Prenatal Assessment of Atypical Adrenal Glands

Emmanuelle Lesieur, Aurélie Noire, Paul Maurice, Catherine Garel, Jean-marie Jouannic, Katia Chaumoitre, Florence Bretelle, Jean Baptiste Haumonte, Guillaume Gorincour, Edwin Quarello

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Complete List of Authors:	Lesieur, Emmanuelle; Screening and diagnosis Unit Noire, Aurelie; Cabinet de Gynécologie et Obstétrique Maurice, Paul; APHP, Service de Médecine Fœtale, Hôpital Armand Trousseau Garel, Catherine; APHP, Department of pediatric imaging, Hôpital d'Enfants Armand-Trousseau Jouannic, Jean-Marie; APHP, Service de Médecine Fœtale, Hôpital Armand Trousseau Chaumoitre, Katia; APHM, : Service d'Imagerie Médicale, AP-HM Hôpital Nord Bretelle, Florence; APHM, Department of Gynaecology and Obstetrics, Gynepole Haumonte, Jean-Baptiste; Screening and Diagnosis Unit, Obstetrics and Gynecology Gorincour, Guillaume; Image2 Center Quarello, Edwin; Unite dechographies obstetricales et de diagnostic antenatal, Hopital Saint Joseph
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Abstract:	

TITLE

Prenatal assessment of atypical adrenal glands: a systematic approach for diagnosis

AUTHORS

Emmanuelle Lesieur [(1)], Aurélie Noire [(2)], Paul Maurice [(3)], Catherine Garel [(4)], Jean-Marie Jouannic [(3)], Katia Chaumoitre [(5)], Florence Bretelle [(6)], Jean Baptiste Haumonte [(1)], Guillaume Gorincour [(7)], Edwin Quarello [(1,7)]

[(1)]: Screening and Diagnosis Unit, Obstetrics and Gynecology Department, St Joseph Hospital, 26 Bd de Louvain, Marseille Cedex 08, France.

[(2)] : Cabinet de Gynécologie et Obstétrique, 7 Av Gambetta, 83400 Hyères, France

[(3)]: Service de Médecine Fœtale, Hôpital Armand Trousseau, APHP. Sorbonne Université, 26 avenue A Netter, 75012 Paris, France.

[(4)] : Department of pediatric imaging, Hôpital d'Enfants Armand-Trousseau APHP. Sorbonne Université, 26 avenue A Netter, 75012 Paris France.

[(5)] : Service d'Imagerie Médicale, AP-HM Hôpital Nord, Chemin des Bourrely, 13015 Marseille, France.

[(6)]: Department of Gynaecology and Obstetrics, Gynepole, AP-HM, Assistance Publique-Hôpitaux de Marseille,Hôpital Nord, Chemin des Bourrely, 13015 Marseille AMU, Aix-Marseille Université, France.

[(7)] : IMAGE^2 Center, 6 rue Rocca, Marseille 13008, France

Correspondence :

Dr Edwin QUARELLO

Image 2 Center

6 rue Rocca

Marseille 13008

France

e.quarello@me.com

SUMMARY

The aim of this study was to identify specific unusual prenatal ultrasonographic patterns of the adrenal gland and to propose a systematic approach for diagnosis. Six foetuses with unusual aspects of one or both adrenal glands, detected during routine prenatal ultrasound screening, were evaluated. Prenatal and postnatal management are described. A checklist of ultrasound features was created in order to perform a detailed analysis of adrenal lesions and guide prenatal management; this includes: time of appearance, location, growth, vascularization, structure, and the presence of findings suggestive of malignancy.

Prenatal – ultrasound – adrenal gland – MRI – counseling

INTRODUCTION

With the widespread use of foetal ultrasound (US), identification of atypical suprarenal masses has become more common. Yet, optimal prenatal diagnosis and prognosis remain challenging.[1] Identifying characteristic imaging findings can help achieve the most relevant diagnosis.[2] Evaluation of the adrenal glands is not included in standard guidelines. Atypical presentation often results from an increased size and / or abnormal appearance (cystic, enlarged, pseudo-tumoural).

Although sufficient epidemiological knowledge of these atypical suprarenal entities is still lacking, five diagnoses stand out according to their location and characteristics: neuroblastoma (NB), congenital adrenal hyperplasia (CAH), adrenal haemorrhage (AH), adrenocortical macrocyst (AM), and adrenal cyst (AC). The main diagnostic issue is the exclusion of malignant neuroblastoma.[3–5] The principal differential diagnosis is subdiaphragmatic extralobar pulmonary sequestration (SEPS).[6] Other less frequent causes can, however, be considered such as enteric duplication cyst, some renal cystic diseases, kidney duplication with upper pole moiety dilatation, and focal renal dysplasia.[7–9]

The definitive diagnosis of an atypical suprarenal entity using US is challenging, especially since the complications specific to each diagnosis imply very different prognoses and postnatal care.[10] Although in most cases the diagnosis cannot be given prenatally, the distinction between specific US features provides a clearer picture to support parental counselling. Based on a series of six cases of atypical adrenal glands, the aim of this study was to propose a systematic US approach in order to aid diagnosis and improve perinatal care and counselling.

PATIENTS AND METHODS

We retrospectively reviewed the US descriptions of cases with an atypical aspect of one or both adrenals detected during routine prenatal US screening in three different prenatal diagnostic centres, in Marseille and Paris, France over a five-year period. In accordance with our country's regulations, the retrospective use of descriptive data does not require specific authorization in France (IRB or equivalent). Patients, all of whom are informed during US examinations of the possible use of their data for scientific purposes (informed consent), may at any time indicate their refusal.

During the period 2015-2020, cases were investigated in order to characterise different atypical adrenal entities. Six cases were encountered, leading to the characterization of six different entities. This analysis focused only on prenatal US description, and all recorded foetal US images were reviewed. The prenatal and postnatal management of each case is described. All US examinations were performed by expert clinicians. If magnetic resonance imaging (MRI) was performed, a precise evaluation of the lesion was carried out. Based on the data, a checklist of US features was then created in order to establish detailed analysis of the adrenal lesion and guide prenatal management.

RESULTS

Six unusual foetuses, detected during routine prenatal US screening, were assessed. In the first case, congenital hyperplasia of the adrenal gland was diagnosed antenatally followed by postnatal management. In the second case, an atypical adrenal gland was described in a patient with Beckwith-Wiedemann syndrome. The third illustrates the prenatal diagnosis of neuroblastoma together with postnatal management. In the fourth and fifth cases, a complex and a simple haemorrhagic cyst were diagnosed antenatally respectively. The last case involved extralobar pulmonary sequestration, a differential diagnosis that was established faced with an atypical adrenal mass. The description of these cases is presented in Table 1

DISCUSSION

Based on US foetal screening, the adrenal gland is one of the anatomical landmarks necessary to accurately define the abdominal perimeter in the mid and late trimesters of pregnancy. The normal appearance of adrenal glands changes with gestational age. In the first trimester, adrenal glands appear as hypoechoic triangles above the kidneys and measure about half the height of the kidney ***(Figure 1)***. They then gradually lengthen and take an inverted V shape above the kidney, to measure more than a third of the length of the kidney. In the third trimester, the appearance of corticomedullary differentiation is observed with a hypoechoic cortex and hyperechoic medulla ***(Figure 1)***.[11]

When an atypical adrenal gland is identified, six possible diagnoses should be initially considered, even if other, less frequent, causes are not excluded, as mentioned above ***(Figure 2).***[12]

First, the bilateral or unilateral presentation should be considered, followed by its sonographic appearance. When bilaterally increased in size and associated with normal sonographic appearance, this may indicate adrenal hypertrophy which can be encountered in some cases of gestational diabetes, intra-uterine growth retardation, and foetal inflammatory syndrome, especially in cases of premature rupture of the membranes.[13,14]

In bilateral cases with abnormal sonographic appearance, congenital adrenal hyperplasia (CAH) should be suspected ***(Table 1 - Case 1, Figure 3)***. This autosomal recessive disorder may be indicated by the association with two US features: a typical aspect of “cerebriform” adrenal glands, associated with virilization of the genitalia. Supported by a family history, these two US features favour the diagnosis of CAH. The prognosis is excellent with appropriate treatment.[15,16]Second, the presence of bilateral cysts with mixed content, possibly partially haemorrhagic, can raise suspicion of an adrenocortical macrocyst in the setting of Beckwith-Wiedemann syndrome. Other US features should be investigated, such as foetal macrosomia with polyhydramnios, macroglossia, and omphalocele ***(Table 1 – Case 2, Figure 4)***.[17–19]

When unilateral with an abnormal US appearance, neuroblastoma is the most frequent congenital malignant tumour of the adrenal (90%). It is most often on the right side (60%), but can be bilateral. Appearance is variable, and cystic in 50% of cases ***(Table 1 – Case 3, Figure 5)***. The contours of neuroblastoma are regular, and the presence of thick walls, vegetations or partitions can be suggestive. The prognosis is variable and depends on its appearance, time at onset and possible secondary locations.[20,21] Overall, a pure cystic form has

a good prognosis. Early detection is associated with a good outcome in more than 90% of cases. A few cases with secondary localization[22] and placental dissemination, with a high risk of foetal hydrops and maternal preeclampsia, have been described, most often with a poor prognosis.[23,24]

An adrenal haemorrhage presents as a rounded or oval, echogenic, heterogeneous and avascular mass of the adrenal area with a changing sonographic appearance, which may help diagnosis. Its size gradually decreases during pregnancy follow-up. Bilateral localization can help diagnosis, as well as specific MRI features ***(Table 1 – Case 4, Figure 6)***. A foetal adrenal haemorrhage can regress and disappear spontaneously during the prenatal period. Adrenal insufficiency is found very rarely, even in cases of bilateral adrenal hemorrhage.[25]

Isolated adrenal cysts ***(Table 1 – Case 5, Figure 7)*** can occur unilaterally. Differential diagnoses of neuroblastoma (cystic form) and adrenocortical macrocyst (Beckwith-Wiedemann syndrome) should be kept in mind. Spontaneous involution is most likely. An absence of malignancy must be confirmed at birth.[26,27]

The differential diagnosis for neuroblastoma is difficult during the prenatal period.[28]

Extralobar pulmonary sequestration is also generally diagnosed early in pregnancy, more commonly in the mid trimester ***(Table 1 – Case 6, Figure 8)***. It is defined as a portion of lung tissue that is totally discontinuous from the tracheobronchial tree and usually has its own pleural covering with an anomalous systemic blood supply.[6] It can have a variable sonographic appearance, and is more frequently left-sided. The US diagnosis is based on the demonstration of a feeding systemic artery that can be identified on colour Doppler imaging. Most often, the artery is derived from the terminal portion of the descending thoracic aorta or the upper part of the abdominal aorta.[29]

All specific prenatal features and prognostic factors of these three entities are summarized in Table 2.

MRI can be a useful adjunct in the prenatal diagnosis of unusual suprarenal entities. Indeed, MRI confirms US diagnosis, complements US in equivocal diagnoses, and may lead to detection of additional findings.[30]

Regarding term at delivery, although some authors have suggested that the increase in size of the adrenal gland may be related to preterm delivery,[31] especially when associated with polyhydramnios, others believe that there is no relationship between size of the adrenal gland and gestational age at delivery.[32]

The treatment of such entities has not yet been determined, and recommendations have changed in recent years. Initially, surgery was favoured in all cases[33,34], then a wait-and-see attitude, based on close prenatal and

postnatal US follow-up, was promoted.[4,35] Overall, patients prenatally diagnosed with extralobar pulmonary sequestration have an excellent prognosis and a wait-and-see attitude, followed by possible postnatal embolization and/or resection, is recommended.[36] As far as adrenal haemorrhage is concerned, therapeutic abstention is required. Regarding neuroblastomas, surgical excision is performed immediately for tissue / mixed forms that have increased in volume. For prenatal cystic and stable forms, a wait-and-see attitude could be proposed initially, to be re-evaluated on a case-by-case basis.

Appropriate prenatal assessment and close sonographic monitoring may avoid surgery in cases of benign masses such as adrenal haemorrhage or spontaneously regressing neuroblastomas.

CONCLUSION

Prenatal US diagnosis of atypical adrenal glands requires a detailed analysis of the lesion, since the prognosis and morbidity vary according to final diagnoses. Knowledge and distinction of relevant US signs are necessary for optimal management. The analysis of atypical adrenal glands underlines the complexity of foetal US and the gap between prenatally suspected conditions and final postnatal diagnosis, which may be potentially very different. Optimization of US analysis may improve perinatal care and prenatal counselling.

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	DIAGNOSIS	Congenital adrenal hyperplasia	Adrenocortical macrocyst Beckwith Wiedemann Syndrome	Solid neuroblastoma	Adrenal haemorrhage	Isolated adrenal cyst	Left extralobar pulmonary sequestration
PRENATAL MANAGEMENT	PATIENT'S AGE (years)	37	31	26	32	26	29
	TRIMESTER AND WG AT DISCOVERY (EGA)	Mid trimester 24	Mid trimester 25	Late trimester 35	Late trimester 34	Late trimester 32	Mid trimester 24
	LOCATION	Bilateral	Bilateral	Unilateral left	Unilateral right	Unilateral left	Unilateral left
	FETAL GENDER	Male	Male	Male	Male	Female	Female
	ANTENATAL ULTRASOUND FEATURES ▪ Size (mm) ▪ Structure ▪ Vascularized ▪ Systemic vessel ▪ Associated findings	 Increased Cerebriform aspect No No Penis increased in size Family history of CAH	 50 x 40 Multicystic with mixed content Heterogeneous No No macroglossia	 22 x 32 Hyperechoic Homogeneous Yes No No	 38 x 29 Altered content Heterogeneous No No No	 10 x 8 Hypoechogenic Homogeneous No No No	 30 x 20 Mixed component Heterogeneous Yes Yes (from the aorta) No
	FETAL MRI ▪ When (WG) ▪ Location ▪ Structure ▪ Associated findings	 NR NR NR NR	 28 Bilateral Cystic and heterogeneous formation Macroglossia	 37 Unilateral left Prerenal Retrogastric Well limited, Heterogeneous, No hemorrhagic signs No	 35 Unilateral right Cystic and heterogeneous formation No	 NR NR NR NR	 29 and 33 Thoraco abdominal junction Plurilocular cystic formation a systemic posterior vessel arising from the aorta
	PRENATAL EVOLUTION	Stable	Increase	Increase	Decrease	Stable	Increase
	PROPOSED PRENATAL DIAGNOSIS	Congenital adrenal hyperplasia	Adrenocortical macrocyst Beckwith Wiedemann Syndrome	Solid neuroblastoma, Adrenal haemorrhage	Adrenal haemorrhage, Cystic neuroblastoma	Isolated adrenal cyst	Left extralobar pulmonary sequestration
POSTNATAL MANAGEMENT	COMPLEMENTARY EXAMS ▪ Urinary catecholamine ▪ Androgenic marquors ▪ Postnatal ultrasound / MRI Lesion confirmed Associated elements ▪ Histological findings post-surgery	 Negative 21-H deficiency Yes No -	 NR NR NR NR NR	 Positive Normal Yes Liver metastases (present at 1 month) Malignant cells	 Negative Normal Yes No NR	 NR NR Yes No No malignant cells	 Negative Normal Yes No Lung cells – no malignant cells
	EVOLUTION	Normal aspect at one week and one month with treatment	Termination of pregnancy Pathology: fetal macrosomia, macroglossia, bilateral nephromegaly, bilateral adrenal masses with haemorrhagic lesion on the left. No malignant cells.	Spontaneous regression, then stabilization	Spontaneous regression	Stabilization	Stabilization
	THERAPEUTIC PROTOCOL	Hydrocortisone and fludrocortisone therapy	NR	Close monitoring, then, Surgery	Close monitoring	Monitoring (spontaneous regression)	Close monitoring

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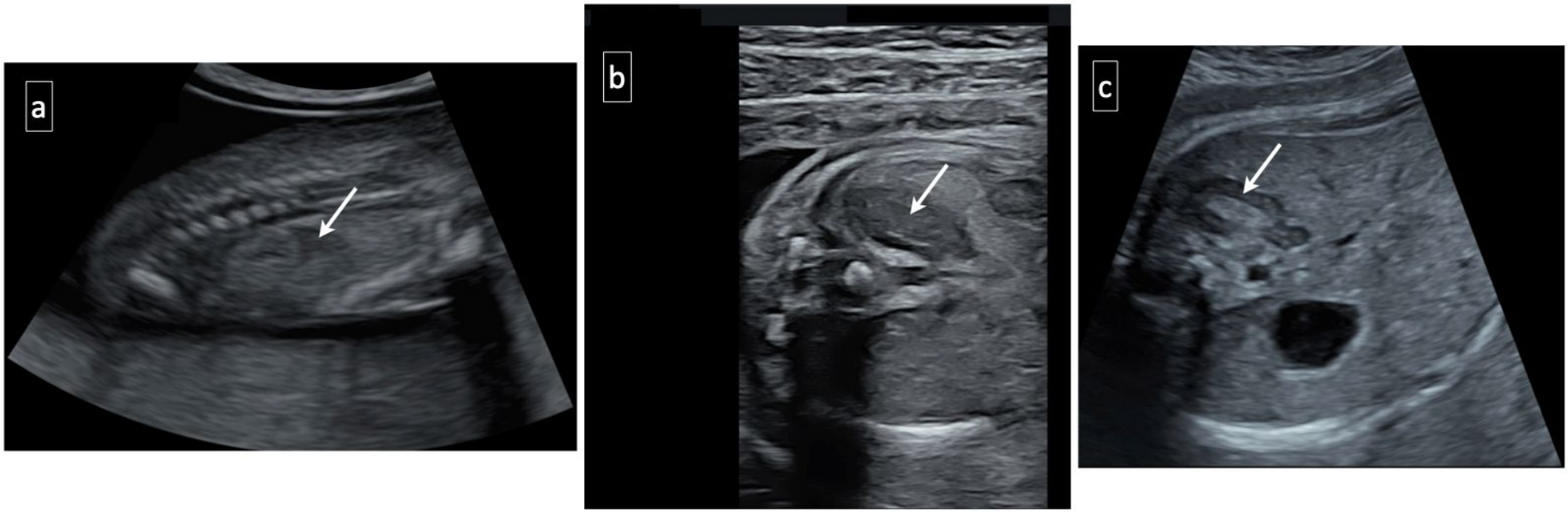
Table 1: Observations of fetuses with atypical adrenal gland detected during routine prenatal ultrasound. (EGA: Estimated Gestational Age ; NR: Not Realize)

		BILATERAL LOCATION			UNILATERAL LOCATION			DIFFERENTIAL DIAGNOSIS
		Abnormal appearance		*Normal appearance*	*Abnormal appearance*			*Abnormal appearance*
		Congenital Adrenal Hyperplasia	**Adrenocortical macrocyst** *(Beckwith Wiedemann Syndrome)*	**GDM FGR FIS**	**Neuroblastoma**	**Adrenal haemorrhage**	**Adrenal Cyst**	**Extralobar pulmonary sequestration**
Characteristic ultrasound signs	**Trimester at discovery**	Mid trimester Late trimester	Mid trimester Late trimester	Mid trimester Late trimester	Late trimester	Late trimester	Mid trimester Late trimester	Mid trimester Late trimester
	Preference Location	Bilateral	Bilateral ++ *(possible unilateral)*	Bilateral	Right	No preference	No preference	Left
	Prenatal Evolution Decrease Stable Increase	 - +++ -	 - + +++	 + +++ +	 + ++ +++	 +++ ++ +	 +++ ++ +	 + ++ +++
	Vascularization Vascularized mass Systemic artery	 No No	 No No	 No No	 Yes Yes	 No No	 No No	 Yes Yes
	Description of the lesion Well limited Structure	 Yes Cerebriform pattern	 No Cystic, Heterogeneous	 Yes Increase in size without abnormal aspect	 Yes Homogeneous *(solid form)* or Heterogeneous *(cystic form)*	 Yes Heterogeneous	 Yes Homogeneous	 No Homogeneous *(nodular form)* or Heterogeneous *(cystic-nodular form)*
	Elements of malignity *Partition, vegetation*	No	No	No	Yes	No	No	No
Prognostic Elements	**Fetal complications**	No	Organomegaly, Macroglossia, Omphalocele Polyhydramnios	No	Possible metastases *(liver ++, lungs, skull, bone marrow, placenta)*	No	No	Mass effect *(fattening diaphragmatic cupolas +/- pleural effusion)*
	Prognosis	Excellent with treatment	Dependent on associated malformations	Excellent	Good *(90% cure if early detection)*	Excellent	Excellent	Good

Table 2: Check list of characteristic ultrasound signs according to more frequent diagnosis of suprarenal mass and prognostic elements associated.

275 *(GDM: Gestational Diabetes Mellitus, FGR: fetal growth restriction, FIS: Fetal inflammatory syndrome*



276

277 *Figure 1: Normal appearance of adrenal glands (arrow) according to the trimester of pregnancy. (a) in the first trimester, in parasagittal view it appears as*

278 *hypoechoic triangle measuring grossly half the height of the kidney. (b) Then, from the second trimester onward, in axial view it takes an oval structure, (c)*

279 *with appearance of a hypoechoic cortex and a hyperechoic medullary during late trimester ultrasound.*

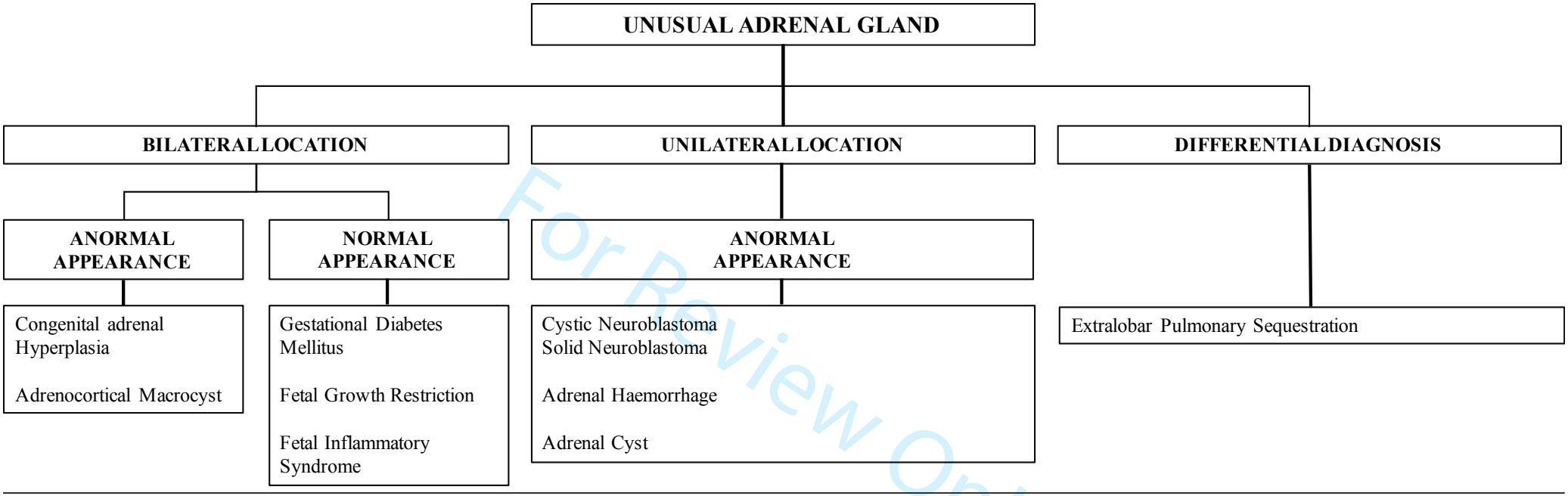


Figure 2: Diagnostic orientation of an atypical adrenal gland according to its type of location and appearance

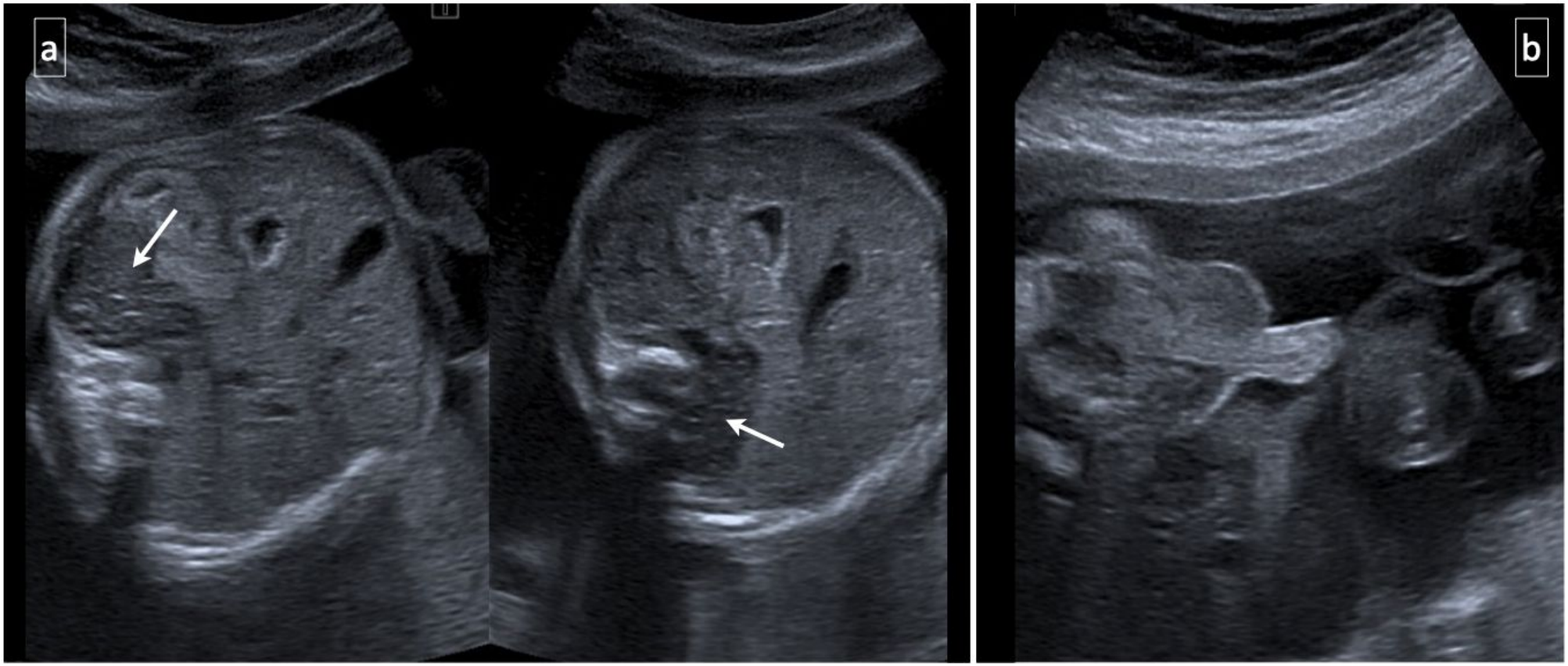


Figure 3: Congenital adrenal hyperplasia at 24 estimated gestational age, with a typical "cerebriform aspect" (a, arrow), associated with a virilization of the genitalia (b) in a male fetus.

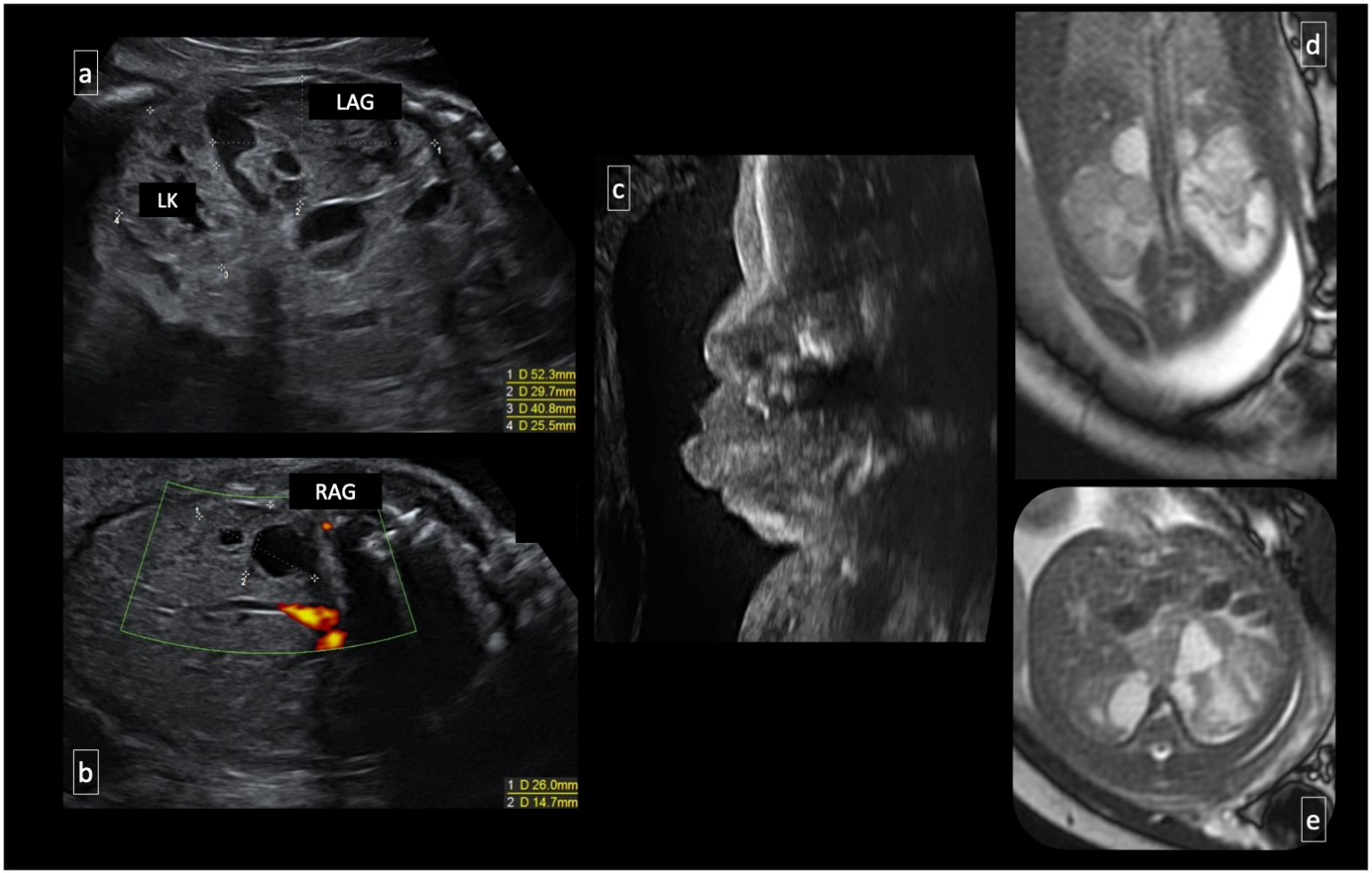


Figure 4: Ultrasound at 25 estimated gestational age in a male fetus showing bilateral partially hemorrhagic cysts on both adrenal glands. This typical ultrasound appearance, on the left(a) and on the right (b) associated with macroglossia (c) was consistent with adrenocortical macrocyst in the setting of Beckwith – Wiedemann syndrome. Fetal MRI was helpful, confirming the atypical appearance of the adrenals, here in frontal (d) and transverse view (e) on BFTE sequences. (LAG: Left Adrenal Gland; LK: Left Kidney; RAG: Right Adrenal Gland)

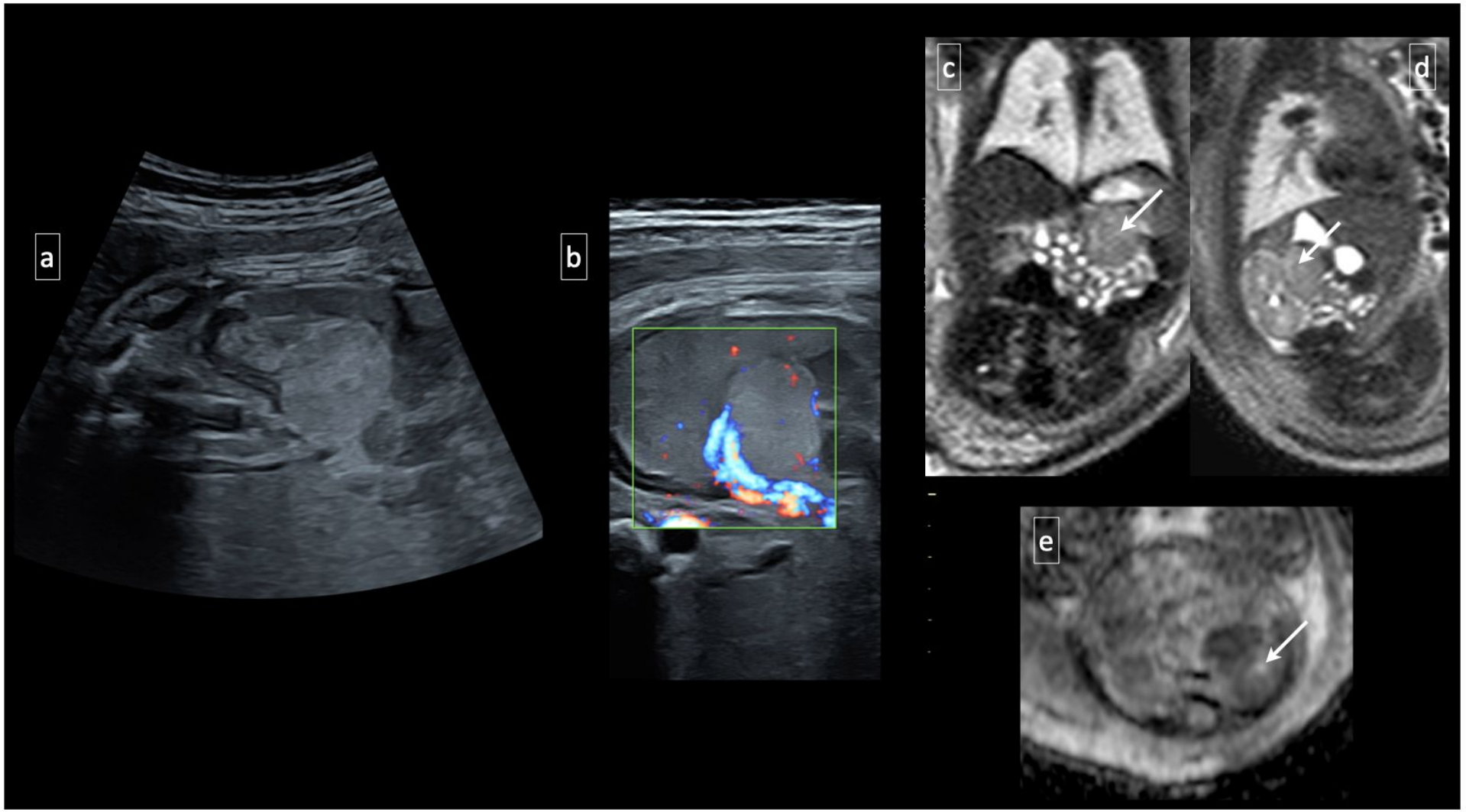


Figure 5: A prenatal well limited, heterogeneous (a) and vascularized (b) mass was diagnosed as a solid neuroblastoma at 35 estimated gestational age in a male fetus. Coronal (c) and sagittal (d) T2-weighted MR images show slightly hyperintense mass of the left adrenal compartment. (e) Apparent diffusion coefficient map shows hypointensity mass that confirming the malignant hypothesis.

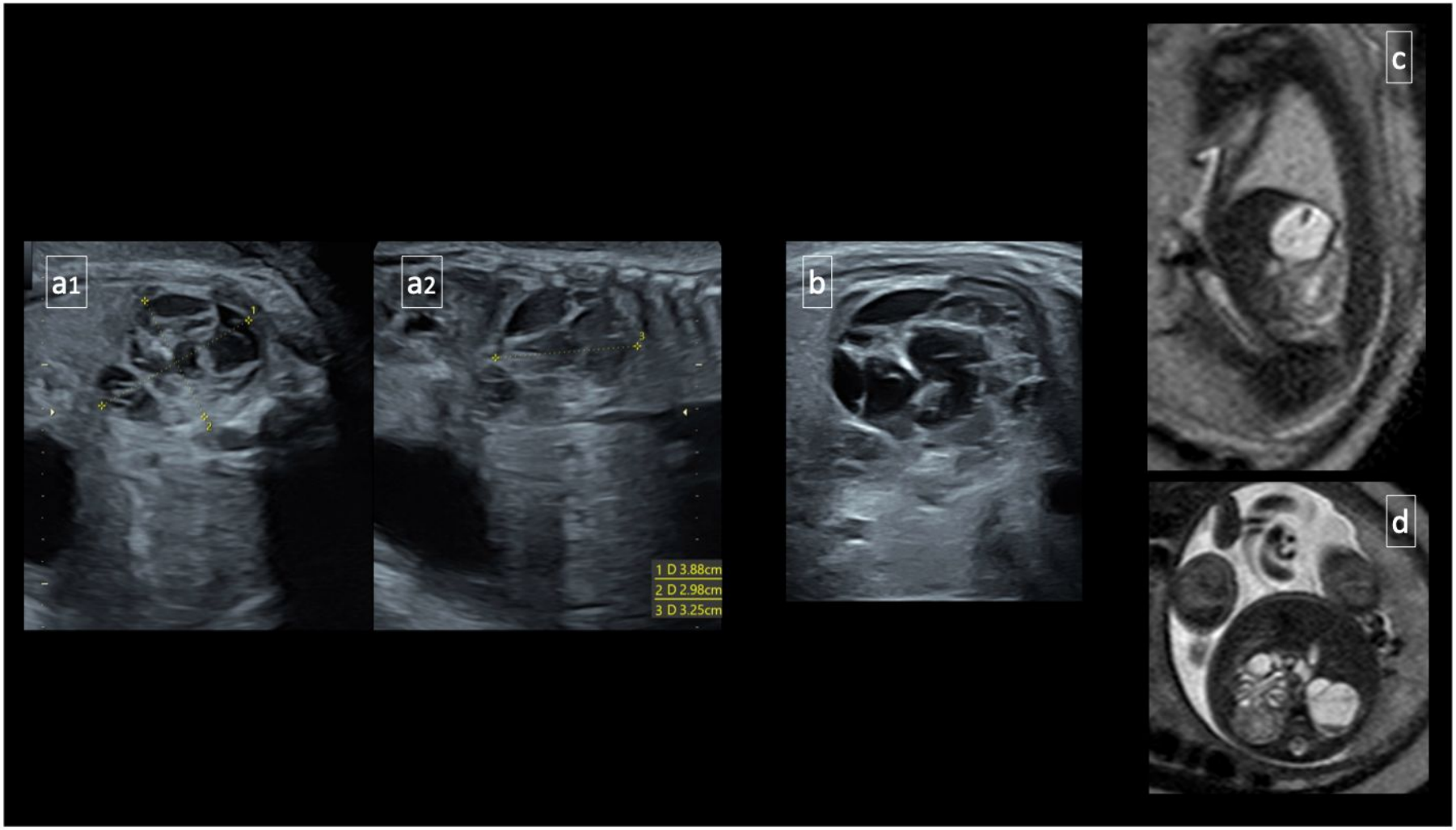


Figure 6: A heterogeneous and avascular mass of the right adrenal gland, with a changing sonographic pattern through follow-up, on a axial (a1), parasagittal (a2) and frontal views (b) is the typical aspect of an adrenal hemorrhage, at 34 weeks estimated gestational age, in a male fetus. Parasagittal (c) and transverse (d) T2- HASTE weighted images show hematic sediment confirming the hemorrhagic composition of the mass.

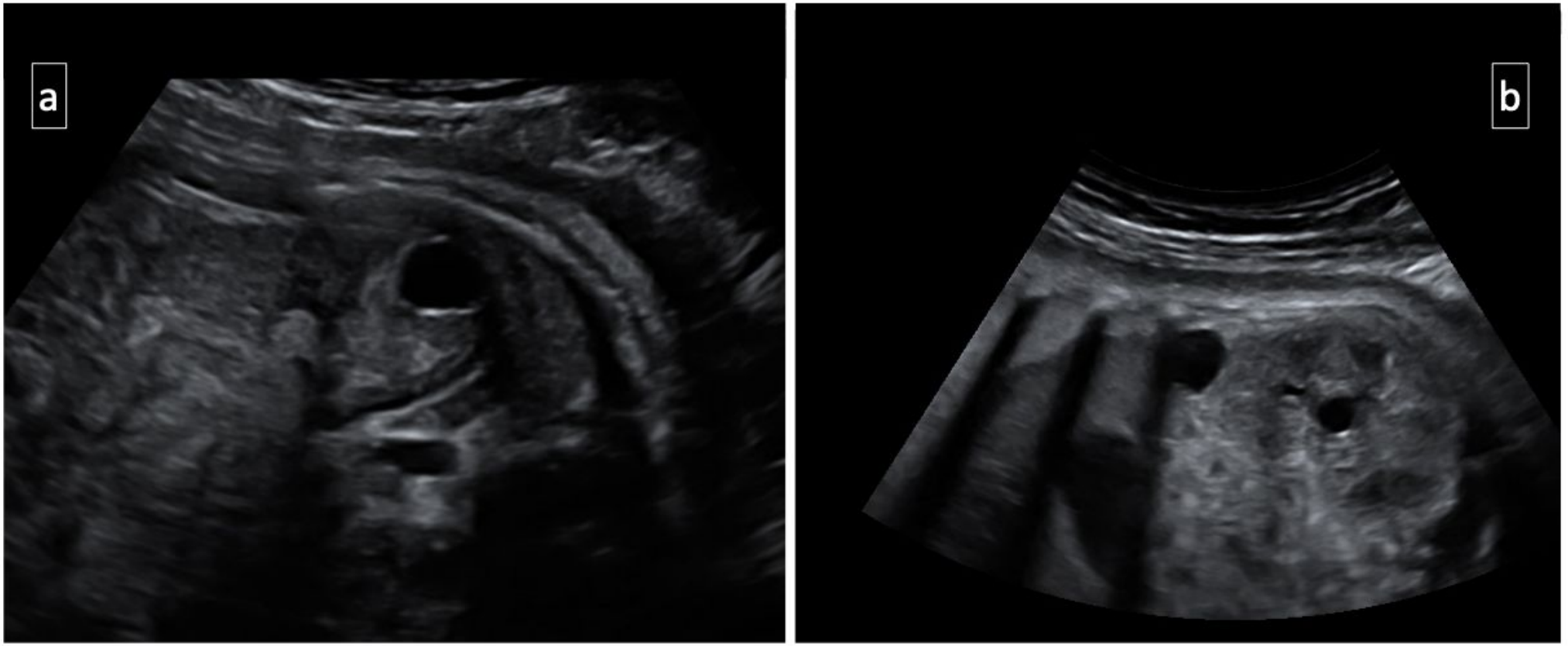


Figure 7: A well limited, isolated, hypoechogenic and homogeneous cyst located above the left kidney in axial (a) and parasagittal (b) views at 32 weeks estimated gestational age in a female fetus, consistent with an adrenal cyst.

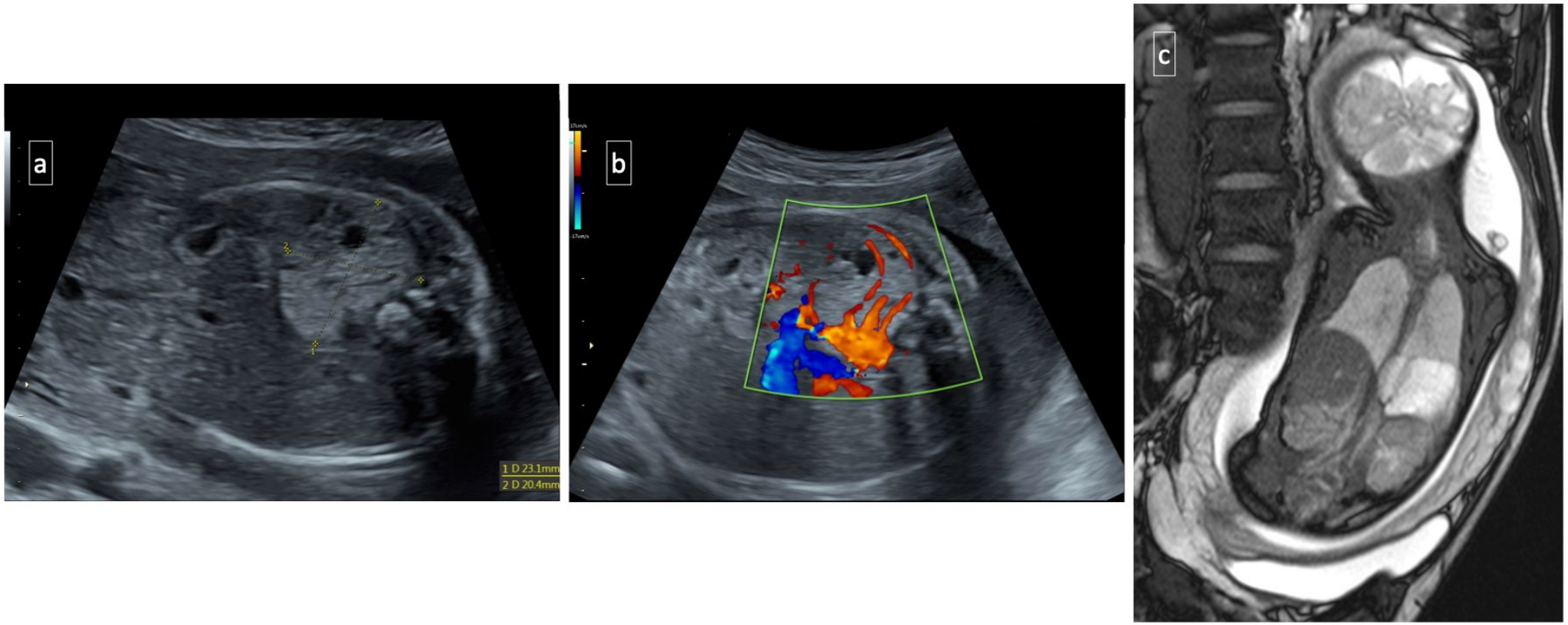


Figure 8: An extralobar pulmonary sequestration in a female fetus, represented by a heterogeneous mass, with mixed component, under the left diaphragm (a) vascularized by a multiple feeding arteries identified on Color Doppler Imaging (b) at 24 weeks estimated gestational age. (c) Coronal SSFSE T2w confirms the left lower lobe mass with systemic feeding vessels (arrow) coursing into the mass.

TITLE

Prenatal assessment of atypical adrenal glands: a systematic approach for diagnosis

AUTHORS

Emmanuelle Lesieur [(1)], Aurélie Noire [(2)], Paul Maurice [(3)], Catherine Garel [(4)], Jean-Marie Jouannic [(3)], Katia Chaumoitre [(5)], Florence Bretelle [(6)], Jean Baptiste Haumonte [(1)], Guillaume Gorincour [(7)], Edwin Quarello [(1,7)]

[(1)]: Screening and Diagnosis Unit, Obstetrics and Gynecology Department, St Joseph Hospital, 26 Bd de Louvain, Marseille Cedex 08, France.

[(2)] : Cabinet de Gynécologie et Obstétrique, 7 Av Gambetta, 83400 Hyères, France

[(3)]: Service de Médecine Fœtale, Hôpital Armand Trousseau, APHP. Sorbonne Université, 26 avenue A Netter, 75012 Paris, France.

[(4)] : Department of pediatric imaging, Hôpital d'Enfants Armand-Trousseau APHP. Sorbonne Université, 26 avenue A Netter, 75012 Paris France.

[(5)] : Service d'Imagerie Médicale, AP-HM Hôpital Nord, Chemin des Bourrely, 13015 Marseille, France.

[(6)]: Department of Gynaecology and Obstetrics, Gynepole, AP-HM, Assistance Publique-Hôpitaux de Marseille,Hôpital Nord, Chemin des Bourrely, 13015 Marseille AMU, Aix-Marseille Université, France.

[(7)] : IMAGE^2 Center, 6 rue Rocca, Marseille 13008, France

Correspondence :

Dr Edwin QUARELLO

Image 2 Center

6 rue Rocca

Marseille 13008

France

e.quarello@me.com

SUMMARY

The aim of this study was to identify specific unusual prenatal ultrasonographic patterns of the adrenal gland and to propose a systematic approach for diagnosis. Six foetuses with unusual aspects of one or both adrenal glands, detected during routine prenatal ultrasound screening, were evaluated. Prenatal and postnatal management are described. A checklist of ultrasound features was created in order to perform a detailed analysis of adrenal lesions and guide prenatal management; this includes: time of appearance, location, growth, vascularization, structure, and the presence of findings suggestive of malignancy.

Prenatal – ultrasound – adrenal gland – MRI – counseling

INTRODUCTION

With the widespread use of foetal ultrasound (US), identification of atypical suprarenal masses has become more common. Yet, optimal prenatal diagnosis and prognosis remain challenging.[1] Identifying characteristic imaging findings can help achieve the most relevant diagnosis.[2] Evaluation of the adrenal glands is not included in standard guidelines. Atypical presentation often results from an increased size and / or abnormal appearance (cystic, enlarged, pseudo-tumoural).

Although sufficient epidemiological knowledge of these atypical suprarenal entities is still lacking, five diagnoses stand out according to their location and characteristics: neuroblastoma (NB), congenital adrenal hyperplasia (CAH), adrenal haemorrhage (AH), adrenocortical macrocyst (AM), and adrenal cyst (AC). The main diagnostic issue is the exclusion of malignant neuroblastoma.[3–5] The principal differential diagnosis is subdiaphragmatic extralobar pulmonary sequestration (SEPS).[6] Other less frequent causes can, however, be considered such as enteric duplication cyst, some renal cystic diseases, kidney duplication with upper pole moiety dilatation, and focal renal dysplasia.[7–9]

The definitive diagnosis of an atypical suprarenal entity using US is challenging, especially since the complications specific to each diagnosis imply very different prognoses and postnatal care.[10] Although in most cases the diagnosis cannot be given prenatally, the distinction between specific US features provides a clearer picture to support parental counselling. Based on a series of six cases of atypical adrenal glands, the aim of this study was to propose a systematic US approach in order to aid diagnosis and improve perinatal care and counselling.

PATIENTS AND METHODS

We retrospectively reviewed the US descriptions of cases with an atypical aspect of one or both adrenals detected during routine prenatal US screening in three different prenatal diagnostic centres, in Marseille and Paris, France over a five-year period. In accordance with our country's regulations, the retrospective use of descriptive data does not require specific authorization in France (IRB or equivalent). Patients, all of whom are informed during US examinations of the possible use of their data for scientific purposes (informed consent), may at any time indicate their refusal.

During the period 2015-2020, cases were investigated in order to characterise different atypical adrenal entities. Six cases were encountered, leading to the characterization of six different entities. This analysis focused only on prenatal US description, and all recorded foetal US images were reviewed. The prenatal and postnatal management of each case is described. All US examinations were performed by expert clinicians. If magnetic resonance imaging (MRI) was performed, a precise evaluation of the lesion was carried out. Based on the data, a checklist of US features was then created in order to establish detailed analysis of the adrenal lesion and guide prenatal management.

RESULTS

Six unusual foetuses, detected during routine prenatal US screening, were assessed. In the first case, congenital hyperplasia of the adrenal gland was diagnosed antenatally followed by postnatal management. In the second case, an atypical adrenal gland was described in a patient with Beckwith-Wiedemann syndrome. The third illustrates the prenatal diagnosis of neuroblastoma together with postnatal management. In the fourth and fifth cases, a complex and a simple haemorrhagic cyst were diagnosed antenatally respectively. The last case involved extralobar pulmonary sequestration, a differential diagnosis that was established faced with an atypical adrenal mass. The description of these cases is presented in Table 1

DISCUSSION

Based on US foetal screening, the adrenal gland is one of the anatomical landmarks necessary to accurately define the abdominal perimeter in the mid and late trimesters of pregnancy. The normal appearance of adrenal glands changes with gestational age. In the first trimester, adrenal glands appear as hypoechoic triangles above the kidneys and measure about half the height of the kidney ***(Figure 1)***. They then gradually lengthen and take an inverted V shape above the kidney, to measure more than a third of the length of the kidney. In the third trimester, the appearance of corticomedullary differentiation is observed with a hypoechoic cortex and hyperechoic medulla ***(Figure 1)***.[11]

When an atypical adrenal gland is identified, six possible diagnoses should be initially considered, even if other, less frequent, causes are not excluded, as mentioned above ***(Figure 2).***[12]

First, the bilateral or unilateral presentation should be considered, followed by its sonographic appearance. When bilaterally increased in size and associated with normal sonographic appearance, this may indicate adrenal hypertrophy which can be encountered in some cases of gestational diabetes, intra-uterine growth retardation, and foetal inflammatory syndrome, especially in cases of premature rupture of the membranes.[13,14]

In bilateral cases with abnormal sonographic appearance, congenital adrenal hyperplasia (CAH) should be suspected ***(Table 1 - Case 1, Figure 3)***. This autosomal recessive disorder may be indicated by the association with two US features: a typical aspect of “cerebriform” adrenal glands, associated with virilization of the genitalia. Supported by a family history, these two US features favour the diagnosis of CAH. The prognosis is excellent with appropriate treatment.[15,16]Second, the presence of bilateral cysts with mixed content, possibly partially haemorrhagic, can raise suspicion of an adrenocortical macrocyst in the setting of Beckwith-Wiedemann syndrome. Other US features should be investigated, such as foetal macrosomia with polyhydramnios, macroglossia, and omphalocele ***(Table 1 – Case 2, Figure 4)***.[17–19]

When unilateral with an abnormal US appearance, neuroblastoma is the most frequent congenital malignant tumour of the adrenal (90%). It is most often on the right side (60%), but can be bilateral. Appearance is variable, and cystic in 50% of cases ***(Table 1 – Case 3, Figure 5)***. The contours of neuroblastoma are regular, and the presence of thick walls, vegetations or partitions can be suggestive. The prognosis is variable and depends on its appearance, time at onset and possible secondary locations.[20,21] Overall, a pure cystic form has

a good prognosis. Early detection is associated with a good outcome in more than 90% of cases. A few cases with secondary localization[22] and placental dissemination, with a high risk of foetal hydrops and maternal preeclampsia, have been described, most often with a poor prognosis.[23,24]

An adrenal haemorrhage presents as a rounded or oval, echogenic, heterogeneous and avascular mass of the adrenal area with a changing sonographic appearance, which may help diagnosis. Its size gradually decreases during pregnancy follow-up. Bilateral localization can help diagnosis, as well as specific MRI features ***(Table 1 – Case 4, Figure 6)***. A foetal adrenal haemorrhage can regress and disappear spontaneously during the prenatal period. Adrenal insufficiency is found very rarely, even in cases of bilateral adrenal hemorrhage.[25]

Isolated adrenal cysts ***(Table 1 – Case 5, Figure 7)*** can occur unilaterally. Differential diagnoses of neuroblastoma (cystic form) and adrenocortical macrocyst (Beckwith-Wiedemann syndrome) should be kept in mind. Spontaneous involution is most likely. An absence of malignancy must be confirmed at birth.[26,27]

The differential diagnosis for neuroblastoma is difficult during the prenatal period.[28]

Extralobar pulmonary sequestration is also generally diagnosed early in pregnancy, more commonly in the mid trimester ***(Table 1 – Case 6, Figure 8)***. It is defined as a portion of lung tissue that is totally discontinuous from the tracheobronchial tree and usually has its own pleural covering with an anomalous systemic blood supply.[6] It can have a variable sonographic appearance, and is more frequently left-sided. The US diagnosis is based on the demonstration of a feeding systemic artery that can be identified on colour Doppler imaging. Most often, the artery is derived from the terminal portion of the descending thoracic aorta or the upper part of the abdominal aorta.[29]

All specific prenatal features and prognostic factors of these three entities are summarized in Table 2.

MRI can be a useful adjunct in the prenatal diagnosis of unusual suprarenal entities. Indeed, MRI confirms US diagnosis, complements US in equivocal diagnoses, and may lead to detection of additional findings.[30]

Regarding term at delivery, although some authors have suggested that the increase in size of the adrenal gland may be related to preterm delivery,[31] especially when associated with polyhydramnios, others believe that there is no relationship between size of the adrenal gland and gestational age at delivery.[32]

The treatment of such entities has not yet been determined, and recommendations have changed in recent years. Initially, surgery was favoured in all cases[33,34], then a wait-and-see attitude, based on close prenatal and

postnatal US follow-up, was promoted.[4,35] Overall, patients prenatally diagnosed with extralobar pulmonary sequestration have an excellent prognosis and a wait-and-see attitude, followed by possible postnatal embolization and/or resection, is recommended.[36] As far as adrenal haemorrhage is concerned, therapeutic abstention is required. Regarding neuroblastomas, surgical excision is performed immediately for tissue / mixed forms that have increased in volume. For prenatal cystic and stable forms, a wait-and-see attitude could be proposed initially, to be re-evaluated on a case-by-case basis.

Appropriate prenatal assessment and close sonographic monitoring may avoid surgery in cases of benign masses such as adrenal haemorrhage or spontaneously regressing neuroblastomas.

CONCLUSION

Prenatal US diagnosis of atypical adrenal glands requires a detailed analysis of the lesion, since the prognosis and morbidity vary according to final diagnoses. Knowledge and distinction of relevant US signs are necessary for optimal management. The analysis of atypical adrenal glands underlines the complexity of foetal US and the gap between prenatally suspected conditions and final postnatal diagnosis, which may be potentially very different. Optimization of US analysis may improve perinatal care and prenatal counselling.

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	DIAGNOSIS	Congenital adrenal hyperplasia	Adrenocortical macrocyst Beckwith Wiedemann Syndrome	Solid neuroblastoma	Adrenal haemorrhage	Isolated adrenal cyst	Left extralobar pulmonary sequestration
PRENATAL MANAGEMENT	PATIENT'S AGE (years)	37	31	26	32	26	29
	TRIMESTER AND WG AT DISCOVERY (EGA)	Mid trimester 24	Mid trimester 25	Late trimester 35	Late trimester 34	Late trimester 32	Mid trimester 24
	LOCATION	Bilateral	Bilateral	Unilateral left	Unilateral right	Unilateral left	Unilateral left
	FETAL GENDER	Male	Male	Male	Male	Female	Female
	ANTENATAL ULTRASOUND FEATURES ▪ Size (mm) ▪ Structure ▪ Vascularized ▪ Systemic vessel ▪ Associated findings	 Increased Cerebriform aspect No No Penis increased in size Family history of CAH	 50 x 40 Multicystic with mixed content Heterogeneous No No macroglossia	 22 x 32 Hyperechoic Homogeneous Yes No No	 38 x 29 Altered content Heterogeneous No No No	 10 x 8 Hypoechogenic Homogeneous No No No	 30 x 20 Mixed component Heterogeneous Yes Yes (from the aorta) No
	FETAL MRI ▪ When (WG) ▪ Location ▪ Structure ▪ Associated findings	 NR NR NR NR	 28 Bilateral Cystic and heterogeneous formation Macroglossia	 37 Unilateral left Prerenal Retrogastric Well limited, Heterogeneous, No hemorrhagic signs No	 35 Unilateral right Cystic and heterogeneous formation No	 NR NR NR NR	 29 and 33 Thoraco abdominal junction Plurilocular cystic formation a systemic posterior vessel arising from the aorta
	PRENATAL EVOLUTION	Stable	Increase	Increase	Decrease	Stable	Increase
	PROPOSED PRENATAL DIAGNOSIS	Congenital adrenal hyperplasia	Adrenocortical macrocyst Beckwith Wiedemann Syndrome	Solid neuroblastoma, Adrenal haemorrhage	Adrenal haemorrhage, Cystic neuroblastoma	Isolated adrenal cyst	Left extralobar pulmonary sequestration
POSTNATAL MANAGEMENT	COMPLEMENTARY EXAMS ▪ Urinary catecholamine ▪ Androgenic marquors ▪ Postnatal ultrasound / MRI Lesion confirmed Associated elements ▪ Histological findings post-surgery	 Negative 21-H deficiency Yes No -	 NR NR NR NR NR	 Positive Normal Yes Liver metastases (present at 1 month) Malignant cells	 Negative Normal Yes No NR	 NR NR Yes No No malignant cells	 Negative Normal Yes No Lung cells – no malignant cells
	EVOLUTION	Normal aspect at one week and one month with treatment	Termination of pregnancy Pathology: fetal macrosomia, macroglossia, bilateral nephromegaly, bilateral adrenal masses with haemorrhagic lesion on the left. No malignant cells.	Spontaneous regression, then stabilization	Spontaneous regression	Stabilization	Stabilization
	THERAPEUTIC PROTOCOL	Hydrocortisone and fludrocortisone therapy	NR	Close monitoring, then, Surgery	Close monitoring	Monitoring (spontaneous regression)	Close monitoring

271

272 *Table 1: Observations of fetuses with atypical adrenal gland detected during routine prenatal ultrasound. (EGA: Estimated Gestational Age ; NR: Not Realize)*

		BILATERAL LOCATION			**UNILATERAL LOCATION**			**DIFFERENTIAL DIAGNOSIS**
		Abnormal appearance		*Normal appearance*	*Abnormal appearance*			*Abnormal appearance*
		Congenital Adrenal Hyperplasia	**Adrenocortical macrocyst** *(Beckwith Wiedemann Syndrome)*	**GDM FGR FIS**	**Neuroblastoma**	**Adrenal haemorrhage**	**Adrenal Cyst**	**Extralobar pulmonary sequestration**
Characteristic ultrasound signs	**Trimester at discovery**	Mid trimester Late trimester	Mid trimester Late trimester	Mid trimester Late trimester	Late trimester	Late trimester	Mid trimester Late trimester	Mid trimester Late trimester
	Preference Location	Bilateral	Bilateral ++ *(possible unilateral)*	Bilateral	Right	No preference	No preference	Left
	Prenatal Evolution Decrease Stable Increase	 - +++ -	 - + +++	 + +++ +	 + ++ +++	 +++ ++ +	 +++ ++ +	 + ++ +++
	Vascularization Vascularized mass Systemic artery	 No No	 No No	 No No	 Yes Yes	 No No	 No No	 Yes Yes
	Description of the lesion Well limited Structure	 Yes Cerebriform pattern	 No Cystic, Heterogeneous	 Yes Increase in size without abnormal aspect	 Yes Homogeneous *(solid form)* or Heterogeneous *(cystic form)*	 Yes Heterogeneous	 Yes Homogeneous	 No Homogeneous *(nodular form)* or Heterogeneous *(cystic-nodular form)*
	Elements of malignity *Partition, vegetation*	No	No	No	Yes	No	No	No
Prognostic Elements	**Fetal complications**	No	Organomegaly, Macroglossia, Omphalocele Polyhydramnios	No	Possible metastases *(liver ++, lungs, skull, bone marrow, placenta)*	No	No	Mass effect *(fattening diaphragmatic cupolas +/- pleural effusion)*
	Prognosis	Excellent with treatment	Dependent on associated malformations	Excellent	Good *(90% cure if early detection)*	Excellent	Excellent	Good

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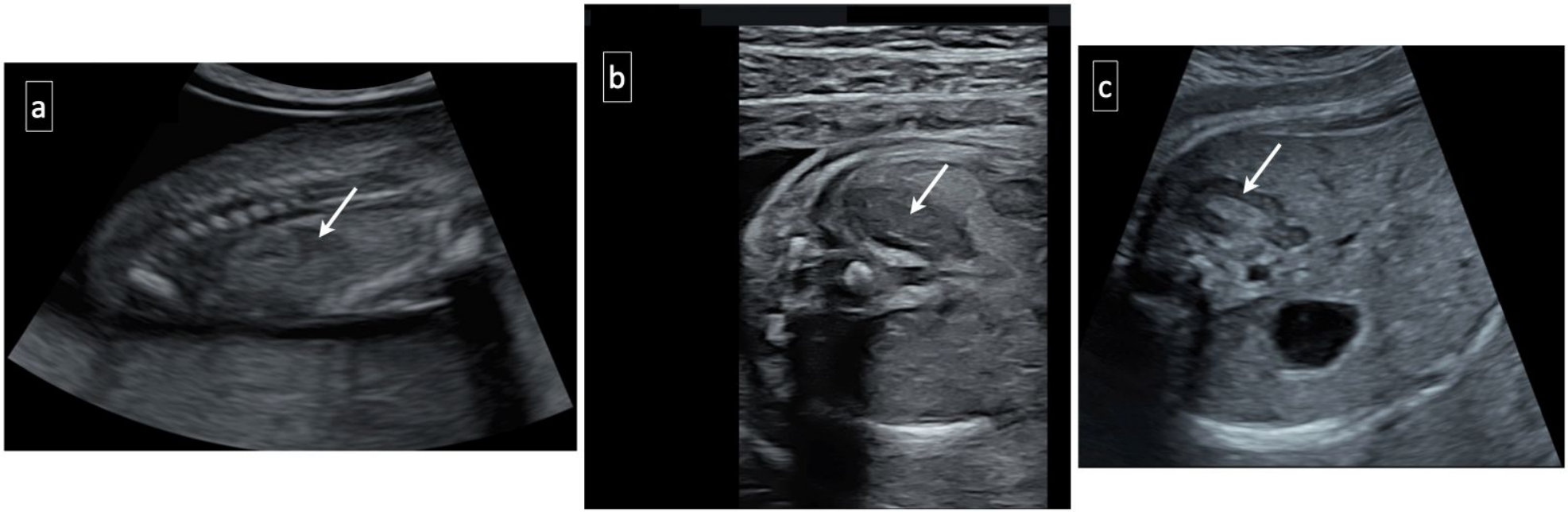
274 *Table 2: Check list of characteristic ultrasound signs according to more frequent diagnosis of suprarenal mass and prognostic elements associated.*

275 *(GDM: Gestational Diabetes Mellitus, FGR: fetal growth restriction, FIS: Fetal inflammatory syndrome*



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277 *Figure 1: Normal appearance of adrenal glands (arrow) according to the trimester of pregnancy. (a) in the first trimester, in parasagittal view it appears as*

278 *hypoechoic triangle measuring grossly half the height of the kidney. (b) Then, from the second trimester onward, in axial view it takes an oval structure, (c)*

279 *with appearance of a hypoechoic cortex and a hyperechoic medullary during late trimester ultrasound.*

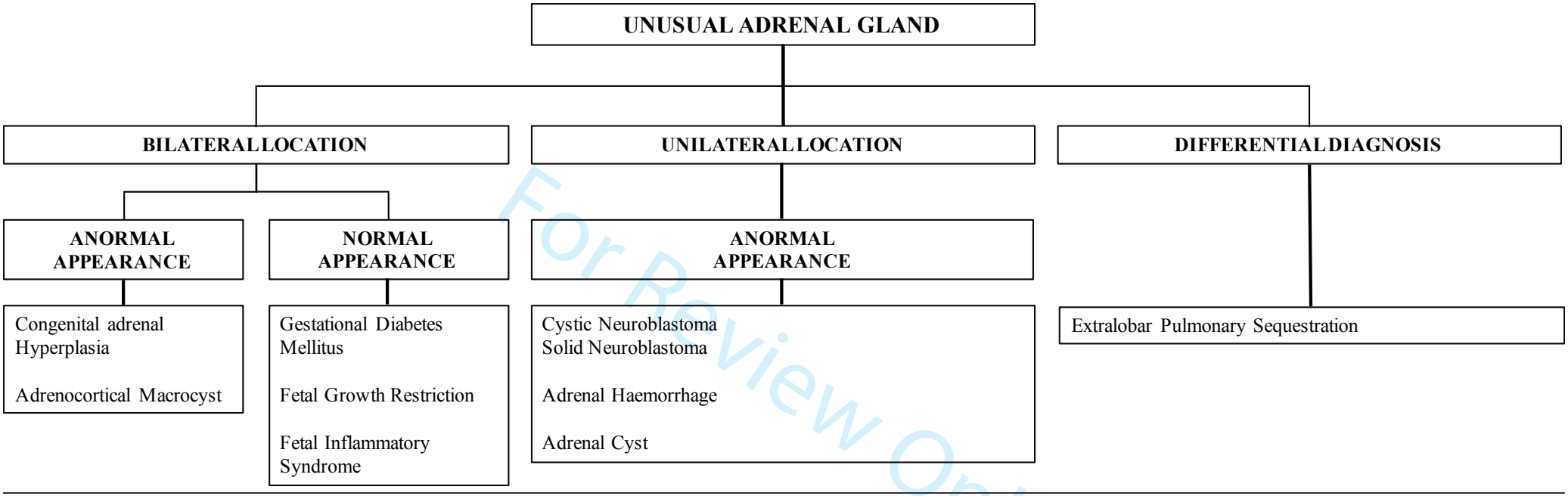


Figure 2: Diagnostic orientation of an atypical adrenal gland according to its type of location and appearance

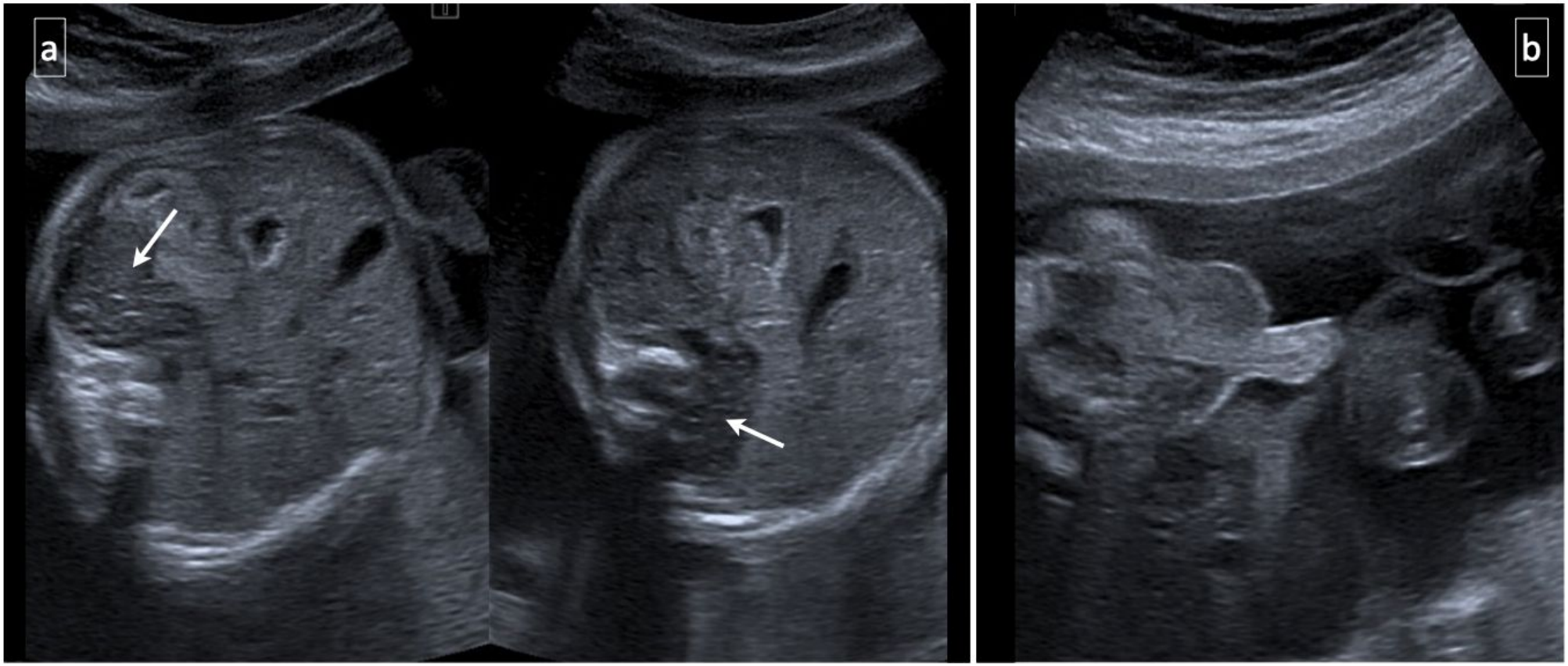
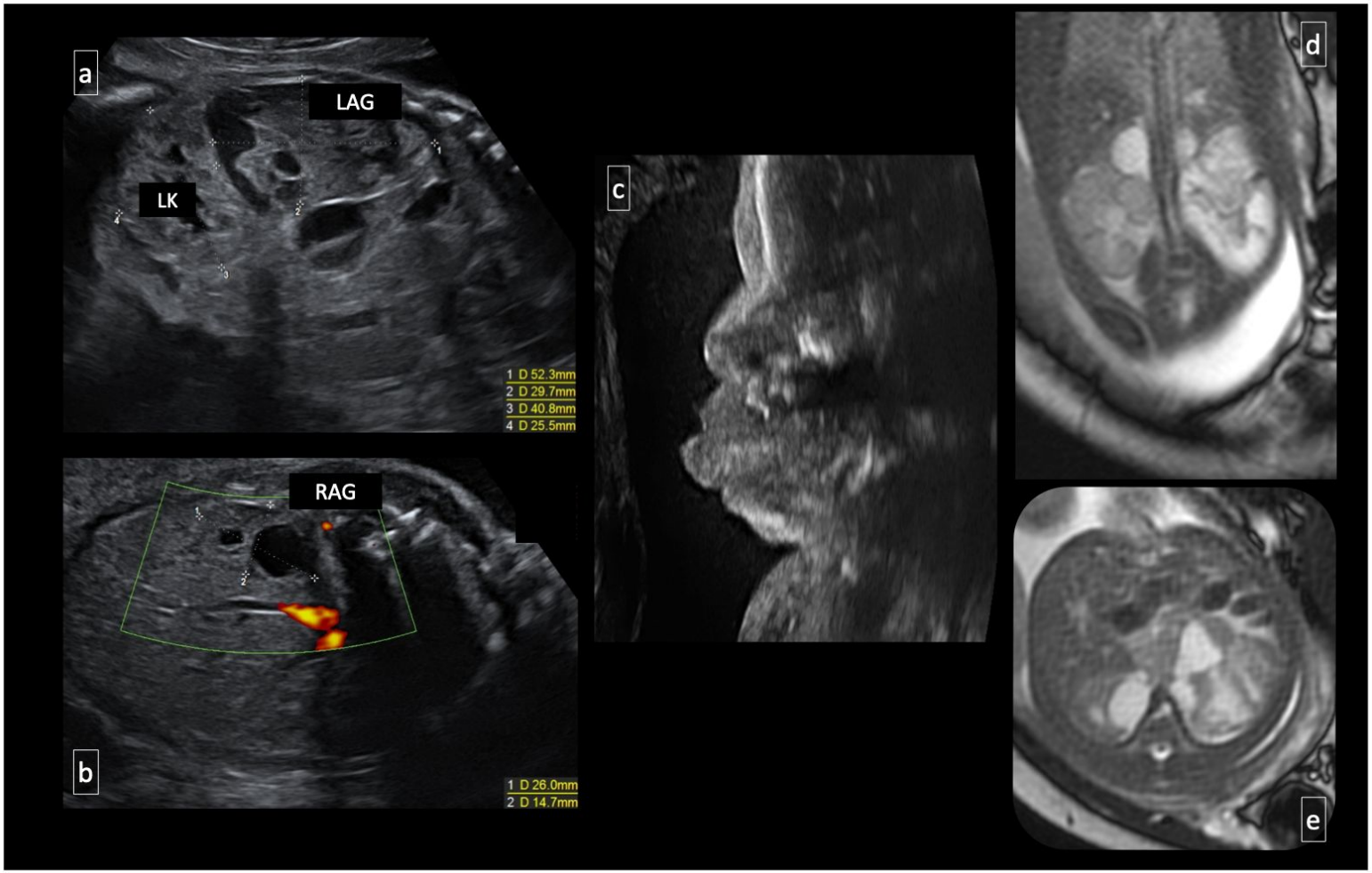


Figure 3: Congenital adrenal hyperplasia at 24 estimated gestational age, with a typical "cerebriform aspect" (a, arrow), associated with a virilization of the genitalia (b) in a male fetus.



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289 *Figure 4: Ultrasound at 25 estimated gestational age in a male fetus showing bilateral partially hemorrhagic cysts on both adrenal glands. This typical*

290 *ultrasound appearance, on the left(a) and on the right (b) associated with macroglossia (c) was consistent with adrenocortical macrocyst in the setting of*

291 *Beckwith – Wiedemann syndrome. Fetal MRI was helpful, confirming the atypical appearance of the adrenals, here in frontal (d) and transverse view (e) on*

292 *BFTE sequences. (LAG: Left Adrenal Gland; LK: Left Kidney; RAG: Right Adrenal Gland)*

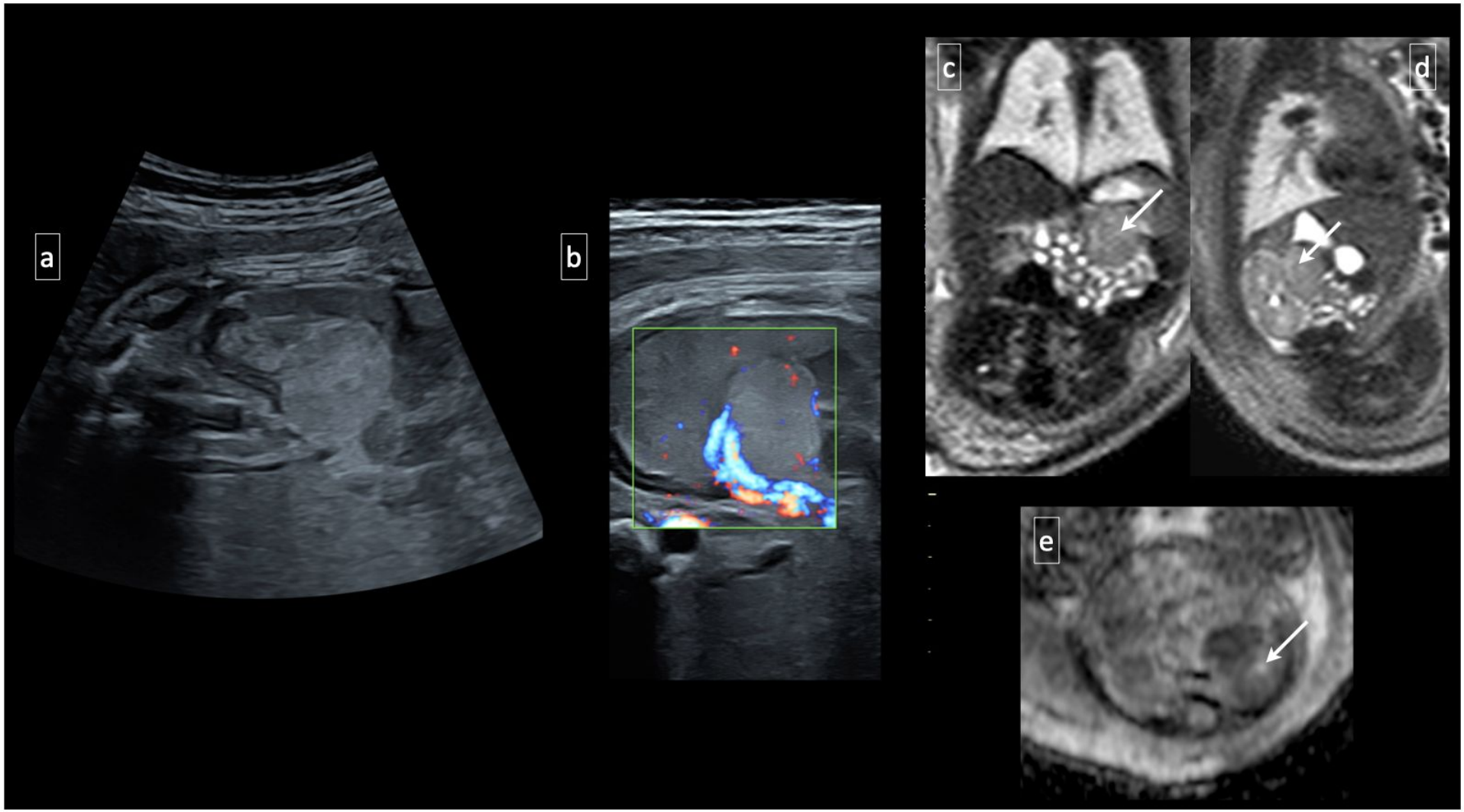


Figure 5: A prenatal well limited, heterogeneous (a) and vascularized (b) mass was diagnosed as a solid neuroblastoma at 35 estimated gestational age in a male fetus. Coronal (c) and sagittal (d) T2-weighted MR images show slightly hyperintense mass of the left adrenal compartment. (e) Apparent diffusion coefficient map shows hypointensity mass that confirming the malignant hypothesis.

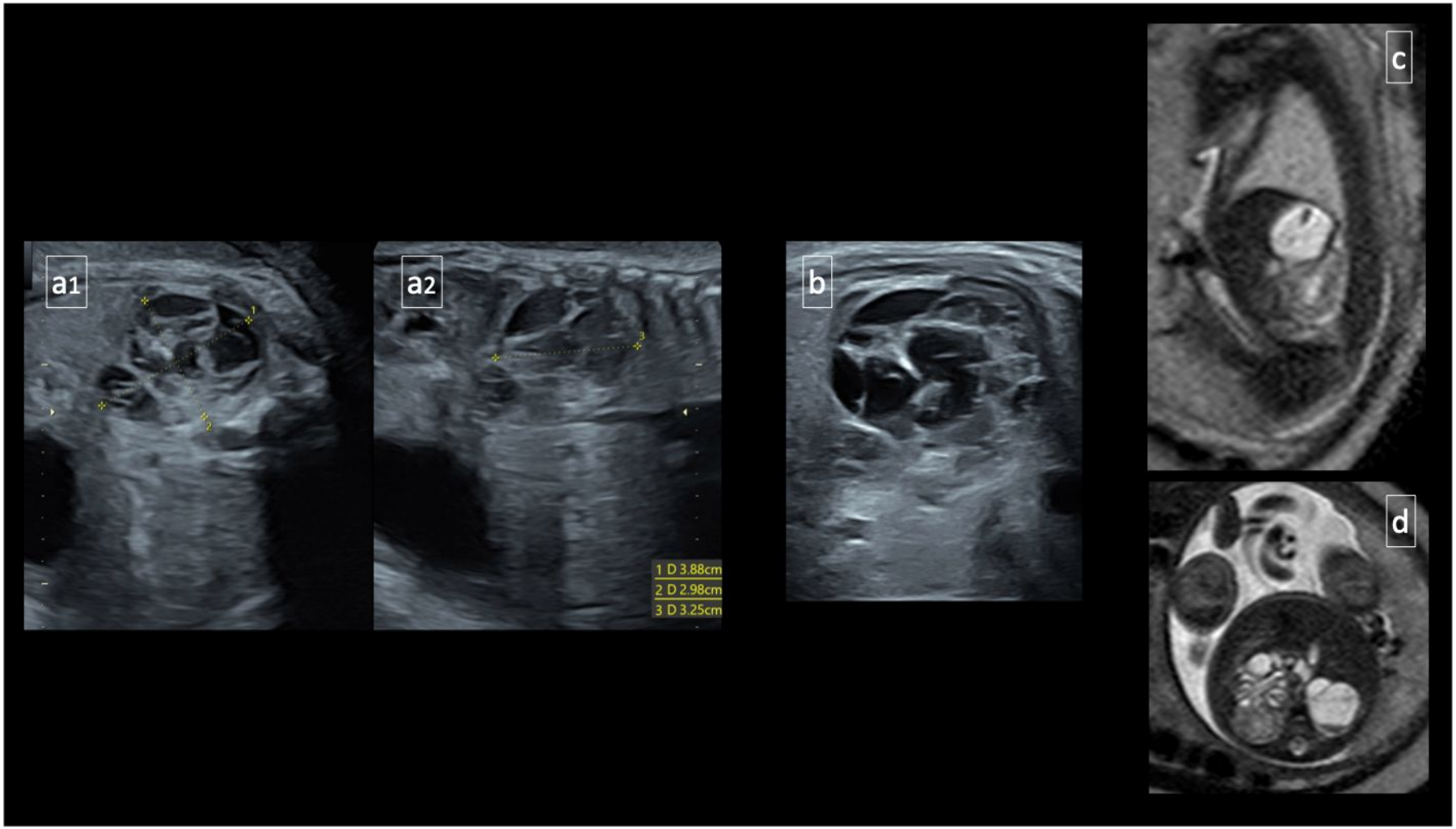
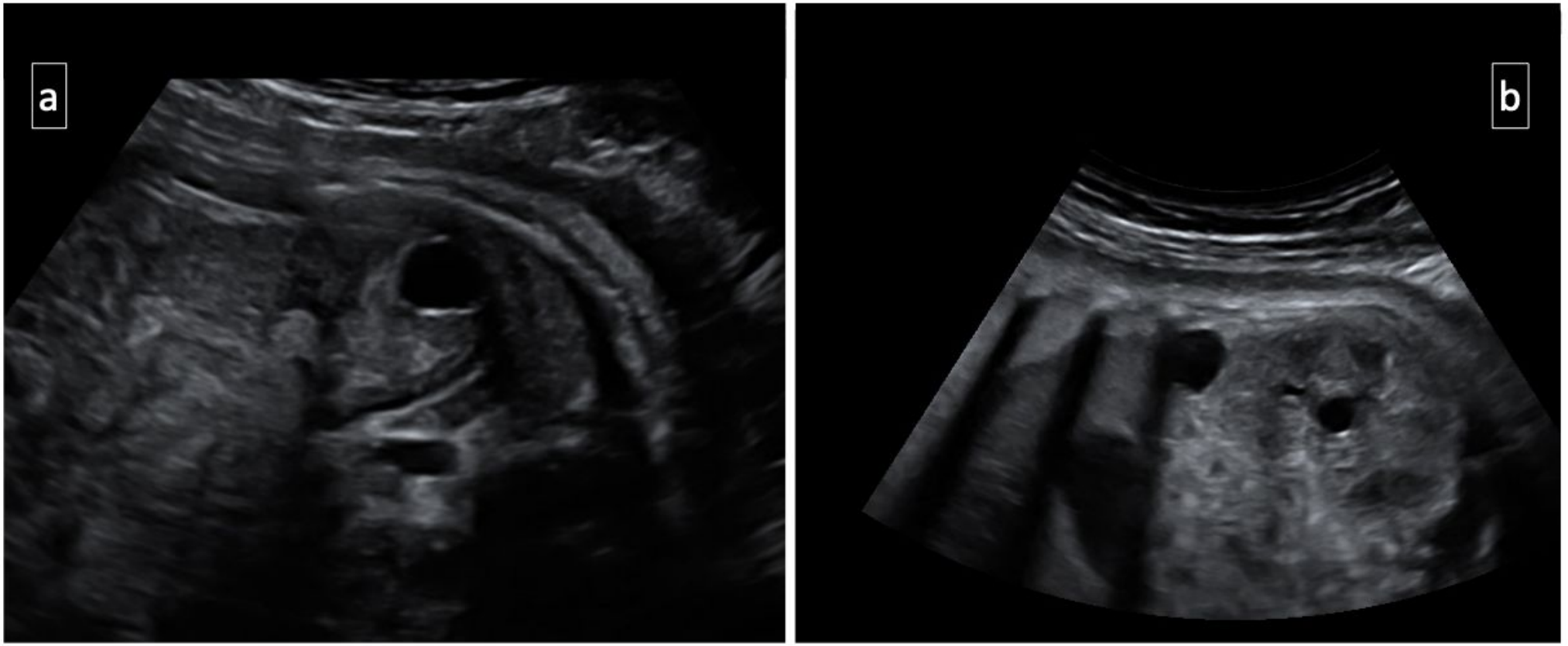


Figure 6: A heterogeneous and avascular mass of the right adrenal gland, with a changing sonographic pattern through follow-up, on a axial (a1), parasagittal (a2) and frontal views (b) is the typical aspect of an adrenal hemorrhage, at 34 weeks estimated gestational age, in a male fetus. Parasagittal (c) and transverse (d) T2- HASTE weighted images show hematic sediment confirming the hemorrhagic composition of the mass.



302

303 *Figure 7: A well limited, isolated, hypoechogenic and homogeneous cyst located above the left kidney in axial (a) and parasagittal (b) views at 32 weeks*
304 *estimated gestational age in a female fetus, consistent with an adrenal cyst.*

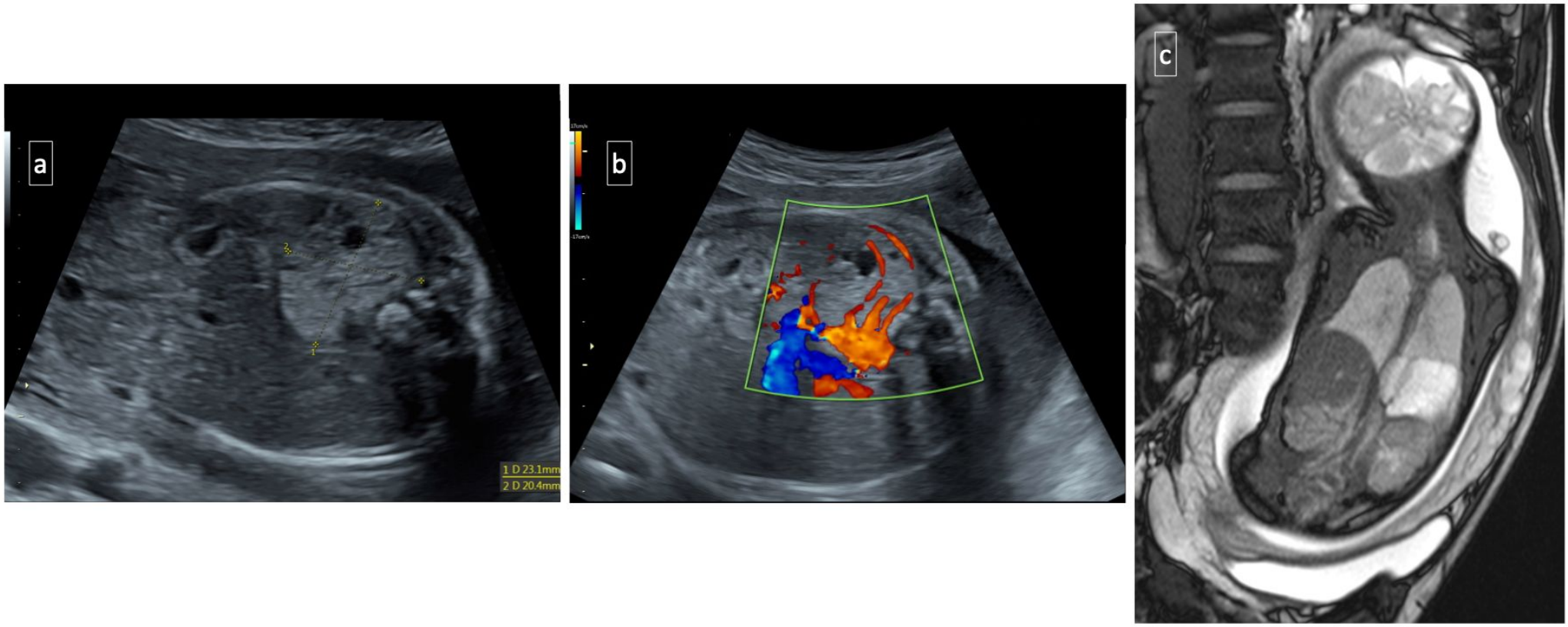
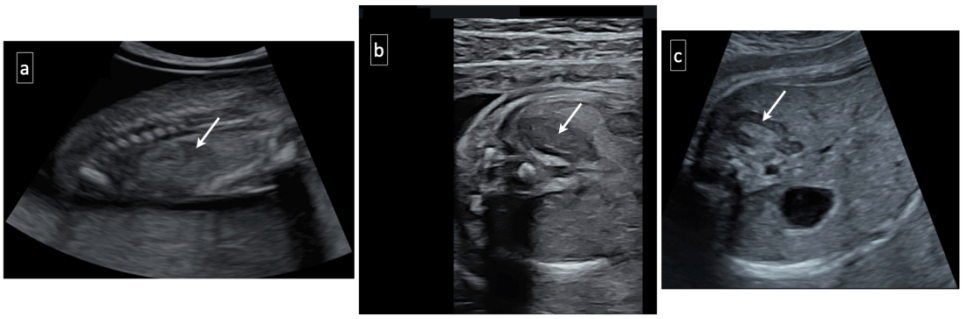
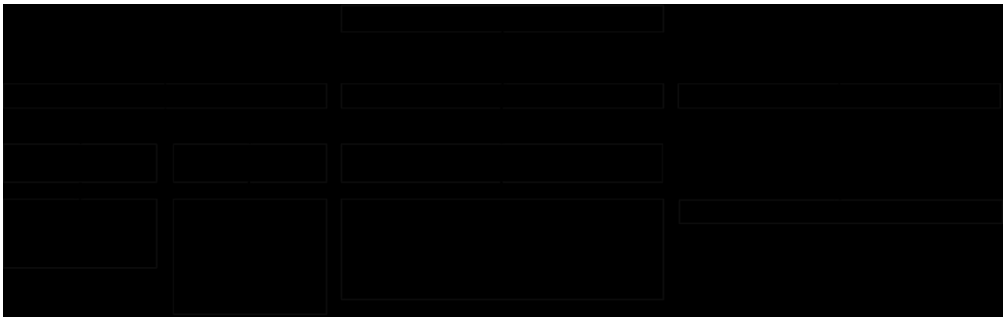


Figure 8: An extralobar pulmonary sequestration in a female fetus, represented by a heterogeneous mass, with mixed component, under the left diaphragm (a) vascularized by a multiple feeding arteries identified on Color Doppler Imaging (b) at 24 weeks estimated gestational age. (c) Coronal SSFSE T2w confirms the left lower lobe mass with systemic feeding vessels (arrow) coursing into the mass.

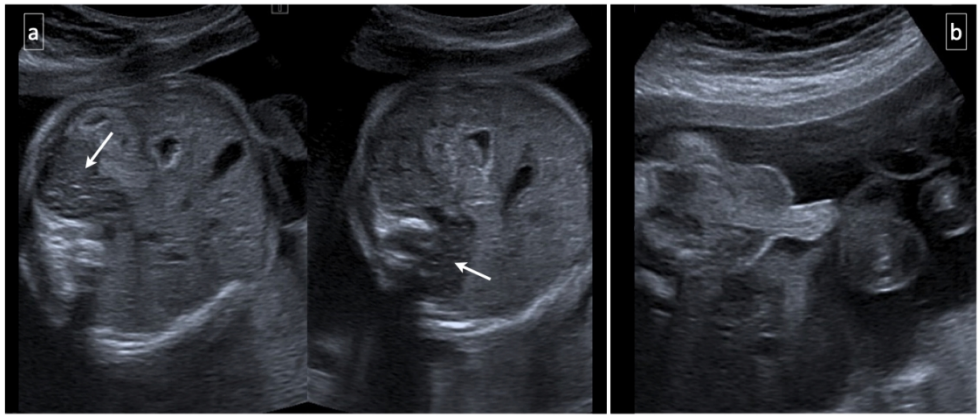


Normal appearance of adrenal glands (arrow) according to the trimester of pregnancy. (a) in the first trimester, in parasagittal view it appears as hypoechoic triangle measuring grossly half the height of the kidney. (b) Then, from the second trimester onward, in axial view it takes an oval structure, (c) with appearance of a hypoechoic cortex and a hyperechoic medullary during late trimester ultrasound.

581x201mm (72 x 72 DPI)



Diagnostic orientation of an atypical adrenal gland according to its type of location and appearance



Congenital adrenal hyperplasia at 24 estimated gestational age, with a typical "cerebriform aspect" (a, arrow), associated with a virilization of the genitalia (b) in a male fetus.

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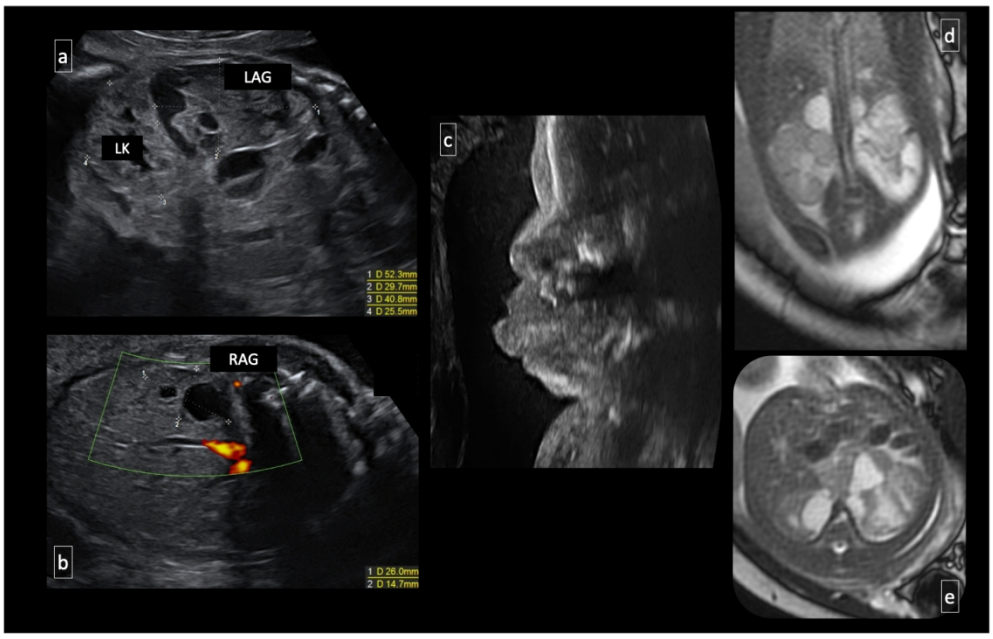

Ultrasound at 25 estimated gestational age in a male fetus showing bilateral partially hemorrhagic cysts on both adrenal glands. This typical ultrasound appearance, on the left(a) and on the right (b) associated with macroglossia (c) was consistent with adrenocortical macrocyst in the setting of Beckwith – Wiedemann syndrome. Fetal MRI was helpful, confirming the atypical appearance of the adrenals, here in frontal (d) and transverse view (e) on BFTE sequences. (LAG: Left Adrenal Gland; LK: Left Kidney; RAG: Right Adrenal Gland)

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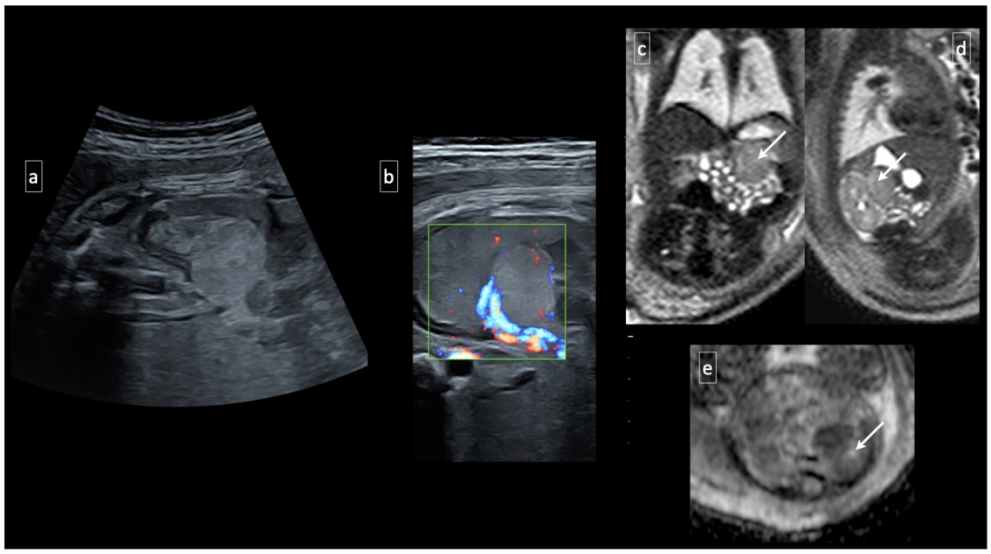

A prenatal well limited, heterogeneous (a) and vascularized (b) mass was diagnosed as a solid neuroblastoma at 35 estimated gestational age in a male fetus. Coronal (c) and sagittal (d) T2-weighted MR images show slightly hyperintense mass of the left adrenal compartment. (e) Apparent diffusion coefficient map shows hypointensity mass that confirming the malignant hypothesis.

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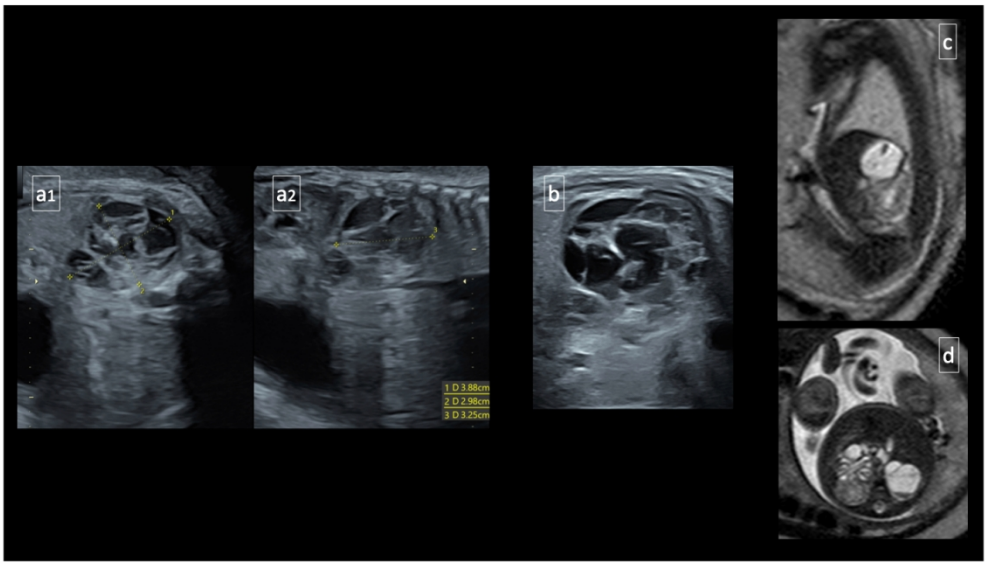

A heterogeneous and avascular mass of the right adrenal gland, with a changing sonographic pattern through follow-up, on a axial (a1), parasagittal (a2) and frontal views (b) is the typical aspect of an adrenal hemorrhage, at 34 weeks estimated gestational age, in a male fetus. Parasagittal (c) and transverse (d) T2-HASTE weighted images show hematic sediment confirming the hemorrhagic composition of the mass.

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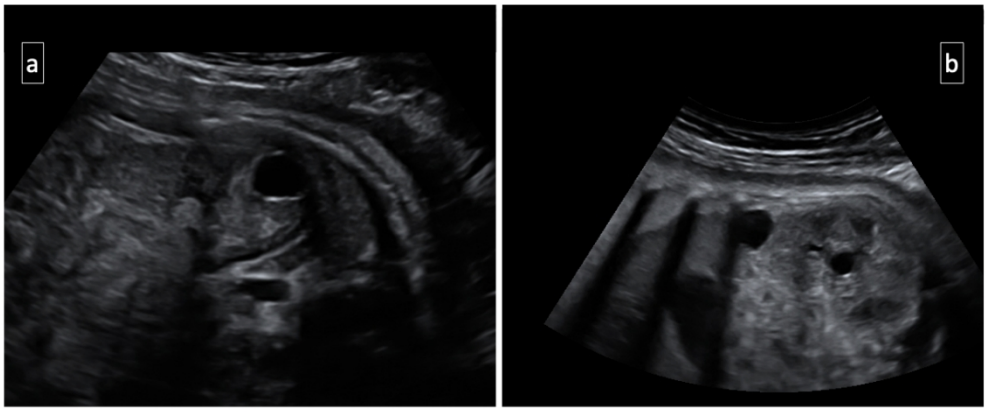

A well limited, isolated, hypoechogenic and homogeneous cyst located above the left kidney in axial (a) and parasagittal (b) views at 32 weeks estimated gestational age in a female fetus, consistent with an adrenal cyst.

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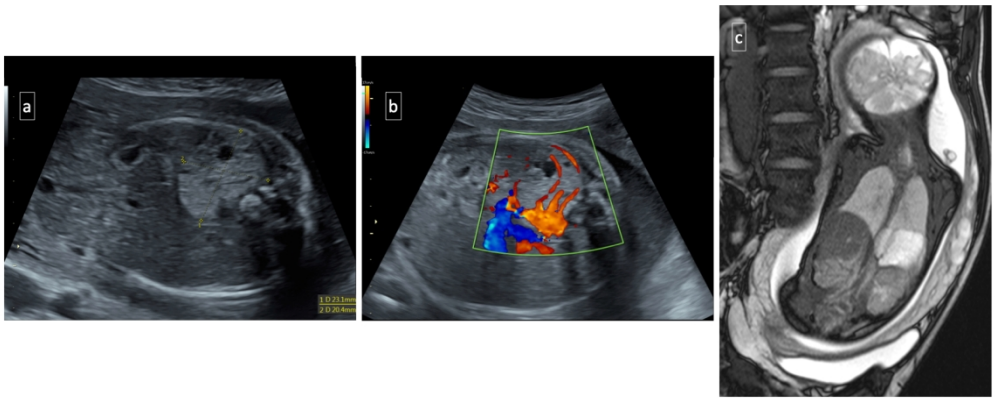

An extralobar pulmonary sequestration in a female fetus, represented by a heterogeneous mass, with mixed component, under the left diaphragm (a) vascularized by a multiple feeding arteries identified on Color Doppler Imaging (b) at 24 weeks estimated gestational age. (c) Coronal SSFSE T2w confirms the left lower lobe mass with systemic feeding vessels (arrow) coursing into the mass.

639x258mm (72 x 72 DPI)