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Update on approaches to urinary lithiasis in pregnancy

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ABSTRACT

Background. Urinary lithiasis is a prevalent and recurring condition in male and female patients and in all age groups. It is the most common cause of abdominal pain of urologic origin during pregnancy. Urinary lithiasis is the primary non-obstetric cause of hospitalization among pregnant patients. Approximately one out of every 200 to 1,500 pregnant women experience renal colic secondary to lithiasis.
Objective. This study provides a critical review of the pathophysiological, diagnostic and therapeutic particularities of this condition based on the best and most recent evidence.
Materials and Methods. A review of literature was carried out for all English language literature. Clinical studies were identified in the bibliographic database such as PubMed (Medline), Ovid and eMedicine (WebMD) using the keywords: hydronephrosis, urolithiasis, kidney stone, urinary tract infection, pregnancy and ultrasound, incidence and epidemiology of renal stones
Conclusions. Diagnostic methods are of particular interest due to maternal and fetal exposure to radiation. Therapy should also be tailored to specific phases of gestation. Physicians must be aware of appropriate approaches to urinary lithiasis in pregnancy to provide safe treatment for patients, with minimal maternal and fetal impacts.

INTRODUCTION

Epidemiology

Urinary lithiasis has been described in male and female patients in all age groups, and is thought to affect up to 15% of global population, depending on geographical location [1-3]. The number of cases of renal colic and related hospital admissions has increased significantly in the last few years [4, 5]. Growing prevalence of urinary lithiasis may reflect poor dietary habits (increased protein and salt intake) or obesity, which increases the predisposition to the disease [6-8]. Improved quality of radiological examinations and higher frequency of medical check-ups may also have contributed to the identification of previously underdiagnosed calculi.
The growing number of cases of urinary lithiasis among women has not been particularly associated with pregnancy [9]. Nonetheless, renal calculi may affect up to 1 out of every 200 pregnant women, with one symptomatic case out of every 3,300 pregnancies [10, 11]. Urinary lithiasis is more common in the second and third trimesters of pregnancy, although complications and symptoms have been more often described in the last months [12, 13].

Pathophysiology of lithiasis in pregnancy

As in the population at large, family history of lithiasis, low fluid intake, obesity, diabetes and diets rich in sodium and red meat are important risk factors for lithogenesis, whereas appropriate hydration and intake of citrate and phytate are protective [14].
Several pregnancy-related anatomical and physiological genitourinary changes, especially urinary stasis in response to maternal hydronephrosis and changes in lithogenic factors, may impact stone formation [15].
During pregnancy, the kidneys are displaced cranially by the fetus and increase approximately 1 cm in size, due to enhanced vascularization and interstitial space enlargement [16].
Maternal hydronephrosis affects 90% of pregnant women [17]. Hydronephrosis signs and symptoms may interfere with appropriate diagnosis of obstructing ureteral lithiasis [18]. Hormone changes, such as higher serum progesterone levels, induce smooth muscle relaxation and decrease ureteral peristalsis, facilitating ureteral dilation. Mechanic factors, such as ureteral compression by the pregnant uterus, particularly on the right side [17], also contribute to this physiologic condition of pregnancy. Urinary tract dilation leads to urinary stasis, facilitating crystallization and calculus formation.
Maternal changes in lithogenic factors involve a dichotomy. On the one hand, hemodynamic changes increase filtration of calcium, sodium and uric acid [19], leading to hypercalciuria. Together, hypercalciuria and enhanced intestinal absorption of calcium due to higher placental production of 1.25-(OH)2 vitamin D, increase the odds of calculus formation. On the other hand, significantly higher urinary pH interferes with renal excretion of citrate, magnesium, uromodulins, nephrocalcin and glycoproteins, which inhibit urinary crystallization and hence calculus formation [12, 16, 20].
According to most studies, the composition of calculi affecting pregnant and non-pregnant women is similar. Still, Ross *et al*. reported higher prevalence of calcium phosphate (hydroxipatyte) calculi during pregnancy (74% and 26%, calcium phosphate and calcium oxalate calculi, respectively) [17]. This is thought to reflect hypercalciuria and higher urinary pH during pregnancy, with resultant urinary supersaturation for brushite and formation of calcium phosphate calculi [12,21]. In pregnant women, lithogenesis clearly has peculiar, pregnancy-related characteristics.

METHODS

A review of literature was carried out for all English language literature. We consulted international databases such as PubMed (Medline), Ovid and eMedicine (WebMD), Cochrane Database of Systematic Reviews and Scielo, with the following terms and their combinations: hydronephrosis, urolithiasis, kidney stone, urinary tract infection, pregnancy and ultrasound, incidence and epidemiology of renal stones. We included all available article published until 2020 in English, with priority for articles after the year 2000, inclusive systematic reviews, meta-analyzes and randomized clinical trials, opinion of experts and editorials. We found 153 records from the preliminary bibliographic search. After the elimination of duplicates and after the excluding the works that were manifestly irrelevant, we carefully examined the 96 most recent or significant papers as it appears below. Exclusion criteria included: articles published in other languages, excluded English language; non-medical articles.

DIAGNOSTIC INVESTIGATION

Clinical and laboratory investigation

The physiologic, pregnancy-related ureteral dilation may facilitate the migration of renal calculi, leading to ureteral obstruction and renal colic [21]. In patients with urinary tract dilation, ureterolithiasis must be distinguished from physiologic hydronephrosis and/or pyelonephritis, which may occur in isolation or result from the first two conditions [22].
Affected patients often present with flank or abdominal pain (85%), microscopic or macroscopic hematuria (95% and 20%, respectively), pyuria (42%), and worsening of lower urinary tract symptoms [23, 24]. However, flank pain and microscopic hematuria may occur during normal pregnancy. Therefore typical clinical signs and symptoms of urolithiasis may be misleading in pregnant women [25, 26].
An estimated 28% of pregnant women with urinary calculi are incorrectly diagnosed as appendicitis, early placental abruption, or diverticulitis, due to diagnostic difficulties [24].
Ancillary laboratory tests may contribute relevant diagnostic information. Serum creatinine levels, complete blood count and C-reactive protein are particularly important for kidney function assessment and investigation of systemic infections [13].

Imaging

Radiologic examinations may have negative impacts on fetal development. Therefore, careful cost-benefit analysis should precede the use of such diagnostic modalities. Gestational age, level of radiation emission associated to the selected radiologic modality, and exposure to intravenous contrast agents must be accounted for, among other factors.
The American Urological Association (AUA), the European Association of Urology (EAU) and the American College of Radiology (ACR) recommend ultrasonography (USG) as the first-line imaging modality in pregnant patients [27, 28] to protect the fetus against teratogenic risks associated with radiation exposure [10, 29]. However, in spite of high specificity (90%), the sensitivity of this method for ureterolithiasis diagnosis is rather low (11-24%) [30]. In USG, calculi appear as echogenic foci with posterior acoustic shadowing, often associated with ureteral dilation [31]. Several measures have been proposed in an effort to improve the diagnostic accuracy of USG, such as investigation of intravesical ureteral jets, transvaginal sonography and renal arterial resistance index (RI) measurement using Doppler US [15]. Shokeir *et al*. have shown that RI does not change in response to physiologic hydronephrosis. In contrast, RI increases significantly in cases of dilation induced by acute ureteral obstruction. Hence, RI measurement may contribute to diagnostic accuracy in pregnant women with suspected urolithiasis [32].
Transvaginal USG may also enhance diagnostic sensitivity for detection of distal ureteral calculi, and differentiation between ureteral obstruction and physiological hydronephrosis. However, limited availability, logistic issues and need of an experienced examiner may preclude widespread use of USG [31, 33].
Magnetic resonance imaging (MRI) is an alternative to computed tomography in cases with inconclusive USG findings, since indirect signs suggestive of calculi, such as ureteritis, incomplete filling of the ureteral lumen and perinephric leakage or edema can be detected on MRI [34].
According to the AUA and the EAU, MRI should be the second line-imaging modality in pregnant patients [27]. Use of gadolinium is indicated for enhanced visualization in most cases. Teratogenic effects of this contrast agent have been demonstrated in animal but not in human studies. For this reason, the American College of Obstetricians and Gynecologists (ACOG) still recommends gadolinium-enhanced imaging in cases in which benefits clearly outweigh potential risks [35]. Magnetic resonance imaging also allows the investigation of non-urological conditions with similar symptoms [15].
In spite of slightly higher predictive value for urolithiasis diagnosis in pregnant women (80% *versus* 77%, for MRI and USG, respectively), the cost-benefit relation does not support widespread use of MRI [33]. A new MR urography protocol using Half-Fourier Single Shot Turbo Spin-Echo (HASTE) has been developed to improve the diagnostic accuracy of MRI and good results have been reported. In a prospective study conducted by Regan *et al*., MRI was as accurate as unenhanced helical CT in detecting acute obstruction by ureteral calculi and more accurate than CT in detecting signs suggestive of obstruction, such as perinephric fluid collection [36, 37].
Computed tomography (CT) is the imaging modality of choice for investigation of lithiasis in the general population. This method should be avoided in pregnant patients, particularly in the first trimester of pregnancy, due to high radiation emission and potential teratogenic effects [38]. The different radiations emitted by the imaging methods are summarized according to **Table 1**. However, according to the ACOG, radiation doses smaller than 50 mGy (< 5 rad) are not associated with fetal anomalies or pregnancy loss [39]. Subtle effects may result from early exposure to radiation doses between 50 mGy and 100 mGy (5-10 rad). Doses higher than 100 mGy (> 10 rad) are associated with risk of spontaneous abortion and fetal malformations in women with gestational age of more than 3 weeks [18].
Low-dose and ultra-low-dose CT [33] (< 3.5 mSv and < 1.9 mSv, respectively) are feasible diagnostic alternatives. In theory, such low doses allow safe use of this imaging modality in pregnancy, in spite of theoretical concerns regarding stochastic effects, including late hematologic malignancy [29, 33]. High sensitivity and specificity (> 96%) and positive predictive value (up to 99%) have been reported in studies investigating the use of low-dose CT for urinary lithiasis diagnosis in non-pregnant individuals [18].
The 2017 ACOG consensus supports the use of CT in selected cases, or when USG and MRI are not readily available, based on the premise that typical CT radiation doses fall below exposure levels associated with fetal harm [40]. In line with ACOG guidelines, the AUA recommends low-dose (< 5 mGy) CT assessment of women in the second or third trimester of gestation in cases with inconclusive USG findings. **Figure 1** provides a suggestion for diagnostic investigation.

MANAGEMENT: RISKS AND PARTICULARITIES

Clinical management

In obstetric patients, the lesser the medical or surgical intervention, the lower the risk of maternal and fetal harm. Whenever possible, conservative management should be the first line of treatment for urinary lithiasis. Upper urinary tract calculi smaller than 10 mm tend to be spontaneously eliminated in 70% to 80% of pregnant patients. Pregnancy-related physiological changes, such as higher glomerular filtration rate and hydronephrosis, translate into higher rates of spontaneous elimination in pregnant relative to non-pregnant women (81% *versus* 47%, respectively) [12, 21, 23].

Table 1. *Radiation doses from different radiologic imaging modalities [33].*

Imaging study	Radiation Dose (mGy)
USG	0
Intravenous pyelogram	1.7 - 10
X Ray	1.4 - 4.2
CT (Conventional)	8 - 49
CT (Low-dose)	< 7

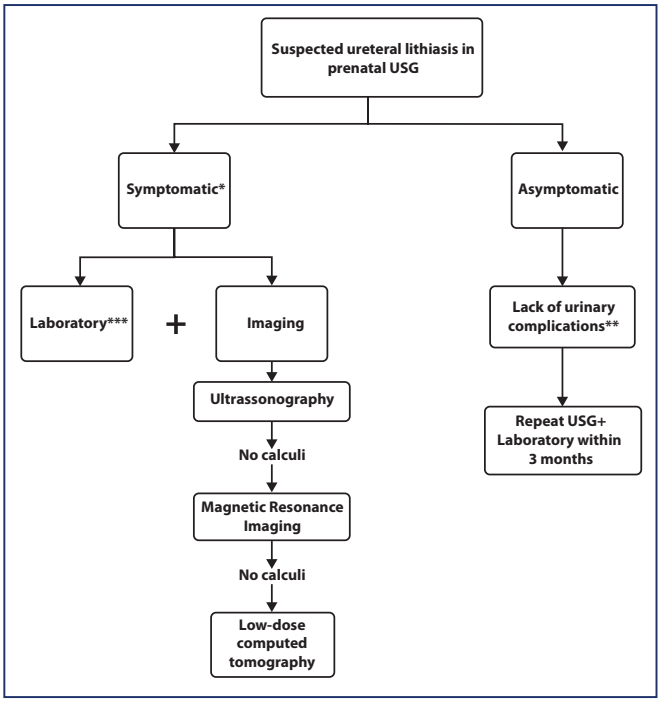

Figure 1. *Diagnostic investigation of ureteral lithiasis in pregnant patients.*

*Symptomatic: flank or abdominal pain, microscopic or macroscopic hematuria, pyuria, and worsening of lower urinary tract symptoms; **Complications: deterioration of kidney function, signs of infection, high renal arterial resistance index (Doppler US), absence of intravesical ureteral jets; *** Laboratory: Complete Blood Count, Sodium, Potassium, Urea, Creatinine, Urinalysis, Urine culture.

However, other conditions requiring immediate intervention must be ruled out prior to selection of a watchful waiting approach. These conditions include urinary tract infection due to obstruction by calculi, intractable pain in spite of clinical management and intense analgesia, acute kidney failure in response to bilateral obstruction, pregnant patients with solitary kidney, and increased frequency of early uterine contractions [13]. Retrospective studies demonstrated renal colic and related complications have been associated with higher risk of prematurity, premature rupture of membranes, low birth weight, preeclampsia, preterm labor, and infant mortality [35].

The selection of medications for conservative management of ureteral lithiasis is based on two pillars: pain management and expulsive therapy.

In pregnant patients, appropriate analgesia must be guided by pain intensity. Oral analgesics, such as paracetamol with codeine, hydrocodone or oxycodone, should be offered first. Non-steroidal anti-inflammatory drugs - the first line of treatment in non-pregnant women - should be avoided due to potential fetal adverse events [17]. Patients should also receive appropriate fluid therapy and antiemetics, as needed [35].

Alpha-1 blockers are the most commonly used agents in expulsive therapy. These drugs have been originally developed for benign prostate hyperplasia and are used off-label to inhibit ureteral smooth muscle contraction, to facilitate the passage of calculi into the bladder [41-43]. The fact that this drug has not been formally approved for use in pregnant women by the Food and Drug Administration (FDA) (Category B) must be emphasized [44]. Successful elimination of calculi following administration of tamsulosin has been reported, with no negative impacts on APGAR scores and mean birth weight [45]. However, in a study conducted by Mervak *et al*., in 2019, short-term use of tamsolusin in the second and third trimesters of pregnancy was not effective in eliminating ureteral calculi. Moreover, fetal safety concerns regarding of off-label use of this drug during pregnancy have been raised.

In the past, calcium channel blockers were used in expulsive therapy in cases of ureteral lithiasis. However, with the advent of alpha-blockers, these drugs are no longer indicated. Calcium channel blockers are thought to be safe in pregnancy and have been approved by regulatory agencies, such as the FDA, for treatment of gestational hyperten-

sion and preterm labor [10]. Hence, these drugs may be a safe alternative to alpha-blockers.
Pregnant women with symptomatic urolithiasis carry a significant risk of secondary urinary infection, which occurs in 52.4% of cases [13]. In cases with urinalysis or clinical findings suggestive of infection, successful management with antimicrobials and appropriate patient follow-up is often indicated, and maternal mortality has not been reported [11]. The range of safe antimicrobials for use in pregnancy is limited and include penicillins, cephalosporins and erythromycin, whereas aminoglycosides, tetracycline, chloramphenicol, fluoroquinolones, and sulfonamides are contraindicated [46].

Surgical management

Surgical management during pregnancy raises maternal and fetal vitality concerns due to surgery- and anesthesia-related morbidity. Still, surgical intervention should be immediately indicated in special cases of ureteral lithiasis with intractable pain, signs of infection, kidney function impairment, solitary kidney, unsuccessful watchful waiting, persistent vomiting, calculi larger than 1 cm, bilateral obstruction or obstetric complications [10]. In such cases, interventional treatment of urinary lithiasis is an emergency surgical procedure. Double-J catheter insertion and percutaneous nephrostomy are equally effective for alleviation of ureteral obstruction [17, 47]. However, high rates of incrustation have been reported following insertion of double-J catheters during pregnancy, possibly due to excessive urinary excretion of phosphate and calcium oxalate [48]. Hence, these catheters should be replaced every 4 to 6 weeks to prevent obstruction and calcification [49]. Strategies aimed to prevent high calcification rates have been investigated. In a clinical study by Takahashi *et al*., lower incrustation rates have been reported following short-term use of the Tria Ureteral Stent with PercuShield and the Polaris Ultra Ureteral Stent with HydroPlus. These catheters share a similar anti-incrustation strategy consisting of hydrogel coating of stent surfaces. Hydrogel-coated surfaces accumulate water in their polymeric network, and act as a superficial protection against hydrophobic bacteria and crystal deposition [50]. In spite of promising short-term results, longer and more detailed studies are warranted.
Nephrostomy is an uncomfortable urinary diversion procedure with greater morbidity. However, this intervention promotes prompt alleviation of the obstruction without catheter manipulation, and is therefore beneficial in cases associated with urinary infection [15].
Need of double-J catheter replacement and transient desobstruction (*i.e*., need of a second surgical intervention for calculus removal) are inconvenient for pregnant patients. Technical and material advancements in endurology led to safe and effective resolution of ureteral lithiasis using ureteroscopy. Stone-free success rates ranging from 73% to 100%, with no need of multiple procedures, have been reported [25, 46]. As per ACOG guidelines, ureteroscopy should be performed in the second trimester of pregnancy to prevent fetal development compromise in the first trimester, and the risk of preterm birth in the third.
Ureteroscopy does not seem to require longer anesthesia and fluoroscopy time relative to double-J catheter insertion, and is associated with low rates of induced preterm labor [51]. Given the high incrustation rates and the need to replace catheters every 4 weeks, ureteroscopy may be a more economical therapeutic alternative across all gestational ages [52]. Shu-Tao Tan *et al*. demonstrated maternal-fetal safety and a success rate in the treatment of stones with ureteroscopy of 87%. This makes us evaluate this procedure as a great alternative for the treatment of ureteral stones in pregnancy [53]. Despite the paucity of literature addressing the outcomes of ureteroscopy in pregnancy, the procedure is thought to be feasible, safe and effective in experienced hands [54].
Extra-corporeal lithotripsy (ECL) and percutaneous nephrolithotripsy (PCNL) are widely used to treat urinary lithiasis in the population at large. However, these methods are contraindicated in pregnant patients. Shock waves used in ECL are associated with higher risk of abortion and early placental abruption [55]. Need of general anesthesia, use of fluoroscopy and difficulties associated with patient positioning justify the contraindication of PCNL in pregnant patients [48].
Lead aprons, proper fluoroscope positioning, low-dose settings and beam collimation may be used to minimize radiation-related concerns in endurological interventions [15]. Procedures may even be performed under ultrasound guidance (i.e., without fluoroscopy) if needed. The follow-the-wire technique is a recent therapeutic alternative. In this method, two guide wires are used for appropriate ureteroscope introduction. High success rates (88%) and only two complications have been reported in a recent meta-analysis evaluating 116 follow-the-wire procedures [56, 57].

With the paradigm shift surrounding surgical management of ureteral lithiasis in mind, Semins *et al*. conducted a study aimed to establish criteria for definitive ureteroscopic treatment. In cases amenable to interventional management, ureteroscopy is preferable to ureteral stenting, with the exception of patients presenting with fever, infection, multiple and/or bilateral calculi, pregnancy complications or anatomical changes, or patients in the first or end of third trimester of pregnancy [10].
Ureteroscopy allows definitive resolution of ureteral lithiasis, carries a lower risk of maternal and fetal complications and is cheaper than double-J catheter insertion, since it does not require multiple interventions [10].
Ideally, surgical interventions should be carried out in the second trimester, since anesthetic and surgical procedures may cause fetal malformations in the first trimester, or induce preterm birth in the third trimester. However, ideal intervention timing is not always possible.
Nitrous oxide should be avoided and regional anesthesia selected to minimize anesthetic risks [13].
Prophylactic use of tocolytics is recommended in women beyond 20 weeks of gestation. Fetal heart rate and uterine activity should be monitored over the course of the perioperative period [13].

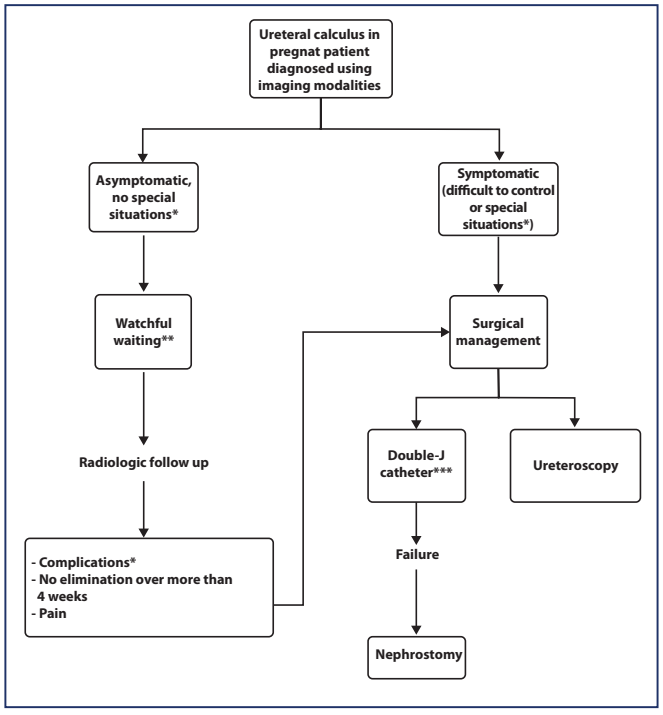

Figure 2. *Management of lithiasis during pregnancy.*

*Special situations: intractable pain, signs of infection, kidney function impairment, solitary kidney, failure in watchful waiting, persistent vomiting, calculi larger than 1 cm, bilateral obstruction, obstetric complications; **Watchful waiting: analgesia + fluid therapy + calcium channel blockers (optional); ***Perform urinary diversion if: fever/infection, multiple and/or bilateral calculi, pregnancy complications, first trimester, anatomical changes, and end of third trimester.

CONCLUSIONS

Urinary lithiasis is a common condition in obstetric patients. Yet, diagnostic and therapeutic approaches remain challenging. Ultrasonography is the diagnostic imaging modality of choice. Doppler US, ureterovesical flow assessment and transvaginal US may be used for optimal outcomes.
Magnetic resonance imaging is the next diagnostic alternative in cases of USG failure. Low-dose CT may be indicated. However, more studies are needed to support the safety of this procedure during pregnancy.
Well-established endurologic techniques are associated with maternal and fetal safety concerns in the obstetric population. Watchful waiting is the therapeutic approach of choice. Literature addressing medical expulsion therapy with alpha-blockers is scarce. Hence, this therapeutic approach may be risky in pregnant patients due to lack of scientific evidence and pharmacological safety criteria. In contrast, calcium channel blockers are widely used in obstetric patients to control gestational disorders. These drugs have a good maternal and fetal safety profile and may be a safe alternative, despite the paucity of scientific evidence of its efficiency.
Given the risk of fetal complications, surgical management, whenever indicated, should be carried out as early as possible. Desobstruction via percutaneous nephrostomy or double-J catheter insertion are effective palliative treatment alternatives. Need of catheter replacement every 4 weeks due to incrustation has led to the development of catheters with lower calcification risks, as well as to wider indication of interventional approaches, such as ureteroscopy for immediate case resolution (**Figure 2**).

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

Each author gave a substantial contribution or the preparation of the manuscript.

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

N/A.

Informed consent

N/A.

Data sharing

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