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REVIEW ARTICLE

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Acute spontaneous non-hemorrhagic adrenal infarction in pregnancy: case-report and literature review

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ABSTRACT

Unilateral non-hemorrhagic adrenal infarction (NHAI) is a very uncommon cause of acute abdomen in pregnancy. Diagnosis is highly challenging due to its rarity, heterogeneity of clinical presentation, and inconclusiveness of the initial workup. Timely recognition is pivotal to ensuring optimal outcomes. Here we describe a case of spontaneous unilateral NHAI diagnosed in a singleton pregnant woman at 32 weeks' gestation at our centre and provide the findings of an extensive literature review on the topic. We identified 22 articles describing 31 NHAI cases in 30 obstetric patients: NHAI occurs more frequently on the right side and in the third trimester, and diagnosis is formulated more than 24 h after clinical presentation in 50% of cases; second-level imaging is always necessary to reach a definitive diagnosis and start appropriate treatment. A high degree of clinical suspicion is needed to promptly recognize NHAI in pregnancy, thus allowing appropriate multidisciplinary management and timely treatment initiation. Promotion of knowledge and awareness of NHAI as a potential cause of acute abdomen in pregnancy is mandatory to improve clinical practice and, ultimately, perinatal outcomes.

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Adrenal; infarction; thrombosis; pregnancy; pain; acute; abdomen

Introduction

Adrenal infarction (AI) in pregnancy is a very rare, although potentially life-threatening, clinical entity [1]. AI can be hemorrhagic or non-hemorrhagic [2], with the latter being much less frequent. Although antiphospholipid-antibody syndrome has been identified as one of the main risk factors for AI [3], pregnancy, with its hypercoagulability state [4], represents a condition at risk, particularly for non-hemorrhagic AI (NHAI) [1].

Diagnosis of NHAI is challenging due to the rarity of the condition as well as the variability of clinical manifestation, especially in unilateral cases with no adrenal insufficiency [5]. The inconclusiveness of the initial workup further increases the diagnostic challenge, leading clinicians toward more common non-obstetric causes of acute pain in pregnancy, such as biliary or renal colic. Yet, prompt diagnosis is pivotal to implementing appropriate therapeutic management and avoiding clinical deterioration [6].

So far, only case reports or small case series have been reported on the topic, and an extensive review of the literature is lacking [1,2,5,7–11]. Here we describe a case of spontaneous unilateral NHAI in a pregnant woman and perform a literature review to provide an in-depth update on this rare clinical entity.

Methods

Case report

We retrospectively collected the medical records of the woman diagnosed with acute spontaneous unilateral NHAI at our university center. This was the first case of AI identified at our center since its establishment in 1981. A written informed consent was obtained from the patient to use her anonymized clinical information for the purpose of this reporting. Since only anonymized data were employed, approval of the Ethical Committee of Fondazione IRCCS San Gerardo dei Tintori was waived.

Information sources and search strategy

We obtained all articles related to our topic from the international electronic bibliographic databases PubMed/MEDLINE, ISI Web of Knowledge, and Cochrane. The articles were identified using a combination of MeSH terms including the keywords "pregnancy", "adrenal", "infarction". The search was limited to

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This article has been corrected with minor changes. These changes do not impact the academic content of the article.

studies reported in English, French, and Italian. We did not employ temporal or publication status limits to restrict our search. Once an article was considered relevant, the full text was retrieved. The references included in the selected articles were also reviewed for related citations. Data collection and analysis were performed between 1 February 2022 and 31 May 2022.

Study selection and data retrieval

Three independent researchers (S.O., F.F., E.M.) screened the titles and abstracts obtained to select the most relevant articles. The three researchers selected the final studies to be included in the review after applying the eligibility criteria independently. Any conflict between researchers was resolved by senior consultants' assessment (I.C., P.V.). Studies were considered eligible for review if they investigated clinical and radiological presentation in obstetric patients with a diagnosis of unilateral or bilateral NHAI. The following data were collected: authors, year of publication, maternal age at diagnosis, gestational age (GA; weeks, days) at diagnosis, obstetric history, side of NHAI, presenting symptoms and vitals, results of blood workup, type and findings of imaging, treatment, clinical course, GA at and mode of delivery, and follow-up.

Results

Clinical case

A 21-year-old woman, gravida 2 para 1, with a spontaneously conceived pregnancy presented at $32^{2/7}$ weeks' gestation to the Emergency Department (ED) of a nearby mother and child hospital for uterine contractions. Her obstetric history included an uncomplicated pregnancy two years before with a term spontaneous vaginal delivery of a healthy male neonate. The patient reported no previous use of hormonal contraception and family history was unremarkable. Her pregestational Body Mass Index (BMI) was 29 Kg/m^2. A two-days hospitalization had occurred two weeks before for intravenous iron administration due to severe iron deficient anemia (Hb 8.9 g/dL).

On hospital presentation, vital signs were normal; irregular uterine contractions were identified, and a transvaginal ultrasound scan showed a shortened cervix of 20 mm. The patient was admitted and given intravenous tocolysis and intramuscular steroids for fetal lung maturation. Nasopharyngeal swab for SARS-CoV-2 detection performed upon admission was negative.

Ten hours after admission, the woman started complaining of a sudden-onset right upper quadrant and flank pain, associated with nausea and two bouts of non-bloody emesis. She was afebrile and had moderate right upper quadrant and flank tenderness. There were no contractions and cervical length was stable. She was administered intravenous acetaminophen, with transient resolution of the pain, which subsequently recurred and worsened. An abdominal ultrasound scan performed 5 h after pain's onset was negative.

Considering the progressive worsening of the pain and its unresponsiveness to intravenous analgesics, the woman was transferred to our second-level hospital. Vital signs at admission showed mild hypertension (130/80 mmHg) and tachycardia (95 bpm), with a slightly elevated respiratory rate (RR 24) and normal oxygen saturation (SpO_2 100%); she was afebrile. Clinical examination revealed a severe right upper quadrant and flank tenderness with rebound pain. The absence of uterine contractions and a 20 mm-long cervix were confirmed. The obstetric ultrasound was regular. Electrocardiogram and chest X-ray had negative results. Also, arterial gas analysis was unremarkable. Blood laboratory analyses were notable only for mild leukocytosis and anemia (Table 1). D-dimer was 1516 ng/mL, normal for the patient's gestational age[12]. Urine analysis was unrevealing. An abdominal ultrasound scan was performed (12 h after pain's onset), which showed a 3-mm right perirenal fluid flap (Figure 1(A)). The right kidney's appearance was normal, and there was no ureteral dilation or urolithiasis; Doppler signal in the right renal vein was regular. The woman was administered analgesics, which allowed for temporary pain control until a new episode of acute right flank pain associated with emesis occurred 4 h later. The patient underwent another scan (17 h after pain's onset): the right perirenal fluid flap was stable and a new, minimal periduodenal fluid component was recognized (Figure 1(B)).

Table 1. Blood tests at admission.

	Result	Normal range
White cell count	14.8×10^3/uL	$4.0–11.0\times10^3$/uL
Hemoglobin	8.8 g/dL	12.0–16.0 g/dL
Mean corpuscular volume	80.0 fL	80.0–99.0 fL
Platelets	315×10^3/uL	$140.0–440.0\times10^3$/uL
Glycemia	116 mg/dL	70–110 mg/dL
Sodium	137 mmol/L	136–145 mmol/L
Potassium	4.0 mmol/L	3.5–5.1 mmol/L
Chlorine	105 mmol/L	98–107 mmol/L
Creatinine	0.4 mg/dL	0.5–1.0 mg/dL
Urea	15 mg/dL	17–48 mg/dL
SGOT	17 U/L	<32 U/L
SGPT	18 U/L	<33 U/L
Prothrombin ratio	0.97	0.85–1.20
Activated partial prothrombin ratio	0.74	0.85–1.20
Fibrinogen	323 mg/dL	175–400 mg/dL
D-dimer	1516 ng/mL	0–250 ng/mL
Lactate dehydrogenase	130 U/L	135–214 U/L
Bilirubin	<0.2 mg/dL	<0.9 mg/dL
Amylase	36 U/L	28–100 U/L
Lipase	19 U/L	13–60 U/L
C reactive protein	0.27 mg/dL	<0.50 mg/dL

Being the sonography inconclusive, the woman's pain was severe and only transiently responsive to analgesics, and a definitive diagnosis was absent, a computed tomography (CT) scan with contrast was performed (21 h after pain's onset). The scan revealed an enlarged and edematous right adrenal gland with preserved morphology and no enhancement following intravenous contrast; stranding at ipsilateral peri-adrenal and peri-para-renal fat was also identified (Figure 2), with no evidence of bleeding. The left adrenal gland was normal. Altogether, the findings suggested a diagnosis of right unilateral NHAI.

Endocrinologist and haematologist consultations were requested. Doppler ultrasound of lower extremities was performed and turned out negative. Analgesics and prophylactic anticoagulation with enoxaparin 4000 IU once a day were established, with complete pain remission in 24 h (48 h after pain onset). Table 2 displays the findings of endocrinological and thrombophilia screening. Clinical and biochemical follow-up showed the absence of adrenal insufficiency.

The patient was discharged after 8 days of hospitalization. Spontaneous onset of labor occurred at $37^{4/7}$ weeks' gestation and the woman gave birth vaginally to a healthy female neonate of 2805 grams. She was discharged on day 3 postpartum with 4000 IU enoxaparin to be continued for 6 weeks. An endocrinological follow-up 6 weeks after discharge showed regular adrenal function.

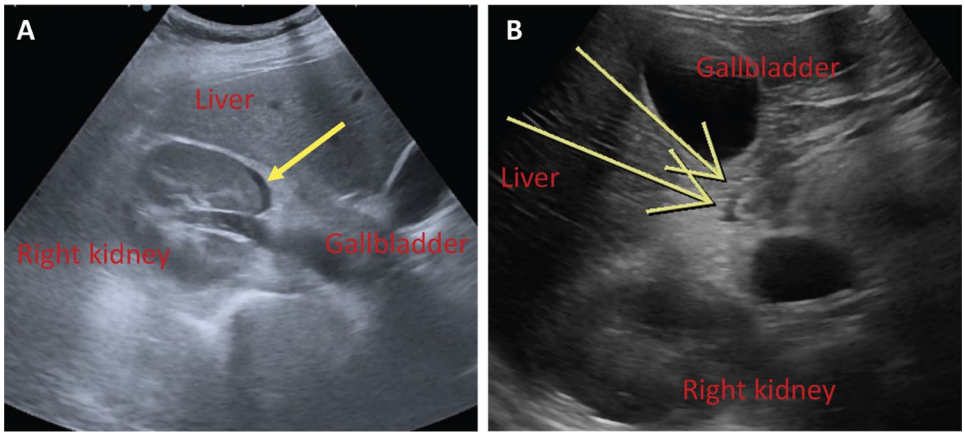

Figure 1. (A, B). Abdominal ultrasound scans. Minimal perirenal (1A) and periduodenal (1B) fluid (yellow arrows).

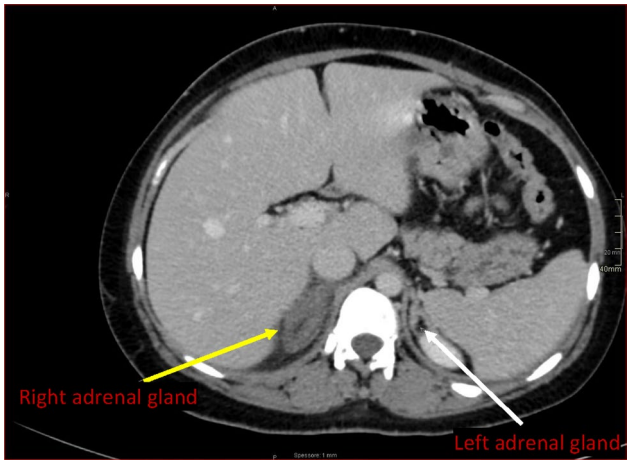

Figure 2. CT scan with contrast. CT scan displays an enlarged and edematous right adrenal gland with preserved morphology, no enhancement following intravenous contrast and inflammatory peri-adrenal fat stranding (yellow arrow). Note usual enhancement of the contralateral adrenal gland (white arrow).

Table 2. Endocrinological and thrombophilia and screening.

	Result	Normal range
Serum cortisol	32.7 mcg/mL	6.24–18 mcg/mL
ACTH [a]	72.1 pg/mL	7.2–63.3 pg/mL
Saliva free cortisol	0.25 mcg/dL	<0.21 mcg/dL
24-h urine cortisol	219 mcg	10–100 mcg
Aldosterone	8.5 ng/dL	1.17–23.6 ng/dL
Renin (clinostatism)	6.4 microIU/mL	2.9–39.9 microIU/mL
24-h urine metanephrine	65 mcg	64–302 mcg
24-h urine normetanephrine	346 mcg	162–527 mcg
Basal homocysteine	3.5 micromol/L	0–12 micromol/L
Thyroid-stimulating hormone	1.67 microIU/mL	0.27–4.20 microIU/mL
Protein C	94%	55–125%
Protein S	48%	55–160%
Factor V Leiden G1691A	Heterozygosis mutation	No mutation detected
Factor II G20210A	No mutation detected	No mutation detected
MTHFR C667T [b]	No mutation detected	No mutation detected
MTHFR A1298C	Homozygosis mutation	No mutation detected
Factor II	110%	60–130%
Factor V	78%	60–130%
Factor VIII	223%	50–170%
Antithrombin III	84%	80–120%
Lupus-like anticoagulant	Negative	Negative
Anti-nucleus Ab [c]	Negative	Negative
Anti-extractable nuclear antigen Ab	Negative	Negative
Anti-DNA native Ab	4.7 UI/mL	<27 UI/mL
Anti-cardiolipin Ab	Negative	Negative
Anti-beta2glycoprotein I Ab	Negative	Negative
Anti-neutrophil cytoplasmic Ab	Negative	Negative
Complement C3	135 mg/dL	90–180 mg/dL
Complement C4	44 mg/dL	10–40 mg/dL

[a] Adrenocorticotropic hormone.
[b] MTHFR, methyl tetrahydrofolate reductase.
[c] Ab, antibodies.

Review of the literature

We found 22 articles describing a total of 31 NHAI cases that occurred in 30 obstetric patients (Table 3). The median maternal age was 25 years (IQR, 24–29.8), with two (6.7%) women >35. Three (10%) patients had a BMI ≥30 kg/m^2. One (3.3%) case smoked during pregnancy, and another had a history of ulcerative colitis. There were two twin pregnancies.

In 23(74.2%) cases, the NHAI occurred after 28 weeks gestation. There was one postpartum event (day 1, n. 14). NHAI was unilateral in 28 (90.3%) cases, with involvement of the right gland in 21 (75%). The remaining three cases were bilateral: two simultaneous (n. 11 and 21) and one sequential (n. 26, 27).

Pain was identified as presenting symptom in all cases, with upper quadrant and/or flank localization in 29/31 events. Accompanying nausea and vomiting was described in 14 (45.2%) cases. Prodromal symptoms were recognized in 4 women (n. 1, 3, 5, and 17) and preempted the diagnosis of NHAI by a time interval ranging from a few hours to 2 weeks. Pyelonephritis was suspected in one case (n. 3), whereas in the remaining three pain was thought to be of colic origin. In one case (n. 26), a condition of painful myoma syndrome was initially suspected [1].

Vitals at presentation were reported in 54.8% of events: 8 (47.1%) women showed abnormal vitals, with mild tachycardia and tachypnea being the most common ($n = 5$ each). Fever was present only in one case (n. 15). Blood tests were normal in 15/29 cases; mild-to-moderate leukocytosis was described in 13 (44.8%) and slightly-to-modestly increased C-reactive protein (CRP, median 5.1 mg/dL, IQR 3.1-7.5 mg/dL) in 6 (20.7%).

Abdominal ultrasound was employed as first-line imaging in 27 (87.1%) events, with an inconclusive report in 19 (70.4%). Abnormal findings included swollen adrenal gland (n. 10 and n. 6), peri-adrenal fluid (n. 10), trace fluid in the Morrison's pouch (n. 26), gallbladder sludge (n. 5 and n. 17), and pyelocaliceal dilation with evidence of kidney stones (n. 8). Twenty-two women underwent a CT scan, with the use of contrast in 20/22.

Table 3. Review of cases of NHAI in obstetric patients.

#	Author, year	Age(y)	GA(wks)	History & current pregnancy data	Side	Presenting symptoms	Vitals at presentation	Blood workup
1	Shah et al. 2022 [7]	25	$32^{0/7}$ wks	1st pregnancy ED access at $32^{0/7}$ wks for left flank pain, resolved with analgesics	Left	Left flank pain, back pain, central lower chest pain, vomiting (few hours after 1st ED access)	BP 100/64 mmHg HR 108 bpm RR 24-26 breaths/m Afebrile	Leukocytosis, lactic acidosis
2	Warda et al. 2021 [8]	24	30 wks	NA	Left	LUQ pain, nauseaand vomiting	NA	NA
3	Mathew et al. 2021 [31]	24	29 wks	3 prior term pregnancies, 1 prior miscarriage Hospital admission for suspected left pyelonephritis at 27 wks, treated with empiric antibiotics	Left	LUQ and flank pain, nausea, and vomiting	BP 115/60 mmHg HR 105 bpm RR 24 breaths/m SpO2 97% on 2 L nasal cannula Afebrile	Leukocytosis
4	Padilla et al. 2021 [32]	25	2nd trimester	4 prior term pregnancies, 9 prior miscarriages Ulcerative colitis, seizure disorder, anemia, cholelithiasis Twin pregnancy	Right	Colicky RUQ pain, nausea	NA	Normal
5	Jerbaka et al. 2021 [33]	36	$36^{5/7}$ wks	7 prior term pregnancies, 2 prior miscarriages ED access at $36^{5/7}$ wks for left upper quadrant abdominal pain, resolved with anti-spasmodics	Left	LUQ and flank pain (a few hours after 1st ED access)	Normal	Anemia (Hb 8.9 g/dL)
6	Chagué et al. 2021a [10]	33	37 wks	3 prior pregnancies	Right	Right-sided abdominal pain	NA	Leukocytosis CRP 4.9 mg/dL D-dimer 1070 ng/L
7	Chagué et al. 2021b [10]	38	26 wks	History of kidney stones	Right	Right flank and back pain	NA	Leukocytosis CRP 1.7 mg/dL
8	Chagué et al. 2021c [10]	19	32 wks	Twin pregnancy Left acute obstructive pyelonephritis during pregnancy	Right	Right flank and back pain	NA	Leukocytosis CRP 8.2 mg/dL
9	Chagué et al. 2021d [10]	34	31 wks	1st pregnancy	Right	RUQ pain	NA	Leukocytosis CRP 2.5 mg/dL D-dimer 1500 ng/L
10	Chagué et al. 2021e [10]	31	36 wks	2 prior miscarriages	Left	Left upper back and lower back chest pain	NA	Leukocytosis CRP 18.7 mg/dL D-dimer 820 ng/L

(*Continued*)

Imaging	Imaging findings	Thrombophilia screening	Treatment	Pregnancy & clinical course	Delivery(wks)	Follow up
ECG Chest X-ray US CT w/ contrast	Negative Negative Negative Hypodense enlarged left gland	NA	Hydrocortisone PP Warfarin PP	pPROM, fetal breech presentation ($32^{1/7}$ weeks) Adrenal insufficiency 1 day PP (basal serum cortisol 78 nmol/L)	Emergent CS (32)	No adrenal insufficiency 4 months PP Normal left gland at MRI 6 months PP
MRI w/out contrast	T2 hyperintense enlarged left gland, hypointense perirenal fat	Factor VIII >200% Hz MTHFR C677T and A1298C	Hydrocortisone Enoxaparin (therapeutic)	Adrenal insufficiency (basal serum cortisol 10.3 ug/dL; ACTH stimulation test: 9.1, 10.7 and 11 ug/dL at T0, T30, and T60) Pain remission	VD (39)	NA
US MRI w/out contrast	Negative T2 enlarged and hyperintense left gland, left kidney superior pole edema (recent pyelonephritis)	Factor VIII >200% Protein S 54%	Intravenous fluids, morphine, antiemetic therapy Hydrocortisone (for 1 month) Enoxaparin (therapeutic)	Adrenal insufficiency (abnormal ACTH stimulation test but no cortisol values reported) Pain remission	VD (39)	No adrenal insufficiency 1 month after diagnosis Enoxaparin (therapeutic) for 6 months PP
US MRCP w/out contrast (DWI sequences) MRI w/out contrast (DWI sequences)	Negative Negative T1 edematous and hypointense right gland	ANCA (1:180)	Morphine, antiemetic therapy Enoxaparin (prophylactic)	Pain remission	NA	NA
US CT w/contrast (1 day PP)	Gallbladder sludge, oligohydramnios Hypodense enlarged and edematous left gland	Ho MTHFR C677T Hz HPA1 1a/1b	Intravenous fluids, analgesics, PPIs Enoxaparin (therapeutic) PP	IoL for oligohydramnios and persistent pain	VD ($36^{5/7}$)	No adrenal insufficiency at 6 months PP Enoxaparin (therapeutic) for 1 week PP then enoxaparin (prophylactic) for 6 months PP
US MRI w/out contrast CT w/ contrast	Swollen right gland T2 hyperintense right gland Hypodense enlarged right gland	Negative	Opioids Enoxaparin (therapeutic) PP	IoL for persistent pain	VD (37)	Atrophic right gland with partial restoration of glandular enhancement at CT at 7 months PP Enoxaparin (therapeutic) PP for 11 months
US CT w/ contrast	Negative Hypodense enlarged right gland, right adrenal vein thrombus	Negative	Opioids Enoxaparin (therapeutic)	Pain remission	NA	Atrophic right gland with partial restoration of glandular enhancement at CT at 3 months PP Warfarin for 6 months PP
US CT w/ contrast MRI w/out contrast	Right pyelocaliceal dilation, kidney stones Hypodense enlarged right gland, right adrenal vein thrombus T2 hyperintense right gland	Negative	Opioids Enoxaparin (therapeutic)	Pain remission	NA	Isolated residual atrophy of the lateral arm of the right gland Warfarin for 3 months PP
US CT w/ contrast MRI w/out contrast	Negative Hypodense enlarged right gland T2 hyperintense right gland, peri-adrenal fluid	Negative	Opioids Enoxaparin (therapeutic)	Pain remission	NA	T1 hyperintense right gland at MRI at 1 month PP
US CT w/ contrast MRI w/out contrast	Swollen left gland and peri-adrenal fluid Hypodense enlarged left gland T2 hyperintense left gland, peri-adrenal fluid	Negative	Opioids Enoxaparin (therapeutic)	Pain remission	NA	Swollen left gland, reduced peri-adrenal fluid, partial restoration of glandular enhancement at MRI 4 months PP

(*Continued*)

Table 3. Continued.

#	Author, year	Age(y)	GA(wks)	History & current pregnancy data	Side	Presenting symptoms	Vitals at presentation	Blood workup
11	Chagué et al. 2021f [10]	22	30 wks	1st pregnancy	Left, right	Left flank pain; right flank pain 24 h later	NA	CRP 5.2 mg/dL
12	Sidibe et at., 2021a [34]	25	30 wks	1st pregnancy Obesity (BMI 30)	Right	RUQ and RLQ pain, fever	NA	Mild leukocytosis
13	Sidibe et at., 2021b [34]	22	38 wks	1 prior term pregnancy, 1 prior TOP Appendectomy, active smoking	Left	Acute abdominal pain	NA	Normal
14	Cunningham et al. 2019 [35]	25	PP day 1	1st pregnancy, normal course, OVD at $40^{4/7}$	Right	RUQ and back pain starting 2 h PP	BP 139/111 mmHg right arm, 158/131 mmHg left arm HR 80 bpm RR 20 breaths/m Afebrile	Leukocytosis
15	Fei et al. 2019 [36]	21	$29^{4/7}$wks	1 prior miscarriage	Right	RUQ and flank pain, nausea and vomiting	BP 134/77 mmHg HR 122 bpm RR 18 breaths/m Fever (38.1 °C, onset a few hours after ED admission)	Leukocytosis
16	Chasseloup et al. 2019 [5]	30	32 wks	3 prior term pregnancies, 1 prior stillbirth	Right	RUQ pain, uterine contractions	Normal	Normal
17	Hynes et al. 2019 [37] & Agarwal and Soe, 2019 [38] (same case reported in two different journals)	21	$28^{4/7}$ wks	1st pregnancy Asthma, iron deficiency anemia, obesity ED access at 28 wks for right upper quadrant abdominal pain, resolved with analgesics	Right	RUQ pain, nausea, vomiting, and chills	NA	Leukocytosis, anemia (Hb 8 g/dL)
18	Glomski et al. 2018a [1] (Case B in the paper)	24	33 wks	NA	Left	LUQ pain, vomiting, diarrhea	NA	Normal
19	Glomski et al. 2018b [1] (Case D in the paper)	33	16 wks	NA	Right	Persistent RLQ pain 1 week after appendicectomy	NA	Normal
20	Aljenaee et al. 2017 [39]	29	24 wks	4 prior term pregnancies	Right	RUQ pain, nausea and vomiting	BP 132/70 mmHg HR 110 bpm RR 22 breaths/m SpO2 99% Afebrile	Normal
21	Molière et al. 2017 [40]	29	30 wks	NA	Right, left	Epigastric, back, and both flanks pain, nausea	Normal	Normal

(*Continued*)

Table 3. Continued.

Imaging	Imaging findings	Thrombophilia screening	Treatment	Pregnancy & clinical course	Delivery(wks)	Follow up
US CT w/ contrast MRI w/out contrast	Negative Hypodense enlarged left and right gland, right adrenal vein thrombus T2 hyperintense left and right gland	Positive LAC abs	Opioids Enoxaparin (therapeutic) Hydrocortisone (started at CT & MRI result)	Adrenal insufficiency (no cortisol values reported) Pain remission	NA	Adrenal insufficiency at 4 months PP
US CT w/ contrast	Negative Hypodense enlarged and edematous right gland, right adrenal vein thrombus	Negative	NSAIDs Enoxaparin (therapeutic)	Pain remission	VD (38)	No adrenal insufficiency at 3 months PP Warfarin for 3 months PP
CT w/ contrast (1 day PP)	Hypodense enlarged left gland	Negative	Warfarin PP	Delivery for vasovagal syncope and fetal arrhythmia (few hours after ED access) Left lumbar pain 1 day PP	Emergent CS (38)	No adrenal insufficiency at 3 months PP Warfarin for 3 months PP
US CT w/ contrast	Negative Hypodense enlarged right gland	Negative (only acquired thrombophilia)	Morphine and acetaminophen Oral labetalol, intravenous magnesium for suspected preeclampsia (stopped at CT result) Dalteparin (therapeutic)	Pain remission	–	Dalteparin (therapeutic) for 3 months
US Chest X-ray CT w/out contrast	Negative Negative Enlarged and hypodense right gland, surrounding fat stranding	Hz MTHFR Hz prothrombin G20210A	Intravenous antibiotic for suspected pyelonephritis (stopped at CT result) Intravenous fluids Enoxaparin (therapeutic)	Pain remission	OVD (40)	Enoxaparin (therapeutic) for 6 weeks PP
US CT w/ contrast	Negative Hypodense enlarged right gland	Negative	Analgesics Tocolytic therapy Enoxaparin (therapeutic) PP	Delivery for persistent pain and uterine contractions unresponsive to analgesics and tocolytic therapy	Emergent CS (32)	Right gland atrophy at CT 6 months PP No adrenal insufficiency at 6 months PP Enoxaparin (therapeutic) for 6 months PP
US MRI w/out contrast CT w/ contrast Lower extremity Doppler US Echocardiogram	Gallbladder sludge T2 hyperintense right gland, minimal peri-adrenal gland fluid Hypodense enlarged right gland Negative Patent foramen ovale	Negative	Morphine Enoxaparin (therapeutic)	Pain remission	NA	No adrenal insufficiency at 2 months PP Recommended enoxaparin (therapeutic) for 6 weeks PP, not taken
US MRI w/out contrast	Negative T2 hyperintense enlarged left gland	NA	Intravenous fluids Analgesics	Pain remission	VD (37)	NA (NHAI diagnosis not performed at the time of presentation; this is a retrospective review)
US MRI w/out contrast	Negative T2 hyperintense enlarged right gland	NA	Intravenous fluids Analgesics	Pain remission	VD (41)	NA (NHAI diagnosis not performed at the time of presentation; this is a retrospective review)
US CT w/ contrast	Negative Hypodense enlarged right gland	Factor VIII 303% (confirmed at 3 months PP)	Enoxaparin (therapeutic)	Pain remission	VD (38)	Enoxaparin (therapeutic) for 2 weeks PP Lifelong anticoagulation recommended at 3 month-PP assessment
US MRI w/out contrast	Negative Bilateral enlarged glands, peri-adrenal fluid, and multiple DWI hyperintense foci; restricted ADC in left gland	Negative	Morphine Anticoagulation (dosage not specified)	Pain remission (no adrenal insufficiency)	NA	Anticoagulation PP

(*Continued*)

Table 3. Continued.

#	Author, year	Age(y)	GA(wks)	History & current pregnancy data	Side	Presenting symptoms	Vitals at presentation	Blood workup
22	Reichman et al. 2016 [11]	28	$28^{1/7}$ wks	2 prior term pregnancies	Right	RUQ and flank pain	Normal	Normal
23	Sormunen-Harju et al. 2016 [41]	31	38 wks	1 prior term pregnancy	Right	RUQ pain	BP 125/70 mmHg Afebrile	Normal
24	Lamba, 2015 [42] (Conference abstract)	20	22 wks	1 prior term pregnancy	Right	Right flank pain, vomiting	BP 139/79 mmHg HR 96 bpm Afebrile	NA
25	Guenette et al. 2015a (case A in Glomski et al. 2018) [1]	20	$27^{4/7}$wks	1st pregnancy	Right	RUQ and flank pain, vomiting	Slight hypertension Afebrile	Leukocytosis
26	Guenette et al. 2015b (1st episode) (case C in Glomski et al. 2018) [1]	29	$17^{5/5}$ wks	1 prior term pregnancy	Right	RUQ and flank pain, nausea	BP 82/47 mmHg Afebrile	Normal
27	Guenette et al. 2015b (2ndepisode) (case C in Glomski et al. 2018) [1]		$35^{5/7}$ wks		Left	LUQ and flank pain, exacerbated by breathing	Normal	Normal
28	Green et al. 2013 [9]	25	28 wks	1 prior miscarriage, 1 prior 2nd trimester pregnancy loss History indicated cervical cerclage placed at 13 wks Obesity (BMI 40 Kg/m^2)	Right	RUQ and flank pain, nausea, vomiting	BP 114/56 mmHg HR 103 bpm RR 20 breaths/m Afebrile	Leukocytosis
29	Hoen et al. 2011a [43]	25	36 wks	1st pregnancy	Right	Right flank pain, nausea	Normal	Normal
30	Hoen et al. 2011b [43]	27	37 wks	1st pregnancy	Right	Right flank and epigastric pain	Normal	Normal
31	Schmitt et al. 2010 [44]	29	36 wks	1st pregnancy	Right	RUQ and flank pain	NA	Normal

Table 3. Continued.

Imaging	Imaging findings	Thrombophilia screening	Treatment	Pregnancy & clinical course	Delivery(wks)	Follow up
US Chest X-ray MRI w/out contrast	Negative Negative T2 hyperintense enlarged left gland, hyperintense perirenal fat	Protein S 45%	Morphine Enoxaparin (therapeutic)	Pain remission	NA	NA
CT w/ contrast (1 day PP) MRI w/ contrast (1 day PP)	Hypodense enlarged and edematous right gland, right adrenal vein thrombus T2 hyperintense enlarged right gland and adjacent fat, right adrenal vein thrombus, restricted ADC in right gland	Negative	Epidural analgesia in labor Opioids PP Enoxaparin (therapeutic) PP	IoL for suspected preeclampsia Pain recrudescence (1 day PP) Pain remission in 2 weeks PP	VD (38)	Right gland atrophy at MRI 3 months PP No adrenal insufficiency at 3 months PP Enoxaparin (therapeutic) for 3 months PP, followed by LDA for 1 year
MRI w/out contrast	T2 hyperintense right gland	NA	NA	NA	NA	NA
US MRI w/out contrast CT w/ contrast	Negative Negative Hypodense enlarged and edematous right gland	Negative	Oxycodone, hydromorphone UFH (in-patient), fondaparinux (therapeutic, out-patient)	Pain remission	39 (VD)	NA
US MRI w/out contrast	Trace fluid in Morrison's pouch Trace fluid in Morrison's pouch, 6-cm uterine fibroid	NA	Indomethacin, hydromorphone (for suspected fibroid-related pain)	Pain remission	–	- (NHAI diagnosed after 2nd episode occurred, by review of MRI findings)
US MRI w/out contrast CT w/ contrast	Negative Left perirenal trace fluid Hypodense enlarged and edematous left gland, normal right gland	Factor VIII 178%	Hydromorphone UFH	Delivery for persistent pain unresponsive to analgesics	CS ($36^{5/7}$)	NA
US CT w/ contrast	Negative Hypodense enlarged and edematous right gland	Hz MTHFR C677T	Intravenous fluids, PPIs, analgesics UFH (in-patient), enoxaparin (therapeutic, out-patient)	Pain remission pPROM at 32 wks, uterine contractions at 33 wks	VD (33)	Enoxaparin (therapeutic) for 6 weeks PP
ECG US CT w/ contrast MRI w/ contrast (4 h PP)	Negative Negative Hypodense enlarged and edematous right gland Right adrenal vein thrombus	Protein S 31% (2 months PP)	Analgesics Enoxaparin (therapeutic) PP	Delivery for persistent pain unresponsive to analgesics (24 h after ED access)	CS ($36^{1/7}$)	Normal right gland at CT w/ contrast 4 months PP Enoxaparin (therapeutic) for 6 months PP
ECG US CT w/ contrast	Negative Negative Hypodense enlarged and edematous right gland, possible right adrenal vein thrombus	Negative	Analgesics Enoxaparin (therapeutic) PP	Delivery for persistent pain unresponsive to analgesics	CS (37)	Enoxaparin (therapeutic) for 6 months PP
US CT w/out contrast CT w/ contrast (1 day PP)	Negative Negative Hypodense enlarged and edematous right gland, right adrenal vein thrombus	Hz factor V Leiden	Morphine Enoxaparin (therapeutic)	Delivery for persistent pain unresponsive to analgesics and lack of definitive diagnosis	CS (36)	Normal right gland at CT w/ contrast 3 months PP Warfarin for 3 months PP

BMI: body mass index; RUQ: right upper quadrant; LUQ: left upper quadrant; RLQ: right lower quadrant; BP: blood pressure; HR: heart rate; RR: respiratory rate; TOP: termination of pregnancy; VD: vaginal delivery; OVD: operative vaginal delivery; NA: not available; NSIADs: non-steroidal-anti-inflammatory drugs; y: years; wks: weeks; pPROM: preterm premature rupture of the membranes; CS: cesarean section; US: abdominal and pelvic ultrasound; PP: postpartum; LDA: low dose aspirin; ANCA: antineutrophil cytoplasmic antibodies; Hz: heterozygous; Ho: homozygous; PFO: patent foramen ovale; MRCP: magnetic resonance cholangiopancreatography; DWI: diffusion weighted imaging; IoL: induction of labor; PPIs: proton pump inhibitors; HPA1: platelet glycoprotein IIIa GPIIIa (HPA1); UFH: unfractionated heparin; ED: Emergency Department; ADC: apparent diffusion coefficient; LAC abs: lupus anticoagulant antibodies; CRP: C reactive protein; MTHFR: methyl tetrahydrofolate reductas.

In all cases, an enlarged hypodense adrenal gland was recognized. MRI was performed in 19 women; it was an adjunction to the CT scan in 10 of them.

Analgesics were the first-line approach in 26/30 cases, and anticoagulant therapy was employed after diagnosis of NHAI in 27 (90%). The three patients with no anticoagulation had been retrospectively diagnosed by radiological imaging review (n. 18, 19, and 26).

Four cases needed cortisone supplementation due to adrenal insufficiency (n. 1–3, 11); only one of them presented a bilateral event (n. 11). The second bilateral NHAI case (n. 21) showed normal adrenal function, likely due to just a minor ischemic involvement of the contralateral gland. Similarly, the woman with metachronous bilateral involvement did not require cortisone supplementation due to the resolution of the first ischemic event (n. 26) by the time the second occurred (n. 27).

Complete pain remission allowing pregnancy's continuation was obtained in 19/30 pregnant women, whereas 7 (23.3%) required immediate delivery ($n = 5$ urgent cesarean sections, CS, and $n = 2$ induction of labor) for persistent pain unresponsive to analgesics.

The median gestational age at delivery was 37 weeks (IQR 36–38$^{5/7}$ weeks, min-max 32–41;), with 7 (36.8%) preterm births <37 weeks. Results of thrombophilia screening were positive in 12/26 cases, and the most common abnormal finding was factor VIII elevation ($n = 4$ cases), which, in one case (n. 20), was also confirmed 3 months postpartum. Atrophy of the affected adrenal gland was identified in 5/9 patients with an available follow-up radiological investigation.

Data regarding anticoagulation management after hospital discharge were available in 18 (60%) women. Either low molecular weight heparin or warfarin were employed, for a duration of time ranging from 2 weeks to 11 months. Only the patient with simultaneous bilateral NHAI (n. 11) showed persistent adrenal insufficiency requiring cortisol supplementation at 4 months postpartum.

Discussion

Here we describe a rare case of spontaneous acute unilateral NHAI in a pregnant woman in the third trimester with a favorable outcome. We also provide an extensive review of this condition to promote knowledge and increase awareness among obstetricians and frontline healthcare workers managing pregnant women with an acute abdomen. AI is a very rare cause of non-uterine abdominal or flank pain in pregnancy. It can be hemorrhagic or non-hemorrhagic [2], with NHAI being far less common than the hemorrhagic form and, thus, more rarely suspected.

The first case of AI in pregnancy has been reported in 1936 [13]; since then, only thirty-one cases of NHAI in pregnancy have been described. The actual prevalence of NHAI during gestation is still not known, although a recent retrospective review of MRI examinations in pregnant women with acute abdominal pain has reported a figure of 1.3% [1].

Adrenal vein thrombosis is thought to be the primary event in both HAI and NHAI, with gland hemorrhage occurring during the reperfusion phase of necrotic or damaged vessels after thrombosis [13–15]. A recently published retrospective review of adrenal vein thrombosis in pregnancy has identified a prevalence of 1.5 per 10,000 births [16].

The anatomy of the adrenal gland makes it prone to infarction in hypercoagulable states. The arterial supply is rich, but the venous drainage is limited to a single vein [17]. Thus, conditions characterized by a pro-thrombotic status, such as antiphospholipid-antibody syndrome [3], inflammatory bowel diseases [18,19], and pregnancy are at increased risk for AI [4,20]. Additional pregnancy-related risk factors include heightened gland stimulation and local blood flow [21] and reduced venous drainage due to the compression from the gravid uterus, which all become more marked during the third trimester. Of note, we identified 23 out of 31 (74.2%) cases occurring >28 weeks' gestation. In our patient, the event happened at 32 weeks.

AI can be unilateral or bilateral, with bilateral cases mostly identified among individuals with antiphospholipid-antibody syndrome [3].

When unilateral, AI more commonly occurs in the right gland, due to a short, direct venous drainage into the inferior vein cava, which favors venous stasis and thrombosis. This is particularly true during pregnancy for the mechanical compression caused by the dextroposition of the uterus [5,16]. Among 31 NHAI cases identified in our review, 22 (71%) saw involvement of the right gland, as it was in our patient. Diagnosis of AI is challenging due to the rarity of the condition as well as the variability of clinical manifestation, especially in unilateral cases with no biological signs of adrenal insufficiency [5,9].

Unilateral AI can present with acute-onset, severe, upper right or left abdominal quadrant and/or flank pain non-responsive to analgesics and usually associated with emesis. This is what we observed in our case. However, the clinical presentation of unilateral AI may vary from patient to patient. This further increases the difficulty in correctly diagnosing unilateral AI by pointing to other more common non-obstetric causes of acute pain, including biliary or renal colic, cholecystitis, pyelonephritis, appendicitis, pneumonia, or pleuritis. Placental abruption, uterine rupture, pulmonary embolism, acute pancreatitis, gonadic vein thrombosis, and ovarian torsion should also be included in the differential diagnosis. In some cases, uterine contractions can be present, thus deceitfully suggesting threatened preterm labor [5]. It is unclear whether the threatened preterm labor diagnosed in our patient was a prodromal sign of the unilateral NHAI or a separate event.

A challenge in diagnosing unilateral AI is additionally increased by the inconclusiveness of the initial workup. Blood laboratory analyses can identify a mild reactive leukocytosis in some cases, as we observed in our patient.

Ultrasonography may be limited because of the challenging location of the gland, the patient's habitus, and the gravid uterus. Rarely, a small amount of perirenal fluid can be identified [2,10], as occurred in our patient but only at the second scan performed 12 h after pain's onset al. so, in a few cases a swollen adrenal gland has been recognized [10]. In turn, both CT scans and MRI can provide diagnostic information [22–24]. However, potential fetal risks related to ionizing radiation and iodinated contrast material exposure contra indicate CT use in favor of MRI before 25 weeks' gestation. Yet, MRI is usually not available in an emergency context and the use of gadolinium-based contrast enhancement during pregnancy is still controversial [25,26], thus making CT scan the most frequently performed imaging in these cases [10]. Considering the advanced gestational age at the presentation of our case and the unavailability of MRI in the ED, we decided to perform a contrast-enhanced CT scan, which showed an enlarged hypodense adrenal gland without hyperenhancement and inflammatory peri-adrenal fat stranding.

The challenge in correctly identifying unilateral AI explains the delay usually observed between clinical presentation and diagnosis, which has been reported to be greater than 24 h in

50% of cases[16]. We needed 21 h to reach a definitive diagnosis. The later the diagnosis is formulated, the later the appropriate therapeutic management is initiated, thus possibly increasing the risk of contralateral gland involvement and clinical status deterioration [6].

Since the underlying cause of AI in pregnancy is believed to be adrenal vein thrombosis [13–15], evaluation for thrombophilia is pivotal. A condition of thrombotic microangiopathy should also be excluded. Abnormal congenital or acquired thrombophilia screening has been identified in several cases of NHAI in pregnant women. Yet, NHAI can also occur in pregnancies with no evidence of thrombophilia disorders, likely due to the increased thrombogenic risk posed by the gestation itself [20]. Nonetheless, additional risk factors for thrombosis can be identified in most of the published cases, including age >35 years, overweight or obese BMI, active smoking, and chronic inflammatory diseases. This suggests that NHAI should be even more suspected if risk factors for thrombosis, alongside gestation, are identified in women presenting with an acute abdomen and inconclusive initial workup.

Our case showed overweight BMI, substantially increased factor VIII activity (223%), homozygosity for MTHFR A1298C mutation, and heterozygosity for factor V Leiden G1691A mutation. This is the first case with a combination of three different thrombophilia disorders. Of note, both high factor VIII levels and factor V Leiden mutation constitute clinically relevant risk factors for venous thromboembolism [27,28].

Alongside thrombophilia and thrombotic status assessment, an endocrinological evaluation is necessary to identify women requiring cortisone supplementation [8]. Interpretation of blood cortisol levels in pregnancy can be challenging, due to a physiological increase in both total and free cortisol levels [6]. The use of trimester-specific cutoffs is mandatory to correctly identify adrenal insufficiency [29]. In our case, a basal cortisol value of 32.7 mcg/dL was widely above the specific cutoff for the third trimester (21 mcg/dL), thus ruling out the need for cortisone supplementation. We identified four cases of NHAI in pregnancy with adrenal insufficiency (3 unilateral and 1 bilateral), and only one of them showed clinical signs (hypotension). Pain medications are the cornerstones of the therapeutic management of NHAI [5,30].

In addition, anticoagulation should always be considered to avoid ischemic events in the contralateral gland [2]. However, awareness of an increased risk for adrenal hemorrhage as well as hemorrhage at childbirth for pregnant women has to be maintained, especially with therapeutic doses of anticoagulants. Since no standard anticoagulation protocol is currently available for NHAI, hematology consultation is mandatory. Our review identified two pregnant patients not receiving anticoagulation who experienced complete remission and an uncomplicated perinatal outcome[1]; however, in a third case, a contralateral NHAI occurred 18 weeks after the first event [2]. Also, 27 of the 31 published cases were treated with therapeutic doses of anticoagulant, with only one woman receiving prophylactic dosage. The hematologist consulted for our case suggested a prophylactic dosage of enoxaparin, to be continued till delivery and for 6 weeks afterwards. Of note, there is also a lack of consensus on the appropriate duration of anticoagulation after delivery, with published data ranging from two weeks to 11 months.

Mode of delivery is usually not influenced by the occurrence of NHAI unless pain persists notwithstanding analgesic therapy and anticoagulation [11]. Five out of 31 NHAI cases required an urgent cesarean section for inadequate pain control. Our patient had a complete resolution of symptoms, thus allowing for pregnancy continuation.

Follow-up of patients with NHAI is pivotal to identifying those at higher risk for adrenal insufficiency [5,16], although no consensus on the type of investigations as well as on follow-up duration exists [7]. NHAI can either completely resolve or evolve into gland atrophy, with the latter scenario increasing the risk of adrenal insufficiency in case of a contralateral event. This is particularly relevant if another pregnancy is planned, which may then require prophylactic anticoagulation. In our case, an endocrinological follow-up was performed 6 weeks postpartum and was regular.

In conclusion NHAI is a very rare cause of non-uterine abdominal pain in pregnant women. However, it can be life-threatening for both the mother and the fetus if associated with adrenal insufficiency. Early recognition and prompt multidisciplinary management are pivotal to improve outcomes. Thus, knowledge of all the potential clinical and radiological patterns of presentation is mandatory. Our work provides an extensive update on the topic and promotes awareness of this condition as a differential diagnosis among frontline healthcare professionals managing pregnant women with acute onset of abdominal pain.

Ethical approval

Since only anonymized data were employed, approval of the Ethical Committee of Fondazione IRCCS San Gerardo dei Tintori was waived.

Consent form

A written informed consent was obtained from the patient to use her anonymized clinical information for the purpose of this reporting.

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Data availability statement

All data generated or analyzed during this study are included in this published article.

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