Nephrolithiasis in Pregnancy: Treating for Two

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OBJECTIVES To review the literature regarding the epidemiology of stone disease and develop a management algorithm based on current evidence and societal guidelines.

METHODS A structured literature review was performed to determine highest quality of evidence guiding care for pregnant patients with symptomatic nephrolithiasis. PUBMED and EMBASE databases were searched using terms "pregnancy," "nephrolithiasis," or "pregnancy" and "renal colic" alone and in combination with "stone", "kidney stone," "ultrasound," "MRI," "CT," "percutaneous nephrostomy," "ureteral stent," or "ureteroscopy." All English-language abstracts were reviewed for relevance and full-length articles were reviewed for content. Articles published prior to 1990 were excluded, and priority for inclusion was given to multi-institutional studies and larger institutional studies, reflecting the highest level of current available evidence and most contemporaneous practice patterns.

RESULTS Symptomatic nephrolithiasis affects less than 1% of pregnancies but poses unique diagnostic challenges due to the physiologic changes of pregnancy and risks of ionizing radiation exposure to the fetus. Ultrasound remains the imaging modality of choice. Most patients may be managed non-operatively, but drainage with percutaneous nephrostomy or ureteral stent may be performed if warranted. Growing evidence also supports the safety and efficacy of definitive stone treatment.

CONCLUSIONS Though rare, symptomatic nephrolithiasis poses significant clinical challenges due to the need to minimize risk for both mother and fetus with diagnostic and therapeutic interventions. A multidisciplinary approach is paramount, as is shared decision making with the patient at each step of care. UROLOGY 151: 44–53, 2021. © 2020 Elsevier Inc.

Nephrolithiasis affects an estimated 7.1% of women in the United States, with increasing prevalence.[1] A stone event during pregnancy affects both maternal and fetal well-being, and poses specific diagnostic and therapeutic challenges in management. Herein, we review the literature regarding the epidemiology of stone disease and consider the unique challenges of managing acute renal colic during pregnancy. We propose a management algorithm based on current evidence and guidelines from the American Urological Association (AUA) and European Urological Association (EAU).[2-4]

METHODS

We performed a structured review of the current literature to determine the highest quality of evidence guiding care for pregnant patients with symptomatic nephrolithiasis. PUBMED and EMBASE databases were searched using the terms "pregnancy" and "nephrolithiasis" or "pregnancy" and "renal colic" alone and in combination with any of the following terms: "stone," "kidney stone," "ultrasound," "MRI," "CT," "percutaneous nephrostomy," "ureteral stent," or "ureteroscopy." All English-language abstracts were reviewed by a single reviewer (JCD) and full-length articles were reviewed if they pertained to the epidemiology, pathophysiology, diagnosis, management, or outcomes of nephrolithiasis in pregnant patients. Reference lists for each article were then reviewed to identify additional pertinent articles. Only articles published after 1990 were included, with priority for multi-institutional studies and larger institutional series to reflect the highest level of available evidence and most contemporaneous technology and practice patterns.

EPIDEMIOLOGY

The reported incidence of stone disease in the pregnant population varies widely. Rates of hospitalization for stone episodes in institutional series range from 0.03% to 0.4% of all deliveries.[5-8] Larger population-level studies utilizing national insurance claims data estimate the prevalence of nephrolithiasis diagnoses from 0.14% to 0.8% of all deliveries.[9-11] Stone recurrence rates among pregnant women appear higher than the general population (29% recurrence rate, mean follow-up 51 months).[12] However, the prevalence of stone disease among pregnant women does

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Table 1. Diagnoses of renal colic or nephrolithiasis during pregnancy

Study	# of Diagnoses	Metric of Diagnosis	Common Presenting Symptoms	Method of Stone Confirmation	# of Confirmed Stones	Initial Misdiagnosis
Strothers et al, 1992[5]	80	Hospital discharge diagnosis	• Flank pain (89%) • Microhematuria (69%) • Nausea (61%) • Abdominal pain (46%) • Gross hematuria (28%) • Chills (13%) • Fever (9%)	• Visualization of passed stone • IVP • Stone retrieved during operation	57 (71%)	Other (28%) • Placental abruption • Appendicitis • Diverticulitis
Parulkar et al, 1998[20]	72	Hospital discharge diagnosis	• Renal colic (99%) • Microhematuria (83%) • Preterm labor (19%) • Pyelonephritis (9%)	• US • IVP	42 (58%) 7 patients did not undergo imaging (known history of nephrolithiasis)	Not reported
Butler et al, 2000[6]	57	Hospital discharge diagnosis	• Flank pain (84%) • Hematuria (81%) • Nausea (37%) • Pain with radiation to the groin (37%) • Chills (7%)	• US • Plain abdominal x-ray • IVP • Visualization of passed stone • Urine straining for calculi	57 (100%)	• Pyelonephritis (21%) • Other (18%) ○ Term labor ○ Hematuria ○ Hyperemesis ○ Suspected appendicitis
Lifshitz et al, 2002[21]	10	Clinical	• Flank pain (100%) • Microscopic hematuria (60%) • Gross hematuria (20%) • Nausea/vomiting (20%) • Fever (10%)	• US • IVP • Ureteroscopy	8 (80%)	Not reported
Burgess et al, 2011[12]	117	ICD-9 codes	• Flank pain (80%) • Microscopic hematuria (57%) • Gross hematuria (15%)	• Stone seen on imaging • Stone identified at time of surgical intervention • Visualization of passed stone • Symptoms during pregnancy + stone diagnosis within 6 months of delivery	90 (77%)	Not reported
White et al, 2013[23]	51	Clinical	Not reported	• US • CT • MRI • Ureteroscopy	44 (86%)	Not reported
Isen et al, 2012[24]	36	Clinical	• Colicky flank pain (100%) • Hematuria (94%) • Nausea/vomiting (69%) • Fever (11%)	• US • Ureteroscopy • Spontaneous stone passage	36 (100%)	Not reported

CT, computed tomography; IVP, intravenous pyelography; MRI, magnetic resonance imaging; US, ultrasound.

not appear to be increasing over time in parallel to the growing prevalence of stone disease among women.[13]

A unique set of physiologic changes during pregnancy affects stone risk. Lithogenic factors in pregnancy include increasing oxaluria, uricosuria, natriuria, and calciuria; the latter may be related to placental secretion of vitamin 1,25-dihydroxycholecalciferol.[14,15] Additionally, urinary stasis in the kidney and ureter from the gravid uterus and progesterone-mediated ureteral smooth muscle relaxation further promote urinary crystallization. These factors are counter-balanced by increased renal blood flow and glomerular filtration rates, as well as increased urinary levels of stone inhibitors such as citrate, nephrocalcin, magnesium, glycosaminoglycans, and uromodulin.[14,15] Stone composition also differs in pregnancy, with pregnant patients more than twice as likely to have calcium phosphate stones (66%-88%) than their non-pregnant counterparts.[5,12,16,17] This is hypothesized to be driven, in part, by the hypercalciuria of pregnancy, as well as higher urine pH, which may be due to increased urinary citrate.[17]

DIAGNOSIS

Symptoms

Most stone episodes are diagnosed during the second or third trimester (38% and 33%-48%, respectively).[9,16] Admissions for renal colic are also most common

Table 2. Reported sensitivity and specificity of ultrasonography for the detection of nephrolithiasis among pregnant women

Study	Type	# of Subjects	Years of Study	Confirmatory Method	Sensitivity	Specificity
Strothers et al, 1992[5]	Retrospective, single center	80	1979-1990	• Stone passage, directly visualized • Stone retrieved at time of intervention • Stone seen on fluoroscopic imaging (IVP or RPG)	34%	86%
Parulkar et al, 1998[20]	Retrospective, single center	70	1984-1995	• Stone visualized on IVP (only 8% of cases receiving US)	95.2%	87%
Butler et al, 2000[6]	Retrospective, single center	57	1986-1999	• Stone visualized on IVP • Stone passage, directly visualized	60%	-
Lifshitz and Lingeman 2002[21]	Retrospective, single center	10	1998-2000	• Intra-operative findings (URS)	28.5%	-
Burgess et al, 2011[12]	Retrospective, single center	112	1997-2009	• Stone passage, directly visualized • Stone identified on imaging (US, x-ray, CT, or MRI) • Stone identified at surgical intervention	54%	78.6%
White et al, 2013[23]	Retrospective, multi-center (5 tertiary care centers)	51	2004-2012	• Ureteroscopy findings	77%	-
Isen et al, 2012[24]	Retrospective, single center	Clinical	2002-2011	• US • Ureteroscopy • Spontaneous stone passage	69%	-

CT, computed tomography; IVP, intravenous pyelography; MRI, magnetic resonance imaging; RPG, retrograde pyelogram; URS, ureteroscopy; US, ultrasound.

during the second and third trimesters (27% and 68%, respectively).[18] Nephrolithiasis is the most common reason for pain-related hospitalization during pregnancy.[19,20]

Most patients present with flank pain and hematuria, though additional symptoms may include nausea or fevers; abdominal pain is rarely the sole presenting symptom.[5,12,20,21] These are similar to presenting symptoms in non-pregnant individuals. There is nearly equal laterality of flank pain on initial presentation and nearly a quarter of pregnant patients with renal colic are diagnosed clinically with nephrolithiasis without confirmatory imaging.[5,12,19]

However, clinical misdiagnosis is common. Stothers et al reported that 28% of pregnant women ultimately diagnosed with stones were initially incorrectly diagnosed with appendicitis, placental abruption, or diverticulitis.[5] Understanding rates of false positive diagnoses is difficult due to lack of consistent confirmatory studies for each case (Table 1). In many cases, the diagnosis of nephrolithiasis is not confirmed by imaging, endoscopy, or visualization of the passed stone.

Imaging

Ultrasonography. Renal Ultrasonography (US) is the first-line imaging modality for pregnant women with suspected nephrolithiasis.[2,3] The reported sensitivity of US for detection of nephrolithiasis in this population varies widely from 29% to 95% (Table 2). The reported negative ureteroscopy rate from US imaging alone is 14%, with a 77% positive predictive value of US for intra-operative stone.[22] When the presence of stones is confirmed by spontaneous passage, surgical retrieval, or fluoroscopic imaging, the false negative rate of US for stone detection among pregnant women has been reported as high as 68%.[5] Thus, US as a sole imaging modality for nephrolithiasis in this population has limitations.

A major challenge of diagnosing symptomatic stones using US in pregnant women is the reliance on indirect indicators of stone presence when the stone itself is not visualized. As physiologic hydronephrosis of pregnancy is reported in up to 90% of patients, typical findings of ureteral dilation or hydronephrosis are unreliable.[15] In cases of physiologic dilation, ureteral dilation typically extends down to the level of the iliac vessels, beyond which the ureter tapers; in a series of 105 pregnant women with distal ureteral stones, ureteral dilation was seen distal to the iliac vessels in all.[23] Thus, distal dilation of the ureter on US may be a key sonographic feature to differentiate stone-related obstruction from physiologic dilation.

The intra-renal resistive index (RI) has been suggested as a sonographic feature that may improve the diagnostic accuracy of US for obstructing stones in pregnancy. Shokeir et al demonstrated that among pregnant women with renal colic and confirmed stones, a mean RI of 0.7 had a 45% sensitivity and 91% specificity for the diagnosis of an obstructing stone. Moreover, a difference in RI between kidneys of 0.06 was found to have a 95% sensitivity and

100% specificity for stones in the same population. Both values were significantly higher than those of asymptomatic, pregnant women, and non-pregnant women without nephrolithiasis, who had similar RI and difference in RI (0.6 and 0.006, respectively). These findings further demonstrate that neither RI nor difference in RI between kidneys is affected by the physiologic hydronephrosis of pregnancy, and both measures may help differentiate this from hydronephrosis from acute obstruction.[24]

Ureteral jets are another sonographic feature that may improve the diagnostic accuracy of US. Absence of ureteral jets has been reported in some series to have high sensitivity and specificity (100% and 91%, respectively) for detection of ipsilateral obstruction in non-pregnant patients.[14] However, unilateral absence of ureteral jets has been described in pregnant women without nephrolithiasis, and may also be positionally dependent, limiting the use of this feature in isolation in pregnant patients.[14,25] When noted together with an elevated RI, the absence of a ureteral jet improves the diagnostic accuracy of US from 56.2% to 71.9%.[26] Such features may enhance the utility of US in diagnosing stones among pregnant women and may help guide clinical decision-making for the urologist.

Transvaginal US has been suggested as an adjunctive modality to abdominal sonography, particularly for the diagnosis of distal ureteral stones. Laing et al evaluated 13 women (6 pregnant) with distal ureteral stones using both abdominal and transvaginal US. Abdominal US definitively diagnosed a distal stone in only 2 of 13 cases, whereas all cases were diagnosed with transvaginal US.[27] Notably, hydronephrosis was absent in 3 patients and symmetric ureteral jets were noted in 2 patients, further affirming that indirect indicators alone may be insufficient for accurate diagnosis of distal ureteral stones.[27] More evidence is needed to support routine adoption of transvaginal US in diagnosing distal ureteral stones in pregnant women. Sonographer experience and availability may limit more widespread use of this modality.

Magnetic Resonance Imaging. Magnetic Resonance Imaging (MRI), and in particular, magnetic resonance urography (MRU), has been suggested as an alternative cross-sectional imaging modality for the diagnosis of nephrolithiasis in pregnant women, which lacks the radiation exposure risks of computed tomography (CT). Both the AUA and EAU recommend MRI as second-line imaging for pregnant patients.[2,3] Gadolinium contrast has been shown to be teratogenic in animals, but not human studies. Thus, the American College of Obstetricians and Gynecologists (ACOG) still recommends use of gadolinium contrast for scenarios where the benefit clearly outweighs the potential risks.[28] Even without gadolinium contrast, static-fluid T2-weighted imaging, such as weighted half-Fourier single-shot turbo-spin echo MRU, provides cross-sectional imaging that can successfully differentiate between hydronephrosis of pregnancy from stone-related obstruction in 89% of cases.[29] Moreover, these image sequences can be more rapidly acquired than traditional MRI.

Obstructing stones on MRU appear as signal voids. Proximal ureteral dilation, perirenal or periureteral fluid, and the "double kink" sign (ureteral kinking at the pelvic brim with a column of urine seen down to the level of the ureterovesical junction) are other features suggestive of obstructing ureteral stones.[29,30] When corroborated with ureteroscopy findings, the positive predictive value of MRI for diagnosis of stones among pregnant women is 80%.[22] However, studies on the role of MRU in this context are limited. Use of this modality is further limited by cost, time, and MRI availability.

Computed Tomography. Though CT is the gold standard for detection of nephrolithiasis, it is not recommended as first-line imaging for pregnant patients.[2,3] The teratogenic effects of fetal radiation exposure are significant, ranging from pregnancy loss, congenital anomalies, growth retardation, severe mental retardation, and microcephaly. These effects are dependent on both gestational age and level of exposure, with most significant effects occurring before or during the first trimester.[28,31] The risk of fetal abnormalities is negligible at levels below 50 mSv, and there are no reported cases of abortion, fetal anomalies, or growth restriction below this exposure.[28,31] The risk of childhood cancers related to early radiation exposure remains unclear.[14,31]

The median estimated radiation exposure for a non-contrast CT of the abdomen and pelvis lies well below 50 mSv.[2] Moreover, use of low-dose CT techniques and ultra-low dose CT techniques can achieve exposures of <4 mSv and even <1 mSv, respectively.[2] White et al reported a mean radiation dose of 0.65 mSv for low dose CT obtained for suspected nephrolithiasis in 24 pregnant women at 5 tertiary care centers.[22] However, adoption of these techniques remains limited, and wide variability in exposures for "low dose" scans across institutions remains.[32]

The 2017 consensus statement from ACOG supports the use of CT if deemed necessary, or if imaging with US or MRI is not readily available, citing the fact that typical radiation dose from CT lies below the exposures associated with fetal harm.[28] However, in the absence of definitive evidence demonstrating safety of ionizing radiation exposure to the fetus at any level, it remains prudent to utilize imaging modalities without radiation risk, such as US or MRI, particularly in the earlier stages of pregnancy.[2,3] Selection of imaging modality, particularly if considering CT, should be part of a shared decision making process with the patient, radiology, and obstetrics team. Moreover, discussion of potential risks of even low radiation exposures should be included.

Abdominal Plain-Films and Intravenous Pyelography. Abdominal plain-film x-ray kidneys, ureter, bladder (KUB) and intravenous pyelography were historically used but are uncommonly used in contemporaneous practice due to

growing use of cross-sectional imaging modalities.[5,6,19] Despite low exposures, both still expose the developing fetus to ionizing radiation. Moreover, detection of a stone may be limited, due to overlying bowel or fetal skeleton.[15] At some institutions where ultra-low-dose CT protocols have been developed, cross-sectional imaging can be obtained with radiation exposures at levels similar to kidneys, ureter, bladder (KUB) and less than intravenous pyelography, further limiting the utility of these imaging modalities for pregnant patients.

TREATMENT

The management of pregnant women with renal colic from obstructing stones is a unique situation with implications for both mother and fetus. Each option comes with risks and benefits that must be carefully balanced. Multidisciplinary, patient-centered care should be prioritized at each step, with frequent re-evaluation of maternal and fetal well-being. Moreover, decisions regarding care of these patients must be tailored to the patient's clinical scenario, considering the mother's preferences and risk tolerance.

Expectant Management

Timely, appropriate management of renal colic and suspected nephrolithiasis in pregnancy is paramount, due to obstetrical repercussions. Retrospective studies have demonstrated a higher risk of preterm, premature rupture of membranes, low birth weight, pre-eclampsia, preterm delivery, and infant death among pregnant women with renal colic.[7,11,18,19,26,33] Nonetheless, expectant management is recommended as the first line approach to the pregnant stone patient without overt infection.[4,15,19] This includes hydration, anti-emetics, and adequate analgesia, typically with acetaminophen and narcotics if needed.

Most patients pass their stones spontaneously, though reported rates of stone passage vary widely. Stothers et al reported an 84% spontaneous passage rate among pregnant women with confirmed stones.[5] Parulkar et al described a spontaneous passage rate of 64%.[19] In contrast, Burgess et al reported a stone passage rate of only 48%; however, nearly a quarter of patients in their study did not have imaging-confirmed stones.[12] Hoscan et al have reported spontaneous passage rates as low as 23%.[21] However, stone location, size, and use of medical expulsive therapy (MET) was not clearly reported in these studies.

Regardless, expectant management must be considered carefully. Febrile infections during pregnancy are particularly serious, given altered cell-mediated immunity; patients without overt signs of infection initially may progress to more serious infection with conservative management. In cases where initial urinalysis or presentation is equivocal for infection, observation with antibiotic therapy has been practiced, without reports of maternal mortality.[5,6,19] Up to 17% of women admitted for nephrolithiasis and renal colic have concomitant pyelonephritis, but the true rate of progression to febrile infection during a trial of conservative management remains unknown.[18]

Pregnancy also influences medication use in expectant management. Nonsteroidal anti-inflammatory and codeine-containing medications should be avoided in pregnancy due to teratogenic effects.[4,14] If antibiotics are administered, a limited number of options exist that are safe in pregnancy, such as penicillins, cephalosporins, and erythromycin. Aminoglycosides, tetracycline, chloramphenicol, fluoroquinolones, and sulfa antibiotics are contraindicated in pregnancy.[14]

Medical Expulsive Therapy

The role of MET for nephrolithiasis in pregnancy is poorly studied. Use of alpha-blockers for MET in the general population is "off-label," and there are additional safety and effectiveness considerations to discuss with the pregnant patient.[4] Alpha-1 selective antagonists and calcium channel blockers have shown either no fetal risk in animal studies, or adverse effects in animal studies that have not been observed in controlled first-trimester human studies (Category B). Thus, these are considered reasonable for use among pregnant women if deemed clinically necessary.[34]

To date, only 2 retrospective single-institution studies have examined the safety and efficacy of MET with alpha-blockers in the setting of pregnancy. Bailey et al evaluated 27 pregnant women who received tamsulosin as part of expectant management (median duration 3 days, range 1-110 days). Delivery occurred at a mean gestational age of 38.1 weeks (SD 2.4 weeks) with preterm birth in 22%, though no spontaneous abortions, intrauterine demise, or congenital anomalies were reported.[34] A retrospective study of 207 pregnant women with renal colic showed no significant difference in spontaneous stone passage rate between 69 patients receiving tamsulosin and 138 controls (79 vs 75%, respectively), despite similar stone sizes and locations. Additionally, there were no differences between groups in mean gestational age, birth weight, Appearance, Pulse, Grimace, Activity, and Respiration scores, length of hospital stay, or need for intervention.[35]

Among urologists, self-reported use of alpha-blocker therapy in pregnant women is significantly less than for non-pregnant patients (44% vs 98%).[36] The most common reason cited for not using alpha-blockers is fear of legal risk (53%), followed by safety concerns (24%).[36] More evidence is needed to understand use of alpha blockers in pregnant women to assuage these medicolegal and safety concerns.

Intervention

Indications for Intervention. Indications for intervention among pregnant patients include intractable symptoms (eg, uncontrolled pain, nausea, vomiting), obstructing stone with infection, progressive hydronephrosis, obstruction of a solitary kidney or bilateral ureteral obstruction, or severe hydronephrosis indicating high-grade obstruction; additionally, obstetric complications such as

preterm labor or pre-eclampsia may also prompt intervention.[5,14,15] Though most patients can be managed conservatively, 26%-30% of symptomatic patients ultimately require acute intervention.[10,12,18] Rates of preterm labor for those requiring intervention are nearly triple those managed conservatively (14% vs 5%).[26] Ultimately, consideration of mode of intervention requires shared decision making with the patient, and multidisciplinary collaboration with experienced obstetricians, urologists, and anesthesiologists.

Percutaneous Nephrostomy Tube. Temporization with nephrostomy tube placement has been successfully used in the pregnant stone patient. To minimize fetal and maternal risk, nephrostomy tube placement may be performed under US guidance with minimal anesthesia, if local interventional radiology availability and expertise allow. However, tube revision is common, and frequent exchanges (every 4-6 weeks) are recommended due to high risk of calcification or occlusion in this population.[4,14,15] As many as 45%-80% of women who receive nephrostomy tubes for initial management of their stones require subsequent tube manipulation or exchange for occlusion or dislodgement, with up to 1-3 exchanges required per patient.[37,38] The rate of septic complications approaches 12.5%, and preterm delivery has been reported in up to 25% in small case series.[37,38] Following initial placement, spontaneous stone passage has been reported in 13%-16%.[37,38]

Ureteral Stent. Ureteral stenting is an alternative to percutaneous nephrostomy tube placement when acute intervention is indicated.[20,21] To minimize maternal and fetal risk, stents may be placed under general anesthesia, monitored anesthesia care, or spinal anesthesia, and with US-guidance and minimal to no fluoroscopy.[39] Rates of stent placement complications during pregnancy are as high as 16%, and include stent migration, stent removal for stent intolerance, stent failure, and preterm labor.[5] Stent toleration is poorly understood, and 42%-47% of pregnant women who receive ureteral stents ultimately undergo early induction due to poor pain control related to stent placement.[12,40] Moreover, labor within 24 hours of stent placement has been described in as many as 11% of patients.[12]

Arguably the biggest concern for ureteral stents during pregnancy is encrustation. Frequent stent exchanges are recommended at least every 4-6 weeks, and careful patient counseling is critical to avoid the management challenges of encrusted stents in this population.[15] The risk of multiple anesthetic exposures for stent exchanges is also pertinent due to concerns regarding the potential effect of anesthetics on the developing fetus.[40] Rivera et al demonstrated that 40% of women initially managed with stents required multiple stent exchanges, with a median of 1.47 anesthetic exposures during the pregnancy (IQR 1-3).[40]

Ureteroscopy

In recent years, as endoscopic technology and technique have improved, there has been a shift toward initial stone treatment with ureteroscopy. In many cases, definitive treatment obviates the need for multiple procedures. Stone-free rates are 73%-100% among those treated endoscopically with lithotripsy or basketing.[14,26,41-46] The recommended timing of non-obstetric surgery by ACOG is during the second trimester, as this minimizes the risk to fetal development during the first trimester and the risk of preterm labor associated with surgical procedures during the third trimester.[45] Nonetheless, ureteroscopy has been successfully performed in both the first and third trimesters.[22,47]

Measures to minimize anesthetic and radiation exposure have been described to further minimize risk to mother and fetus. Though typically performed under general anesthesia, ureteroscopy can be performed under local or spinal anesthesia.[14,44,45] If possible, general anesthetic use should be minimized during the critical period of fetal neural synaptogenesis during the third trimester and beyond, with a recent FDA warning regarding fetal anesthetic exposures during this time.[48] US-only techniques have also been reported, though used in less than a quarter of cases.[45] When fluoroscopy is used, radiation-minimizing strategies should be employed, including selective use for critical portions of the procedure, low-dose and pulsed settings, cone-beam imaging, and pelvic shielding.[40] When pelvic shielding is used, the C-arm should be set to manual exposure mode; leaving this on automatic brightness control may actually result in increased delivered radiation, as exposures are automatically increased in attempt to penetrate through the shielding lead.

Evidence regarding the risks and outcomes of ureteroscopy remains limited, with most cases reported by tertiary care centers. A meta-analysis by Semins et al examined ureteroscopy complications among pregnant women and determined an overall 8% complication rate.[46] Of these, 1.8% were classified as Clavien I complications, 5.5% were classified as Clavien II complications, and 0.9% were classified as Clavien III complications (1 case of ureteral perforation managed with ureteral stent). Notably, there was no difference in UTI or ureteral injury rates between pregnant women and the published AUA/EAU rates for ureteroscopy.[46] Obstetric complications following ureteroscopy are also low, with a preterm labor rate of 4%.[45] Reported cases of preterm labor following ureteroscopy occurred during the third trimester, and were not associated with general anesthesia or duration of stone treatment.

Compared to temporizing ureteral stent placement, ureteroscopy does not appear to have a longer mean anesthetic or fluoroscopy time; moreover, it is associated with a lower rate of induced preterm labor.[40] Decision-analytic models comparing ureteroscopy to serial stent exchanges every 4 weeks also support ureteroscopy as a more cost-effective management strategy at all gestational ages.[49] Though literature regarding the outcomes of ureteroscopy in pregnancy remains sparse, reported experiences provide

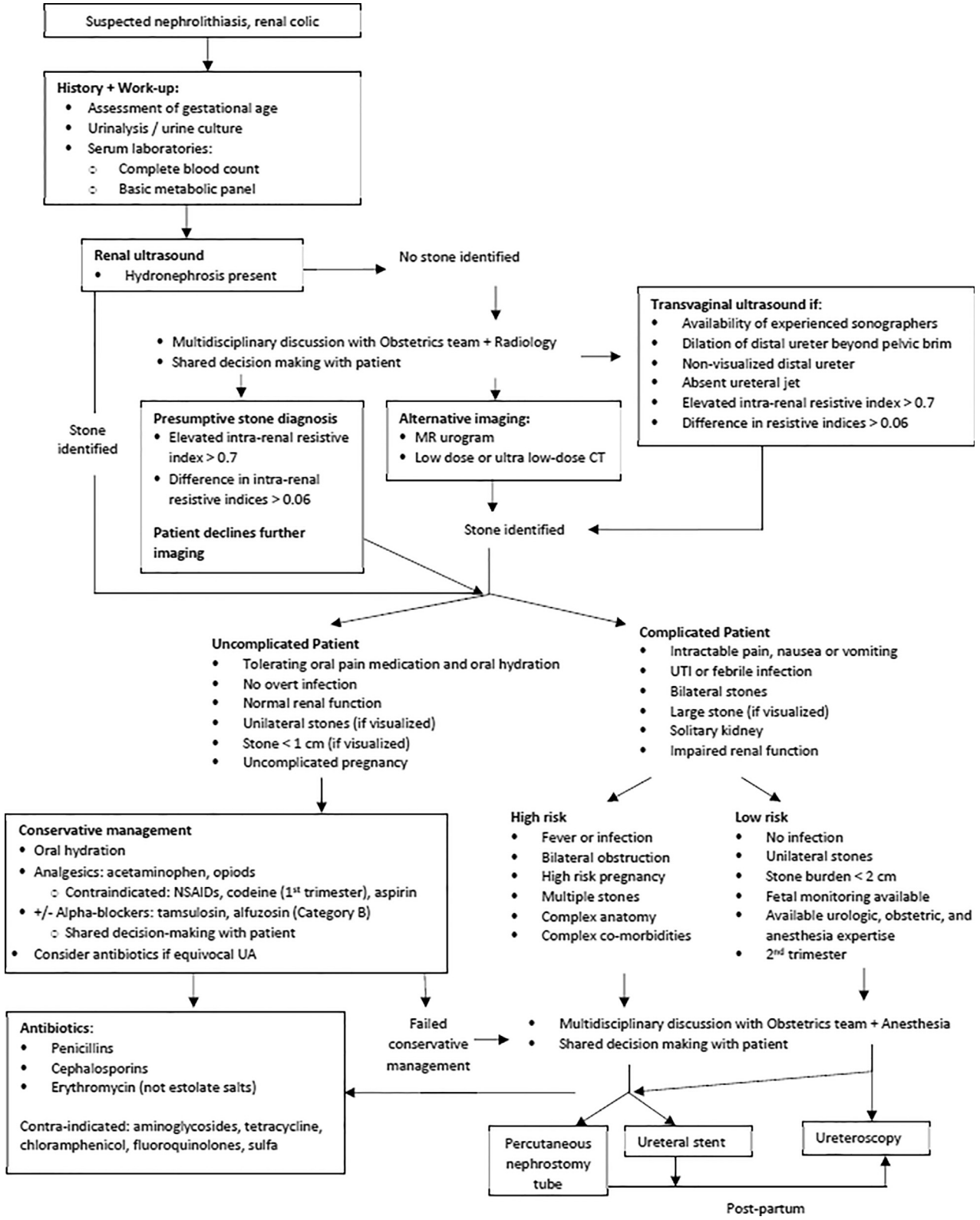

Figure 1. Proposed management algorithm for symptomatic nephrolithiasis in the pregnant patient.

evidence for the feasibility, safety, and efficacy of this approach in experienced hands.[4]

Other Treatment Considerations. Though percutaneous nephrolithotomy and shockwave lithotripsy (SWL) have been successfully performed in the pregnant patient, these treatment approaches are not recommended in pregnancy.[4,14] Though successful birth has been reported following inadvertent SWL in unrecognized pregnancy, SWL is contraindicated in pregnancy, with associated

risks of miscarriage, congenital malformation, intrauterine growth retardation, placental disruption, and fetal demise.[4,14,15] Percutaneous nephrolithotomy remains a high-risk procedure for the pregnant woman due to prone positioning, general anesthesia requirement, and radiation exposure with traditional fluoroscopy-based techniques.

Based on the current literature, we therefore propose a management algorithm for nephrolithiasis in pregnancy (Fig. 1). Care for these patients must involve shared decision making and a multi-disciplinary approach with obstetrics, radiology, and anesthesia and urology to ensure optimal care in the context of the clinical scenario and patient preferences. Moreover, specific discussion with the patient regarding diagnostic and treatment risks, as well as anticipated outcomes, should be provided at each step.

Follow Up

Patients who do not pass their stones during pregnancy warrant close post-partum urologic follow-up for re-imaging and discussion regarding appropriate stone management. When stones are either passed or treated, close follow-up remains warranted to ensure resolution of hydronephrosis and provide counseling on stone prevention strategies, as parity remains a significant risk factor for future stone formation.[12,50] However, even within this population, an individualized, risk-adapted strategy for stone prevention should be considered. Prior stone history and stone composition during pregnancy (eg, calcium phosphate vs calcium oxalate) may help determine which patients may be inherently at higher risk for stone formation and recurrence in the non-pregnant state, and thus benefit most from further prevention work-up with 24-hour urine studies and longer term follow up.

CONCLUSIONS

Nephrolithiasis in pregnancy presents a complex clinical scenario requiring engagement between the patient, urologists, obstetricians, radiologists, and anesthesiologists. Careful and frequent re-assessment of maternal and fetal well-being, as well as consideration of the risks and benefits of any diagnostic study or intervention is critical. Clinical decisions must be individualized with attention to patient preferences, values, and risk perception.

US is the initial imaging modality of choice. Features such as an elevated RI and absence of ureteral jet can be used to help the astute clinician in stone diagnosis. Transvaginal ultrasound may be helpful in identifying distal ureteral stones but requires additional resources and sonographer experience. In selected cases use of MRI or low-dose CT may be appropriate. Conservative management and supportive care are appropriate for most patients; experience with alpha-blocker therapy in this setting remains limited. When intervention is necessary, temporary drainage with percutaneous nephrostomy tube or ureteral stent placement may be considered with frequent exchanges. Additionally, mounting evidence supports the safety and efficacy of ureteroscopy and primary treatment of the stone, particularly in the second trimester. However, more well-powered studies using standardized diagnostic and outcome metrics are needed to better delineate outcomes, as well as to elucidate the risks and benefits of specific stone management approaches in pregnant women. Further research in this area may improve quality of care delivery for this population.

References

1. Scales CD, Smith AC, Hanley JM, Saigal CS. Prevalence of kidney stones in the United States. *Eur Urol.* 2012;62:160–165. https://doi.org/10.1016/j.eururo.2012.03.052.
2. Fulgham PF, Assimos DG, Pearle MS, Preminger GM. Clinical effectiveness protocols for imaging in the management of ureteral calculous disease: AUA technology assessment. *J Urol.* 2013;189:1203–1213. https://doi.org/10.1016/j.juro.2012.10.031.
3. Turk C, Petrik A, Sarica K, et al. *EAU Guidelines on Urolithiasis*. European Association of Urology. Available at: https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Urolithiasis-2019.pdf. Published 2019. Accessed February 16, 2020.
4. Assimos D, Krambeck A, Miller NL, et al. Surgical management of stones: american urological association/endourological society guideline, PART II. *J Urol.* 2016;196:1161–1169. https://doi.org/10.1016/j.juro.2016.05.091.
5. Stothers L, Lee L. Renal colic in pregnancy. *J Urol.* 1992;148:1383.
6. Butler E, Cox S, Eberts E, Cunningham F. Symptomatic nephrolithiasis complicating pregnancy. *Obs Gynecol.* 2000;96:753–756.
7. Lewis D, Robichaux A, Jaekle R, Marcum N, Stedman C. Urolithiasis in pregnancy: diagnosis, management, and pregnancy outcome. *J Reprod Med.* 2003;48:28.
8. Rosenberg E, Sergienko R, Abu-Ghanem S, et al. Nephrolithiasis during pregnancy: characteristics, complications, and pregnancy outcome. *World J Urol.* 2011;29:743–747. https://doi.org/10.1007/s00345-011-0719-7.
9. Sohlberg EM, Brubaker WD, Zhang CA, et al. Urinary stone disease in pregnancy: a claims-based analysis of 1.4 million patients. *J Urol.* 2019. https://doi.org/10.1097/JU.0000000000000657.
10. Drescher M, Blackwell RH, Patel PM, Kuo PC, Turk TMT, Baldea KG. Antepartum nephrolithiasis and the risk of preterm delivery. *Urolithiasis*. 2019;47:441–448. https://doi.org/10.1007/s00240-018-1085-3.
11. Ordon M, Dirk J, Slater J, Kroft J, Dixon S, Welk B. Incidence, treatment, and implications of kidney stones during pregnancy: a matched population-based cohort study. *J Endourol.* 2020. https://doi.org/10.1089/end.2019.0557.
12. Burgess KL, Gettman MT, Rangel LJ, Krambeck AE. Diagnosis of urolithiasis and rate of spontaneous passage during pregnancy. *J Urol.* 2011;186:2280–2284. https://doi.org/10.1016/j.juro.2011.07.103.
13. Riley J, Dudley AG, Semins MJ. Nephrolithiasis and pregnancy: has the incidence been rising? *J Endourol.* 2014;28:383–386.
14. Srirangam SJ, Hickerton B, Van Cleynenbreugel B. Management of urinary calculi in pregnancy: a review. *J Endourol.* 2008;22:867–875. https://doi.org/10.1089/end.2008.0086.
15. Semins M, BR M. Kidney stones during pregnancy. *Nat Rev Urol.* 2014;11:163–168.
16. Meria P, Hadjadj H, Jungers P, Daudon M. Stone formation and pregnancy: pathophysiological insights gained from morphoconstitutional stone analysis. *J Urol.* 2010;183:1412–1416. https://doi.org/10.1016/j.juro.2009.12.016.
17. Ross AE, Handa S, Lingeman JE, Matlaga BR. Kidney stones during pregnancy: an investigation into stone composition. *Urol Res.* 2008;36:99–102. https://doi.org/10.1007/s00240-008-0138-4.
18. Swartz MA, Lydon-Rochelle MT, Simon D, Wright JL, Porter MP. Admission for nephrolithiasis in pregnancy and risk of adverse birth outcomes. *Obstet Gynecol.* 2007;109:1099–1104. https://doi.org/10.1097/01.AOG.0000259941.90919.c0.

19. Parulkar BG, Hopkins TB, Wollin MR, Howard PJJ, Lal A. Renal colic during pregnancy: a case for conservative treatment. *J Urol*. 1998;159:365–368. https://doi.org/10.1016/s0022-5347(01)63918-1.
20. Lifshitz DA, Lingeman JE. Ureteroscopy as a first-line intervention for ureteral calculi in pregnancy. *J Endourol*. 2002;16:19–22. https://doi.org/10.1089/089277902753483664.
21. Hoscan MB, Ekinci M, Tunckiran A, Oksay T, Ozorak A, Ozkardes H. Management of symptomatic ureteral calculi complicating pregnancy. *Urology*. 2012;80:1011–1014. https://doi.org/10.1016/j.urology.2012.04.039.
22. White WM, Johnson EB, Zite NB, et al. Predictive value of current imaging modalities for the detection of urolithiasis during pregnancy: a multicenter, longitudinal study. *J Urol*. 2013;189:931–934. https://doi.org/10.1016/j.juro.2012.09.076.
23. MacNeily AE, Goldenberg SL, Allen GJ, Ajzen SA, Cooperberg PL. Sonographic visualization of the ureter in pregnancy. *J Urol*. 1991;146:298–301. https://doi.org/10.1016/s0022-5347(17)37775-3.
24. Shokeir AA, Mahran MR, Abdulmaaboud M. Renal colic in pregnant women: role of renal resistive index. *Urology*. 2000;55:344–347. https://doi.org/10.1016/s0090-4295(99)00475-6.
25. Karabulut N, Karabulut A. Colour doppler evaluation of ureteral jets in normal second and third trimester pregnancy: effect of patient position. *Br J Radiol*. 2002;75:351–355. https://doi.org/10.1259/bjr.75.892.750351.
26. Andreoiu M, MacMahon R. Renal colic in pregnancy: lithiasis or physiological hydronephrosis? *Urology*. 2009;74:757–761. https://doi.org/10.1016/j.urology.2009.03.054.
27. Laing FC, Benson CB, DiSalvo DN, Brown DL, Frates MC, Loughlin KR. Distal ureteral calculi: detection with vaginal US. *Radiology*. 1994;192:545–548. https://doi.org/10.1148/radiology.192.2.8029429.
28. Committee on Obstetric Practice: Joshua Copel, Yasser El-Sayed, R. Phillips Heine, Kurt R Wharton. *Obstet Gynecol*. 2017;130:e210–e216. https://doi.org/10.1097/AOG.0000000000002355.
29. Mullins JK, Semins MJ, Hyams ES, Bohlman ME, Matlaga BR. Half Fourier single-shot turbo spin-echo magnetic resonance urography for the evaluation of suspected renal colic in pregnancy. *Urology*. 2012;79:1252–1255. https://doi.org/10.1016/j.urology.2011.12.016.
30. Spencer JA, Chahal R, Kelly A, Taylor K, Eardley I, Lloyd SN. Evaluation of painful hydronephrosis in pregnancy: magnetic resonance urographic patterns in physiological dilatation versus calculous obstruction. *J Urol*. 2004;171:256–260. https://doi.org/10.1097/01.ju.0000102477.19999.b2.
31. Patel SJ, Reede DL, Katz DS, Subramaniam R, Amorosa JK. Imaging the pregnant patient for nonobstetric conditions: algorithms and radiation dose considerations. *Radiographics*. 2007;27:1705–1722. https://doi.org/10.1148/rg.276075002.
32. Weisenthal K, Karthik P, Shaw M, et al. Evaluation of kidney stones with reduced-radiation dose CT: progress from 2011-2012 to 2015-2016-not there yet. *Radiology*. 2017:170285. https://doi.org/10.1148/radiol.2017170285.
33. Chung S-D, Chen Y-H, Keller JJ, Lin C-C, Lin H-C. Urinary calculi increase the risk for adverse pregnancy outcomes: a nationwide study. *Acta Obstet Gynecol Scand*. 2013;92:69–74. https://doi.org/10.1111/aogs.12016.
34. Bailey G, Vaughan L, Rose C, Krambeck A. Perinatal outcomes with tamsulosin therapy for symptomatic urolithiasis. *J Urol*. 2016;195:99–103. https://doi.org/10.1016/j.juro.2015.06.097.
35. Theriault B, Morin F, Cloutier J. Safety and efficacy of Tamsulosinas medical expulsive therapy in pregnancy. *World J Urol*. 2019. https://doi.org/10.1007/s00345-019-03022-z.
36. Lloyd G, Lim A, Hamoui H, Nakada S, Kielb S. The use of medical expulsive therapy during pregnancy: a worldwide perspective among experts. *J Endourol*. 2016;30:354–358.
37. Kavoussi L, Albala D, Basler J. Percutaneous management of urolithiasis during pregnancy. *J Urol*. 1992;148:1069.
38. Khoo L, Anson K, Patel U. Success and short-term complication rates of percutaneous nephrostomy during pregnancy. *J Vasc Interv Radiol*. 2004;15:1469–1473. https://doi.org/10.1097/01.RVI.0000140639.57131.6D.
39. Jarrard D, Gerber G, Lyon E. Management of acute ureteral obstruction in pregnancy utilizing ultrasound-guided placement of ureteral stents. *Urology*. 1993;42:263–267.
40. Rivera ME, McAlvany KL, Brinton TS, Gettman MT, Krambeck AE. Anesthetic exposure in the treatment of symptomatic urinary calculi in pregnant women. *Urology*. 2014;84:1275–1278. https://doi.org/10.1016/j.urology.2014.07.007.
41. Travassos M, Amselem I, Filho NS, et al. Ureteroscopy in pregnant women for ureteral stone. *J Endourol*. 2009;23:405–407. https://doi.org/10.1089/end.2008.0181.23.3.
42. Rana AM, Aquil S, Khawaja AM. Semirigid ureteroscopy and pneumatic lithotripsy as definitive management of obstructive ureteral calculi during pregnancy. *Urology*. 2009;73:964–967. https://doi.org/10.1016/j.urology.2008.12.054.
43. Polat F, Yesil S, Kirac M, Biri H. Treatment outcomes of semirigid ureterorenoscopy and intracorporeal lithotripsy in pregnant women with obstructive ureteral calculi. *Urol Res*. 2011;39:487–490. https://doi.org/10.1007/s00240-011-0376-8.
44. Isen K, Hatipoglu NK, Dedeoglu S, Atılgan I, Çaça FN, Hatipoglu N. Experience with the diagnosis and management of symptomatic ureteric stones during pregnancy. *Urology*. 2012;79:508–512. https://doi.org/10.1016/j.urology.2011.10.023.
45. Johnson EB, Krambeck AE, White WM, et al. Obstetric complications of ureteroscopy during pregnancy. *J Urol*. 2012;188:151–154. https://doi.org/10.1016/j.juro.2012.02.2566.
46. Semins MJ, Trock BJ, Matlaga BR. The safety of ureteroscopy during pregnancy: a systematic review and meta-analysis. *J Urol*. 2009;181:139–143. https://doi.org/10.1016/j.juro.2008.09.029.
47. ACOG Committee on Obstetric Practice: ACOG Committee Opinion No. 474: Nonobstetric surgery during pregnancy. *Obs Gynecol*. 2011;117:420.
48. Olutoye OA, Baker BW, Belfort MA, Olutoye OO. Food and Drug Administration warning on anesthesia and brain development: implications for obstetric and fetal surgery. *Am J Obstet Gynecol*. 2018;218:98–102. https://doi.org/10.1016/j.ajog.2017.08.107.
49. Wymer K, Plunkett BA, Park S. Urolithiasis in pregnancy: a cost-effectiveness analysis of ureteroscopic management vs ureteral stenting. *Am J Obstet Gynecol*. 2015;213:691.e1–691.e8. https://doi.org/10.1016/j.ajog.2015.07.024.
50. Reinstatler L, Khaleel S, Pais VMJ. Association of pregnancy with stone formation among women in the United States: a NHANES analysis 2007 to 2012. *J Urol*. 2017;198:389–393. https://doi.org/10.1016/j.juro.2017.02.3233.

EDITORIAL COMMENT

Management of urologic conditions in pregnancy can be quite challenging for both the patient and the physician. As the authors suggest in this excellent review, we are essentially "treating for two"; but beyond this we are also more limited in our diagnostic and treatment options during pregnancy. One key take home message is the importance of pursuing further imaging when ultrasound is equivocal. Whether that be with magnetic resonance urography or low dose computed tomography, additional imaging permits a definitive diagnosis and risk stratification. In selection of the most appropriate diagnostic imaging modality, a multidisciplinary discussion with Obstetrics and Radiology is quite valuable. The goal remains as low as reasonably achievable. Any radiation exposure from diagnostic imaging

and/or therapeutic treatment (eg, intraoperative fluoroscopy) must be documented in the electronic medical record.

Over the past decade, there has been increasing utilization of ureteroscopy for endoscopic stone treatment during pregnancy, particularly in the second trimester in order to minimize the risk to fetal development (first trimester) and the risk of preterm labor (third trimester). Decision-analytical modeling has suggested ureteroscopy is more cost effective then temporizing ureteral stent placement.[1] However, in the era of COVID 19, the potential benefits of definitive management cannot be understated. Limiting exposure for the mother and baby is paramount. Again, the value of a multidisciplinary approach and shared decision making (SDM) is readily apparent.

While SDM has become an almost cliché term in medicine, I cannot think of another clinical scenario where SDM is more important than the pregnant patient with a stone. SDM is "an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences."[2] In the symptomatic pregnant patient, SDM is imperative in selection of imaging modality, pain management, and stone treatment. The risks and benefits must be considered for both the mother and baby.

One question that remains unanswered is how proactive we should be in treating asymptomatic stones in our kidney stone patients of child-bearing age? While many pregnancies are unplanned, there are clearly clinical scenarios in which stone formation during pregnancy is predictable and may lead to complications such as the patient with cystinuria. In these high-risk patients and/or those with larger stones, I generally favor getting them stone free before a planned pregnancy to decrease the risk of a stone event.

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References

1. Wymer K, Plunkett BA, Park S. Urolithiasis in pregnancy: a cost effectiveness analysis of ureteroscopic management versus ureteral stenting. *Am J Obstet Gynecol.* 2015;213:691.e1–691.e8.
2. Elwyn G, Frosch D, Thomson R, et al. Shared decision making: a model for clinical practice. *J Gen Int Med.* 2012;27:1361–1367.

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