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ORIGINAL PAPER

Ureteroscopy in pregnant women with complicated colic pain: Is there any risk of premature labor?

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Summary *Objective: Clinical presentation of ureteral stones during pregnancy is generally with renal colic pain. The aim of this study is to present our experience in the management of renal colic during pregnancy in emergency settings.*

Materials and methods: 208 pregnant patients who presented to emergency department with renal colic pain and underwent ureteroscopy (URS) due to failed conservative therapy were enrolled in the study. Urinary tract stones were diagnosed either with ultrasound (US) examination or during URS. Laser lithotripsy and double J (DJ) stent placement were routinely done in all patients with ureteral stones. The incidence of infective complications and premature uterine contractions (PUC) due to URS were compared.

Results: No stone was identified in 36.1% (n = 75) of patients with using US and diagnostic URS. Of the remaining 133 patients, 30 (22.6%) had no stone at US but stones were diagnosed during diagnostic URS. The type of anesthesia had no significant effect on PUC. An increased risk of sepsis and PUC was found in patients with fever at the initial presentation. Interestingly, PUC was more frequent in patients with lower serum magnesium levels. There was a significant correlation with time delay until the intervention and the risk of urosepsis and PUC, individually.

Conclusions: Ureteroscopy is a safe option for evaluation of pregnant patients with unresolved renal colic. According to the current findings, timing of the operation is the most important factor affecting the septic risks and abortion threat. Surgical intervention with URS must be planned as soon as possible.

KEY WORDS: *Pregnancy; Urinary calculi; Renal colic.*

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INTRODUCTION

The management of urinary stones during pregnancy is a major challenge for urologists (1). The incidence of urolithiasis during pregnancy is estimated to be between 0.02-0.53%, complicating from 1:200 to 1:2000 pregnancies, and urolithiasis may also be a contributing factor in up to 40% of premature births (2).

Several elements are capable of increasing the risk of urolithiasis and hydronephrosis during pregnancy, including the mass-effect of gravid uterus, reduced peristalsis and dilation of the urinary tract due to elevated progesterone levels, and increased risk of infection and electrolyte imbalance (decreased secretion of urinary stone inhibitors, such as citrate and magnesium) (3).

Renal colic is the most common non-obstetric cause of abdominal pain and subsequent hospitalization during pregnancy (3). The clinical presentation of ureteral stones during pregnancy is primarily after 20 weeks of gestation; alongside renal colic, tenderness, fever, dull aching pain and hematuria (4).

As is the case with the general population, a conservative approach that makes use of analgesia and monitoring for spontaneous passage is often the most appropriate initial treatment for acute renal colic in the pregnant patient. However, if spontaneous passage does not occur or if complications develop, placement of a ureteral stent or a percutaneous nephrostomy is necessary. In such cases, *ureteroscopy* (URS) has also become a reasonable alternative due to patients' low tolerance for these devices (5).

The aim of this study is to present our experience managing renal colic during pregnancy in emergency settings.

MATERIALS AND METHODS

From November 2000 to August 2014 pregnant patients who presented to *Emergency Departments* (EDs) of *University of Messina* and *Magna Graecia University* with complicated renal colic were included in the study. We refer to as complicated when it is unresponsive to con-

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servative analgesic treatment or there is leucocytosis, fever and vomiting. Patients were endoscopically treated with either a *double J* (DJ) stent placement or semirigid ureterolithotripsy. Data were retrospectively analyzed.
As standard protocol at the *University Hospitals* in which the study was carried out, each patient signed an informed consent agreement upon admission allowing data collection for research purposes. The study design is in accordance with the *Helsinki Declaration*, conforms to the *Committee on Publication Ethics* (COPE) guidelines and was approved by the *Institutional Review Board* (IRB) of the *University Hospitals* in which the study was conducted. All design, analysis, interpretation of data, drafting and revisions followed the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) Statement: guidelines for reporting observational studies, available through the EQUATOR (*Enhancing the Quality and Transparency of Health Research*) network (6).
Assessment included general evaluation at presentation, routine urine and blood tests, urine culture, blood culture if necessary, *urinary system ultrasonography* (USG), and consultation with the *Department of Obstetrics & Gynecology*. No *computed tomography* (CT) scan, *Kidney-Ureter-Bladder* (KUB) graphy, or other ionizing radiation study was performed due to risk of foetal radiation exposure. All patients presented to the ED with complicated HN received analgesics and *intravenous* (IV) hydration treatment in a conservative approach; those who failed to respond and still had renal colic underwent ureteroscopy and were included in the study. Stones were fragmented using a *holmium:yttrium-aluminum-garnet* (Holmium:YAG) laser and DJ stents were routinely placed in all patients. All operations were performed by two surgeons with a large amount of experience in endourology (performing more than 500 procedures each).
Follow-up protocols included obstetric examination and ultrasound, to check both maternal and fetal health status, and urological follow-up consisted of clinical assessment of general well-being and symptomatology, USG examination, routine urine and blood tests, and urine culture.
DJ stents were removed four weeks after post-op.
The primary endpoints of the study were to examine whether URS increases *premature uterine contractions* (PUC) and the rate of premature labor, defined as regular uterine contractions that induce thinning and shortening of the uterine cervix before 37 weeks of pregnancy according to NICE guidelines (7). Uterine contractions were specifically defined as regular if they were of high intensity and occurred 3 or more times in 10 minutes measured by cardiotocography.
Modification of the uterine cervix was evaluated by vaginal examination and, in case patients were 30 weeks pregnant or more, by transvaginal ultrasound and if cervical length was more than 25 mm we excluded the diagnosis of preterm labor (8). We also evaluated whether delaying the operation increases the risk of premature labor and whether early intervention is beneficial over delayed URS in terms of urosepsis, Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection and Organ dysfunction can be identified as an acute change in total Sequential (*Sepsis-Related*). *Organ Failure Assessment Score* (SOFA) score ≥ 2 points consequent to the infection. Urosepsis is mainly due to obstructed uropathy of the upper urinary tract (9). The secondary endpoints were to evaluate whether the rate of preterm labor and sepsis are effected by having a urinary stone and undergoing laser lithotripsy or by having a negative diagnostic URS, to see if there are parameters that can be used to determine the risk of preterm labor and urosepsis.

Statistical analysis

Statistical analyses were performed using original SPSS software, version 20.0 (*IBM Corp, NY, USA*). Statistical significance was set at $p < 0.05$. Baseline variables were described using means and standard deviations or percentages, as appropriate. Mann-Whitney U tests were used to evaluate the difference between quantitative measurements that have non-parametric distribution. Chi-squared tests were used for categorical data. Cut off values for quantitative measurements were found by using *Receiver Operating Characteristics* (ROC).
Sensitivities, specificities, and predictive values with 95% confidence intervals were calculated.

Results

A total of 208 patients were included in the study. All enrolled patients were in the second (from the 13th to the 27th week) or third trimester (from the 28th week onward) of pregnancy. Patients in the second trimester had a gestational age of 26.1 ± 0.8 weeks, whereas patients in the third trimester had a gestational age of 31.8 ± 2.2 weeks.
The grade of hydronephrosis was 1, 2 and 3 in 102 (48.1%), 75 (35.4%), 35 (16.5%) patients, respectively. A total of 133 of these patients had a ureteral stone diagnosed with urinary system *ultrasonography* (USG) or during diagnostic ureteroscopy and underwent laser lithotripsy and DJ stent placement. The mean stone size was 8.3 ± 2.2 mm. The stone was in the lower, middle and upper ureter in 78 (58.6%), 46 (34.6%) and 9 (6.7%) patients, respectively. In 10 patients, stone retropulsion occurred during laser lithotripsies and only two of these patients had PUC. The remaining 75 patients underwent diagnostic ureteroscopy, no stone was encountered, and a DJ stent was placed.
The mean duration of the operation was 29.4 ± 4.6 minutes. Different parameters about patients with and without PUC are given in Table 1.
8.7% of patients with a stone (encountered before or during URS and treated) underwent preterm labour - something they are at higher risk of than patients in whom no stone is revealed during either preoperative evaluation or diagnostic URS (1.4% of these patients underwent preterm labour, $p < 0.05$, Odd's ratio: 3.8, confidence interval: 1.1-13.2).
Patients with signs of urinary tract infection (UTI) are considered to have a fever at the time of diagnosis, as they have positive urine culture and urosepsis after ureteroscopy and were at greater risk for the presence of PUC when compared to patients without signs of UTI ($p < 0.005$, Odd's ratio: 6.6, confidence interval: 1.8-12.1). Nine out of 35 patients (25.7%) with and 12 out of 173 patients (6.9%) without signs of UTI underwent preterm labour.

Table 1.
Time elapsed prior to operation (hours) and serum magnesium level (mmol/L) of patients diagnosed and treated for urinary stone disease and patients who underwent diagnostic ureteroscopy, subgrouped by having premature uterine contrations (PUC). Values are expressed as median (minimum, maximum).
*(*p < 0.05, **p < 0.01, ***p < 0.001, when compared with patients having PUC).*

		Time elapsed until operation	Serum magnesium level
Stone +	PUC +	37.5 (min 19, max 43)	0.73 (min 0.62, max 0.84)
	PUC -	21 (min 6, max 42)***	0.78 (min 0.54, max 1.86)**
Stone -	PUC +	34.5 (min 30, max 42)	0.96 (min 0.83, max 1.17)
	PUC -	22 (min 6, max 47) *	0.82 (min 0.58, max 1.36)*

The number of patients with signs of UTI experiencing preterm labour was not statistically different in subgroups where the patients were operated upon for an existing stone or where they had a diagnostic URS and DJ stent placement (p: 0.488). However when patients without signs of UTI were considered, having a stone and undergoing lithotripsy increased the risk of preterm labour more than in patients with no urinary stone ($p < 0.05$, Odd's ratio: 7.3, confidence interval: 0.9-57.6).
When we analyze the data, having a fever at the time of diagnosis is the highest risk factor for preterm labour (Odd's ratio: 19.3, confidence interval: 6.1-60.8).
Additionally, delaying operation by more than 36 hours increases the risk by a factor of 10 (Odd's ratio: 10, confidence interval: 1.8-12.1). However being stone-free at operation's end increases the risk of preterm labour (Odd's ratio: 6.2, confidence interval: 2.8-13.5).
This situation may indicate that, to be stone-free, patients need complete stone removal which may require longer operation times and can therefore lead to a risk of increased preterm labour. Upon univariate analysis of the data, having a fever at time of diagnosis, being stone-free at the end of the procedure and a delay of > 36 hours until operation have a statistically significant relationship with having PUC ($p < 0.0001$).
The mean time elapsed until operation was significantly longer in patients with preterm labour than in both subgroups of patients without preterm labour; in whom a stone was not revealed ($p < 0.05$) or whom had a diagnosed stone either with US or URS ($p < 0.001$). The cut-off value of a 30.5 hour-delay till operation in patients without a stone has a sensitivity of 75% and specificity of 71% on a ROC curve analysis (AUC: 0.792). On the other hand, for patients with a urinary stone, the cut-off value of 29.5 hours has a sensitivity of 83% and a specificity of 79% (AUC: 0.86). Additionally, the serum magnesium levels of patients who had a stone were significantly lower in patients with preterm labour than in patients without preterm labour ($p < 0.01$). Interestingly, when patients without a stone were considered, the opposite relationship is encountered; patients in this group with a PUC had significantly higher levels of serum magnesium ($p < 0.05$). The data is reported in Table 2.
For patients with a diagnosed urinary stone (either with US or during URS) who subsequently underwent laser lithotripsy, elapsed time until operation ($p < 0.05$), urine density ($p < 0.05$), serum uric acid (UA) level ($p < 0.05$) and serum glucose level ($p < 0.05$) all have statistically significant relationships to urosepsis. The median values for all these parameters are given in Table 3. However, these parameters did not have statistically significant relationships in patients without urinary stones.

Discussion

Hydronephrosis and the accompanying persistent renal colic during pregnancy is a urological and obstetric emergency. It is a relatively rare occurrence in 0.05% of all pregnancies (10). Different urological, obstetrical, gynecological and general surgical evaluations are needed to make a differential diagnosis and exclude other emergency situations such as an acute twisted ovarian cyst, aortic aneurysms or appendicitis (11).
The first diagnostic step is an ultrasonographic examination. Real-time USG demonstrates the renal parenchyma, calyceal system, dilated ureter, and occasionally the offending calculus, without radiation exposure. There are limitations of USG however; the first being low sensitivity of standard USG for urolithiasis which is between 34-86% (12, 13). The second limitation is the impossibility of evaluating the ureter below the level of the pelvic brim/iliac artery in most cases as well as situations in which the

Table 2.
Median values of time elapsed prior to operation (hours), urine density, serum uric acid level (µmol/L) and serum glucose level (mmol/L) in patients with diagnosed urinary stone who had urosepsis.
Values are expressed as median (minimum, maximum).
*(*p < 0.05, when compared with patients who didn't have urosepsis).*

		Urosepsis +	Urosepsis -
Stone +	Time elapsed until operation	38 (min 32, max 40)	21 (min 6, max 43)*
	Urine density	1010 (min 1000, max 1020)	1015 (min 1010, max 1030)*
	Serum uric acid level	350 (min 260, max 430)	238 (min 121, max 2785)*
	Serum glucose level	4.28 (min 4.03, max 4.48)	4.82 (min 3.45, max 8.07)*

investigator is unable to differentiate between secondary ureteral obstruction from calculi and the physiologic hydronephrosis of pregnancy (14). Transvaginal USG is another diagnostic tool that can be used to accurately detect distal ureteral stones as demonstrated in the literature and can be performed to evaluate the length of the uterine cervix in a one-step procedure (15).

In pregnant patients, ionizing radiation may have teratogenic effects on the fetus and should be avoided, diminishing clinicians' diagnostic options in complicated cases. However, *European Association of Urology* (EAU) guidelines permit the use of a low-dose CT as a last resort in selected cases. Magnetic resonance imaging (MRI) can also be used as it may define the level of urinary tract obstruction and visualize stones as filling defects (5). In our cohort of patients we did not use low-dose CT, KUB X-ray, *intravenous urography* (IVU) or MRI.

In patients with complicated hydronephrosis with colic pain, ureteroscopy can be used as a diagnostic procedure thanks to low complication rates in this patient group and due to a potentially high number of diagnosed ureteral stones in carefully selected patients, something that was reflected by our results in this study (16-18). According to *Wymer et al.* study, ureteroscopy is less costly and more effective than routine stenting, especially in early pregnancy (19). Of all the patients presented to the *Emergency Department*, 133 were found to have a ureteral stone.

Ultrasonography revealed the stone in 103 patients (77.4%), and 30 patients (22.6%) were found to have ureteral calculi during ureteroscopy.

This finding demonstrates that USG is a decisive diagnostic method for patients with renal colic during pregnancy and that ureteroscopy can be used as an auxiliary measure (20). About 20-30% of ureteral stones during pregnancy are not expelled spontaneously and need active treatment (21).

The first step in active treatment is the placement of a ureteral DJ stent or percutaneous nephrostomy. DJ stent placement is a rapid way to decompress the urinary system, and can be performed with a retrograde or antegrade approach (22).

Retrograde approach may be performed under local anesthesia using USG guidance, thus avoiding fluoroscopic radiation exposure. Limited fluoroscopic imaging can only be performed if there is any difficulty advancing the guidewire up the ureter (23). However, *Denstedt* and *Razvi* suggest that a ureteral stent should be reserved for the later stages of pregnancy (24). In cases where a DJ stent is placed during the first trimester of pregnancy, it is advised that the stent be changed on a monthly basis (21).

Percutaneous nephrostomy insertion in pregnant patients has several advantages. It's a minimally invasive procedure, provides immediate and effective decompression of the kidney cavities and can be performed even in sepsis situations and under local anesthesia without the need for ionizing radiation.

The procedure also allows urine collection for culture, and permits access for future percutaneous nephrolithotomy procedures (25). Percutaneous nephrostomy may be preferred over DJ stents during early pregnancy due to easier replacement techniques if necessary (21, 26).

Ureteroscopy and laser lithotripsy for ureteral calculi during pregnancy has gained popularity in the last few years and studies on urinary tract stones in pregnant patients are increasing.

Zhang et al. reported that out of 117 pregnant patients, 12 had PUC and 5 had renal colic for more than 24 hours - a statistically significant condition (18).

In our study, we found that time elapsed until operation is a major risk factor for PUC and that there is a significant difference between patients with and without PUC in both groups as well as with and without urinary system stones. The delay is caused by the need to perform tocolysis and maternal corticosteroid administration to induce fetal lung maturation according to *Royal College of Obstetricians and Gyneacologists Guidelines* (27-30). However, early intervention should be suggested in cases of complicated HN patients. The delayed operation was also found to be a risk factor for urosepsis in our cohort of patients.

The situation becomes a two-sharp-edged sword; delay is necessary but can be a risk factor for sepsis. A delay is associated with increased sepsis risk, especially in patients who had urinary stones.

This delay is not significant in patients without stones, which may depend on the duration of the operation (in patients with a stone, operation time may be longer due to the additional procedure of laser lithotripsy).

Unfortunately operation times are not recorded, so statistical analysis could not be performed. So, we can potentially suggest that a simple DJ stenting may be preferred over laser lithotripsy in cases where the operation can be performed after > 36 hours of admission to the ED or in patients with signs of UTI upon admission, in order to reduce the rate of PUC.

Mitrovic-Jovanovich et. al. reported in their study how serum levels of magnesium and calcium can be predictors of preterm delivery (31).

In our study cohort, we observed that serum levels of magnesium are significantly lower in patients who had uterine contractions during URS. However, the serum levels of calcium did not differ in patients with or without uterine contractions.

The significant differences in serum glucose levels in patients with and without sepsis can be attributed to increased catabolic activity. *Jeon et al.* found that an increased glucose level upon hospital admission is associated with increased blood stream infections (32). Similarly, in our study, the serum glucose levels were significantly higher in patients who had urosepsis.

Although the mechanism is not clear, the serum levels of UA increased in cases of severe sepsis.

This is either caused by an increase in production due to hypoxia and ischemia, which results in increased conversion of xantine and hypoxantine to UA; or is caused by decreased excretion from the kidneys due to decreased renal perfusion in sepsis (33, 34).

It was hypothesized by *Chuang et al.* that serum UA levels are correlated with total antioxidant capacity of patients and helps to counterbalance increased pro-inflammatory cytokines. Whether hyperuricemia is a risk factor for sepsis is unknown, but it is shown that higher levels of UA are associated with poorer outcomes in sepsis patients (35).

Our study has some limitations. The first limitation is the retrospective nature of the study and the second is that duration of time prior to operation wasn't exactly recorded but classified into categories so the analyses with this parameter could not be carried out to provide exact mean values.

Conclusions

Ureterolitotripsy and DJ stent placement are valid and safe choices in pregnant patients with complicated hydronephrosis.

In our opinion, the most important issue is timing, evaluating all the parameters including blood tests, radiology, general status of the fetus and patient. Delaying an operation can lead to an over exposure to septic risks and PUC may increase.

The perfect timing should be planned step-by-step with a multi-disciplinary approach.

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