

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

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#### 36 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.

43 Prenatal – ultrasound – adrenal gland – MRI – counseling

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#### 45 **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.<sup>1</sup> Identifying characteristic imaging findings can help achieve the most relevant diagnosis.<sup>2</sup> 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.<sup>3–5</sup> The principal differential diagnosis is subdiaphragmatic extralobar pulmonary sequestration (SEPS).<sup>6</sup> 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.<sup>7–9</sup>

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.<sup>10</sup> 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.

#### 92 **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

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#### 100 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)*.<sup>11</sup>

108 When an atypical adrenal gland is identified, six possible diagnoses should be initially considered, even if 109 other, less frequent, causes are not excluded, as mentioned above *(Figure 2).*<sup>12</sup>

First, the bilateral or unilateral presentation should be considered, followed by its sonographic appearance. 110 When bilaterally increased in size and associated with normal sonographic appearance, this may indicate 111 adrenal hypertrophy which can be encountered in some cases of gestational diabetes, intra-uterine growth 112 retardation, and foetal inflammatory syndrome, especially in cases of premature rupture of the membranes.<sup>13,14</sup> 113 In bilateral cases with abnormal sonographic appearance, congenital adrenal hyperplasia (CAH) should be 114 suspected (Table 1 - Case 1, Figure 3). This autosomal recessive disorder may be indicated by the association 115 with two US features: a typical aspect of "cerebriform" adrenal glands, associated with virilization of the 116 genitalia. Supported by a family history, these two US features favour the diagnosis of CAH. The prognosis 117 is excellent with appropriate treatment.<sup>15,16</sup>Second, the presence of bilateral cysts with mixed content, possibly 118 partially haemorrhagic, can raise suspicion of an adrenocortical macrocyst in the setting of Beckwith-119 Wiedemann syndrome. Other US features should be investigated, such as foetal macrosomia with 120 polyhydramnios, macroglossia, and omphalocele (Table 1 – Case 2, Figure 4).<sup>17–19</sup> 121

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.<sup>20,21</sup> 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<sup>22</sup> and placental dissemination, with a high risk of foetal hydrops and maternal
preeclampsia, have been described, most often with a poor prognosis.<sup>23,24</sup>

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.<sup>25</sup>

135 Isolated adrenal cysts (Table 1 - Case 5, Figure 7) can occur unilaterally. Differential diagnoses of

136 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.<sup>26,27</sup>

138 The differential diagnosis for neuroblastoma is difficult during the prenatal period.<sup>28</sup>

139 Extralobar pulmonary sequestration is also generally diagnosed early in pregnancy, more commonly in the

140 mid trimester (*Table 1 – Case 6, Figure 8*). It is defined as a portion of lung tissue that is totally

141 discontinuous from the tracheobronchial tree and usually has its own pleural covering with an anomalous

142 systemic blood supply.<sup>6</sup> It can have a variable sonographic appearance, and is more frequently left-sided.

143 The US diagnosis is based on the demonstration of a feeding systemic artery that can be identified on colour 144 Doppler imaging. Most often, the artery is derived from the terminal portion of the descending thoracic aorta

145 or the upper part of the abdominal aorta.<sup>29</sup>

146 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.<sup>30</sup> Regarding term at delivery, although some authors have suggested that the increase in size of the adrenal gland may be related to preterm delivery,<sup>31</sup> especially when associated with polyhydramnios, others believe that there is no relationship between size of the adrenal gland and gestational age at delivery.<sup>32</sup>

152 The treatment of such entities has not yet been determined, and recommendations have changed in recent 153 years. Initially, surgery was favoured in all cases<sup>33,34</sup>, then a wait-and-see attitude, based on close prenatal and postnatal US follow-up, was promoted.<sup>4,35</sup> 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.<sup>36</sup> 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.
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#### 163 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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			<b>Adrenocortical</b>				
	DIAGNOSIS	<mark>Congenital adrenal</mark> hyperplasia	<mark>macrocyst</mark> Beckwith Wiedemann Syndrome	Solid neuroblastoma	Adrenal haemorrhage	Isolated adrenal cyst	Left extralobar pulmonary sequestration
	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		50 - 40	22 - 22	28 - 20	10 - 9	20 - 20
	<ul> <li>Size (mm)</li> <li>Structure</li> </ul>	Cerebriform aspect	S0 x 40 Multicystic with mixed content	22 x 32 Hyperechoic Homogeneous	Altered content Heterogeneous	10 x 8 Hypoechogenic Homogeneous	30 x 20 Mixed component Heterogeneous
	<ul> <li>Vascularized</li> </ul>	No	Heterogeneous	Yes	No	No	Yes
PRENATAL MANAGEMENT	<ul> <li>Systemic vessel</li> </ul>	No	No	No	No	No	Yes (from the aorta)
	<ul> <li>Associated findings</li> </ul>	Penis increased in size Family history of CAH	No macroglossia	No	No	No	No
	FETAL MRI						
	<ul> <li>When (WG)</li> </ul>	NR	28	37	35	NR	29 and 33
	<ul> <li>Location</li> </ul>	NR	Bilateral	Unilateral left	Unilateral right	NR	Thoraco abdominal
				Prerenal	Custia and hataraganaous		junction
	Structure	NR	Cystic and heterogeneous	Well limited	formation	NR	
	Structure		formation	Heterogeneous	Tormation		Plurilocular cystic
				No hemorrhagic signs	No		formation
	<ul> <li>Associated findings</li> </ul>	NR	Macroglossia	No		NR	a systemic posterior vessel
							arising from the aorta
	PRENATAL EVOLUTION	Stable	Increase	Increase	Decrease	Stable	Increase
	PROPOSED PRENATAL DIAGNOSIS	Congenital adrenal	Adrenocortical macrocyst	Solid neuroblastoma,	Adrenal haemorrhage,	Isolated adrenal cyst	Left extralobar pulmonary
		hyperplasia	Beckwith Wiedemann	Adrenal haemorrhage	Cystic neuroblastoma		sequestration
	COMPLEMENTARY EXAMS		Syndrome				
	<ul> <li>Urinary catecholamine</li> </ul>	Negative	NR	Positive	Negative	NR	Negative
	<ul> <li>Androgenic marquors</li> </ul>	21-H deficiency	NR	Normal	Normal	NR	Normal
	<ul> <li>Postnatal ultrasound / MRI</li> </ul>						
	Lesion confirmed	Yes	NR	Yes	Yes	Yes	Yes
	Associated elements	NO	INK	Liver metastases (present at	INO	NO	INO
	<ul> <li>Histological findings post- surgery</li> </ul>	-	NR	Malignant cells	NR	No malignant cells	Lung cells – no malignant cells
MANAGEMENT	EVOLUTION	Normal aspect at one week	Termination of pregnancy	Spontaneous regression,	Spontaneous regression	Stabilization	Stabilization
MANAGEMENT		and one month with	Pathology: fetal	then stabilization			
		treatment	macrosomia,				
			nacrogiossia, bilateral				
			adrenal masses with				
			haemorrhagic lesion on the				
			left. No malignant cells.				
	THERAPEUTIC PROTOCOL	Hydrocortisone and	NR	Close monitoring, then,	Close monitoring	Monitoring	Close monitoring
		fludrocortisone therapy		Surgery		(spontaneous regression)	

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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		
		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
	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
Characteristic ultrasound signs	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)
	<b>Elements of malignity</b> <i>Partition, vegetation</i>	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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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 <u>Figure 1</u>: 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)
- with appearance of a hypoechoic cortex and a hyperechoic medullary during late trimester ultrasound.

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



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<u>Figure 3</u>: 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.





- 289 <u>Figure 4</u>: 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)



<u>Figure 5</u>: 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.



- 298 <u>Figure 6</u>: A heterogeneous and avascular mass of the right adrenal gland, with a changing sonographic pattern through follow-up, on a axial (a1), parasagittal
- 299 (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
- 300 *transverse (d) T2- HASTE weighted images show hematic sediment confirming the hemorrhagic composition of the mass.*



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- 302 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
   303 estimated gestational age in a female fetus, consistent with an adrenal cyst.



- 307 *the left lower lobe mass with systemic feeding vessels (arrow) coursing into the mass.*
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#### 1 TITLE

- 2 Prenatal assessment of atypical adrenal glands: a systematic approach for diagnosis
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#### 36 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.

43 Prenatal – ultrasound – adrenal gland – MRI – counseling

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#### 45 **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.<sup>1</sup> Identifying characteristic imaging findings can help achieve the most relevant diagnosis.<sup>2</sup> 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.<sup>3–5</sup> The principal differential diagnosis is subdiaphragmatic extralobar pulmonary sequestration (SEPS).<sup>6</sup> 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.<sup>7–9</sup>

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.<sup>10</sup> 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.

#### 92 **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

n of the.

#### 100 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)*.<sup>11</sup>

108 When an atypical adrenal gland is identified, six possible diagnoses should be initially considered, even if 109 other, less frequent, causes are not excluded, as mentioned above *(Figure 2).*<sup>12</sup>

First, the bilateral or unilateral presentation should be considered, followed by its sonographic appearance. 110 When bilaterally increased in size and associated with normal sonographic appearance, this may indicate 111 adrenal hypertrophy which can be encountered in some cases of gestational diabetes, intra-uterine growth 112 retardation, and foetal inflammatory syndrome, especially in cases of premature rupture of the membranes.<sup>13,14</sup> 113 In bilateral cases with abnormal sonographic appearance, congenital adrenal hyperplasia (CAH) should be 114 suspected (Table 1 - Case 1, Figure 3). This autosomal recessive disorder may be indicated by the association 115 with two US features: a typical aspect of "cerebriform" adrenal glands, associated with virilization of the 116 genitalia. Supported by a family history, these two US features favour the diagnosis of CAH. The prognosis 117 is excellent with appropriate treatment.<sup>15,16</sup>Second, the presence of bilateral cysts with mixed content, possibly 118 partially haemorrhagic, can raise suspicion of an adrenocortical macrocyst in the setting of Beckwith-119 Wiedemann syndrome. Other US features should be investigated, such as foetal macrosomia with 120 polyhydramnios, macroglossia, and omphalocele (Table 1 - Case 2, Figure 4).<sup>17-19</sup> 121

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.<sup>20,21</sup> Overall, a pure cystic form has

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

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.<sup>25</sup>

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.<sup>26,27</sup>

138 The differential diagnosis for neuroblastoma is difficult during the prenatal period.<sup>28</sup>

139 Extralobar pulmonary sequestration is also generally diagnosed early in pregnancy, more commonly in the

140 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

142 systemic blood supply.<sup>6</sup> It can have a variable sonographic appearance, and is more frequently left-sided.

143 The US diagnosis is based on the demonstration of a feeding systemic artery that can be identified on colour 144 Doppler imaging. Most often, the artery is derived from the terminal portion of the descending thoracic aorta

145 or the upper part of the abdominal aorta.<sup>29</sup>

146 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.<sup>30</sup> Regarding term at delivery, although some authors have suggested that the increase in size of the adrenal gland may be related to preterm delivery,<sup>31</sup> especially when associated with polyhydramnios, others believe that there is no relationship between size of the adrenal gland and gestational age at delivery.<sup>32</sup>

152 The treatment of such entities has not yet been determined, and recommendations have changed in recent 153 years. Initially, surgery was favoured in all cases<sup>33,34</sup>, then a wait-and-see attitude, based on close prenatal and postnatal US follow-up, was promoted.<sup>4,35</sup> 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.<sup>36</sup> 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.

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#### 163 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
	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
PRENATAL MANAGEMENT	ANTENATAL ULTRASOUND FEATURES    Size (mm)  Structure  Vascularized  Systemic vessel  Associated findings   FETAL MRI  When (WG)  Location  Structure	Increased Cerebriform aspect No No Penis increased in size Family history of CAH NR NR NR	50 x 40 Multicystic with mixed content Heterogeneous No No macroglossia 28 Bilateral Cystic and heterogeneous formation	22 x 32 Hyperechoic Homogeneous Yes No No 37 Unilateral left Prerenal Retrogastric Well limited, Heterogeneous,	38 x 29 Altered content Heterogeneous No No No 35 Unilateral right Cystic and heterogeneous formation	10 x 8 Hypoechogenic Homogeneous No No No NR NR NR	30 x 20 Mixed component Heterogeneous Yes Yes (from the aorta) No 29 and 33 Thoraco abdominal junction Plurilocular cystic
	Associated findings	NR	Macroglossia	No hemorrhagic signs No	No	NR	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 <ul> <li>Urinary catecholamine</li> <li>Androgenic marquors</li> <li>Postnatal ultrasound / MRI</li> <li>Lesion confirmed</li> <li>Associated elements</li> </ul> Histological findings post- surgery EVOLUTION	Negative 21-H deficiency Yes No - Normal aspect at one week and one month with treatment	NR NR NR NR NR Termination of pregnancy Pathology: fetal macrosomia, macroglossia, bilateral nephromegaly, bilateral adrenal masses with haemorrhagic lesion on the left. No malignant cells.	Positive Normal Yes Liver metastases (present at 1 month) Malignant cells Spontaneous regression, then stabilization	Negative Normal Yes No NR Spontaneous regression	NR NR Yes No No malignant cells Stabilization	Negative Normal Yes No Lung cells – no malignant cells Stabilization
	THERAPEUTIC PROTOCOL	Hydrocortisone and fludrocortisone therapy	NR	Close monitoring, then, Surgery	Close monitoring	Monitoring (spontaneous regression)	Close monitoring

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		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
	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
Characteristic ultrasound signs	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)
	<b>Elements of malignity</b> <i>Partition, vegetation</i>	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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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 <u>Figure 1</u>: 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)
- with appearance of a hypoechoic cortex and a hyperechoic medullary during late trimester ultrasound.

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



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<u>Figure 3</u>: 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.



- 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)



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<u>Figure 5</u>: 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.



- 298 *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.

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- 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.



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.

490x210mm (72 x 72 DPI)



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)

553x352mm (72 x 72 DPI)



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.

570x320mm (72 x 72 DPI)



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.

507x290mm (72 x 72 DPI)



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.

433x182mm (72 x 72 DPI)



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)