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Review

Stones in pregnancy and pediatrics

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Abstract Urinary stone disease is a highly prevalent condition affecting approximately 10% of the population, and has increased in incidence significantly over the past 20 years. Along with this, the rate of stone disease among women and children is also on the rise. The management of stone disease in specific populations, such as in children and during pregnancy can present unique challenges to the urologist. In both populations, a multi-disciplinary approach is strongly recommended given the complexities of the patients. Prompt and accurate diagnosis requires a high degree of suspicion and judicious use of diagnostic imaging given the higher risks of radiation exposure. In general, management proceeds from conservative to more invasive approaches and must be individualized to the patient with careful consideration of the potential adverse effects. However, innovations in endourologic equipment and techniques have allowed for the wider application of surgical stone treatment in these patients, and significant advancement in the field. This review covers the history and current advances in the diagnosis and management of stone disease in pregnant and pediatric populations. It is paramount for the urologist to understand the complexities of properly managing stones in these patients in order to maximize treatment efficacy, while minimizing complications and morbidity.
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1. Introduction

Urolithiasis is a highly prevalent condition across the globe, with incidence rates ranging from 1% to 5% in Asia, 7%–13% in North America, and 5%–9% in Europe [1]. The incidence of kidney stone disease has been increasing worldwide over the past few decades. In Japan, the annual incidence of first-episode upper urinary tract stones increased from 54.2 to 134.0 per 100 000 over a 40-year period [2]. A similar increase has been shown in the United States, where the overall prevalence of kidney stones rose 3.6% from 1988 to 1994 [3]. With stone disease becoming increasingly more common, it is important to understand the subtleties and implications of treating urolithiasis in special populations; this review will focus on the specific management of stone disease in pediatric and pregnant populations.

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2. Pregnancy

2.1. Epidemiology

Recent evidence suggests that the incidence and prevalence of urinary stone disease are increasing substantially in the female population. In the United States, the overall prevalence of nephrolithiasis in women has increased at a rate of 1.9% annually over the past 30 years, and there has been a 52% increase in stone-related hospital admissions of female patients [4,5]. Overall, pregnant women are not at a higher risk of stone formation compared with non-pregnant women of similar age and demographics [6]. However, the true incidence of urolithiasis during pregnancy remains largely unknown and reports in the literature vary widely from one out of every 200 to 3 800 pregnancies [7,8]. Literature reports that there has been no change in the incidence of stone disease among pregnant women over the past 2 decades [9]. Although not common, urolithiasis during pregnancy represents a difficult clinical situation, which poses potential serious risks to both the mother and fetus, and requires careful diagnostic and management strategies.

2.2. Etiology of stones during pregnancy

Multiple changes occur in genitourinary anatomy and physiology throughout the course of pregnancy that may impact potential stone formation, including urinary stasis and changes to urinary lithogenic factors. Gestational hydronephrosis is very common occurring in up to 90% of women by the end of their third trimester, however, it can be present as early as 6 weeks of gestation and persist until 6 weeks postpartum [10]. The cause of collecting system dilatation during pregnancy is multi-factorial and includes elevated renal filtration, hormonal changes, and extrinsic compression from the gravid uterus. During the first trimester, there is a significant increase in cardiac output and circulating blood volume, along with a decrease in systemic vascular resistance, all of which result in an increase in the glomerular filtration rate (GFR) by 40%—65% [11]. In addition, elevated levels of progesterone result in smooth muscle relaxation and subsequent dilatation of the urinary collecting system [12]. However, extrinsic compression of the ureters by the uterus or ovarian vein plexus at the level of the pelvic brim is thought to be the most important contributing factor to gestational hydronephrosis [13]. Typically, hydroureteronephrosis is greater on the right-side due to dextrorotation of the uterus and shielding of the left ureter by the sigmoid colon [14]. In the majority of cases gestational hydronephrosis is asymptomatic and not associated with significant obstruction, however, in certain cases it can result in flank pain and even forniceal rupture. Hydronephrosis during pregnancy results in urinary stasis and increases contact time with urinary lithogenic factors, which may increase the potential for crystallization and stone formation. Dilatation of the urinary tract may also allow for easier migration of stones from the kidney into the ureter, potentially explaining the observation that ureteric calculi are twice as common as renal calculi during pregnancy [15].

Significant changes also occur to the urinary milieu during pregnancy. Renal filtration increases along with the GFR, and results in a corresponding increase of multiple lithogenic constituents of the urine including calcium, oxalate, uric acid and sodium [16,17]. In addition, hypercalciuria also results from the placental production of 1,25-dihydroxycholecalciferol (1,25-vit D), which causes increased gastrointestinal absorption and bone resorption of calcium, and suppresses parathyroid hormone levels [8,16]. All of these effects of placental 1,25-vit D act to increase filtration and decrease resorption of calcium by the kidney, thereby causing hypercalciuria. In addition, many pregnant women may be taking additional calcium supplementation based on evidence that it significantly reduces the risk of pre-eclampsia, maternal morbidity and mortality, and preterm birth [18]. While investigators have found a trend towards an increased risk of urolithiasis with calcium supplementation during pregnancy, it was not statistically significant [19]. The benefits of calcium supplementation in pregnancy must be carefully balanced against the potential risks, especially in women at high risk of urolithiasis.

The increase in lithogenic factors during pregnancy is balanced by a similar increase in the excretion of urinary stone inhibitors such as citrate, magnesium, glycosaminoglycans, nephrocalcin, uromodulin and thiosulfate, all which inhibit crystal growth and aggregation [20]. Elevation of citrate levels in the urine not only directly inhibits stone formation, but also increases urinary pH thereby reducing the risk of calcium oxalate and uric acid stone formation [17]. However, this alkalinization of the urine increases the likelihood of calcium phosphate stone formation. Studies have demonstrated an increased incidence of calcium phosphate stones among pregnant women [21]. The elevated GFR also increases urine volume, which further serves to decrease the risk of stone formation [22]. The sum effect of these changes to urinary factors ultimately results in no overall difference to the risk of stone disease during pregnancy compared to non-pregnant women.

2.3. Clinical presentation

The diagnosis of acute renal colic can be difficult during pregnancy due to the high prevalence of non-specific flank and abdominal pain, nausea and vomiting, lower urinary tract symptoms, and hematuria [23]. Elevated levels of progesterone can lead to nausea and vomiting, most commonly within the first trimester, but can be present throughout the entire pregnancy [15]. Up to 84% of women report back and abdominal pain secondary to the stretching of ligaments and musculature [15]. Hematuria can result from the rupture of small renal pyramid veins caused by renal enlargement, and up to 52% of women without urolithiasis may have gross or microscopic hematuria during their pregnancy [24]. A high index of suspicion is required to ensure a prompt and accurate diagnosis of urolithiasis during pregnancy, as up to 30% of cases will be mis-diagnosed [24].

Urolithiasis most commonly presents in the second (39%) and third (46%) trimesters of pregnancy [21]. A prior history of stone disease is important to elicit as up to 30% of patients will have had a previous stone, and approximately 3.7% will have had a prior stone episode during pregnancy [21]. Patients will most typically present with flank or abdominal pain (85%), microscopic (95%) or gross (20%) hematuria, pyuria (42%) and worsening lower urinary tract voiding symptoms [10,23]. Patients less frequently present with complications of urolithiasis including urosepsis, premature labor, premature rupture of membranes, pregnancy loss, hypertension, or pre-eclampsia [25]. The rates of reported complications from renal colic during pregnancy vary widely from 0 to 67%, and multiple studies have found no association between acute renal colic and adverse perinatal outcomes [25,26].

2.4. Initial investigations

All patients who present with symptoms suggestive of urinary stone disease should undergo a thorough history and physical exam. Initial laboratory investigations include a complete blood count, electrolytes, urea, creatinine, uric acid and calcium level, as well as a urinalysis and urine culture. If a metabolic evaluation including 24 h urine studies is indicated based on the clinical presentation, then this should be delayed until completion of the pregnancy and weaning of breastfeeding, as the associated hormonal changes may significantly alter urine chemistries [8].

2.5. Imaging considerations

Diagnostic imaging is the cornerstone of investigating renal colic in pregnancy given the difficulty of making an accurate diagnosis based on history and physical examination alone. Multiple imaging modalities including ultrasonography, X-ray examination of the kidneys, ureters, and bladder (KUB), intravenous pyelogram (IVP), computed tomography (CT), and magnetic resonance urography (MRU) have been utilized. However, the need for an accurate and timely diagnosis must be carefully balanced with the potential risks of radiation exposure to the mother and fetus.

The risk of teratogenicity from radiation exposure to the fetus is dependent on gestational age at the time of exposure. The estimated threshold to induce teratogenesis or miscarriage in the first trimester is 20 mGy, compared with 50 mGy in the second and third trimesters [27]. However, radiation is thought to have a stochastic effect on carcinogenesis, where there is no absolute "safe threshold" of exposure. The risk of childhood cancer secondary to the *in utero* exposure of 10 mGy of radiation is estimated to be one in 10 000 [27]. The current opinion of the American College of Obstetricians and Gynecologists (ACOG) is that radiation doses of less than 50 mGy during pregnancy are safe for the fetus, with no increased risk of pregnancy loss or fetal anomalies [28]. The approximate fetal doses of radiation for common imaging modalities are listed in Table 1 [29].

Table 1 Estimated fetal doses of radiation associated with maternal radiologic procedures [29].

Imaging study	Radiation dose (mGy)
US	0
IVP (3 film)	1.7–10
XR KUB	1.4–4.2
CT (conventional)	8–49
CT (low dose)	≤7
MRU	0

CT, computed-tomography; IVP, intravenous pyelogram; MRU, magnetic resonance urography; US, ultrasonography; XR KUB, X-ray of the kidneys, ureters, and bladder.

2.5.1. Ultrasound

Ultrasound is the preferred initial diagnostic modality for evaluating pregnant patients with potential renal colic given that there is no ionizing radiation, it is safe to both the mother and fetus, and is easily obtained. The sensitivity of ultrasound to detect urolithiasis during pregnancy is highly operator dependent and varies from 34% to 86% [23]. A definitive diagnosis with ultrasound can be difficult secondary to the patient's body habitus, position of the fetus, or location of the calculi within the ureter. Physiologic hydronephrosis further confuses the diagnosis, as it can be difficult to distinguish between acute obstruction and physiologic hydronephrosis if a definitive stone is not visible [7,12].

In attempts to improve the diagnostic accuracy of ultrasonography a number of adjunct measurements have been utilized including urinary jets, endovaginal ultrasound, and resistive indices (RI). The location of hydroureteronephrosis can be suggestive of acute obstruction; for instance, hydroureter distal to the iliac vessels or severe left hydroureteronephrosis can be indicative of pathologic obstruction [30]. The visualization of urinary jets can suggest the absence of obstructing calculi, however, 13% of pregnant patients without stones will have an absence of their urinary jet [31]. The use of endovaginal ultrasound can assist in the detection of distal ureteric calculi and urinary jets, but is contraindicated in the presence of ruptured or prolapsed membranes [30]. Doppler ultrasound with the measurement of RI has also been utilized to distinguish physiologic hydronephrosis from pathologic obstruction. An elevated RI of 0.70 or greater has been suggested as a marker of obstruction, however, RI is non-specific and can be elevated in normal kidneys, and may not be increased during the early phases of obstruction when there is vascular dilatation [32].

2.5.2. Low-dose CT

Low-dose and ultra-low-dose CT protocols have been developed in order to minimize radiation exposure while maintaining a high sensitivity and specificity for the detection of urolithiasis. Ideally, patients undergoing low-dose CT protocols have a body mass index (BMI) of less than 30 kg/m^2 allowing for the sensitivity and specificity of the scan to be maintained above 90% [33]. A previous series examining low-dose CT scans in pregnancy confirmed very low radiation exposure of 7.1 mGy [29]. In addition, a multi-institutional study demonstrated that low-dose CT had the highest positive predictive value (96%) of all imaging modalities for detecting urolithiasis in pregnancy [34]. Newer software may allow for further reductions in radiation dose and are currently under investigation. The American Urological Association (AUA) recommends low-dose CT scan (defined as <5 mGy) as an appropriate imaging modality for women in the second or third trimester when initial ultrasound is non-diagnostic, based on the endorsement from the ACOG that this is well below the radiation threshold of 50 mGy, and is not associated with fetal loss or anomalies [28,33].

2.5.3. MRU

MRU, using a T2-weighted half-Fourier single-shot turbo-spin echo (HASTE) protocol, has emerged as a promising option for the diagnostic imaging of urolithiasis in pregnancy. It avoids ionizing radiation; there are no known harmful effects to the fetus; it has a fast acquisition time of approximately 15 min; it can evaluate for non-urologic causes of symptoms [35]. However, its utilization is limited by cost, availability, and the inability to be used in patients with metallic implants. While there is no specific stone signal on MRU, characteristic findings of pathologic obstruction include direct visualization of a stone at a point of ureteral constriction, renal edema or peri-renal extravasation, and the "double-kink" sign where constriction is present at the pelvic brim and ureterovesical junction [35]. A small series has demonstrated HASTE MRU to have a sensitivity of 84%, a specificity of 100%, and a diagnostic accuracy of 100% for the diagnosis of acute ureteral obstruction in pregnancy [36].

Despite significant advances in diagnostic imaging, the accurate and safe diagnosis of urolithiasis in pregnancy remains challenging. A recent study examining renal colic in pregnancy showed an overall 14% rate of negative ureteroscopy [34]. Rates of negative ureteroscopy varied on the imaging modality utilized and was highest for ultrasound alone (23%), compared with ultrasound plus low-dose CT (4.2%) and ultrasound plus MRU (20%) [34]. The AUA recently released recommendations for imaging of renal colic in pregnancy based on the available published evidence [33]. While their recommendations are based mostly on lower-strength observational studies, ultrasound is recommended as the initial investigation of all pregnant women suspected of renal colic [33]. If ultrasound is non-diagnostic then non-contrast MRU should be considered in the first trimester or low-dose CT in the second and third trimesters [33].

2.6. Management considerations

As a result of the complexities and potential complications associated with treating urolithiasis in pregnancy, a multidisciplinary approach with involvement of a urologist, obstetrician, radiologist, neonatologist, and possibly an anesthesiologist is highly recommended. In general, first line treatment for renal colic in pregnancy is expectant management. However, indications for acute intervention include active infection, obstructed solitary kidney or bilateral obstruction, unremitting pain or emesis, progressive renal obstruction, or signs of impending obstetrical complications such as pre-term labor and pre-eclampsia. Ideally, surgical intervention is best preformed in the second trimester when the risk of miscarriage and pre-term labor is minimized [37]. Options for acute intervention include temporizing measures with placement of an indwelling ureteral stent or external nephrostomy tube, or ureteroscopy. Shock wave lithotripsy (SWL) and percutaneous nephrolithotomy (PCNL) are contraindicated during pregnancy.

2.6.1. Expectant management

Expectant management with a trial of spontaneous passage is the general first line treatment for ureteric calculi in the pregnant population. It has been estimated that approximately 70%—80% of pregnant patients with symptomatic upper tract calculi will pass their stone spontaneously, and a higher spontaneous passage rate has been demonstrated among pregnant women compared with non-pregnant women (81% *vs*. 47%) [10,15,21]. The higher rate of successful spontaneous passage has been attributed to the effects of progesterone, which result in smooth muscle relaxation and ureteral dilatation [51]. However, a recent study demonstrated a spontaneous passage rate of only 48%, suggesting that the initial rates of spontaneous passage may be an overestimate secondary to erroneous diagnosis and incomplete follow-up [24]. Observation with serial ultrasounds is recommended throughout the duration of the pregnancy and once the patient has delivered routine management of the stone can be undertaken. If the stone does not pass during pregnancy, approximately 50% of them will pass spontaneously during the first month postpartum [51].

An important component of expectant management is aggressive fluid resuscitation and symptom control with analgesia and anti-emetics. Potential maternal or fetal adverse effects of medications administered during pregnancy must be carefully considered when managing this population. While nonsteroidal anti-inflammatories are classically used for analgesia in renal colic, they are contraindicated in pregnancy due to the risk of premature closure of the patent ductus arteriosus and the association with fetal pulmonary hypertension [38]. Codeine has been shown to have teratogenic effects if administered in the first trimester [39]. Opioids are considered the mainstay of analgesia during pregnancy and are considered safe [23,39].

2.6.2. Medical expulsive therapy (MET)

MET with α-blockers or calcium channel blockers is frequently utilized in the non-pregnant population to increase the likelihood of spontaneous ureteric stone passage [40,41]. These medications are currently classed as a category B medication in pregnancy and thought to be safe with no harmful effects having been demonstrated in humans [42]. A recent retrospective matched cohort study examined the safety and efficacy of MET in pregnancy and found no association with adverse maternal or fetal outcomes, and a 24% rate of improved stone passage with the use of tamsulosin [43]. While this recent study is promising, more rigorous evidence is required before the use of MET in pregnancy can be widely adopted. The recent AUA/Endourology Society Surgical Management of Stones Guideline recommends that if MET is being considered in a pregnant patient, the patient should be counseled that these medications have not been well studied for use in pregnancy and are being utilized for an "off-label" purpose [41].

2.6.3. Urinary drainage

When temporizing drainage is required, either an indwelling ureteral stent, or an external nephrostomy tube may be used. Both drainage types have distinct advantages and disadvantages and the selection of drainage device ultimately depends on the clinical scenario, availability of resources, and surgeon and patient preference. Either drainage device can become infected, dislodged, blocked, or encrusted [44]. Numerous reports have demonstrated the accelerated encrustation of foreign bodies in the urinary tract during pregnancy secondary to the metabolic changes that occur. This necessitates the frequent exchange of either ureteric stents or nephrostomy tubes every 4—6 weeks [45]. External nephrostomy tubes may be associated with flank discomfort and require additional care as there is an external tube. Indwelling ureteric stents can cause lower urinary tract voiding symptoms, suprapubic and flank discomfort. While both stents and nephrostomy tubes can be inserted with minimal anesthesia under ultrasound guidance, stent insertion is typically performed under limited fluoroscopic guidance and therefore not ideal during the first trimester [44]. Nephrostomy tube insertion results in rapid decompression of the collecting system, avoids ureteric manipulation, has a high success rate, and may be preferred in the setting of sepsis [46]. Recent evidence suggests that drainage with ureteric stents and nephrostomy tubes is equivalent in terms of patient outcomes [47].

2.6.4. Ureteroscopy

Temporary drainage and delaying of definitive stone management until the postpartum period were the mainstay of treatments for urolithiasis in pregnancy until the mid 2000s. However, this treatment strategy is associated with many drawbacks including frequent tube changes and significant discomfort from the drainage tube. Definitive surgical management with ureteroscopy is now an accepted alternative for patients who fail expectant management. Contraindications include active infection, large stone burden, multiple calculi, abnormal anatomy, obstetrical complications, or inadequate obstetric, urological or anesthetic resources [47]. Given the higher teratogenic risks of anesthesia in the first trimester, ureteroscopy is reserved for the second and third trimesters of pregnancy [37].

Ureteroscopy has been shown to be both feasible and safe during the second and third trimesters of pregnancy, with comparable stone-free rates to non-pregnant patients. Several retrospective case series have demonstrated stone-free rates ranging from 63% to 93% [48,49]. A meta-analysis has demonstrated no difference in the incidence of ureteric injury or urinary tract infection (UTI) in pregnant patients compared with non-pregnant patients [49]. In addition, multiple studies have demonstrated a low rate of preterm labor (0—1%) associated with ureteroscopy [48,49]. Finally, a recent retrospective review found that ureteroscopy was associated with the least number of complications, compared with ureteric stent or nephrostomy tube drainage, for the treatment of ureteric calculi in pregnancy [50].

Ureteroscopy may be performed under general, spinal or local anesthetic. The patient should be positioned in the lithotomy position with the right side of the abdomen elevated to avoid uterine compression of the inferior vena cava. Fetal monitoring should be performed during and after the procedure [51]. Radiation exposure should be limited by positioning the C-arm image source underneath the patient and coning the image to include only the kidney [51]. Lead shielding should be placed underneath the contralateral side of the abdomen, and only limited fluoroscopy images should be obtained with low-dose pulse imaging [51]. Typically, ureteric dilatation is unnecessary given the dilated ureters of pregnancy. There is a paucity of evidence regarding the optimal intracorporeal lithotripter to use during pregnancy. There are theoretical concerns regarding the potential for stimulating uterine contractions with electrohydraulic lithotripsy and adverse impacts on fetal ear development with ultrasonic lithotripsy [48]. Holmium:YAG (Ho:YAG) lasers and pneumatic lithotripters are felt to be safe, and are the currently recommended methods for intracorporeal stone disruption during pregnancy [48]. A post-procedural ureteric stent is most commonly placed to minimize the risk of complications and may be removed at the surgeon's discretion postoperatively [49].

2.6.5. PCNL

PCNL is contraindicated in pregnancy secondary to the need for prone positioning, prolonged anesthetic and fluoroscopy times. A few case reports have described PCNL in pregnancy utilizing supine positioning and ultrasound guided access, and have reported no complications [52,53]. However, if PCNL is required in a pregnant patient, it is best performed in the postpartum period.

2.6.6. SWL

SWL is also contraindicated during pregnancy due to potential risks to the fetus. It has been associated with miscarriage, congenital malformations, intrauterine growth retardation and placental displacement [54]. Although case reports exist of inadvertent SWL during pregnancy that have resulted in no complications, there is currently insufficient evidence to support the safe use of SWL during pregnancy [55].

The incidence of stone disease in females has increased over the past few decades and as such it is expected the incidence of urolithiasis in pregnancy may also increase in the future. Acute renal colic in pregnancy is a difficult clinical situation which has potential serious complications for both the mother and the fetus, and requires a thoughtful, multi-disciplinary approach to management. The diagnostic and treatment recommendations of this review are summarized in an algorithm [47] (Fig. 1).

3. Pediatrics

3.1. Epidemiology

Similar to the overall trends in urolithiasis, stone disease in the pediatric population has also been increasing over the past several decades. In the United States, the incidence of pediatric stone disease has risen 4% per year from 1984 to 2008 [56]. Similar trends have been noted in the United Kingdom, Japan, and Iceland [2,57,58]. Given the rising

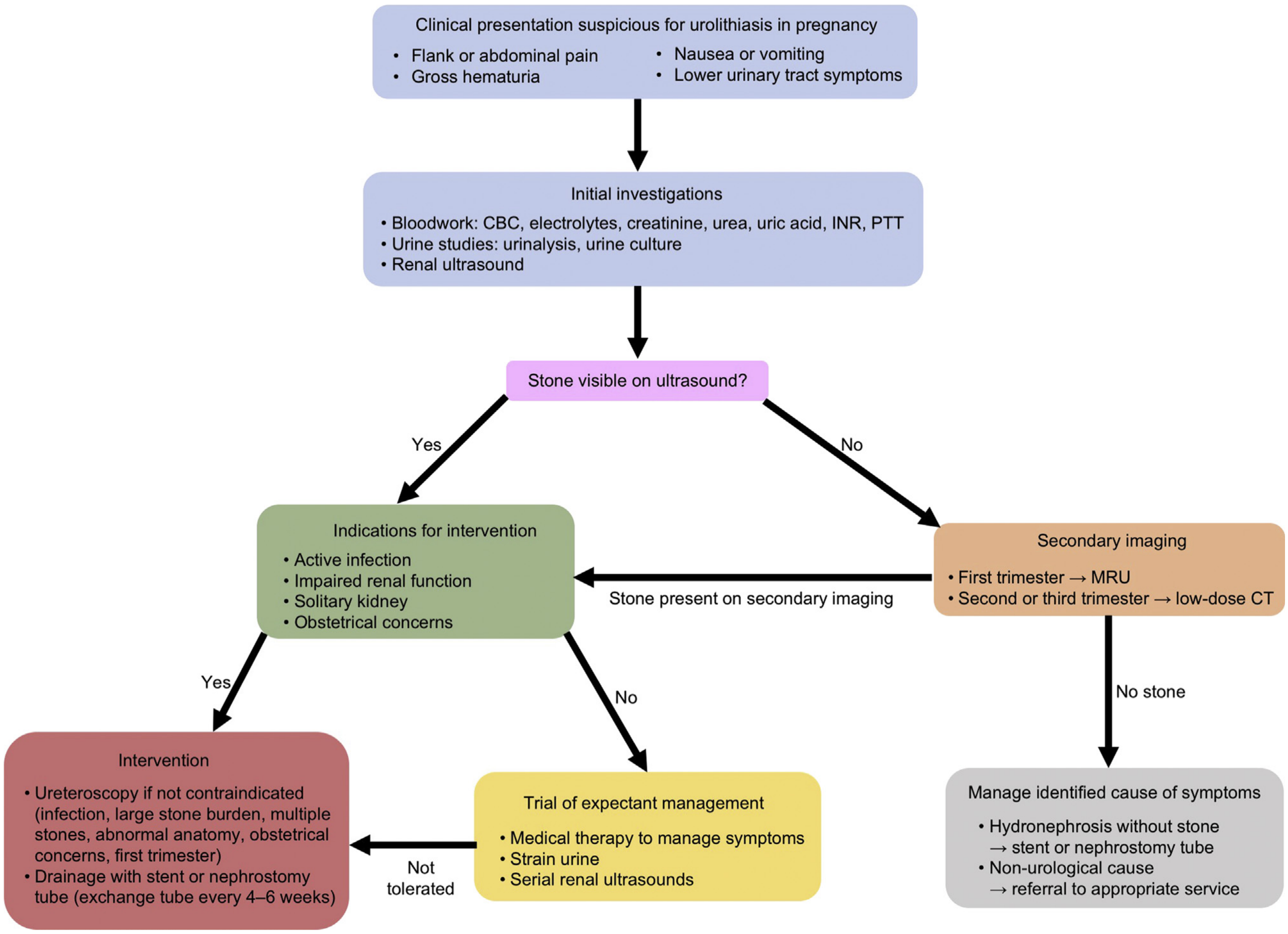

Figure 1 Treatment algorithm for the management of suspected urolithiasis in pregnancy. CBC, complete blood count; CT, computed tomography; INR, international normalized ratio; MRU, magnetic resonance urography; PTT, partial thromboplastin time. Adapted from reference [47].

incidence of pediatric stone disease, it is important to understand the intricacies of managing urolithiasis in this population.

3.2. Etiology of pediatric stone disease

While the etiology of the increasing incidence of pediatric stone disease has not been well established, there has been a well-documented increase in metabolic-induced stones and a corresponding decrease in infectious based stones [58]. There are many theories regarding the rising incidence of pediatric urolithiasis including changing dietary patterns, higher rates of childhood obesity, and the increased detection of stones. Changes in diet including decreased water and calcium consumption, along with increased intake of dietary sodium, protein, and sweetened soft drinks have been linked to stone disease [59]. It is well established that low-fluid intake is an important risk factor for pediatric stone formation [59]. Elevated dietary sodium increases the excretion of calcium within the urine, and inadequate calcium intake may increase urinary oxalate levels [59]. Rising childhood obesity rates have been associated with the increasing prevalence of stone disease in kids, and higher rates of hyperoxaluria, hypocitraturia and hyperuricosuria have been shown in obese children [60]. However, a recent study has refuted these findings and shown that urinary calcium and citrate levels are more closely associated with dietary intake than BMI in children [61]. Finally, given the widespread availability and utilization of CT scans it has been postulated that the rise in pediatric nephrolithiasis is secondary to improved detection abilities [62].

3.3. Clinical presentation

The presentation of nephrolithiasis in children can be highly variable depending on the age of the patient. In younger patients less than 5 years old, stones are most frequently discovered incidentally or following imaging to investigate urinary tract infections [63]. However, they can present with nonspecific abdominal pain, irritability, nausea or vomiting, or gross hematuria [63]. School-aged children and adolescents tend to present with more classic severe colicky flank or abdominal pain [63].

3.4. Initial investigations

All pediatric patients who present with symptoms and findings suggestive of stone disease should undergo a thorough history and physical exam. Family history of stone disease is important to elicit as it is present in 22%—75% of cases of pediatric nephrolithiasis [64]. Features suggestive of a possible hereditary etiology include infantile or early childhood presentation, recurrent stones, renal insufficiency, nephrocalcinosis, acidosis, growth retardation, rickets, or dysmorphism. Initial laboratory investigations include a urinalysis and urine culture [64].

A metabolic stone evaluation should be performed on all pediatric first time stone formers given their high risk of recurrent stone disease. Even in the presence of an underlying anatomic abnormality, such as ureteropelvic junction obstruction, a metabolic evaluation is still warranted due to the high incidence of metabolic derangements detected in these cases [65]. The metabolic stone evaluation includes a complete metabolic blood profile, and a 24-h urine collection. There are some challenges in performing metabolic evaluations in the pediatric population, including the feasibility of an accurate 24-h urine collection depending on the toilet training status of the child, and the lack of accepted standard reference ranges for the 24-h urine analyses in this population [66]. Random spot urine sample ratios of urine calcium to urine creatinine have been used with promising sensitivities and specificities of 90% and 84% respectively [67]. However, this test is limited to a single urinary metabolite and cannot adequately evaluate for overall metabolic disturbances. The majority of kidney stones in children are calcium based including calcium oxalate (40%—60%) and calcium phosphate (10%—20%) [68]. The remainder of other pediatric stone types are less common including uric acid (2%—10%) and cystine stones (6%—10%) [68]. The incidence of struvite stones has decreased over the past several decades due to improvements in the management of urinary tract anomalies and are currently found in 17%—30% of cases of pediatric nephrolithiasis [68].

3.5. Imaging

Diagnostic imaging for the assessment of pediatric stone disease must be easily accessible, economic and safe. The imaging modality of choice should provide an accurate assessment of stone size, location, and density, as well as other important aspects of urinary tract anatomy. There is currently no accepted consensus regarding the optimal imaging regimen for the assessment of a suspected urinary tract stone in children. Consequently, there is significant practice variation among different providers [62].

Ultrasound is a commonly used modality to assess for urolithiasis. While it has been shown to be less accurate compared with CT imaging, it has the distinct advantage of avoiding ionizing radiation. In the acute symptomatic setting, ultrasonography may miss ureteric stones, but has a high sensitivity when there is associated hydronephrosis [69]. The overall sensitivity and specificity for ultrasonography in detecting pediatric stone disease is 59%—78% and 100% respectively [69]. Ultrasonography is typically recommended as the first line imaging modality for the assessment of pediatric stone disease and can be used in conjunction with KUB in order to improve the sensitivity for radio-opaque stones [51].

Unenhanced CT scans are the gold standard imaging modality for the assessment of adult urinary stone disease due to their high reported sensitivity of 94%—99% [70]. CT imaging also has the added benefit of being able to assess for alternative diagnoses and secondary signs of acute urinary obstruction such as hydroureteronephrosis, renal enlargement or perinephric stranding [70]. CT, however, involves exposure to ionizing radiation which carries the potential long-term risk of malignancy, which is significantly higher in children [71]. Current estimates suggest that childhood radiation exposure from a 10 mGy abdominal CT scan results in a lifetime risk of solid organ cancer ranging from 13 to 33 cases per 100 000 [71]. Currently it is recommended that CT scans for stone disease in children be limited to cases where ultrasound quality is limited, and the diagnosis remains uncertain, or for surgical planning of complex stone cases [51]. When selecting the best imaging modality for a pediatric patient with stone disease it is important to consider the high likelihood for recurrent stone disease and the cumulative effects of radiation exposure.

3.6. Management considerations

A multidisciplinary approach including a urologist, nephrologist, and dietician is highly recommended for the management of urolithiasis in pediatric patients. Comprehensive care of the pediatric stone patient requires not only treatment of the stone, but a focus on prevention through dietary and possibly medical management. In general, first line treatment for stone disease in the pediatric population is expectant management. However, indications for surgical intervention include the presence of fever, active infection, obstructed solitary kidney, bilateral obstruction, persistent nausea or vomiting, refractory pain, or failed expectant management. There are some important considerations for the surgical management of stone disease in children including the importance of preserving renal development and function, and minimizing radiation exposure and the need for re-treatment. Given the lack of prospective randomized trials comparing treatment modalities there is currently no consensus regarding the most effective surgical management. The goal of surgical management in pediatric stone disease should be complete stone clearance in order to minimize re-treatment rates, as evidence has suggested adverse clinical outcomes in 69% of cases with residual stone fragments of less than 5 mm in size [72]. The decision regarding the most efficacious treatment modality must be individualized to the patient, and consider patient age, anatomy, stone size, location and composition as well as surgical expertise. Current surgical treatment options include SWL, ureteroscopy, and PCNL.

3.6.1. Expectant management

Expectant management with a trial of spontaneous passage is considered the first line treatment for ureteric calculi in the pediatric population. The rate of spontaneous stone passage is reported to be 41%—63% for ureteric calculi, and it is thought that the pediatric ureter is more elastic than the adult ureter allowing for the easier passage of calculi [73]. As previously discussed MET is commonly utilized in the adult population to increase ureteric stone passage rates. A recent meta-analysis demonstrated similar benefits in the pediatric population with increased rates of spontaneous stone passage with the use of MET [74]. Current data shows a low rate of reported adverse events, with the most common reported side effect being somnolence [74].

3.6.2. SWL

SWL was initially introduced for the treatment of adult urolithiasis in the early 1980s, and has been utilized in the pediatric population since 1986, despite never receiving United States Federal Drug Administration (FDA) approval [75]. Several large series have demonstrated that SWL in children has safety, complication and stone-free rates comparable to the adult population [76—78]. SWL efficacy rates for the primary treatment of upper urinary tract calculi in children range from 68% to 84%, with re-treatment rates ranging from 22% to 49% [76—78]. Lower stone-free rates have been demonstrated in children with a history of urologic conditions or prior urinary tract reconstructions, and ureteric calculi greater than 1 cm; consequently, these patients may be better candidates for alternative surgical treatment such as ureteroscopy or PCNL [78]. A recent multivariate analysis demonstrated that younger age, female gender, small stone burden and lack of prior ipsilateral stone treatment were all positively correlated with stone clearance following SWL [79]. Treatment of ureteric calculi within the mid and distal ureter is typically avoided due to difficulties with stone localization and concerns regarding the potential for injury to developing reproductive systems [80]. The placement of a ureteric stent prior to SWL has been associated with a lower complication rate but no improvement in stone-free rate [81]. Current relative indications for stenting prior to SWL include a solitary kidney, staghorn or large calculi, obstruction, and abnormal anatomy [51]. Complication rates are low (7%—18%) and complications are most commonly UTI, renal coli, and steinstrasse [76—78]. Long-term evaluation following SWL treatment is very limited in children, however, to date there is no association between SWL and long-term renal scarring, or renal, gonadal or pancreatic functional impairment [82—84]. Currently, SWL is considered the preferred treatment modality for uncomplicated renal and proximal calculi less than 20 mm in the pediatric population [85].

3.6.3. Ureteroscopy

Historically ureteroscopy in the pediatric population was reserved for distal ureteric calculi or upper tract calculi failing SWL treatment, due to concerns of potential complications including ureteric ischemia, perforation, and development of ureteric strictures or vesicoureteral reflux [86]. However, recent advances in endourologic instrumentation including increasingly smaller ureteroscopes and the utilization of the Ho:YAG laser, has allowed ureteroscopy to become increasingly accepted as a primary treatment modality for pediatric stone disease. In addition, techniques such as sequential co-axial dilatation of the ureteric orifice, and the use of ureteral access sheaths, have further facilitated the use of ureteroscopy in this population. Even with the current small caliber of ureteroscopes available, pediatric ureters may still require a period of stenting prior to endoscopic management in order to allow for passive ureteric dilatation. The most recent AUA Surgical Stone Management Guideline, however, does not recommend that stents be placed routinely before attempting ureteroscopy [41]. Current contraindications for ureteroscopy include staghorn calculi, anatomic anomalies precluding retrograde access, prior endoscopic failure, and active infection. Current literature suggests stone-free and complication rates similar to that of the adult population [87,88]. For distal ureteric calculi reported stone-free rates range from 79% to 95%, with a risk of ureteral perforation ranging from 4% to 6% [87,88]. A recent randomized trial comparing primary ureteroscopy to SWL for treatment of distal ureteric calculi found ureteroscopy was associated with a significantly higher stone-free rate following a single treatment (94% *vs.* 43%) [87]. Promising results have also been reported for ureteroscopic management of upper ureteric calculi with stone-free rates of 88% and a 6% complication rate [89]. However, a recent report suggests that up to 40% of patients will require at least two procedures in order to treat upper urinary tract calculi, suggesting that the stone-free rate following a single ureteroscopic procedure may not be significantly better than SWL [90]. The majority of published series examining ureteroscopy in children have routinely placed post-procedural stents, however, a recent report demonstrated no sequelae associated with stent-free ureteroscopy in uncomplicated procedures [91].

3.6.4. PCNL

Initially there was significant hesitation regarding the use of PCNL in pediatric patients, secondary to concerns regarding the effect on renal function, prolonged fluoroscopy time and irrigation exposure, and the risk of bleeding. However, PCNL utilizing adult-sized instruments has demonstrated to be safe and efficacious with stone-free and complication rates comparable to the adult population [92]. Studies have also demonstrated no risk of renal function deterioration or renal scarring [93]. Series examining the efficacy of PCNL in children have demonstrated stone-free rates ranging from 87% to 98.5% [92—94]. The development of miniaturized instruments for PCNL has allowed for the wider adoption of PCNL in the pediatric population. Miniaturized PCNL utilizes smaller nephroscopes and access sheaths, including the mini (14—20 Fr), ultra-mini (11—13 Fr) and micro-PCNL (4.85 Fr) techniques. The benefits of miniaturized PCNL include increased manoeuverability, decreased blood loss and transfusion rate, reduced complication rate, lower risk of hypothermia due to decreased irrigation fluid required, and shorter hospital stays [95]. However, the smaller tract size is also associated with longer operative time for larger stone burdens and decreased visual clarity [96]. In addition, the ultra-mini and micro-PCNL techniques do not allow for rigid pneumatic or ultrasonic lithotripters, and micro-PCNL does not enable stone fragment removal thereby increasing the risk of postoperative ureteric obstruction [96]. High stone-free rates are reported for all three miniaturized techniques including mini (76%—95%), micro (80%—100%), and ultra-mini (85%—100%) PCNL, however, the mean stone size treated ranges significantly in these reported series [96,97]. Smaller tract sizes are associated with a lower risk of blood transfusion and pelvicaliceal rupture, however, there is a higher risk of postoperative renal colic from ureteric obstruction [96].

While there is currently no established consensus, indications for PCNL as the primary treatment of urolithiasis in children include large upper tract stone burden (>2 cm), lower pole calculi greater than 1 cm, anatomic abnormality impairing urinary drainage, and cystine or struvite stone composition [85]. PCNL is becoming increasing utilized for the treatment of pediatric stone disease, however, it remains technically challenging and requires surgical expertise in order to optimize efficacy and minimize morbidity.

Pediatric stone disease is becoming increasingly more prevalent worldwide and it is important to understand the complexities of managing these patients appropriately. Technical innovations in endourologic equipment and technique have allowed for the increasing adoption of ureteroscopy and PCNL, and have significantly advanced the treatment of pediatric urolithiasis. However, it is imperative that the treatment of pediatric stone disease focuses not only on surgical management, but also on the prevention of recurrent stone formation as this population is at very high risk for recurrent urolithiasis. The diagnostic and treatment recommendations of this review are summarized in an algorithm [51,85] (Fig. 2).

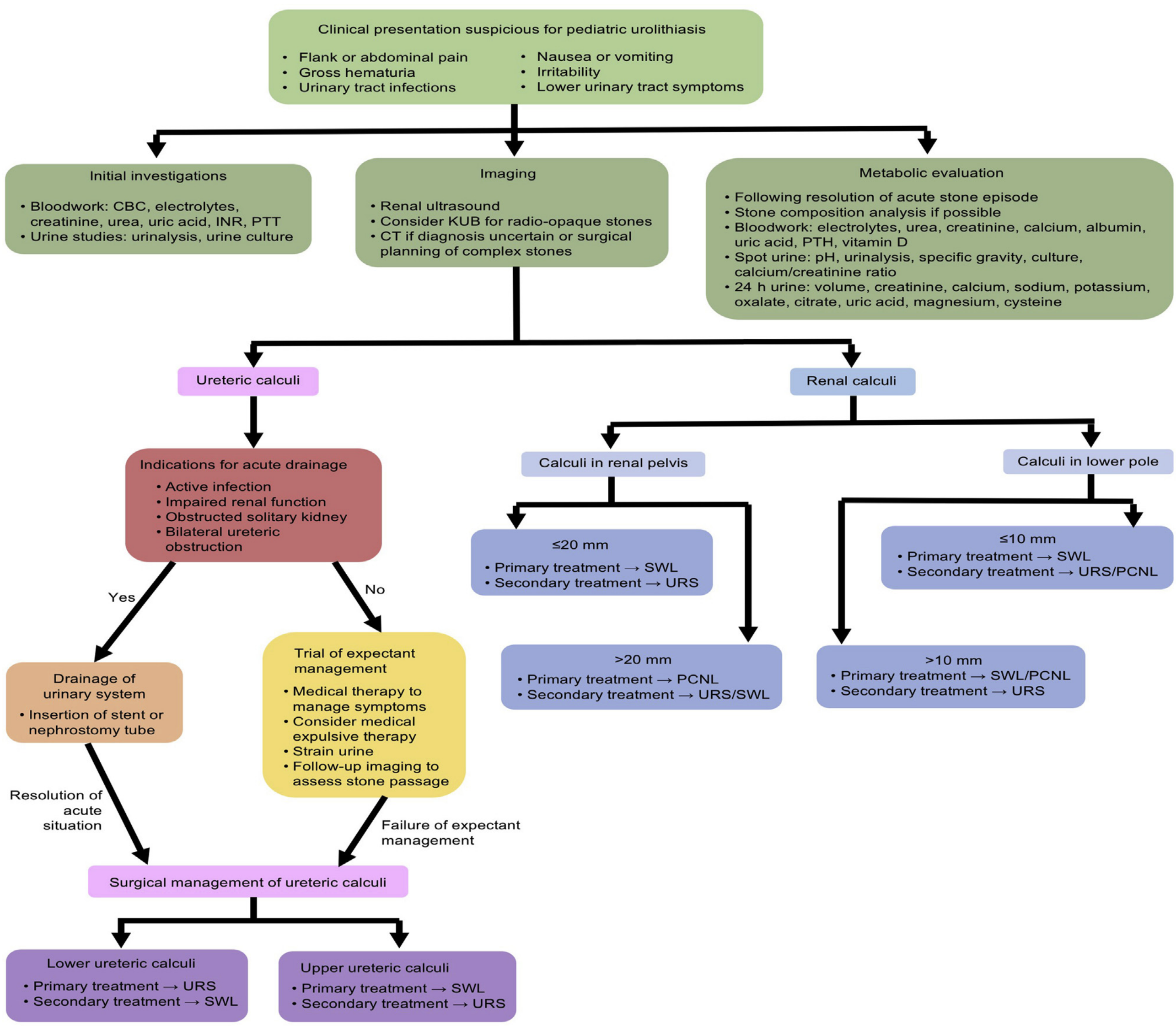

Figure 2 Treatment algorithm for the management of suspected pediatric urolithiasis. Consideration for the best treatment modality must be individualized to the patient, and factor in patient age, collecting system anatomy, stone composition, and available surgical expertise. Specifically, hard stone compositions and collecting system anomalies can significantly impact stone clearance following SWL [51,85]. CBC, complete blood count; CT, computed tomography; INR, international normalized ratio; KUB, X-ray of kidneys, ureters, and bladder; PCNL, percutaneous nephrolithotomy; PTH, parathyroid hormone; PTT, partial thromboplastin time; SWL, shock wave lithotripsy; URS, ureteroscopy.

4. Conclusion

Urolithiasis is a highly common condition worldwide, with increasing rates of incidence among most demographic groups. Along with this, the occurrence of stone disease in special populations, such as children and pregnant women, will also increase. It is important for the urologist to understand the intricacies and complexities of properly managing stones in these patients in order to maximize treatment efficacy while minimizing morbidity.

Author contributions

Study concept and design: Hassan Razvi, Jennifer Bjazevic.
Data acquisition: Jennifer Bjazevic.
Data analysis: Jennifer Bjazevic.
Drafting of manuscript: Jennifer Bjazevic.
Critical revision of the manuscript: Hassan Razvi, Jennifer Bjazevic.

Conflicts of interest

The authors declare no conflict of interest.

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