REVIEW

Ruptured renal artery aneurysm in pregnancy and puerperium: literature review of 53 cases

Goran Augustin[1] · Tomislav Kulis[2] · Nina Kello[3] · Vanja Ivkovic[4]

Abstract

Purpose To summarize and define the most appropriate diagnostic methods and therapeutic options for ruptured renal artery aneurysms in pregnancy based on rarely published data.

Methods Literature searches of English-, German-, Spanish-, and Italian-language articles were performed in PubMed (1946–2018), PubMed Central (1900–2018) and Google Scholar. The search terms included renal artery aneurysm, renal artery rupture, pregnancy, puerperium, nierenarterienaneurysma, schwangerschaft, wochenbett, aneurisma de la arteria renal, el embarazo, puerperio, aneurisma dell'arteria renale and gravidanza. Additional studies were identified by reviewing reference lists of retrieved studies.

Results Fifty-three cases were collected. The average maternal age was 31 ± 6 years; 71.4% were multiparous and significantly older than primiparas. The majority presented in the third trimester (62.3%), followed by second (20.7%) and the first (5.7%), while 11.3% presented postpartum. All postpartum patients presented during the first week postpartum and 50% during the first 24 h postpartum. Parity was not associated with the trimester of presentation. The left renal artery was affected slightly more frequently (58.5% vs. 41.5%). There were no differences in the affected side according to trimester of presentation, including postpartum. 25 out of 53 cases underwent ipsilateral nephrectomy (47.1%) and 18 underwent aneurysm repair or coil embolization (34.0%). There was no difference in maternal (25.8%) vs. 4 (18.1%) and fetal mortality according to the side of rupture. There were no differences in the distribution of maternal or fetal mortality frequency according to the trimester of presentation.

Conclusions The clinical presentation is easily confused with more common conditions and time to diagnosis is often delayed. Diagnostic delay is associated with high maternal and fetal mortality. Ruptured renal artery aneurysm should be included in the differential diagnosis for pregnant or peripartum patients presenting with acute and severe flank pain, especially if followed by a drop in blood pressure. Early diagnosis and immediate intervention are important for achieving better maternal and fetal outcomes. There are several methods of managing asymptomatic or ruptured renal artery aneurysm during pregnancy although no established guidelines exist.

Keywords Renal artery aneurysm · Pregnancy · Differential diagnosis · Maternal mortality · Fetal mortality

Introduction

Renal artery aneurysms (RAA) are rare and account for 0.01–0.5% of all aneurysms [1], with an incidence of approximately 0.09% [2]. Renal artery aneurysms in pregnancy

✉ Goran Augustin
augustin.goran@gmail.com

Extended author information available on the last page of the article

have been reported in the literature, but due to their low prevalence, there is insufficient knowledge on the characteristics, risk factors, diagnosis, management and outcomes of RAA and ruptures in pregnancy.

Pregnancy-related hormonal, hemodynamic and intra-abdominal pressure changes likely increase the risk of RAA rupture [3]. RAA rupture during pregnancy is a dreaded and fatal complication of RAA with high mortality and morbidity rates for both mother and fetus. Diagnosis is often delayed because the clinical presentation is easily mistaken for more common conditions such as placental abruption, nephrolithiasis or pyelonephritis.

We present the largest systematic review and meta-analysis to date of cases on RAA rupture in pregnancy and puerperium, and propose an algorithm for the diagnosis and management of suspected RAA rupture in pregnancy based on these rarely published data. This review included almost twice as many cases as recently published review of the literature [4].

Methods

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [5, 6], we performed a systematic review of English-, German-, Spanish-, and Italian-language articles using PubMed, PubMed Central, and Google Scholar. The search items included: 'renal artery aneurysm', 'renal artery rupture', 'pregnancy', 'puerperium', 'nierenarterienaneurysma', 'schwangerschaft', 'wochenbett', 'aneurisma de la arteria renal', 'el embarazo', 'puerperio', 'aneurisma dell'arteria renale' and 'gravidanza'. Additional studies were identified by reviewing reference lists of retrieved studies (Fig. 1). We included all cases and case series of patients identified as having a renal artery rupture during pregnancy or puerperium. Exclusion criteria included: (1) spontaneous renal rupture with bleeding; (2) bleeding renal angiomyolipoma; (3) non-ruptured RAA; (4) renal artery stenosis with post-stenotic dilatation; and (5) patients not fulfilling the definition of pregnancy or puerperium.

The primary outcome was to identify associations of demographic data (age), obstetric data (trimester of pregnancy, parity), risk factors (such as hypertension, collagen vascular disease, genetic connective tissue disorders), disease-specific data (RAA side, RAA type, duration of symptoms, time to diagnosis) and therapeutic intervention (type of urologic procedure, the order of obstetric and urologic procedure) with maternal and fetal outcomes. The secondary outcome was to identify common initial working diagnoses in the reported cases. The study is exempt from ethics approval because we synthesized data from previously published studies.

Data extraction

A data extraction form was prepared and piloted to determine if changes were required before extracting data from the full review. Three review authors (GA, TK, and NK) independently extracted patient-level data from articles using pre-defined criteria and compared data to achieve maximum reliability. Any disagreements were reviewed and resolved by the authors. Several groups of RAA-related parameters were extracted from the published articles. Obstetric data

included age, GPLA status, and trimester of pregnancy. Clinical/patient characteristics included localization and duration of pain, other symptoms, and possible predictors including the status of contralateral kidney, blood pressure, pulse, body temperature, flank tenderness, and abdominal guarding/rigidity. Diagnostic data included hematuria, vaginal/cervical examination, laboratory parameters, cardiotocography, fetal sonography, gynecologic/abdominal ultrasound, abdominal CT, abdominal MRI, angiography, and working diagnosis. The type of therapeutic intervention and maternal and fetal outcome were collected.
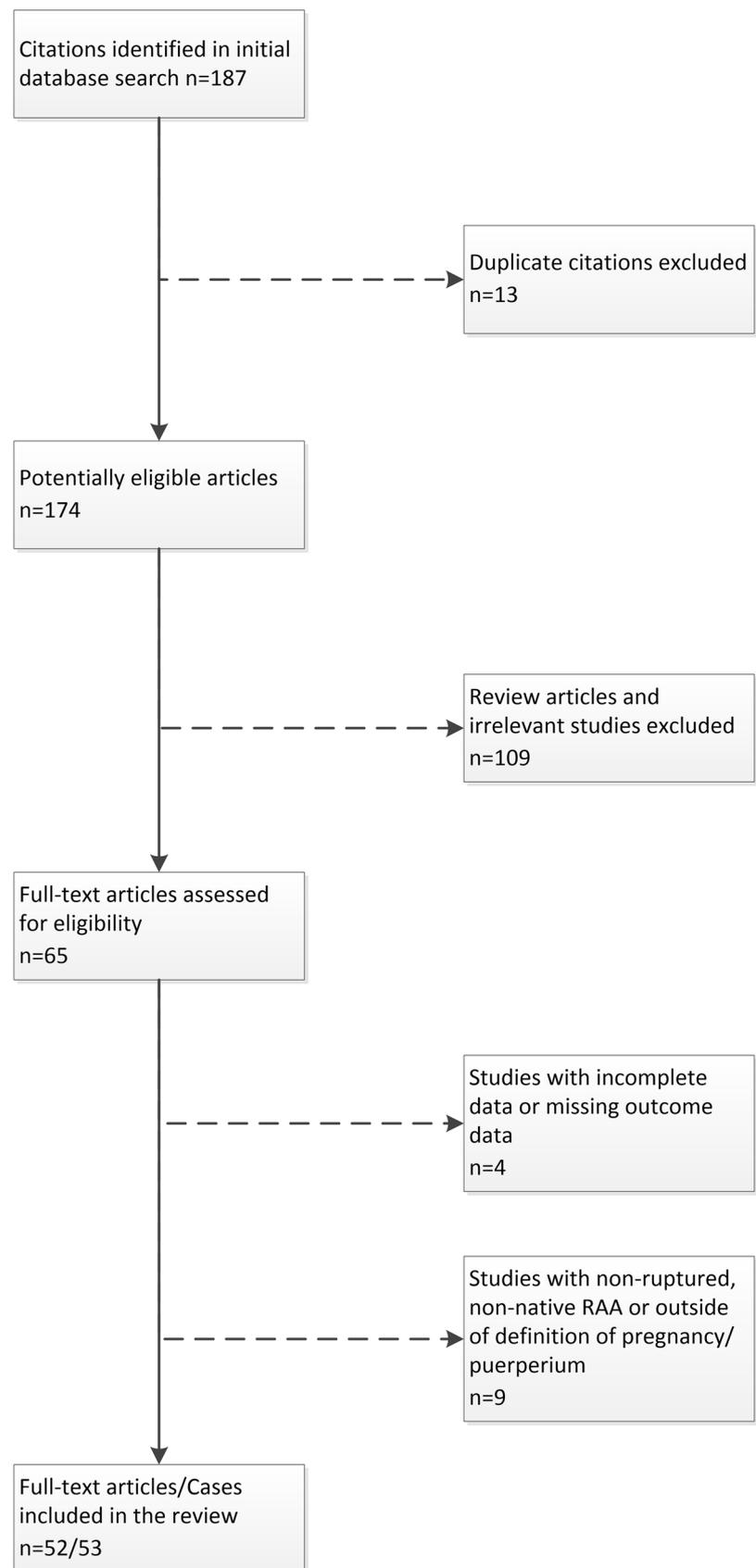
We collected the data that was available from the included studies. However, more than half of the data were missing for several characteristics and are stated as much where applicable.
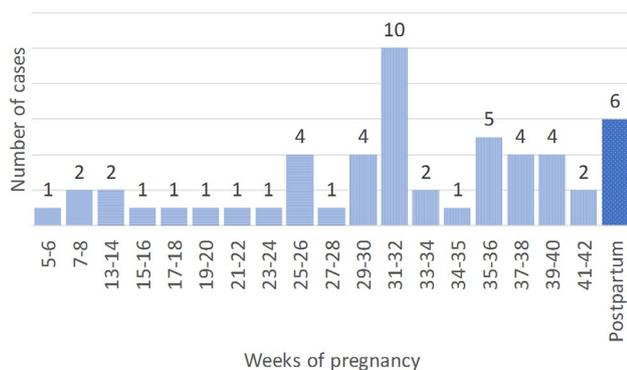
Statistical analysis

Normality of distribution was tested using the D'Agostino–Pearson test. Arithmetical mean, standard deviation, median and interquartile range were used as measures of central tendency. Normally distributed variables are compared using Student's t test for unpaired and paired samples while non-normally distributed variables were compared using the Mann–Whitney test. Correlations were tested using Pearson's and Spearman's tests. Categorical variables were presented as plain numbers and proportions, and were compared with a chi-square test or Fischer's Exact test. Associations between multiple independent variables and a categorical dependent variable were tested using logistic regression. Independent variables (i.e., potential confounders) were selected using a combination of rational clinical judgment and directed acyclic graphs. A two-tailed p value of less than 0.05 was used as a measure of significance. Statistical analysis was done in SPSS v. 21 (IBM Corp., USA).

Results

Of the 187 studies that were identified in our initial database search (Fig. 1), 53 cases of RAA rupture in pregnancy reported from 1926 to 2017 fulfilled the required criteria and were reviewed [3, 4, 7–56]. The data from individual case reports are summarized in Supplementary Table 1. The average maternal age was 31 ± 6 years. Data on parity were available for 49 women of which 35 (71.4%) were multiparous and were significantly older than primiparas (33 ± 5 vs. 28 ± 7 respectively, $p = 0.005$). All cases had data on the trimester of presentation: the majority presented in their third trimester (33, 62.3%), while 3 (5.7%) and 11 (20.7%) presented in the first and second third trimesters, respectively, and 6 (11.3%) cases presented postpartum (Fig. 2). All postpartum patients presented during the first week

Fig. 1 Flow chart for study selection

Citations identified in initial database search n=187

Duplicate citations excluded n=13

Potentially eligible articles n=174

Review articles and irrelevant studies excluded n=109

Full-text articles assessed for eligibility n=65

Studies with incomplete data or missing outcome data n=4

Studies with non-ruptured, non-native RAA or outside of definition of pregnancy/ puerperium n=9

Full-text articles/Cases included in the review n=52/53

Fig. 2 A number of cases regarding trimester of presentation

postpartum and 50% during the first 24 h postpartum. Parity was not associated with the trimester of presentation ($\chi^2(3) = 1.4$, $p = 0.70$). The left renal artery was affected slightly more frequently than the right renal artery (31 (58.5%) vs. 22 (41.5%), respectively). Only seven studies reported data on aneurysm morphology (five saccular and two dissecting RAAs). The vaginal/cervical examination was normal in all reported cases (21/53). The most common working diagnoses were placental abruption/uterine rupture ($N = 14$) (non-specified), acute upper urinary tract disease ($N = 10$), ruptured RAA ($N = 3$), ruptured AAA ($N = 2$) and ruptured ectopic pregnancy ($N = 2$). There were no differences in the affected side according to trimester of presentation, including postpartum ($\chi^2(3) = 0.6$, $p = 0.90$).

The most frequent symptom at presentation was acute and severe pain, most frequently located in the flanks ($N = 37$) and abdomen ($N = 17$), while back pain ($N = 3$) occurred rarely. As for pain characteristics and onset, 33 patients (62.2%) characterized their pain as severe or excruciating and in 32 cases (60.4%) the pain had a sudden onset. Flank tenderness was present in 23 patients and two presented with a pulsatile mass (one with a bruit). Ten patients presented with nausea or vomiting and 17 patients with collapse or fainting. 17 cases reported hematuria, 8 with gross hematuria and 2 with microscopic/dipstick positive hematuria. None of the patients with hematuria died while two patients without hematuria died (0% vs. 22%, $p = 0.51$). There is no statistically significant difference probably due to a small number of patients.

Cases reported before 1988 did not routinely use diagnostic imaging (abdominal CT was used in one case, which was negative). Cases reported after 1988 predominantly used transabdominal ultrasound and abdominal CT (60.6% and 51.5%, respectively). Suspicious or positive findings were present in 70.0% of transabdominal ultrasound and 94.1% of abdominal CT findings, respectively. 25 out of 53 cases underwent ipsilateral nephrectomy (47.1%) and 18 underwent aneurysm repair or coil embolization (34.0%).

Despite the tendency of lower mortality with the performance of the caesarean section, there was no significant impact on maternal survival (19.4% vs. 33.3%, $p = 0.48$). Additionally, due to a small number of cases, it is difficult to compare groups when analyzing the sequence during the same procedure or if several operations were performed. Maternal mortality was 22.6% ($N = 12$), while fetal mortality was 47.2% ($N = 25$). There was no difference in maternal mortality according to the side of rupture (left vs. right 8 (25.8%) vs. 4 (18.1%), $p = 0.75$). There was no difference in fetal or combined maternal and fetal mortality between RAA sides (both $p > 0.05$). Additionally, there were no differences in the distribution of maternal or fetal mortality frequency according to the trimester of presentation (all $p > 0.05$). Combined maternal or fetal mortality was highest in the second trimester (81.8%) compared to the first and third trimesters (33.3% and 45.5% respectively, $p = 0.21$). Multivariate analyses, which included age, hypotension at presentation, hypertensive disorders, side of presentation and parity did not show any predictors of maternal, fetal or combined maternal and fetal mortality. Additionally, a multivariate model including potential predictors of the side of RAA rupture showed no independent predictors.

Discussion

Our systemic review of 53 cases of women with RAA rupture in pregnancy or puerperium is the largest reported to date.

It has previously been reported that the majority of RAA ruptures occur in the third trimester [4, 7, 8], as confirmed in our review with 62.3% of cases presenting in the third trimester. The proposed causes of the increased risk for RAA rupture in the later stage of pregnancy include: (1) expanded intravascular volume with increased systemic blood pressure; (2) rapid increase of blood flow to the kidneys (30–50% in the first trimester) with increased pressure in renal arteries; (3) increased intraabdominal pressure especially during labor; (4) gravid uterine compression on infrarenal aorta and right renal artery due to the physiological clockwise rotation; and (5) weakened structure of the major arteries following increased steroid production [9, 10, 57]. These changes are also supported by data that RAA rupture incidence increases with trimester, as demonstrated in our review with only 5.7% of cases occurring in the first trimester, and 20.7% in the second trimester. The mechanical–physiological changes are still present in the early postpartum period, and this is corroborated in our review by the fact that all postpartum patients presented within 7 days and 50% of these within 24 h of labor.

Our review found that 71.4% of women with RAA rupture were multiparous, indicating that parity could be a

risk factor for RAA rupture. Repeated pregnancies might induce irreversible vessel wall damage that, coupled with the increase in vascular congestion that occurs during pregnancy, may promote a rapid increase in aneurysmal size and even rupture [11]. Furthermore, multiparas are older, and the advancing age carries a biological impact of atherosclerosis and vessel degeneration.

RAAs are more commonly found on the right side in the general population (58.5%), which may be related to the higher incidence of fibrodysplasia on the right side [2, 58, 59], and women account for 64% of all cases of RAA [60]. The first review from 1956 of pregnant patients with ruptured RAA reported eight cases, all with left-sided RAA [12]. The authors concluded that it was far more common on the left side, but since there were so few cases, the conclusions were left open-ended. In the first modern review from 1987 on RAA rupture in pregnancy, authors claimed that 90% of ruptured RAAs in pregnancy was on the left side [7]. Subsequent reviews [4, 8] do not even mention side predilections. Our data show that the ratio of ruptured RAA during pregnancy is in favor of the left side at 1.4:1. Despite the small number of cases and lack of statistical power, it appears to be a shift from a right-sided predilection in the non-pregnant population to a left-sided one in pregnancy. The tendency for left renal artery involvement could be explained by the physiological, clockwise rotation of the enlarged gravid uterus that may compress the aorta and the right renal artery, thus increasing pressure in the left renal artery [10].

In the general population, RAAs show a slightly different natural history in comparison with other visceral artery aneurysms, with a significantly lower risk of rupture and a considerably lower mortality rate. The incidence of true RAAs, excluding microaneurysms and dissections, is approximately 0.1–0.3% [1, 2, 61–63]. The incidence of RAA in pregnancy is not age related but does peak at the age of 35, and then declines, probably due to decreasing incidence of pregnancy in older age. This distribution is likely related to the distribution of pregnancy incidence during the reproductive years.

Risk factors for RAA rupture include incomplete calcification, size > 2 cm, progressive enlargement and mechano-physiological effects of pregnancy [13]. However, treatment of incidental contralateral RAA is not mandatory; it has been reported that active surveillance is safe in the majority of cases [1]. Nevertheless, abrupt onset of RAA progression and rupture, increased risk during pregnancy, in addition to high morbidity and mortality, should warrant early repair of a diagnosed RAA in women planning a pregnancy. Previous recommendations in women of child-bearing age were that surgery should be undertaken for all, even asymptomatic RAAs [3, 64]. Over the last decade, interventional options have shifted towards endovascular techniques over surgical

repair of RAA [65]. This is due to advances in interventional materials and techniques, shorter hospital stay and excellent technical success followed with high renal preservation rates [66].

In the general population, most RAAs are saccular, located in the primary or secondary bifurcations (75%), while intraparenchymal aneurysms occur in less than 10% [1, 58, 59]. Most are asymptomatic [2, 61–63]. Bilateral RAA represents less than 7% of cases and quite often are multiple [67]. In our study, when reported, most RAAs were also saccular.

It is difficult to define the cause of RAA during pregnancy because many studies did not describe the pathologic findings after nephrectomy and there are no specimens in cases when interventional radiology was the only treatment. In the general population, RAAs are strongly associated with arterial hypertension [67], and control of hypertension is essential as it is associated with a lower incidence of RAA rupture [68]. RAAs are usually attributed to medial degeneration and fibrodysplasia with the fragmentation of the internal elastic lamina [2]. Furthermore, in rats, lesions of the renal arteries appeared after the third pregnancy with increased frequency and complexity in subsequent pregnancies [69]. In our review, hypertension was the most frequent risk factor and two patients had Ehlers–Danlos syndrome.

Diagnosis and treatment

Based on collected data, a diagnostic-therapeutic algorithm can be proposed when RAA rupture in pregnancy is suspected (Fig. 3) and could serve as a useful tool for timely diagnosis and early treatment. One must be cautious because due to a small number of cases the algorithm should serve as guidance but without strict recommendations.

RAA rupture should be considered in the differential diagnosis of acute onset of flank or abdominal pain followed by hypotension. Based on our review, the characteristic syndrome of RAA rupture is sudden (60.4%), severe (62.3%), unilateral flank pain commonly followed by hemorrhagic shock. Gross hematuria helps in diagnosis but is not common, or not described (in some cases microhematuria is present). A normal vaginal examination helps to exclude many gynecologic/obstetric causes because the more common causes of hemorrhagic shock during pregnancy are obstetric (placental abruption, placenta previa, ruptured uterus and ectopic pregnancy in early gestation).

Furthermore, given the rarity of ruptured and non-ruptured RAA in pregnancy and puerperium, even if there is a suspicion of RAA in the hemodynamically stable pregnant patient, it could be hard to decide to perform radiation imaging techniques. Transabdominal ultrasound is most commonly the first imaging modality used, and frequently, hemodynamically stable patients are sent to an abdominal

Fig. 3 Proposed diagnostic and treatment algorithm when RAA rupture in pregnancy is suspected
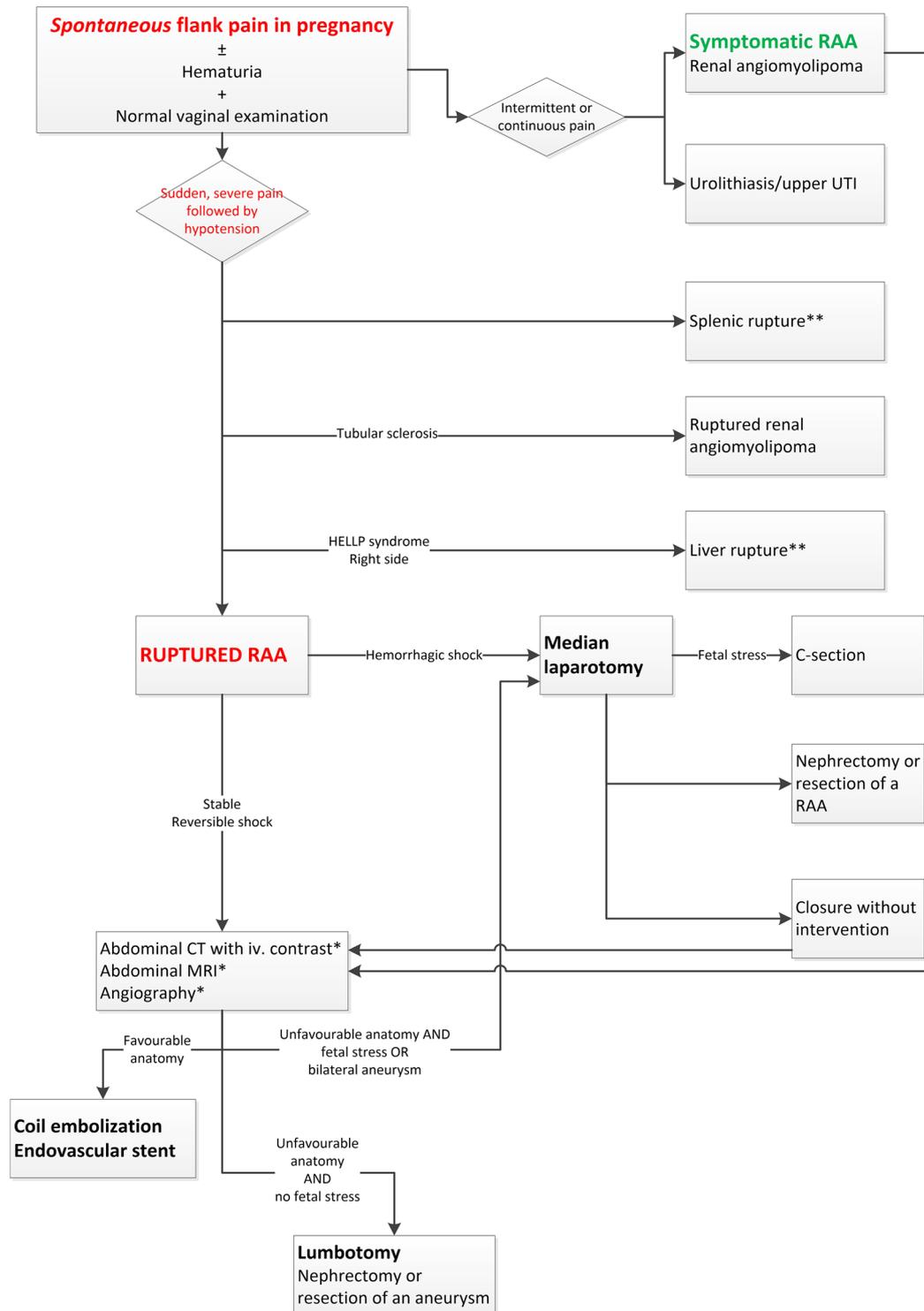
*define type and dimensions of RAA and location and dimensions of retroperitoneal hematoma (when CT or MRI are used). The status of the contralateral kidney and renal artery should be defined.

** Rarely these patients present with isolated flank pain. Mostly these patients have abdominal pain located on the affected side.

RAA – renal artery aneurysm; UTI – urinary tract infection; CT – computed tomography; MRI – magnetic resonance imaging

CT scan. A low-dose CT scan is considered low risk in pregnancy, delivering radiation equivalents of around six abdominal X-rays [70], and is considered highly sensitive (94%), while transabdominal ultrasound, though 70% sensitive, is acceptable. Ultrasound with color Doppler, however, may not clarify the retroperitoneal pathology. MR imaging is often not readily available in emergency settings. The ideal situation is if preoperative imaging can be done. Angiography is diagnostic and defines a treatment modality [33].

The status of the contralateral kidney and eventual RAA should be checked because some degree of congenital/acquired systemic or kidney impairment is common. It is more commonly found in Ehlers–Danlos syndrome, tuberous sclerosis, periarteritis nodosa, etc. Knowledge of the status of the contralateral kidney defines further treatment strategies and a contralateral RAA should be treated accordingly.

Treatment options for rupture of RAA include nephrectomy, repair of RAA and reconstruction of the renal artery, and angiographic embolization. In the hemodynamically unstable patient with confirmed or suspected RAA, exploratory median laparotomy should be performed, with subsequent nephrectomy, resection of RAA, and C-section. In the hemodynamically stable patient, endovascular procedures such as coil embolization and endovascular stenting should be performed if the anatomy is favorable. If the localization of the ruptured RAA is unfavorable and there is no fetal stress, a lumbotomy, nephrectomy or RAA resection is recommended. In the setting of fetal stress or the presence of bilateral RAA, median laparotomy is recommended. In our review, nephrectomy was performed in 23 cases, mostly before 1997. This should be interpreted in the appropriate historical context, since more modern interventions, namely endovascular procedures, started being reported with Prabulos et al in 1997 [38].

Prognosis

Reported maternal and fetal mortality rates have decreased over the decades with improvements in access to high-level care and advancements in interventional techniques. Before 1970, maternal and fetal mortality was 92% and 100%, respectively [42]. In a paper by Cohen et al. from 1987, the reported maternal mortality and fetal mortality of RAA rupture improved to 56% and 82%, respectively [7]. Since then, the reported maternal mortality has been significantly lowered, to 5.1% (2 of 39 cases), $p = 0.0003$. Based on our review of 53 cases from 1926–2017, the average maternal and fetal mortality was 22.6% and 47.2% respectively. Of note, despite a decreasing trend in fetal mortality in the periods above—6/8 (75.0%) before 1956; 5/8 (62.5%) from 1957–1981; and 14/37 (37.8%) from 1982 onwards—there has not been a statistically significant decrease in fetal mortality ($p = 0.93$). The explanation could be that fetal death

from maternal hemorrhage develops early after onset of RAA rupture before any resuscitation or bleeding control procedures can be performed.

Overall, the prognosis of ruptured RAA in pregnancy is dependent on several factors. The delay between the onset of symptoms and the final treatment is most critical. Sometimes, time is lost when the patient is examined first at the local hospital and then sent immediately, after an initial diagnostic workup, or when hemodynamically unstable, to the tertiary center. A significant drop in maternal mortality in the past decades points to advances in education, fast and accurate imaging diagnostics, and immediate treatment.

To conclude, RAA rupture in pregnancy is an extremely rare condition, although more prevalent than in the general population. Our review of RAA rupture in pregnancy, the most thorough to date, demonstrates that this diagnosis still carries high fetal mortality and maternal morbidity, and therefore, we should be aware of it especially in patients with sudden onset of unilateral flank pain followed by hypotension. With timely diagnosis and management, we could avoid fatal maternal and fetal outcomes. In asymptomatic, incidental RAA in women of childbearing age, elective endovascular treatment should be considered as the first method of choice.

Compliance with ethical standards

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Affiliations

Goran Augustin[1] [ORCID] **· Tomislav Kulis[2] · Nina Kello[3] · Vanja Ivkovic[4]**

Tomislav Kulis
tkulis@gmail.com

Nina Kello
ninakello1986@gmail.com

Vanja Ivkovic
vanja.ivkovic@gmail.com

[1] Department of Surgery, University Hospital Centre Zagreb and School of Medicine University of Zagreb, Kišpatićeva 12, 10000 Zagreb, Croatia

[2] Department of Urology, University Hospital Centre Zagreb and School of Medicine University of Zagreb, Kišpatićeva 12, 10000 Zagreb, Croatia

[3] Division of Rheumatology, Northwell Health, 865 Northern Boulevard, Great Neck, NY 11021, USA

[4] Department of Internal Medicine, University Hospital Centre Zagreb and School of Medicine University of Zagreb, Kišpatićeva 12, 10000 Zagreb, Croatia