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Review Articles

Renal tumors in pregnancy: a systematic review

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Summary

Renal tumors are rarely observed in pregnancy, and their symptoms may mimic other pregnancy-related conditions, such as renal calculi, cystitis, and pyelectasia. These tumors are generally characterized by magnetic resonance imaging and ultrasonography. The decision to perform surgery depends on the stage of pregnancy. If a patient is diagnosed as having neoplasms in the first trimester, the best choice is to operate as soon as possible. If the diagnosis is made in the second trimester, a better option would be to wait until the 28th week of pregnancy to optimize a fetus' chances of survival in case preterm labor occurs. If the mass is detected in the third trimester, surgery should be postponed until the end of pregnancy. In this study, the authors reviewed articles on renal tumors during pregnancy published from 1980 to 2015.

Key words: Renal tumors; Calculi; Cystitis; Pylectasia; Pregnancy.

Introduction

Renal tumors rarely occur during pregnancy and are usually accompanied by symptoms that may mimic other pregnancy-related conditions (e.g., renal calculi, cystitis, pyelectasia). Clinical presentation is characterized by a common triad: palpable masses, flank pain, and hematuria. The high occurrence of palpable mass during pregnancy is probably caused by the frequent abdominal examinations that patients undergo during the course of their pregnancy. Flank pain is almost always present, but it can mimic renal colic or pyelonephritis, thus delaying diagnosis. Hematuria (macroscopic and/or microscopic) presents only in less than half of pregnant patients. It occurs when a renal mass ruptures, and blood flows into the renal ducts [1].

Materials and Methods

The authors systematically examined the scientific literature, including papers, reviews, and case reports, published by PubMed from 1980 to 2015. The papers for review were searched using a combination of the following keywords: renal cancer, pregnancy, gestation, and renal mass. No language restrictions were imposed on the selection.

Results

In the last 25 years, 107 diagnoses of renal tumors in pregnancy have been reported in the literature. The most common histotype is renal cell carcinoma (RCC) (88 cases), followed by angiomyolipoma (AML) (82 cases), nephroblastoma (Wilms' tumor) (eight cases), metanephric adenoma (three cases), fibroma (three cases), sarcoma (two cases), lymphoma (three cases), juxtaglomerular cell tumor (three cases), oncocytoma (two cases), reninoma (three cases), carcinoid, angioma, mesoblastic nephroma, teratoma, and renal pelvis carcinoma (one case each) [2]. The diagnoses were performed by ultrasonography and magnetic resonance imaging (MRI) because pregnant women are generally prohibited from undergoing CT scanning given the high exposure of the fetus to radiation during such tests. Ultrasound techniques are also more sensitive than intravenous pielography to small renal masses. CT imaging can be reserved for patients who present symptoms during puerperium [3].

According to Loughlin [1], the treatment of renal tumors typically involves radical nephrectomy. Schematically, the treatment of masses depends on pregnancy period and should be aimed at ensuring a good prognosis for both the mother and the fetus [2]. If a patient is diagnosed as having neoplasms in the first trimester, the best choice is immediate operation. If the condition is diagnosed in the second trimester, a better option is to wait until the 28th week of pregnancy to optimize the fetus' chances of survival in case preterm labor occurs. If the mass is detected in the third trimester, surgery should be scheduled until after the pregnancy.

The type of surgery and other treatment options should be evaluated in accordance with individual cases and prognoses. In certain situations wherein benefits outweigh risks, la-

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paroscopy can be performed. The advantages of laparoscopy are that it involves minimally invasive procedures, reduces morbidity, decreases pain, entails a short recovery period, and enables the fast resumption of regular bowel and bladder function [3]. Despite its benefits, however, it also presents risks. Difficulties may be encountered in implementing techniques because of a large pregnant uterus; the pregnant uterus may be damaged, and abdominal pressure may occur, thereby reducing the amount of blood pumped back to the heart and decreasing placental perfusion. Given the different histotypes, clinical presentations, and prognoses identified in the reviewed papers, the present authors organized the discussion according to the types of tumors diagnosed.

Renal cell carcinoma (RCC)

RCC is the most frequently diagnosed renal tumor in pregnancy. Numerous findings support the idea that pregnancy-related hormonal changes (e.g., high estrogen and progestin levels) stimulate renal cell proliferation. Renal cells have both estrogen and progestin receptors. At the same time, the hyperfiltration of kidneys during pregnancy causes nephrons to develop glomerulosclerosis, thus increasing their susceptibility to carcinogenesis [2]. RCCs double in volume in 500 days, with the tumors demonstrating malignancy but a low replication rate. On the basis of histological characteristics and genetic alterations, the Heidelberg classification (1997) identifies four groups of RCCs: common, papillary, chromophobe, and collecting duct carcinomas [4]. Clear cell carcinoma is the most common of the four types of RCCs. It can also be one of the tumors that grow as a symptom of von Hippel-Lindau (VHL) syndrome, which is an autosomal disorder that induces the development of several benign and malignant tumors in various body districts. These tumors include hemangioblastomas of the retina, cerebellum, brain stem, and spinal cord, adenocarcinomas of the lymphatic sac, cysts or tumors of the pancreas, and renal lesions. In pregnant women with a familial history of VHL disease, ultrasound screening is a suitable diagnostic procedure given that such screening avoids the risk of puncturing the hypervascular tumor of the spinal cord during the administration of epidural anesthesia . This tumor can be very aggressive and spreads early with diffuse metastasis [5].

Chromophobe RCC is a rare condition, with only approximately 50 cases described in the literature. Its main symptoms are microscopic hematuria (47% of cases), which is present in less than half of diagnosed patients, hypertension (18%) that is often be poorly controlled by medical therapy and mimics preeclampsia, and renal masses (88% of patients) that are difficult to identify because of the large dimensions of the uterus [9, 10]. The prognosis for this disease is better than that for clear cell carcinoma, with a five-year survival of 92% (chromophobe RCC) against 50% (clear cell carcinoma) [6].

Collecting duct renal cancer is considerably more malignant than other renal cancers. It often occurs in young patients, and at diagnosis, metastasis has often already spread. The first symptoms are usually bone metastasis and weight loss [7].

Mucinous tubular and spindle cell carcinoma is a low-grade variant of RCC. It is the rarest type and presents non-specific characteristics during MRI and ultrasound screening, thus leading to difficult diagnoses [8]. During the studied period, 88 pregnant patients were diagnosed with renal cancer, 29 of whom were diagnosed from 2000 to 2015. The gestational age at diagnosis was identified in 24 of the 29 cases. Specifically, five, 13, and three patients were diagnosed in the first, second, and third trimesters, respectively. Tumor localization was specified in 12 of 29 cases: in eight and four of the subjects, the tumors were on the right and left kidneys, respectively. Applied therapy was specified in 27 cases: 18 patients underwent laparotomic nephrectomy, and nine were treated laparoscopically. Mode of delivery was indicated in 22 cases: ten patients delivered vaginally; ten underwent a cesarean section (CS) (one of the patients also underwent hysterectomy directly after CS), and two underwent medical abortion. From 1980 to 2015, at least 18 patients gave birth to healthy infants by vaginal delivery [1, 8-16].

Angiomyolipoma (AML)

AML is a benign amartomatous tumor composed of blood vessels, smooth muscle cells, and fat tissue. In 30% of cases, AML is associated with tuberous sclerosis (TS), whereas the remaining 70% occurs in a sporadic manner [17]. It is a rare condition, accounting for only 3% of renal solid masses and presenting in only 0.3% of the general population. AML is usually found in kidneys but may also occur in the spleen, liver, uterus, or tubes [18].

TS is a neurocutaneous hereditary disease that can affect almost every tissue in the body. The most frequent localizations are the skin, brain, kidneys, and heart. TS incidence varies from cosmetic skin alterations to severe organ damage. About 80% of patients with TS present AML [19]. In many cases of TS and AML association, AML and lymphangio-leiomyomatosis coexist; the latter is a lung disease characterized by shortness of breath, pneumothorax, and fatigue and causes severe respiratory impairment [20]. When AMLs are associated with TS, they are often large (generally > 4 cm), multiple, and susceptible to ruptures and massive bleeding [3]. The high risk of bleeding is attributed to increased plasma volume during pregnancy [21].

AML is also strongly correlated with estrogen exposure, both in pregnancy and in combined contraceptive therapy. It is typical of women of fertile age. AML causes morbidity in two ways: bleeding and renal failure [17]. It is frequently asymptomatic. In symptomatic patients, for whom the possibility of AML rupture is a necessary consideration, symptoms are usually flank pain, palpable masses (often

detected in pregnancy because of the high number of abdominal palpations), and hematuria (due to intracapsular or retroperitoneal rupture of aneurysms generated by the vessels of the tumor) [18].

The risk of ruptures increases with tumor dimensions (a tumor > 4 cm can be regarded as presenting high risk), coexistence with TS, and other symptoms. The presence of fat enables ultrasound, MRI, and CT imaging of AML [17]. The disease is effectively diagnosed by ultrasonography because the findings of this technique are strongly suggestive (hyperechoic mass). MRI is then used as a confirmatory screening approach, and a biopsy is rarely performed [21]. In asymptomatic patients with AMLs less than 4 cm, treatment is unnecessary, and ultrasound control every 6 to 12 months is sufficient [22]. Interventions for patients requiring treatment can involve surgery, with partial or radical nephrectomy, and endovascular treatment that entails transcatheter embolization with liquid agents (e.g., NBCA), polyvinyl alcohol particles, gel foam, and metallic coils; these treatments constitute a conservative approach to renal parenchyma [3]. Therapeutic embolization can be used in different cases: (a) in patients whose AMLs are larger than 4 cm, for which preventive intervention is necessary; b) in acute bleeding of AML and in the stabilization of renal function when TS is present. The most common approach to transarterial embolization is the femoral technique because it enables the easiest access to the femoral artery. When this treatment is contraindicated, however, transradial embolization is a suitable alternative. Instances of contraindication are the presence of acute aorto-renal angles, renal artery stenosis, or severe peripheral arterial stenosis, and when avoiding high exposure of the pelvic region to radiations is advised (as is the case in pregnancy). Another alternative treatment is radical nephrectomy, which is considered for patients who are hemodynamically unstable [23-30].

Reninoma

Reninoma differs from other tumors. In fact it is induced by the hormonal secretion of renin, which then activates the renin-angiotensin-aldosterone system. This activation causes hypokalemia and severe hypertension that is unresponsive to most medical treatments. Differential diagnoses of pheochromocytoma include urine catecholamine and metanephrine testing, which generate normal results in the presence of reninoma [31]. Severe hypertension can simulate preeclampsia and lead to abruptio placentae, preterm delivery, and HELLP syndrome, thus threatening the patient's life.

Adult Wilms' tumor

The present authors found six cases of adult Wilms' tumor, which is one of the most common tumors in children and rarely occur in adults. The criteria typically used to diagnose a nephroblastoma are (1) primary renal neoplasms, (2) primitive blastomatous spindle or round cell components, (3) the formation of abortive or embryonal tubular or glomeruloid structures, (4) the absence of hypernephromatous areas, (5) pictorial confirmation of histological findings, and (6) > 15 years of age.

Standard treatment for adult Wilms' tumor should consist of radical nephrectomy accompanied by chemotherapy with or without radiotherapy. During pregnancy, chemotherapy and radiotherapy are contraindicated (primarily in the first trimester because of teratogenic effects, but also in the second and third trimesters because of effects on placental functioning and fetal growth) [32]. Surgical timing should adhere to Loughlin's recommendations [1].

Metanephric adenoma

Metanephric adenoma derives from the same structure as Wilms' tumor and metanephric blastema, one of the embryologic precursors to the development of the kidney. Metanephric adenoma is thus considered the counterpart of Wilms' tumor. It can present not only with the classical symptoms of renal tumors (hematuria, palpable masses, or flank pain), but also with paraneoplastic syndromes, such as polycythemia or hypercalcemia. With imaging findings alone, differential diagnoses of RCC and Wilms' tumor can be very difficult, thus motivating the adoption of an aggressive approach even with a benign tumor. Only two cases of metanephric adenoma are described in the literature [33].

Sarcoma

Renal sarcomas are rare in pregnancy, as evidenced by the only two cases reported in the literature. The first case was a rhabdomyosarcoma, a malignant tumor of mesenchymal origin that presents with non-specific symptoms. Only ten cases of rhabdomyosarcoma are found in the literature, both for pregnant and non-pregnant patients and with no differences in incidence between men and women. Typical presentations are weight loss, fatigue, hematuria, and abdominal pain. It is generally aggressive and prognosis is worse in adults than in children [34]. No standardized treatment is employed and the therapeutic approach should be similar to the classical intervention suggested by Loughlin for solid renal masses, independent of histotype [1]. The second sarcoma case during pregnancy involved a patient who presented gross hematuria without signs of urinary infection [35]. Both of these cases occurred during the third trimester of pregnancy with a unilateral tumor; the patients underwent simultaneous CS and total nephrectomy. Both patients presented free margins of excisions and were disease free after several years of follow-up.

Oncocytoma

Oncocytoma is a benign tumor without invasion or metastasis. It is usually accidentally diagnosed in asymptomatic patients. The literature discusses two cases of oncocytoma in pregnant patients. In one of the patients, the

tumor presented with severe hypertension with superimposed preeclampsia, uncontrollable by therapy, thereby leading to diffuse edema and acute pulmonary edema. This tumor's behavior was uncommon, driving the need for intensive care and radical nephrectomy for the mother and causing fetal death. Blood pressure normalized after the intervention [36].

Teratoma

Only one case of mature cystic teratoma is reported in the literature. The patient, at 25 weeks of gestation, was initially diagnosed with renal abscess. Ultrasound and clinical examination indicated spontaneous abortion with pyometra. The patient underwent nephrectomy and evacuation of retained products of conception and developed sepsis. Diagnosing renal teratoma necessitates the presence of two criteria: the tumor should unequivocally be determined as being of renal origin and must show heterotopic organogenesis [37].

Choriocarcinoma

Choriocarcinoma is a highly aggressive cancer composed of atypical cytotrophoblast and syncytiotrophoblast. In women, it derives frequently from a previous pregnancy, mainly molar. The main site of occurrence is inside the uterus, deriving from eutopic pregnancies, followed by ovarian and fallopian localization (derived from ectopic pregnancy). In rare cases, it has been described as a primary tumor that occurs in other districts of the body. Metastasis is more common in other organs than in genital ones. The literature describes only one case of renal choriocarcinoma (of gestational origin), detected in a patient with three previous full-term deliveries. At diagnosis, the tumor had already spread by pulmonary metastasis. The uterus did not present signs of the tumor. The patient underwent chemotherapy and was disease free at two years of follow-up [38].

Conclusion

Although rare, renal tumors can threaten the lives of pregnant women and infants [18]. These conditions require close examination upon presentation of flank pain, palpable masses, hematuria, and severe hypertension. Accurate differential diagnosis is also essential. Common diseases that can be confused with renal tumors include urinary tract infections (abscesses and pyelonephritis), renal calculi, preeclampsia, and renal endometriosis [39-41] .Given their generally poor progression, the early diagnosis of renal tumors permits a less invasive treatment, thus preserving renal function and securing positive pregnancy outcomes. With the evolution of laparoscopic and endovascular techniques in recent years, minimally invasive therapies are now available and minimize maternal and fetal risks [19, 42, 43].

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