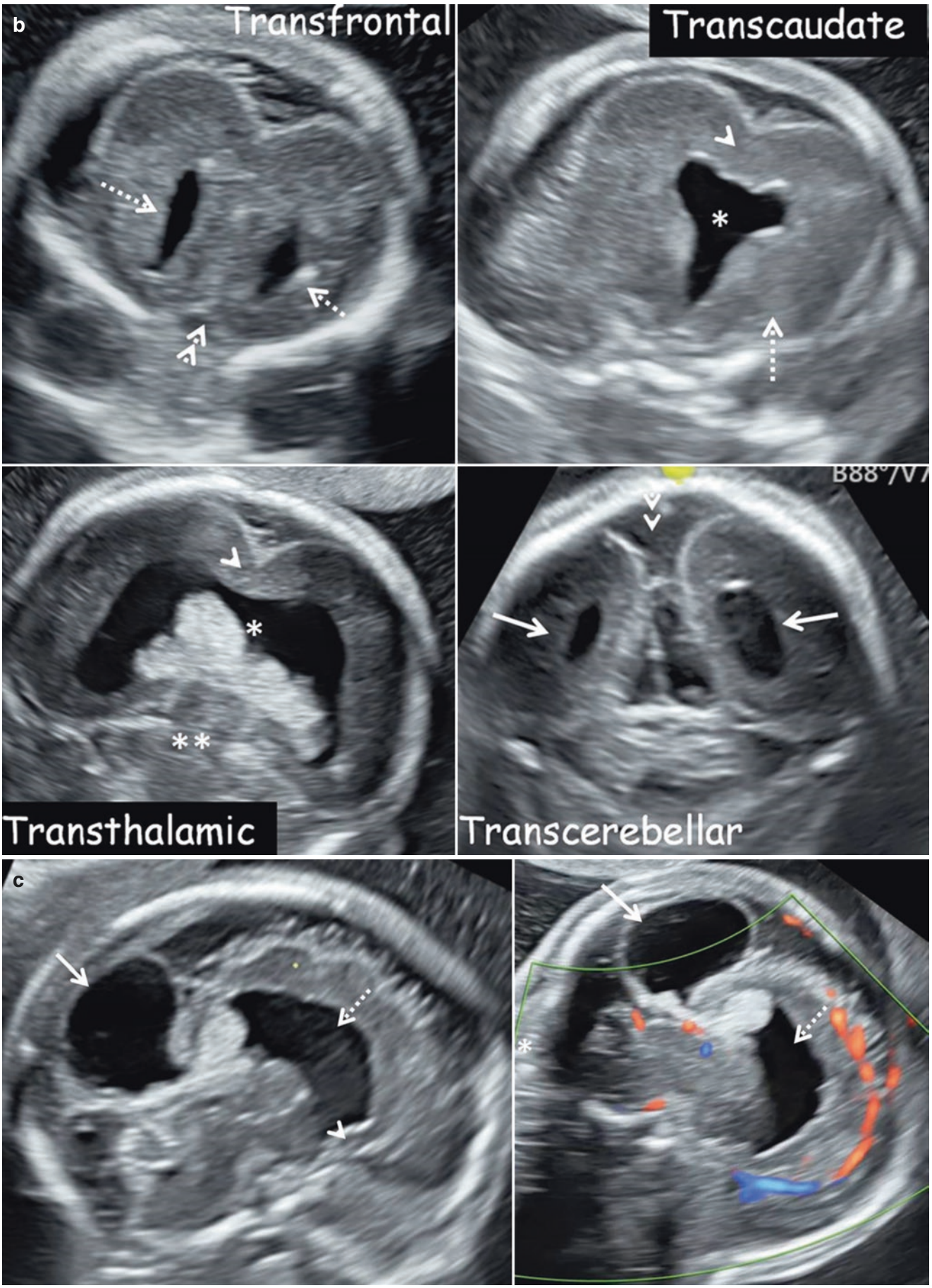


Fig. 3.10 (**a**) 19 weeks (TAS, TVS and 3D US) *middle interhemispheric variant* – axial transventricular sections TAS and TVS, 3D multiplanar midsagittal section with polyline omniview-derived axial section – uncleaved body (*), dorsal interhemispheric cyst (**), genu of CC (arrowhead), cleaved anterior horns (dotted arrow), cleaved posterior horns (solid arrow). (**b**) 19 weeks (TVS) *middle interhemispheric variant* – coronal transfrontal, transcaudate, transthalamic and transcerebellar sections – uncleaved body and posterior region of anterior horns (*), uncleaved thalamus (**), cleaved anterior horns (dotted arrows), cleaved posterior horns (solid arrows), anterior IHF (double arrowheads), posterior frontal and parietal cortex uncleaved with no IHF (single arrowhead), posterior IHF (double small arrowheads). (**c**) 19 weeks (TVS) *middle interhemispheric variant* – midsagittal sections without and with color Doppler – uncleaved body (dotted arrow), dorsal interhemispheric cyst (solid arrow), genu of CC (arrowhead), abnormal course of anterior cerebral artery under the calvarium on color Doppler. (**d**) 19 weeks (TAS and TVS 3D) *middle interhemispheric variant* – axial section through a plane just caudal and parallel to the transcerebellar section and 3D rendered image with inversion – incomplete circle of Willis (solid arrow), uncleaved body with cleaved anterior and posterior horns on inversion mode. Dorsal interhemispheric cyst is seen in posterior IHF (dotted arrows). (**e**) 19 weeks (TAS) *middle interhemispheric variant* – midsagittal, posterior and anterior coronal sections of the fetal face – facial profile (solid arrow), orbits (arrowheads) and upper lip (dotted arrow) are normal



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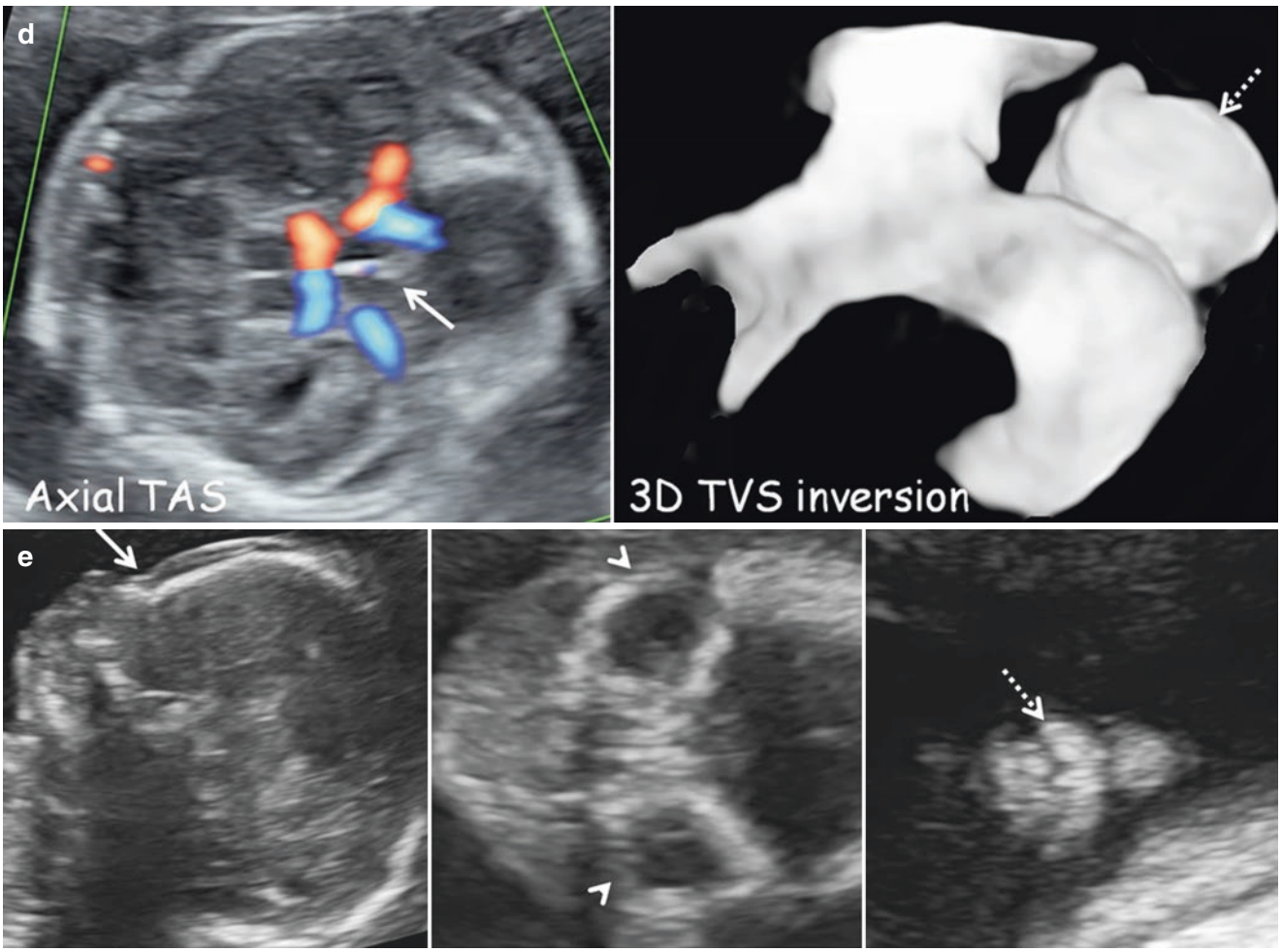


Fig. 3.10 (continued)

5. The splenium, genu and rostrum of the CC are seen. The body of the CC is absent.
6. The circle of Willis is abnormal.

3.1.5 Common Findings in All Types of HPE

1. CSP is absent.
2. CC is segmentally absent in the uncleaved regions.
3. IHF is absent in the uncleaved regions.
4. The circle of Willis and course of anterior cerebral artery are abnormal.

3.1.6 Midline Facial Defects in HPE

Ninety percent of cases of alobar and semilobar HPE have midline facial defects. The face is therefore normal in the other 10% (Figs. 3.10e and 3.11). The facial defects in lobar HPE are less common and subtle.

The following are the facial defects:

1. Cyclopia: Single midline orbit with single or partially cleaved globes is seen. Presence of a tubular proboscis is seen arising superior to the midline orbit (Fig. 3.13a).
2. Arrhinia: The nose, nasal bones and septum are absent (Figs. 3.2, 3.6c, 3.7b, 3.12a and 3.13a).
3. Hypotelorism: Interorbital distance is less than fifth percentile (Figs. 3.2b and 3.12a).
4. Ethmocephaly: Hypotelorism with a proboscis (tubular appendage) attached to the forehead above the level of the orbits. The nose is absent (Figs. 3.12a and 3.13a).
5. Cebocephaly: Hypotelorism with nose having a single nostril (Fig. 3.5).
6. Median cleft lip may be seen (Figs. 3.2b, 3.6c and 3.7b).
7. Low-set ears may be present.

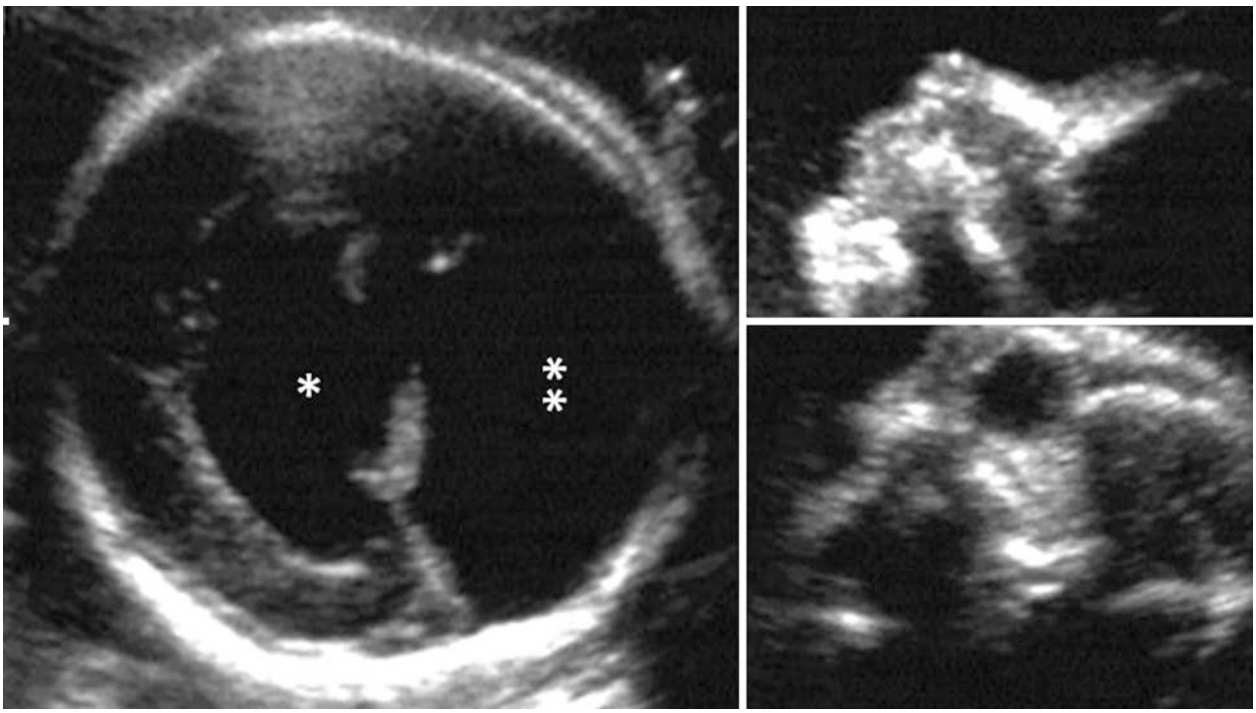


Fig. 3.11 24 weeks (TAS) *alobar holoprosencephaly with normal face* – axial transventricular section of cranium, midsagittal section of face and axial section of the orbits – primitive monoventricle (*), dorsal sac (**), no abnormality seen in the fetal face

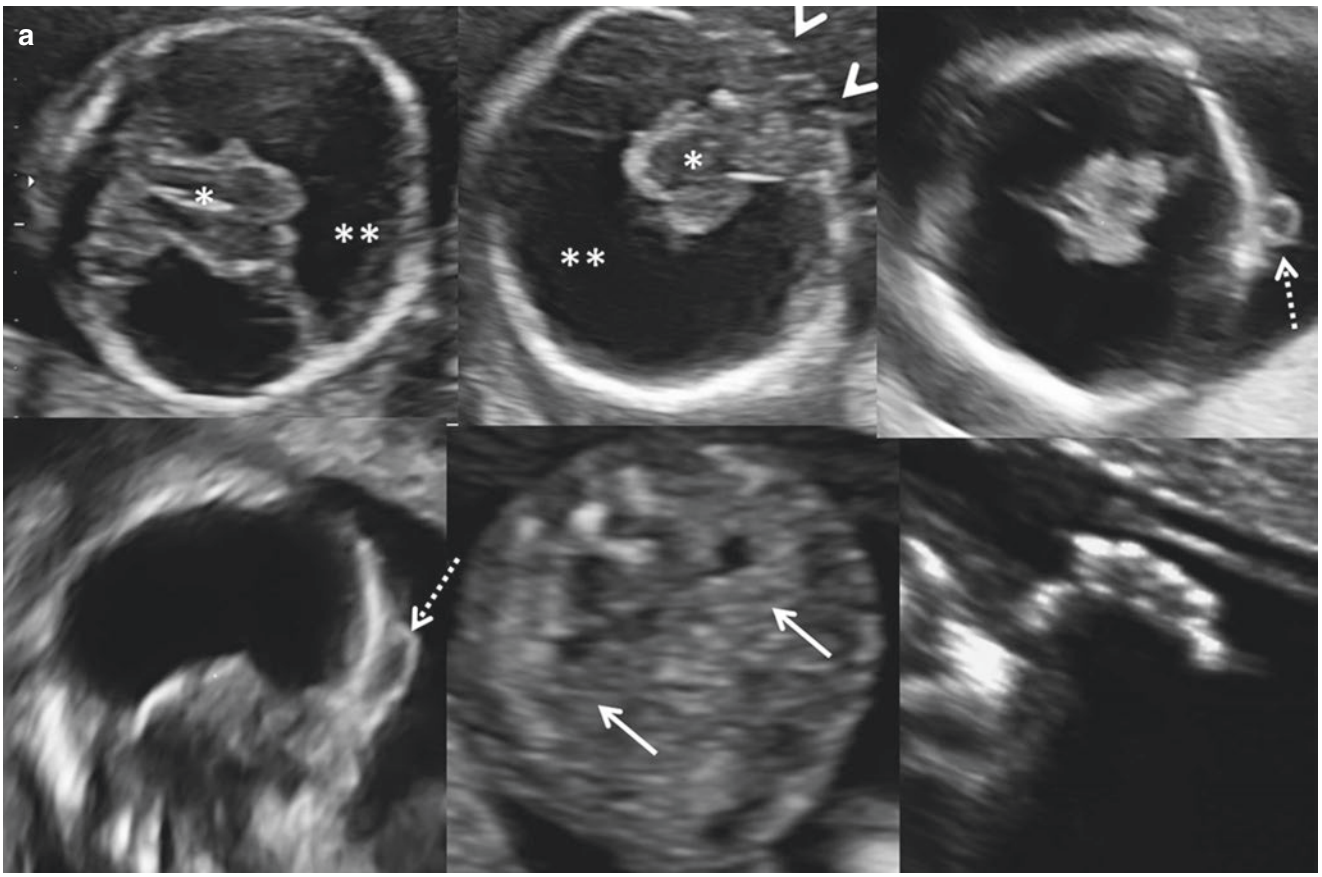
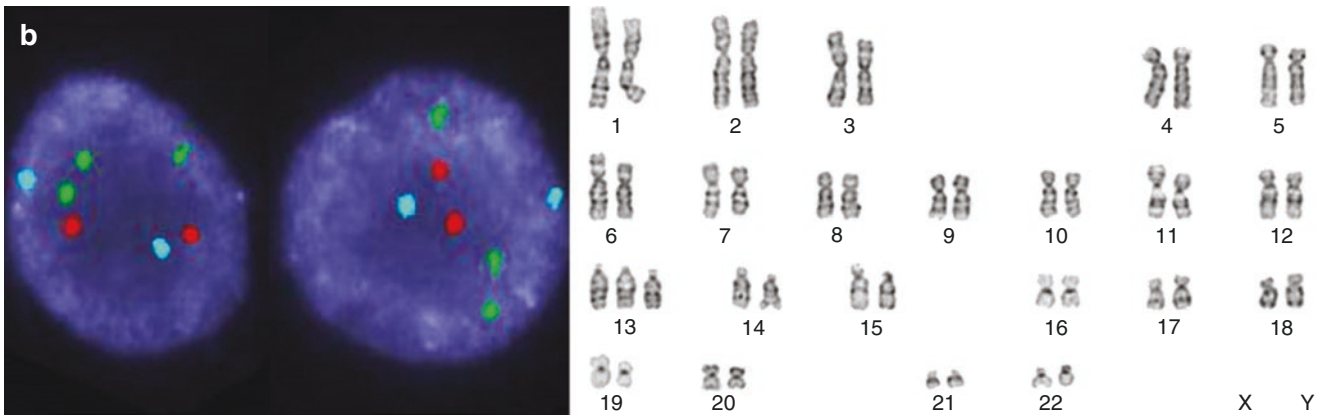


Fig. 3.12 (**a**) 17 weeks (TAS) *alobar holoprosencephaly with extracraniofacial anomalies, trisomy 13* – axial transcerebellar, axial section through the orbits, axial section through the proboscis, midsagittal section of face, axial section of the abdomen and section through fetal hand – uncleaved thalamus (*), monoventricle (**), bilateral microphthalmia and hypotelorism (arrowheads), proboscis (dotted arrows), hyperechoic kidneys (solid arrows) and polydactyly – trisomy 13 (next figure). (**b**) 17 weeks *alobar holoprosencephaly with extracraniofacial anomalies, trisomy 13* – amniocentesis – three green signals seen in the interphase FISH, three copies of chromosome 13 in the karyotype



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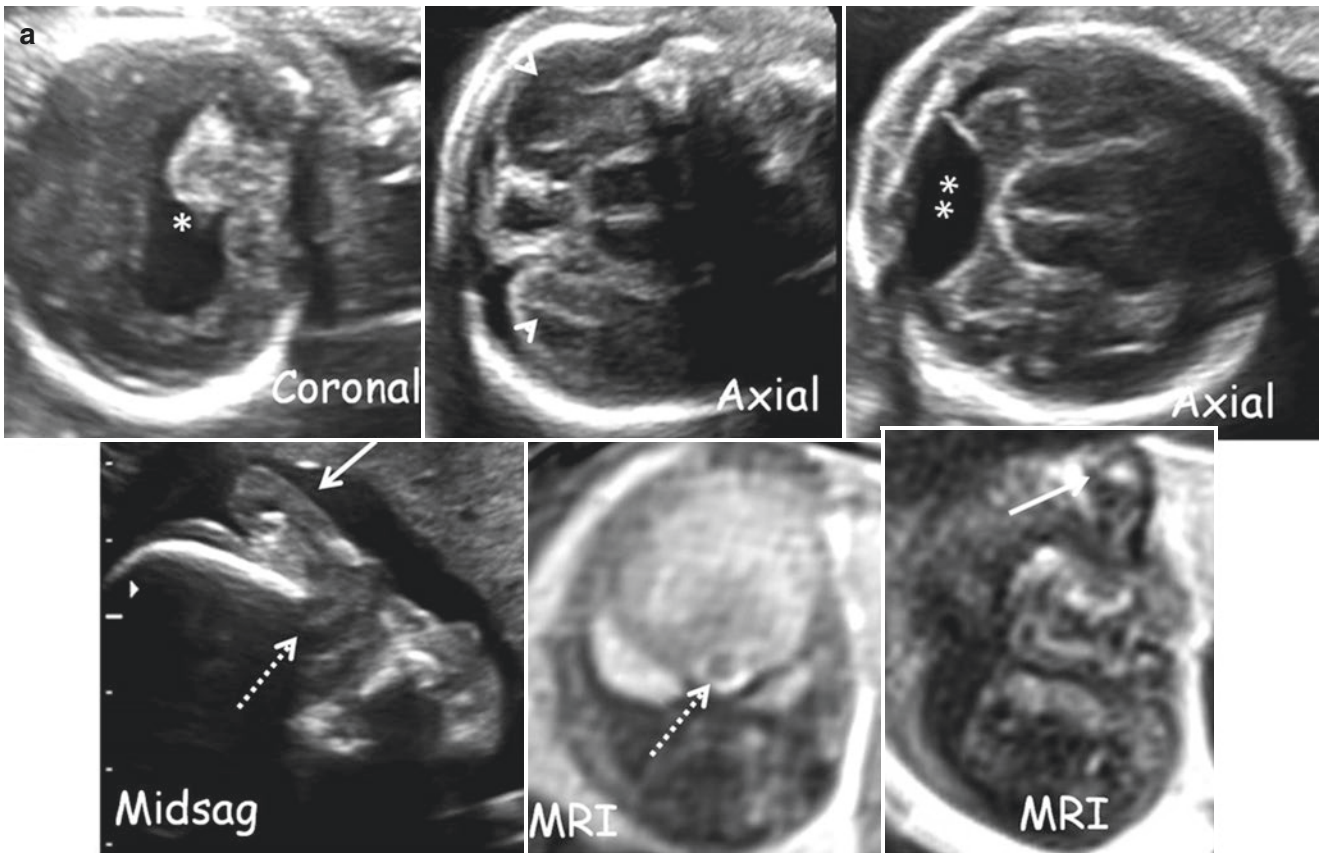
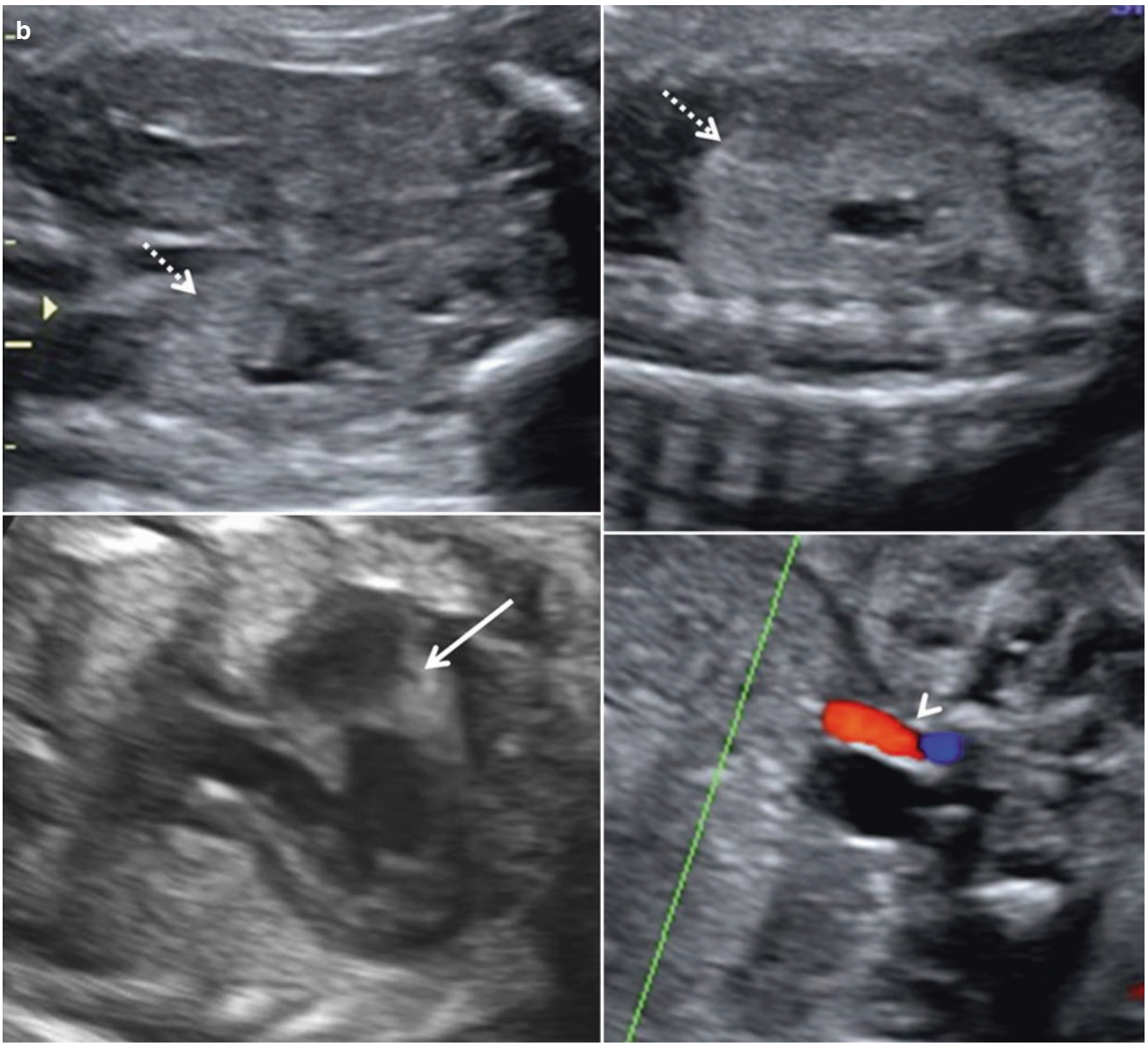


Fig. 3.13 (**a**) 23 weeks (TAS and MRI) *semilobar holoprosencephaly with extracraniofacial anomalies, trisomy 13* – coronal transfrontal, axial transventricular and transcerebellar sections of the cranium, midsagittal section of face, T2W coronal images of the face – CSP is not seen, anterior horns are uncleaved (*), occipital lobes are cleaved (arrowheads), Dandy-Walker malformation (PCF cyst) (**), cyclopia (dotted arrows), proboscis (solid arrows). Associated anomalies in the following figure. (**b**) 23 weeks (TAS) *semilobar holoprosencephaly with extracraniofacial anomalies, trisomy 13* – bilateral hyperechoic kidneys (dotted arrows), congenital heart disease (solid arrow) and single umbilical artery (arrowhead). Fetal karyotyping and picture of abortus in the following figure. (**c**) 23 weeks *semilobar holoprosencephaly with extracraniofacial anomalies* – fetal blood sampling for karyotyping reveals trisomy 13 (13:14 translocation). Parental karyotyping is indicated. Picture of face of abortus



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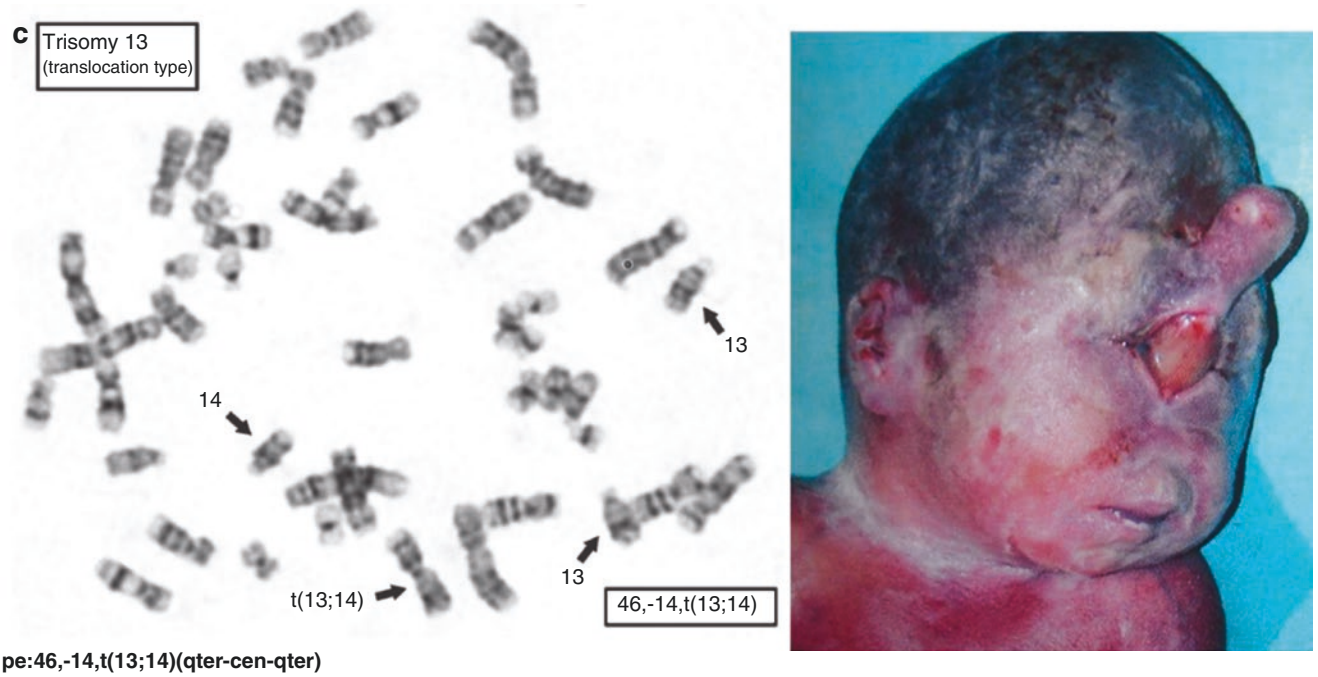

Fig. 3.13 (continued)

3.1.7 Associated Anomalies

Associated anomalies are common and include cardiac, skeletal, renal and other defects. When associated anomalies are present, there is a high risk of chromosomal abnormalities (trisomy 13, triploidy, trisomy 18, deletions, duplications and translocations) (Figs. 3.12a, b and 3.13a–c). Nonchromosomal syndromes should also be considered depending on the nature of the associated anomalies. These include Smith-Lemli-Opitz and Meckel syndromes. Nonsyndromic, autosomal dominant HPE must be considered in cases of recurrence. Incomplete penetrance and variable expression may make clinical detection of the abnormality in the parents difficult. Maternal diabetes increases the risk of HPE.

Suggested Reading

1. McGahan JP, Nyberg DA, Mack LA. Sonography of facial features of alobar and semilobar holoprosencephaly. AJR. 1990;154:143–8.
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