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Pregnancy and thrombosis: Adrenal vein thrombosis. A retrospective descriptive study of 14 cases

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ABSTRACT

Objectives: Adrenal vein thrombosis during pregnancy is a rare thromboembolic event but is not exceptional. The objective of this study was to described the symptoms, diagnosis, treatment and follow-up of patients with this condition.
Study design: This was a retrospective descriptive study of 14 cases (13 patients, one recurrence) that occurred in the three university maternity hospitals in Lyon (France) from 2008 to 2016.
Results: Adrenal vein thrombosis occurred exclusively in the third trimester (gestational age > 28 weeks), with most patients presenting unilateral lumbar pain (13/14 cases, 93%) and vomiting (8 cases, 57%), mimicking renal colic. To establish the diagnosis, all patients were examined by abdominal CT and all but three (79%) by abdominal ultrasonography. Ten patients (71%) were treated by low molecular weight heparin and the remaining four (29%) by unfractionated heparin. The delay between presentation and diagnosis, and thus before treatment was initiated, was greater than 24 h in 50% of cases. Thrombosis occurred predominantly (11 vs 3 cases) on the right adrenal vein. Labor inducing or cervical ripening agents were used after temporarily interrupting treatment for 9/14 patients (64%). Epidural anesthesia was possible for 11 patients (79%) and 2 (14%) had postpartum hemorrhage. Eleven patients received hemostatic function investigations with anomalies detected in four cases (36%). One of the six patients (16%) who had a second full-term pregnancy during the study period had a contralateral recurrence.
Conclusions: Adrenal vein thromboses are rare events requiring curative anticoagulant therapy and labor management to minimize the risk of hemorrhage. Patients should receive thromboprophylaxis for subsequent pregnancies and a full thrombophilia investigation.

Introduction

Pregnancy induces hypercoagulability and increased blood stasis (two elements in Virchow's triad) due to abdominal compression by the gravid uterus, increasing the risk of thromboembolic events. In the general population, adrenal vein thrombosis occurs bilaterally and induces acute then chronic adrenal failure, and leads in most cases to the discovery of an underlying life-threatening antiphospholipid syndrome [1,2].

Here, we describe cases of adrenal vein thrombosis occurring during pregnancy, which appear to be rare but not exceptional events that are always unilateral. Diagnosis is complicated by the non-specific nature of the symptoms and the absence of acute adrenal failure. The most common presentation is indeed unilateral lumbar pain and vomiting, without fever, mimicking renal colic. The aim of this study was to systematically describe the symptoms, mode of diagnosis, treatment and follow-up of patients with adrenal vein thrombosis occurring during pregnancy.

Materials and methods

We retrospectively investigated the medical files of patients treated in the three university maternity hospitals in Lyon, France between January 2008 and December 2016. We searched for the International Classification of Diseases (ICD-10) code O223 to identify patients who had had deep vein thrombosis during their pregnancy. We then studied each medical file to only include those

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who had presented adrenal vein thrombosis and carried out a descriptive study.

Results

There were 89,618 births during the study period in the three hospitals involved and 265 (roughly 3%) of the mothers had deep vein thrombosis (ICD-10 code O223). There were 14 cases (13 patients, one recurrence) of adrenal vein thrombosis during pregnancy, giving a an estimated prevalence in this study of 1.5 per 10,000 births.

Clinical characteristics

The patients' clinical characteristics are summarized in Fig. 1.

Nine of the 13 patients in the study group were primiparous at diagnosis, with a mean age of 30.2 years (range, 23–42 years). All patients had classic risk factors for venous thromboembolic disease: a BMI above 25 (11 patients, of which 5 were obese) and/or a smoking habit (8/14 patients). One patient, with a twin pregnancy, was the only one to present a risk factor associated specifically with pregnancy. Two patients had a chronic inflammatory disease, one, rheumatoid arthritis, and the other, Crohn's disease, which was diagnosed postpartum. One other patient was being treated with aspirin following a previous early miscarriage due to chronic histiocytic intervillositis. Three patients developed gestational diabetes mellitus with no associated fetal macrosomia. All fourteen cases of adrenal vein thrombosis occurred in the third trimester of pregnancy (gestational age > 28 weeks) with nonspecific symptoms suggestive of renal colic and with opioid-resistant pain for 8 patients (57% of the study group, Fig. 1).

Diagnosis

Diagnosis was based on patient reports of persistent pain with no obvious cause and imaging results. For half the study group, this lead to a delay of more than 24 h in establishing the diagnosis (Fig. 1), which nonetheless was reached within 48 h of hospitalization in all but one case. This latter patient was diagnosed on day 6.

No biological anomalies were identified other than moderate leucocytosis, ranging from 12 to 25×10^6 L^{-1} with leucocytosis > 15×10^6 L^{-1} in 8 cases (57%). C-reactive protein levels were always in the normal range.

Eleven patients were initially examined by abdominal ultrasonography, which was uninformative in all but one case, in which it revealed an adrenal hematoma. All patients were subsequently investigated by abdominal CT with a contrast agent, regardless of the ultrasonography results. The CT scans revealed indirect signs of adrenal vein thrombosis (Fig. 2, size asymmetry, poor enhancement after injection of the contrast agent, adrenal hematoma, adrenal gland edema), which allowed the diagnosis to be established in all 14 cases. In 11/14 cases, the thrombosis site was on the right (Table 1). The thrombus itself was never observed. Doppler echocardiography was not deemed useful in any of these cases, the main motivation for the imaging exams having been to eliminate a potentially surgical cause.

Anticoagulant therapy

Curative anticoagulant therapy was administered after diagnosis, using low molecular weight heparin (LMWH) in 10 cases and unfractionated heparin (UF) in 4 cases, as decided by the attending anesthetist. Note that the patients' pain subsided in the first 24 h after heparin treatment was initiated. The wearing of compression stockings, recommended for all pregnant women, was particularly emphasized for these patients.

Delivery method

Induction of labor was scheduled for all patients after a 24 h interruption of their anticoagulant treatment to minimize the risk of hemorrhage. This was carried out for 9/14 patients by oxytocin perfusion. Labor began spontaneously for the 5 remaining patients before the planned induction. Epidural analgesia was possible for 11 patients, notably for all those for whom labor was induced. Only two of the patients who went into labor spontaneously received epidural analgesia, after controlling their hemostatic parameters. A cesarean section was performed for 3/14 patients, one because of poor progression after induction, one because of fetal heart rate anomalies after induction, and one because of unexplained severe abdominal pain at 37 weeks. For this patient, it was the abdominopelvic CT scan performed following the cesarean section that revealed the adrenal vein thrombosis. No neonatal morbidities were observed.

Complications

The absence of any symptoms of acute or chronic adrenal insufficiency meant that the hypothalamic-pituitary-adrenal axis

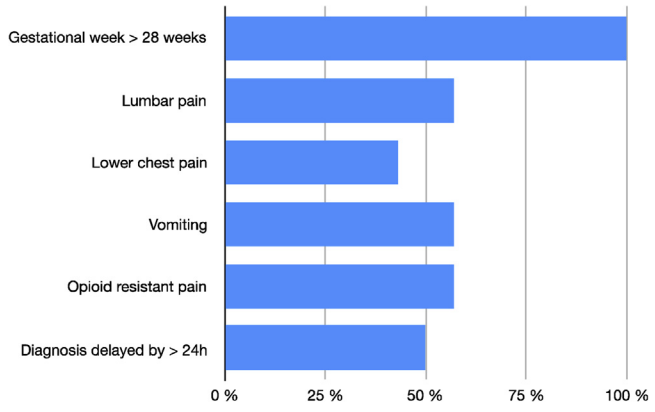

Fig. 1. Clinical characteristics of the study group of 14 cases of unilateral adrenal vein thrombosis during pregnancy.

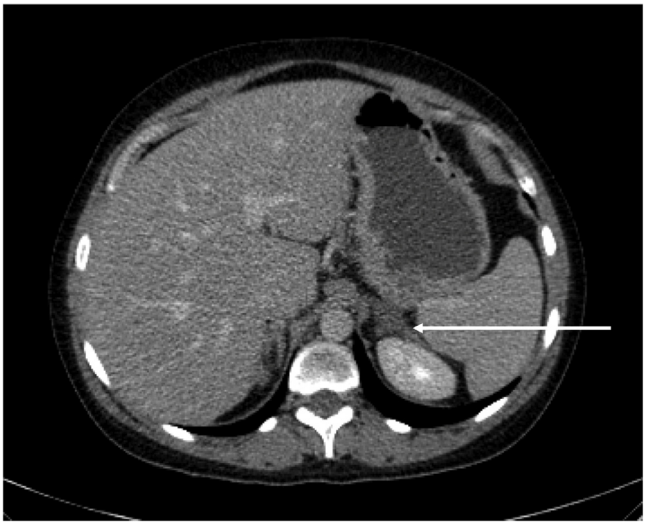

Fig. 2. Abdominal CT scan with contrast agent showing size asymmetry and poor enhancement in the left adrenal gland (adrenal thrombosis).

Table 1
Clinical and paraclinical characteristics, treatment, and type of birth for 14 cases of adrenal vein thrombosis during pregnancy.

Patient	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13
Age	31	42	27	27	25	33	23	29	26	29	24	26	24	26
BMI	23	31	30	37	33	27	23	27	26	19	27	28	33	28
Parity	1	1	1	1	2	3	1	3	1	2	1	1	1	2
Twin pregnancy	–	–	–	–	+	–	–	–	–	–	–	–	–	–
Smoker	–	+	–	+	+	+	+	+	–	–	+	+	–	–
GA at birth	28 + 4	35 + 3	36 + 3	32	33 + 6	32	37 + 2	29 + 6	36 + 1	35 + 2	37	33	33 + 5	36 + 4
Thrombosis	right	left	right	right	right	right	right	left	left	right	right	right	right	right
Urine test	nitrites +	blood +	proteins +	proteins +	blood ++	–	–	–	blood +	–	proteins +	leucocytes +	–	–
Lumbar pain	–	+	+	+	+	+	–	–	–	–	–	+	+	+
Lower chest	+	–	–	–	–	+	+	+	+	+	+	–	–	–
Vomiting	+	–	–	+	+	+	–	–	+	+	–	–	+	+
Anticoagulant	UF	LMWH	LMWH	LMWH	UF	LMWH	UF	LMWH	UF	LMWH	LMWH	LMWH	LMWH	LMWH
Labour induction	+	–	+	+	–	+	–	–	+	–	+	+	+	+
Epidural anesthesia	+	–	+	+	+	+	+	– (lack of time)	+	–	+	+	+	+
Birth type	cesarean (poor progression)	vaginal	vaginal	vaginal	vaginal	vaginal	cesarean (unexplained pain)	vaginal	vaginal	vaginal	vaginal	vaginal	(emergency)	vaginal
Postpartum hemorrhage	–	–	–	+		–	+	–	–	–	–	–	–	–
Antiphospholipid syndrome	–	IgG anticardiolipin antibodies	–	not investigated	–	–	–	–	–	–	lupus anticoagulan	not investigated	lupus anticoagulant	–
Trombophilia investigations	–	–	–	not investigated	heterozygous factor V mutation	–	–	–	–	–	–	not investigated	–	–

GA, gestational age; LMWH, low molecular weight heparin; UF, unfractionated heparin.

was only assessed for 3/14 patients. None of these patients had adrenal dysfunction, probably because only one adrenal vein was obstructed.

Two patients in our study group (14%) had postpartum hemorrhage, one following vaginal delivery of twins, while the other was the patient mentioned above who received an emergency cesarean section because of unexplained abdominal pain, and whose bleeding thus occurred before any treatment for adrenal vein thrombosis (the cause of the pain, diagnosed subsequently) was initiated.

Follow-up

All patients received curative anticoagulant therapy followed by antivitamin K therapy for a total of six months. Twelve of the 14 patients received hemostatic and antiphospholipid tests with a specialist in the late postpartum period and if possible after completing the course of anticoagulant therapy. Two patients were lost to follow up. Blood tests anomalies were discovered for four patients. Three had antiphospholipid syndrome, with lupus anticoagulant in two cases and IgG anticardiolipin antibodies in the other. One patient had congenital thrombophilia with heterozygous Leiden factor V mutation.

A follow-up CT scan was prescribed for 6 of the 14 patients. In one case, this exam revealed the sequelae of adrenal infarction. No biological tests or follow-up had been performed for this patient who did not exhibit any clinical symptoms of adrenal dysfunction.

Prevention and relapse

Six of the 14 patients carried a second pregnancy to term during the study period. Preventive LMWH treatment was prescribed from the first trimester onward following specialist advice. Five of the six patients adhered to the prescribed regimen. The only patient who did not complete the treatment had a contralateral adrenal thrombosis recurrence at $29^{6/7}$weeks of gestation.

Comments

Adrenal vein thrombosis during pregnancy is rare and the literature on this condition is scarce. We indeed found only three existing case reports [3–5].

In this study, the diagnosis rate increased substantially after 2012, with three cases before and 11 after, over similar time periods. The only explanation that comes to mind is that knowledge of this condition and its presentation with nonspecific symptoms probably increased around this date among obstetricians, who subsequently performed the appropriate exams more frequently. This highlights how difficult diagnosing adrenal vein thrombosis during pregnancy is.

The symptoms presented by patients in this study consisted of unilateral lumbar pain, predominantly on the right, vomiting, without fever, which are symptoms commonly associated with renal colic. Urine tests were not informative and no biological signs of inflammation were identified apart from moderate leucocytosis ($12–25 \times 10^6\ L^{-1}$). The patients' renal ultrasound scans, performed as a first test given their symptoms, were also normal. They experienced severe pain, resistant to strong opioids. These findings are consistent with literature data [1,2]. In the cases reported by Hoen et al. [3] and Schmitt et al. [4], the patients underwent an emergency cesarean section, at 36 and 37 weeks gestational age, respectively, because of the unexplained abdominal symptoms. Our study suggests however that there is a clear benefit to prolonging pregnancy under anticoagulant therapy and planning labor induction during an interruption in the treatment. This notably avoids the negative effects of uterine scarring for future pregnancies, bearing in mind that the majority of patients in our group study were primiparous. Furthermore, the risk of neonatal respiratory distress is higher following a cesarean section than after vaginal delivery, particularly before 38 weeks of pregnancy [6].

The nonspecific nature of the clinical symptoms means that additional tests are required to precisely establish the diagnosis. The first imaging exams performed for most patients in our study group were abdominal and renal ultrasound scans, which proved uninformative in all but one case. Nevertheless, ultrasound scans are reproducible, inexpensive and non-irradiating, and can eliminate differential diagnoses, notably renal colic. This technique seems indispensable as a first approach for pregnant women with acute abdominal pain.

None of our patients or those described in the literature were examined by Doppler echocardiography [1–5]. All the diagnoses in the present study were established on the basis of abdominal CT images with contrast enhancement. Computed tomography became indicated because the patients' pain was resistant to appropriate analgesic therapy. A reluctance to examine pregnant women by CT and the rarity of this condition explain why diagnosis occurred more than 24 h after hospitalization for more than half the patients in the study group. In previous studies [3,4], cesarean delivery was performed before CT investigations to avoid the potentially harmful effects of the irradiation or the contrast agent on the fetus.

Studies have shown however that the effects on the fetus of abdominopelvic CT X-rays are sufficiently low to justify performing these exams when the risk-benefit balance favors imaging. Indeed, Golberg et al. [7] evaluated the doses delivered at between 10 and 50 mGy per CT scan and in its 2004 recommendations, the American College of Obstetricians and Gynecologists states that fetal risks are low below 100 mGy and negligible below 50 mGy [8]. At an advanced gestational age furthermore, the risks associated with iodine contrast agents are seemingly low. Several authors have investigated the possible association between neonatal hypothyroidism and in-utero exposure to contrast agents and found no additional risk [9–11]. The injection of a contrast agent seems essential to diagnose the invisible thrombus through indirect signs, in particular poor enhancement after injection.

Thrombosis occurred in the right adrenal vein for most patients (11/14) in our study, which is consistent with previous reports [1–3]. The most plausible explanation seems to be that dextro-rotation of the uterus during the third trimester induces inferior vena cava syndrome by mechanical compression, creating upstream venous stasis. Note that the right adrenal vein connects directly to the vena cava, whereas the left adrenal vein connects to the renal vein. This arrangement is suggestive of a possible embolic risk although no such event has ever been reported.

As for all thromboembolic events, treatment involves curative heparin therapy, in different forms, to be continued after childbirth for six months in total. All the patients in our study group were then treated using antivitamin K (or warfarin if they were breastfeeding). None received new oral anticoagulants.

Only two patients in this study had postpartum hemorrhage, which we defined as blood loss greater than 500 mL for vaginal deliveries and greater than 1000 mL for cesarean sections. One patient had a twin pregnancy, for which the increased uterine distension increases the risk of postpartum hemorrhage. The other patient who had postpartum hemorrhage underwent cesarean section before anticoagulant therapy was initiated; this was therefore not a iatrogenic effect. Planned induction of labor during an interruption in their anticoagulant therapy probably reduced the risk of hemorrhage for these patients.

The hypothalamic-pituitary-adrenal axis was only investigated in 3/14 patients, and no anomalies were detected, contrary to the

cases reported by Schmitt et al. [3] and Hoen et al. [4]. This is probably because the cases in the present study were exclusively unilateral. Furthermore, Ctvrtlik et al. [12] indicate that these evaluations are not recommended in patients, such as those in this study, without symptoms of acute (dehydration, hypotension, digestive disorders, hyponatremia at hypokalemia, hypoglycemia . . .) or chronic (asthenia, melanodermia, hypotension) adrenal insufficiency. It seems appropriate in this context to not systematically perform endocrinological investigations in analogy to the management of adrenal metastases, for which hormonal assessments are only conducted on clinical signs of acute or chronic adrenal insufficiency. Furthermore, the severity of the symptoms and correspondingly rapid treatment, along with the unilateral nature of the thrombosis seem incompatible with the development of chronic adrenal insufficiency. Patients should nonetheless be assessed regularly for signs of chronic adrenal insufficiency to avoid missing a potential long-term complication.

Four of the twelve patients who underwent hemostatic and thrombotic investigations presented anomalies. Other anomalies have also been described [1,2]. Three were found to have antiphospholipid syndrome. It therefore seems appropriate to first investigate antiphospholipid syndrome in patients presenting adrenal vein thrombosis during pregnancy, as soon as the diagnosis is confirmed. These investigations have to be carried out before heparin treatment is initiated, as this affects the concentrations of lupus anticoagulant and makes the results uninterpretable. Thrombophilia tests should preferably be performed once the course of anticoagulant therapy has been completed and outside of pregnancy, which alters blood coagulability notably in terms of protein S. It therefore seems essential to refer these patients to a hemostasis specialist and to properly diagnose all those who undergo such an event, to avoid missing underlying risk factors for potentially severe thromboembolic events. In some cases, genetic testing of family members and preventive treatment outside of pregnancy may be appropriate.

Of the six patients who had another pregnancy within the study period, only one experienced a recurrence. This patient is the only one who had not taken the prescribed prophylaxis treatment. Although no extrapolation can be made on the basis of a single case, this suggests that the risk of recurrence is high in the absence of preventive treatment. There are no specific recommendations for when to begin prophylaxis after a first case of adrenal vein thrombosis but the hemostasis specialists in our treatment centers recommended initiating treatment in the first trimester of pregnancy. The recommendations for pregnant women with a history of thromboembolic events are preventive LMWH therapy from the third trimester onward or earlier, and compression stockings [13], with additional antiplatelet therapy for patients known to have antiphospholipid syndrome.

Conclusions

Our study shows that adrenal vein thrombosis during pregnancy is rare but not exceptional and occurs exclusively in the third trimester. Diagnosis is based on several clinical signs and a CT scan with contrast agent (edema, poor enhancement after injection of the contrast medium). Treatment involves curative anticoagulant therapy, continued postpartum for a total duration of six months. Thrombophilia investigations seem essential in light of the proportion (4/12) of patients in this study who presented an anomaly. Preventive anticoagulant therapy is required during subsequent pregnancies to avoid relapses.

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