MANAGEMENTAND OUTCOMES OF INPATIENT TREATMENT OF URINARY TRACT STONES IN THE OBSTETRIC PATIENT

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ABSTRACT

Objectives: Urinary tract stones are a common occurrence in the general population. Although the prevalence of urinary stones in women has risen in recent years, it is still considered a relatively rare event in pregnancy, with urinary stones complicating an estimated 8 in 1,000 pregnancies. There is substantial literature regarding urolithiasis in pregnancy, however many publications focus on maternal outcomes and management, neglecting neonatal outcomes. Furthermore, there is a paucity of literature comparing inpatient management of urinary calculi in pregnant women with their non-pregnant counterparts. This thesis will be addressing two objectives. The first objective of this thesis is to determine how pregnancy impacts the clinical course and management of urinary stones. Specifically, our first objective is to compare the clinical presentation, inpatient procedure rates, and length of hospital stay, as well as to identify associated clinical conditions of urolithiasis in pregnancy. The second objective of this thesis is to identify the incidence of urolithiasis in pregnancy and to compare maternal and fetal outcomes between pregnancies affected and not affected by urinary tract stones.

Methods: To accomplish the objectives of this thesis, two retrospective cohort studies were conducted. Both studies utilized the National Inpatient Sample (NIS), a population-based database consisting of hospital inpatient admissions in the United States (US) from 1999 to October 1st, 2015. To address the first objective, a cohort of women admitted for urinary tract stones was identified using the ICD-9-CM code for urolithiasis (592.X). Then women who were concurrently pregnant at time of admission for urinary tract stones were identified. Subsequently, a comparison group of non-pregnant women with urinary tract stones was identified within the cohort and age-matched (1:1) to the pregnant women. Conditional logistic regression models, adjusted for baseline maternal characteristics, were used to compare the odds of presenting symptoms, length of hospital stay, clinical course, and procedural management of urinary tract stones among pregnant and non-pregnant women. To address the second objective, a cohort of pregnant women was identified. Within this cohort, pregnant women admitted for urinary stones formed one group, while pregnant women not admitted for urinary stones formed the comparison group. Multivariate logistic regression models, adjusted for the baseline maternal demographic characteristics and co-morbidities, were used to compare the associations between urinary tract stones in pregnancy and maternal and neonatal outcomes.

Results: In the first study, pregnant women with urolithiasis were statistically less likely to present with the classic symptoms of renal colic, such as fever (OR 0.22, 95% CI 0.16-0.30) and flank pain (OR 0.63, 95% CI 0.56-0.70), when compared to their non-pregnant counterparts. They were also less likely to suffer infectious complications of urolithiasis or to undergo invasive medical procedures. However, pregnant women tended to have longer hospital stays than the non-obstetrical cohort (OR 1.07, 95% CI 1.02-1.12 for 3 days or longer). In the second study performed, overall incidence of urolithiasis in pregnancy over the study period was 7.1 per 10,000. When compared with pregnant women without urinary tract stones, the pregnant patients with stones had higher risks of obstetric complications. Specifically, they were at greater risk of hypertensive disorders of pregnancy (OR 1.3, 95% CI 1.24-1.47), gestational diabetes mellitus (OR 1.29, 95%

CI 1.20-1.30), abruptio placenta (OR 1.41, 95% CI 1.22-1.64), placenta previa (OR 1.55, 95% CI 1.27-1.90), and cesarean deliveries (OR 1.20, 95% CI 1.15-1.25). Pyelonephritis (OR 88.87, 95% CI 81.69-96.69) and maternal death (OR 2.85, 95% 1.07-7.60) were also more likely in women with urinary tract stones, and their offspring were at greater risk of congenital anomalies (OR 2.84, 95% CI 2.43-3.3) and preterm birth (OR 1.92, 95% CI 1.82-2.03). Risk of intrauterine fetal death (OR 0.60, 95% CI 0.45-0.81) was lower among pregnancies complicated by urolithiasis.

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Conclusion: Pregnant women tend to have a milder disease course when compared with their non-pregnant counterparts. We hypothesize that frequent visits with their physicians and heightened awareness of symptoms predispose pregnant women to earlier diagnoses and quicker management. When compared with pregnancies not complicated by urinary tract stones, pregnancies complicated by stones were observed to have higher rates of adverse maternal and neonatal outcomes. A high level of suspicion is warranted when pregnant patients present with symptoms of urolithiasis. Prompt diagnosis and management can spare these patients from serious complications and undergoing invasive procedures, as well as sparing the neonate from adverse outcomes.

Keywords: Urinary tract stones; Pregnancy, urolithiasis, pregnant, neonate, outcomes, management

RÉSUMÉ

Objectifs: Les calculs urinaires sont fréquents dans la population générale. Leur prévalence chez les femmes a augmenté aucours des dernières années. Bien qu'il s'agisse encore d'un événement rare pendant la grossesse, la recherche montre que les calculs urinaires compliquent 8 grossesses sur 1000. Il existe une littérature abondante sur les calculs urinaires pendant la grossesse, mais de nombreuses publications se concentrent sur les issues maternelles et la prise en charge, négligeant les issues néonatales. Entre autre, il y a peu de littérature comparant la prise en charge hospitalière des calculs urinaires chez les femmes enceintes avec leurs homologues non enceintes. Cette thèse vise à répondre à ces questions, ainsi qu'à valider les résultats observés dans la littérature existante.

Recherche et méthodes: Pour atteindre les objectifs de cette thèse, deux études de cohorte rétrospectives ont été menées. Les deux études ont utilisé le National Inpatient Sample (NIS), une base de données couvrant environ 20% de toutes les admissions de patients hospitalisés aux États-Unis (États-Unis) de 1999 au 1er octobre 2015. Le NIS fait partie du Healthcare Cost and Utilization Project (HCUP), la plus grande source complète de données sur les soins hospitaliers aux États-Unis. Les cohortes ont été identifiées à l'aide des codes d'un système de codage uniforme et systématisé, appelé International Classification of Diseases, 9^{th} revision, Clinical Modification (ICD-9-CM). Pour répondre au premier objectif, une cohorte de femmes enceintes a d'abord été identifiée. Ensuite, le code ICD-9-CM pour la lithiase urinaire (592.X) a été utilisé pour identifier

les femmes enceintes admises pour des calculs urinaires. Un groupe de comparaison de femmes non enceintes présentant des calculs urinaires a été identifié dans la cohorte et apparié selon l'âge (1: 1) avec les femmes enceintes. Les codes de la ICD-9-CM ont également été utilisés pour identifier les symptômes, la durée du séjour à l'hôpital, les conditions associées et les interventions observées chez ces patients. Pour répondre au deuxième objectif, une cohorte de femmes enceintes a été identifiée. Au sein de cette cohorte, les femmes enceintes admises pour calculs urinaires constituent un groupe, avec les femmes enceintes non admises pour calculs urinaires constituant le groupe de comparaison. Les codes ICD-9-CM ont été utilisés pour identifier les issues maternelles et néonatales.

Résultats: Dans la première étude, les femmes enceintes atteintes de lithiase urinaire étaient statistiquement moins susceptibles de présenter les symptômes classiques de colique rénale, comme la fièvre, OR 0.22 95% CI 0.16-0.30, et la douleur au flanc, 0.63 (0.56-0.70), par rapport à leurs homologues non enceintes. Elles étaient également moins susceptibles de souffrir de complications infectieuses de la lithiase urinaire ou de subir des procédures médicales invasives. Cependant, leur séjour à l'hôpital était généralement plus long chez les femmes enceintes, 1.07 (1.02-1.12). Dans la deuxième étude réalisée, l'incidence globale de la lithiase urinaire pendant la grossesse était de 7.1 pour 10 000. Par rapport aux femmes enceintes sans calculs, les patientes enceintes avec des calculs présentaient des risques plus élevés de complications obstétriques. Ils présentaient un risque plus élevé de troubles hypertensifs de la grossesse, 1.35 (1.24-1.47), de diabète sucré gestationnel, 1.29 (1.20-1.30), d'abruptio placenta, 1.41 (1.22-1.64), de placenta

praevia, 1.55 (1.27-1.90) et d‘accouchement par césarienne, 1.20 (1.15-1.25). La pyélonéphrite, 88.87 (81.69-96.69) et le décès maternel étaient également plus fréquents chez les femmes présentant des calculs urinaires. La progéniture des femmes enceintes souffrant de calculs urinaires était plus à risque d'anomalies congénitales, 2.84 (2.43-3.31 et de prématurité, 1.92 (1.82-2.03). Par contre, ces enfants nés de femmes atteintes de lithiase urinaire avaient des taux inférieurs de mortalité fœtale intra-utérine, 0.60 (0.45-0.81).

Conclusions: Les femmes enceintes ont tendance à avoir une évolution plus légère de la maladie que leurs homologues non-enceintes. Des visites fréquentes avec leur médecin et une conscience accrue des symptômes les prédisposent à des diagnostics précoces et à une prise en charge plus rapide. Par rapport aux grossesses sans calculs urinaires, les grossesses compliquées par des calculs se sont avérées avoir des taux plus élevés d'issues maternelles et néonatales négatives. Un niveau élevé de suspicion est indiqué lorsque les patientes enceintes présentent des symptômes de calculs urinaires. Un diagnostic et une prise en charge rapides peuvent épargner à ces patients des complications graves et subir des procédures invasives, ainsi qu'épargner à la mère et au fœtus des événements obstétricaux indésirables.

Mots clés: Calculs rénaux, grossesse, enceinte, pierres, obstétrique, nouveau-né, prise en charge

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CONTRIBUTION OF AUTHORS

Natasha Sebastian is the primary author of this thesis under the supervision of Dr. Haim A. Abenhaim.

Natasha Sebastian and Dr. Haim A. Abenhaim contributed to the study concept and design.

Nick Czuzoj-Shulman contributed to the data collection.

Natasha Sebastian and Dr. Haim A. Abenhaim contributed to the analysis and interpretation of the data, to drafting the manuscript and to the critical revision of the manuscript for important intellectual content.

The thesis supervisor, Dr. Haim A. Abenhaim, contributed to the initial review and edits of the first draft of this thesis.

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LIST OF ABBREVIATIONS

CCS	Clinical classifications software
CKD	Chronic kidney disease
C/S	Cesarean section
CT scan	Computed tomography scan
DM	Diabetes mellitus
ECMO	Extracorporeal membrane oxygenation
GDM	Gestational diabetes mellitus
GFR	Glomerular filtration rate
HCUP	Healthcare cost and utilization project
HIPAA	Health insurance probability and accountability act
HTN	Hypertension
ICD-9	International classification of diseases, 9th revision
IUFD	Intrauterine fetal demise
IUGR	Intrauterine growth restriction
KUB	Kidney-ureter-bladder
LOS	Length of stay
NIS	National inpatient sample
NSAID	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
POC	Products of conception
PPCM	Peripartum cardiomyopathy
PPH	Postpartum hemorrhage

PROM	Premature rupture of membranes
PPROM	Preterm premature rupture of membranes
PTB	Preterm birth
UTI	Urinary tract infection
VTE	Venous thromboembolism
W/	With
W/O	Without

CHAPTER 1: INTRODUCTION

Urinary tract stones are a common occurrence in the general population affecting almost 10% of the US population. Although men are more likely to suffer from urinary calculi, in recent years, the prevalence of urinary tract stones in women has risen to nearly match the prevalence in men. White non-Hispanic individuals are at a higher risk of developing urinary calculi than their black, non-Hispanic or Hispanic counterparts. Patients suffering from urolithiasis often have comorbidities or systemic illnesses predisposing them to stone formation.[1] For instance, obesity and other chronic conditions, such as diabetes, tend to increase the risk of urinary tract stones.[2] Renal colic, or flank pain, is the most common symptom voiced by patients. Nausea and vomiting often accompany the intense pain. Hematuria may be present. [3]

Management of urolithiasis is usually undertaken in an outpatient setting. Ureteral dilation with drugs like tamsulosin, hydration, and analgesics compose the foundation of urinary calculi treatment.[3] Antibiotics are often used, as urinary tract stones are frequently associated with urinary tract infections (UTI). UTIs can induce stone formation by alkalinizing the urine, as in cases of Proteus mirabilis infection. In turn, ureteral obstruction from an existing stone can cause proximal urinary stasis, leading to infection.[4] However, in some cases, hospital admission is necessary. Over the years, several surgical interventions have been developed to treat these stones[5], with recent developments focusing on non-invasive procedures, such as extracorporeal shockwave lithotripsy. [6]

Urinary tract stones occurring during pregnancy are a rare occurrence. However, it is vital for physicians to have a high clinical suspicion when evaluating patients who present with symptoms of renal colic. Urolithiasis affects 0.8% of pregnancies in the United States.[7] However, the prevalence is thought to be much higher, as patients may be asymptomatic.[8] Nonetheless, renal colic is still considered the most common non-obstetric cause for hospital admissions in pregnant patients.[9] Urinary tract stone events during pregnancy pose unique risks for both the mother and fetus. Ultrasonography remains the imaging modality of choice, however intravenous urography should be performed if necessary. Special care must be taken when treating pregnant women. As in the general population, conservative management is the main focus in treating these patients. Spontaneous passage of the stones is the ultimate goal for pregnant patients. Invasive interventions are usually avoided in this patient population, as they pose a risk for preterm labor.[8]

Literature on urolithiasis in pregnancy is broad. Many studies focus on management and pregnancy outcomes. However, there is lack of comparative research between pregnant and non-pregnant patients. There is also a paucity of research on neonatal outcomes related to maternal urolithiasis. Recognizing these deficiencies in the literature, this thesis aims to acknowledge unanswered questions about differences in care with non-pregnant patients and neonatal outcomes, as well as strive to support existing findings.

CHAPTER 2: LITERATURE REVIEW

The following chapter presents and describes the subject material that will be focused on in the coming chapters. This chapter will be split into three parts. The first will focus on urinary stones, summarizing known literature about the disease including its causes, pathophysiology, treatment, and complications. The second part of this chapter will describe the anatomical and physiological changes that occur to the female body during gestation, as well as potential maternal and neonatal complications of pregnancy. The third part of this chapter will iterate what we already know about urinary tract stones in pregnancy.

2.1 Overview of urolithiasis

2.1.1 Description and symptoms

Urolithiasis is defined as stone formation (lithiasis) in the urinary tract (Uro-), which is composed of the two kidneys, two ureters, a bladder, and a urethra. Although most stones found in the bladder form spontaneously due to urinary stasis or bladder infection, a good proportion originate from the kidney.[10] The most common symptoms seen in patients suffering from urinary tract stones are unilateral abdominal or flank pain, gross hematuria, nausea, vomiting, dysuria, and urgency.[11]

2.1.2 Incidence and epidemiology

Urolithiasis is a very common medical condition in the United States, affecting 1 in 11 individuals. It occurs more commonly in men than women, with a prevalence of 10.6% and 7.1%, respectively. White, non-Hispanic individuals are more likely to develop stones when compared with the Black and Hispanic population. The prevalence of stone disease increases with age. [2]

2.1.3 Causes and risk factors

Urinary calculi are thought to develop due to genetic, dietary, environmental, and lifestyle risk factors. These include, but are not limited to, obesity, hypertension, diabetes, chronic kidney disease, inactivity, high sodium intake, excessive consumption of animal proteins, high intake of sugar and sweeteners, and bacteria.[12] Certain medical conditions, such as idiopathic hypercalciuria, and medications, like vitamin D supplements, can also lead to stone formation. [13,14]

2.1.4 Types of urinary tract stones and stone formation

2.1.4.1 Calcium stones

Calcium stones are the most common type of urinary tract stone seen in the general population. There are two types of calcium stones: calcium oxalate and calcium phosphate. Calcium oxalate is the most common type of stone, representing approximately 70% to 80% of those observed. They tend to occur in patients with lower urine volume, higher urine calcium excretion, higher urine oxalate excretion, and lower urine citrate excretion. Calcium phosphate is found in close to 15% of all urinary stones. They are known to form in alkaline urine ($pH \geqq 6.5$). [15]

2.1.4.2 Uric acid stones

Uric acid is present in about 8% of all analyzed urinary tract stones.

Uric acid stones are more likely to be seen in patients with purine-rich diets, patients suffering from diseases with high cell turnover, such as cancers and Paget's disease of the bone, or in patients taking immunosuppressant therapy for autoimmune diseases, such as lupus. [15,16]

2.1.4.3 Struvite stones

Struvite is seen in roughly 1% of urinary tract stones. Struvite stones are composed of magnesium ammonium phosphate. Due to their association with urinary tract infections, particularly urease-producing Proteus mirabilis, they are often called infection stones.[17] The urease enzyme typically increases the urinary pH above physiologic span (pH ≈ 8.5-9).[15,18] Staghorn calculi, branched stones that partially or completely fill the renal pelvis, are most commonly composed of struvite.[19] Staghorn calculi usually require surgical management.

2.1.4.4 Cystine stones

Cystine stones make up approximately 1% to 2 % of urinary tract stones, although their prevalence in the pediatric population appears to be higher. They occur in patients with a genetic disorder called cystinuria. [20]

2.1.5 Diagnosis and management of urinary tract stones

2.1.5.1 Diagnosis of urinary tract stones

To rule out infectious causes of stone formation, urine culture and urinalysis should be ordered. Imaging of the urinary tract by ultrasonography allows for visualization of a distended kidney and ureter in most cases, illustrating a distal ureteral blockage. Radiography, often known as a KUB (kidneys, ureters and bladder), is no longer the gold standard as some urinary tract stones are radiolucent or hidden by overlying bone structures, thus not appearing on radiographic imaging. [21,22]

2.1.5.2 Medical management

Conservative management of urinary tract stones consists of expulsive therapy, pain control and follow up imaging.[21]

2.1.5.2.1 Tamsulosin

Tamsulosin is an alpha-blocker. It is most often used in patients with benign prostate hyperplasia or prostatitis, as it is a very effective ureteral and urethral dilator. In patients with urinary tract stones, tamsulosin aids in the passage of stone >5mm and ≤10mm in diameter. The most common side effects of Tamsulosin are dizziness and orthostatic hypotension.[23]

2.1.5.2.2 Pain management

Acute renal colic mandates an appropriate pain management protocol. Non-steroidal anti-inflammatory drugs (NSAIDs) are the preferred drugs for pain management as they are effective and have a well-known and limited side effect profile. Ketorolac is the most commonly used NSAID for urolithiasis. If the pain is not controlled by NSAIDs, opioid administration is warranted. [3,21]

2.1.5.3 Surgical management

2.1.5.3.1 Ureteral catheterization

Ureteral catheterization, also known as ureteral stenting, is described by the placement of a hollow-lumen tube in the ureter, allowing passage of urine from the kidney to the bladder when there is present or anticipated obstruction of the ureter. This tube is often called a pigtail stent, JJ stent or double J stent as its extremities are coiled to allow for proper placement of the stent without possibility of movement. It is often used when there is bilateral ureteral obstruction, prophylactically before extracorporeal shockwave lithotripsy, or following ureterendoscopy.[24]

2.1.5.3.2 Pyelogram

Intravenous pyelography refers to a KUB radiograph taken before and after the intravenous administration of iodinated contrast. It is effective at detecting hydronephrosis, however is less effective at detecting the presence of stones when compared with non-contrast computed tomography and sonography.[11]

2.1.5.3.3 Cystoscopy and ureteroscopy

Cystoscopy refers to the visualization of the interior of the bladder by way of flexible or rigid endoscopy through the urethra.

Ureteroscopy refers to the visualization of the interior of the ureters via flexible endoscope. If a stone is visualized in the proximal ureter, it may be fragmented under direct visualization by holmium laser lithotripsy. The fragmentation of the stone allows for easier passage of smaller fragments. Ureteroscopy is the first-line treatment for urinary calculi requiring surgical removal.[25]

2.1.5.3.4 Nephrotomy and nephrostomy

Nephrotomy is described as a surgical incision into a kidney. Nephrostomy signifies an opening between the kidney and the skin. These percutaneous surgical techniques are reserved for larger impacted stones occupying the kidney or proximal ureter, such as staghorn calculi. [25]

2.1.5.3.5 Ultrasonic fragmentation of the calculi

Also known as extracorporeal shockwave lithotripsy, ultrasonic fragmentation of the calculi occurs when high-energy shock waves are transmitted through the body with aid of biplanar fluoroscopy. This energy fragments the stone, allowing for easier passage through the ureter. [26]

2.1.6 Adverse outcomes and complications of urinary tract stones

2.1.6.1 Urinary tract infections

Urinary tract infections (UTIs) are microbacterial infections that may occur in any part of the urinary tract. The term "UTI" encompasses asymptomatic bacteriuria, acute uncomplicated cystitis, recurrent cystitis, catheter-associated UTI, prostatitis, and pyelonephritis.[27] UTIs most commonly occur by bacteria ascending the urinary tract via the urethra. The most frequent microbial cause of UTIs is Escherichia coli. UTIs are more common in women due to their shorter urethra.[28] Although it is known that some urinary tract stones can be caused by urinary tract infections, such as Proteus mirabilis causing struvite stones,[17] the presence of an obstructing urinary tract stone can also lead to a UTI in patients. Urinary stasis secondary to obstruction by the stone can cause bacterial overgrowth and infection.[29]

2.1.6.2 Pyelonephritis

Pyelonephritis refers to an infection of the kidney and/or upper urinary tract. As in other UTIs, pyelonephritis is usually caused by ascending microbacteria via the ureters. It is considered to be a complicated UTI. It is known to cause systemic side effects such as fever, chills, nausea, and vomiting. Together, flank pain and costovertebral angle tenderness are usually indicative of pyelonephritis. [30]

2.1.6.3 Sepsis

By definition, sepsis is the body's extreme response to an infection. It is a life-threatening medical emergency. It is a chain reaction of symptoms occurring due to an infection. Sepsis can affect every organ system, leading to tachycardia, fever, confusion, shortness of breath, extreme pain or discomfort, and perspiration. [31] Septic shock refers to systemic shock caused by sepsis. Shock is a life-threatening emergency, caused by extreme hypotension and tachycardia.[32]

2.1.6.4 Hydroureter and hydronephrosis

When an obstruction blocks the passage of urine through the ureter, the urine builds up in the proximal ureter and renal pelvis. They consequently swell to accommodate the increased fluid volume. Swelling of the proximal ureter is called hydroureter and swelling of the kidney is called, hydronephrosis. These conditions can be a normal finding in pregnancy due to physiological compression of the ureters by the gravid uterus.[33]

2.1.6.5 Acute renal failure

Also known as acute kidney injury, acute renal failure is described as a sudden and reversible decline in the glomerular filtration rate (GFR). A decreased GFR leads to elevated levels of blood urea nitrogen, creatinine, and other metabolic waste products that are usually filtered by the kidney. [34]

2.2 Overview of pregnancy

2.2.1 Anatomical changes in pregnancy

As time goes by, the growing uterus takes increasingly more space in the abdomen. Although the elasticity of the abdominal musculature allows for outward growth of the anterior abdomen, the gravid uterus occupies a lot of space within the abdomen, thus producing mass effect on surrounding structures. Most notably, it may cause mechanical obstruction of the inferior vena cava and ureters, leading to increased pedal edema and dilated proximal ureters and renal pelvises.[35] Progressive uterine distention also leads to superior displacement of the diaphragm, causing decreased lung volumes and expansion. [36]

2.2.2 Physiologic changes in pregnancy

During gestation, the female body undergoes several changes to endure the metabolic and physiologic demands of the growing fetus. Among other modifications, blood volumes increase to maintain steady perfusion of the placenta, lungs increase alveolar ventilation to compensate for increased oxygen demand and reduced lung capacity, and renal blood flow increases, thus accelerating the GFR. [37]

2.2.3 Maternal complications of pregnancy

Complications of pregnancy may arise from preexisting conditions, or may develop during the gestational period (antepartum), during delivery (intrapartum), or after delivery (postpartum).

2.2.3.1 Antepartum complications

2.2.3.1.1 Gestational hypertension, preeclampsia, and eclampsia

Gestational hypertension is described as the development of hypertension (blood pressures over 140/90 mmHg on two occasions, at least 4 hours apart) after 20 weeks' gestation, in the absence of proteinuria or other criteria for preeclampsia.

Preeclampsia is a multiorgan diseases process consisting of hypertension with proteinuria or one of the following presenting after 20 weeks' gestation: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual symptoms. Preeclampsia is hypothesized to be caused by increased vascular resistance in the placental arteries due to failure of vascular remodeling. The increased vascular resistance leads to placental secretions of antiangiogenic factors in the maternal circulation resulting in widespread maternal vascular dysfunction.[38-40] Eclampsia is defined by the occurrence of new-onset, generalized, grand mal seizures or coma in a woman with preeclampsia or gestational hypertension.[41] These hypertensive disorders of pregnancy are associated with high risks of maternal and fetal morbidity and mortality.

2.2.3.1.2 Gestational diabetes mellitus

Pregnancy promotes insulin resistance via placental secretion of diabetogenic hormones, such as growth factor, prolactin, progesterone, etc. Gestational diabetes mellitus (GDM) develops in women whose pancreatic function is insufficient to overcome the insulin resistance associated with the pregnant state. Universal screening at 24 to 28 weeks' gestation helps diagnose GDM. This consists of performing a random glucose tolerance test on the mother.[42] GDM carries an increased risk of several complications for the mother and fetus. These include, but are not limited to, urinary tract infections, preeclampsia, preterm labor, abruptio placentae, postpartum uterine atony, stillbirth, and macrosomia.[43] The risk of developing overt diabetes mellitus after the pregnancy is elevated in women whom experience GDM during their pregnancy.[43,44]

2.2.3.1.3 Preterm premature rupture of membranes

Premature rupture of membranes (PROM) refers to membrane rupture before the onset of contractions. Preterm PROM (PPROM) indicates premature rupture of membranes occurring before the 37th week of gestation. The single most common identifiable risk factor for PPROM is genital tract infections. Delivery occurs within one week of membrane rupture in the majority of pregnancies. The lapse of time between the rupture of membranes and delivery is called the latency period. PPROM increases the risk for oligohydramnios and chorioamnionitis. [45,46]

2.2.3.1.4 Abruptio placentae

Abruptio placentae, also known as placental abruption, is known as the partial or complete detachment of the placenta prior to delivery. It is usually accompanied by vaginal bleeding, abdominal pain, uterine tenderness, and a nonreassuring fetal heart rate pattern. Placental abruption carries increased risks of both maternal and fetal morbidity and mortality. Risk factors include cigarette smoking, hypertensive disorders, and cocaine use. [47]

2.2.3.1.5 Placenta previa

Placenta previa refers to placental tissue that extends inferiorly and partially or completely covers the internal cervical os after 20 weeks' gestation. The most common symptom of placenta previa is vaginal bleeding. The most notable risk factor is previous cesarean delivery. Complications of placenta previa include maternal hemorrhage, amniotic fluid embolism, preterm delivery, and fetal anemia. [48]

2.2.3.2 Intrapartum complications

Intrapartum complications refer to issues that occur during delivery.

2.2.3.2.1 Chorioamnionitis

Chorioamnionitis, or intraamniotic infection, refers to inflammation of the placental membranes and chorion. This inflammation is most commonly caused by an ascending multibacterial infection in women with ruptured membranes. The most common clinical feature is the presence of fever. Other symptoms of infection are also commonly seen, such as tachycardia and leukocytosis. Chorioamnionitis should be treated with broad-spectrum antibiotics and delivery to prevent further sequelae to the mother and fetus. These include maternal sepsis, maternal coagulopathy, fetal/neonatal death, fetal sepsis, fetal neurodevelopmental disabilities, and cerebral palsy. Prophylactic antibiotics can be given to women with PPROM to reduce the risk of clinical chorioamnionitis. [49]

2.2.3.2.2 Cesarean delivery

Although it is most often associated with breech fetal presentation and cephalopelvic disproportion, cesarean delivery is often required to avoid delays in maternal or neonatal treatment in severe complications. Cesarean delivery, also known as cesarean section or c-section, is a surgical procedure whereby an incision is made, most often transversely over the lower uterine segment (Pfannenstiel incision), and extended through the abdominal wall in efforts to expose the anterior uterine wall. A hysterotomy incision is then made through the anterior uterus until the fetus can be seen and extracted and given to another clinician. The placenta is then extracted using gentle traction. Once the placenta is removed, the uterus is exteriorized and closed. Prior to closure of the abdominal wall, the abdominal cavity is inspected to ensure hemostasis. C-section is one of the most common surgical procedures performed in the United States. It can also be requested electively. [50,51]

2.2.3.2.3 Instrumental delivery

Instrumental delivery refers to the use of forceps, a vacuum, or other devices to aid in the delivery of a fetus. These devices are usually employed during vaginal deliveries, however are also rarely used in cesarean deliveries when the fetal head is deeply engaged.[52,53]

2.2.3.3 Postpartum complications

Postpartum complications are issues that occur in the mother after the delivery of the neonate.

2.2.3.3.1 Postpartum hemorrhage

Postpartum hemorrhage is a blood loss of over 1000mL during or after delivery, resulting in maternal hypovolemia. It is most commonly caused by uterine atony, but can also be related to trauma during c-sections, placenta accreta, or maternal bleeding disorders. Uterine atony can be idiopathic or secondary to retained products of conception (POCs). Mild cases can be treated with uterine massage, intrauterine balloon tamponade, and/or oxytocin, whereas some severe cases require manual extraction of the POCs, transfusion of blood and blood products, or hysterectomy. [54]

2.2.3.3.2 Venous thromboembolism

Venous thromboembolism (VTE) refers to the formation of a blood clot, also known as a thrombus, in the deep veins of the lower extremities. The most common cause of VTE in pregnant patients is the rise of estrogens, leading to a hypercoagulable state. These thrombi are at elevated risk of dislodging from their location and travelling through the blood vessels. When this occurs, it is known as an embolus. The embolus most commonly lodges in the small pulmonary blood vessels, giving rise to a pulmonary embolism. VTEs are considered the most common cause of maternal death. [55,56]

2.2.3.3.3 Maternal mortality

Maternal mortality encompasses all deaths related to or aggravated by a pregnancy, occurring during the pregnancy, during delivery, or up to 42 days postpartum. Although maternal mortality rates have been declining worldwide, they have been rising in the United States since the start of the 21st century. Circumstances leading to most maternal deaths are typically multifactorial. [57,58]

2.2.4 Neonatal complications of pregnancy

Throughout gestation, a multitude of factors can compromise the development of the fetus. These factors can be intrinsic – directly related to the fetal development, such as placental insufficiency – or extrinsic – indirectly related to the fetal development, such as trauma. Repercussions can include anatomical abnormalities, growth delays, premature delivery, and fetal death.

2.2.4.1 Congenital anomalies

Congenital anomalies refer to structural abnormalities that occur during fetal development. These anatomical malformations can have medical, surgical and/or cosmetic impact on the neonate's life. They can occur individually or in combination with other anomalies to create a syndrome.[59]

2.2.4.2 Intrauterine growth restriction

Intrauterine growth restriction (IUGR) describes a fetus that has not reached its growth potential due to environmental factors. Causes for IUGR can stem from the mother, the placenta, the fetus itself, or a combination. It is defined by an estimated fetal weight below the 10th percentile for gestation age measure via sonography. Fetal growth restriction can be symmetric, affecting all of the organs proportionally, or asymmetric. Anatomic symmetry is assessed by evaluating multiple anatomical fetal measurements during routine gestational ultrasounds. [60]

2.2.4.3 Intrauterine fetal death

Intrauterine fetal death (IUFD) refers to the demise of the fetus after 20 weeks gestation. It is usually synonymous with the term stillbirth, which refers to the birth of a neonate that has already died. It can be due to maternal, fetal or placental causes.[61]

2.2.4.4 Preterm birth

Preterm birth (PTB) refers to the delivery of a neonate between 20- and 37-weeks' gestation. A delivery before 20 weeks gestation is considered a miscarriage. There are many risk factors that may influence the initiation of preterm labor, including premature rupture of membranes, placenta previa, cervical incompetence, etc. A prior history of these risk factors, or history of prior spontaneous PTBs, increases the risk of recurrence in subsequent pregnancies. High-risk pregnancy specialists typically follow women with prior severe PTB. [62]

2.3 Overview of urinary tract stones in pregnancy

The physiological changes in pregnancy can increase the risk of stone formation in the renal pelvis. [8]

2.3.1 Prevalence

Urinary tract stones occur in 8 per 1,000 pregnancies.[7] Up to 90% of cases occur in the second or third trimester.[8] They occur more commonly in White, non-Hispanic women, when compared to black and Hispanic women. [8,7]

2.3.2 Current management guidelines

Current guidelines from the American Urology Association and the European Association of Urology suggest using conservative management, such as pain control, observation, and supportive therapy as first-line treatment for pregnant patients with urinary tract stones.[63,64] The main goal is to aid in spontaneous passage of the stone. If necessary, some interventions may be performed, such as ureteroscopy, but are reserved for stones refractory to conservative care. Pain management is also important, as the added stress can precipitate preterm labor.[8]

CHAPTER 3: RATIONALE, OBJECTIVES AND HYPOTHESES

Although urinary tract stones are a very common occurrence in the general population, they are quite rare in pregnant patients.[65] Existing research tends to focus on management and outcomes in the mother, however there is little literature comparing the clinical presentation and inpatient management in pregnant patients, compared to non-pregnant patients. Also, there is a paucity of literature focused on neonatal outcomes. [8,66-70] Common findings from publications studying urolithiasis in pregnant patients show an increased risk of preterm labor[71-73], however other studies refute this association[74-76].

In North America, most cases of urolithiasis are treated in an outpatient setting.[77] While medical management is the mainstay of urinary calculi treatment, invasive procedures have been seen to be useful and necessary in some cases.[11] However, in the pregnant population, invasive procedures carry risks of labor induction and harm to the growing fetus.[78] Based on an interpretation of existing literature, we hypothesize that pregnant women have a more difficult disease course compared to their non-pregnant counterparts, and that urinary tract stones pose a considerable risk of preterm labor and delivery, as well as increase the risk of adverse neonatal outcomes. Being able to identify common management trends can aid in generating clinical guidelines for care of future patients. Furthermore, recognition of notable maternal and fetal risks in these patients will help increase physician awareness of this rare complication, and hopefully promote a higher level of suspicion when these patients present with possible urinary calculi symptoms. The potential for this research is to improve patient management and negative maternal and fetal outcomes.

Therefore, the objectives of this thesis are as follows:

1. To compare the clinical presentation, inpatient procedure rates, and length of hospital stay, as well as to identify associated clinical conditions of urolithiasis in pregnancy.
2. To identify the incidence of urolithiasis in pregnancy, as well as to compare maternal and fetal outcomes of urinary tract stones with pregnancies not affected by urinary tract stones.

These objectives were addressed by conducting two separate retrospective cohort studies. In this thesis, the findings of these analyses are presented as two manuscripts with a linking chapter.

CHAPTER 4: CLINICAL PRESENTATION AND MANAGEMENT OF NEPHROLITHIASIS IN THE PREGNANT PATIENT: A MATCHED COHORT STUDY

The following chapter presents the methods and results of objective one: To compare the clinical presentation, inpatient procedure rates, and length of hospital stay, as well as to identify associated clinical conditions of urolithiasis in pregnancy.

The topic presented in this manuscript will be introduced with some background information. The methods will cover comprehensive details on the study population and statistical methods used. Results are described in detail and a thorough discussion provides critical information as well as study limitations and future implications.

Clinical Presentation and Management of Urolithiasis in the Obstetric Patient: A Matched Cohort Study

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4.1 Abstract

Background: Urolithiasis is a common medical condition in pregnancy, but little is known about the clinical presentation and management of this condition in pregnant patients.

Objective: To compare the clinical presentation, inpatient procedure rates, and length of hospital stay, as well as to identify associated clinical conditions of urolithiasis in pregnancy.

Study Design: A cohort of pregnant women was identified within the Healthcare Cost and Utilization Project — Nationwide Inpatient Sample database from 1999 to October 1st, 2015. ICD-9-CM coding was used to identify women diagnosed with urolithiasis within the cohort. A comparison group of non-pregnant women was identified within the cohort and age- matched (1:1) to the pregnant women.

Results: A cohort of 42,113 pregnant patients was identified to have urolithiasis, which were age-matched to 42,113 non-pregnant female patients. Overall baseline characteristics were mostly similar between both groups, except in regards to income, insurance type and weight. Pregnant patients tended to have higher income, more likely to be insured with Medicaid or private insurance, and were less likely to be obese. Pregnant patients were less likely to present with classic clinical symptoms of urinary tract stones, such as flank pain, OR 0.63, 95% CI 0.56-0.70 and fever, 0.22 (0.16-0.30). Pregnant patients were more likely to have hospital stays of 3 days or more, when

compared to the non-pregnant population, 1.07 (1.02-1.12). The non-pregnant patients were more commonly affected by infectious conditions, namely urinary tract infections, 0.56 (0.53-0.59), sepsis, 0.17 (0.14-0.20), and pyelonephritis, 0.34 (0.36-0.44). All invasive and surgical procedures were more frequently practiced in the non-pregnant group.

Conclusion: Pregnant women with urolithiasis were observed to have fewer symptoms, complications, and procedure rates. We hypothesize that pregnant women with urinary tract stones who are admitted to the hospital have a milder disease course than non-pregnant women with stones who are also admitted to the hospital. Due to the pregnancy, further observation is probably warranted leading to longer hospital admissions.

Keywords: Urolithiasis, urinary tract stones, pregnancy, peripartum

4.2 Introduction

Urolithiasis or "urinary tract stones" is a relatively common condition occurring in an estimated 8.8% of the general U.S. population.[1] The prevalence of stones among men and women is 10.6% and 7.1%, respectively. Among those presenting to the emergency room with abdominal pain, 12% are admitted for observation or stone removal.[2] Although not commonly thought of as a complication of pregnancy, a cohort study by Sohlberg et al. concluded that urinary stones complicate 8 in 1000 deliveries.[3] Additionally, a study published by Blanco et al. recognized renal colic as one of the most common non-obstetric reasons for hospital admission in pregnancy.[4] Although such previous studies exist, there is still a lack of knowledge on the clinical presentation and management of urinary tract stones in the obstetric patient, and how these differ from non-pregnant women. The objectives of this study are to compare the clinical presentation and management of urolithiasis in pregnant women with non-pregnant age-matched women in a population-based setting.

4.3 Materials and Methods

4.3.1 Data source

The objectives of this study were achieved using the Healthcare Cost and Utilization Project (HCUP), the largest comprehensive source for inpatient hospital care data in the United States.[5] The HCUP databases adhere to the Health Insurance Portability and Accountability Act (HIPAA) privacy rule, which protects the health care information of Americans. The National Inpatient Sample (NIS) is one of HCUP's nationwide databases and it is the largest publicly accessible all-payer inpatient health care database in the United States. It contains roughly 20% of all inpatient admissions, and excludes rehabilitation hospitals, long-term acute care hospitals, Veteran Affairs hospitals, and other Federal hospitals.[6] The Clinical Classifications Software (CCS) is based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), which itself is a uniform and systematized coding system.

4.3.2 Study Population

Utilizing the HCUP-NIS database, we identified a cohort of women, all of childbearing age (12-51 years old), who had been admitted for urinary tract stones (ICD-9 code 592.X) between 1999 and September 30, 2015, inclusively. Data from October 1 to December 31, 2015 were excluded from this study as the NIS changed their coding system from ICD-9 to ICD-10 on October 1, 2015. The ICD-9 code we used for urinary tract stones is in concordance with other publications studying urolithiasis, such as Nowfar et al.[7] Within the identified dataset, we isolated a group of women whom were known to be pregnant at time of admission by using the ICD-9 codes for pregnancy and delivery (diagnosis codes V22.xx, V23.xx, V27.xx, 634.xx-679.xx, and procedure codes 72.xx-75.xx). This set of codes for the identification of pregnant women represents an algorithm used in many publications, such as Hoang et al.[8] and Nolan et al.[9] This search yielded a total of 573,342 women admitted for urinary tract stones. Of these women, 46,982 were known pregnant at the time of admission. These women were then age-matched at a 1:1 ratio with the remaining 526,360 non-pregnant women admitted with urolithiasis using 5-year age intervals, thus resulting in a cohort of 42,113 pregnancies complicated by urinary stones with 42,113 non-pregnant controls. Additional matching criteria were not applied to allow for a larger cohort, and thus a higher statistical power for this study

4.3.3 Statistical analysis

Our analysis consisted of several steps. First, we compared the frequency of baseline characteristics of study subjects by pregnancy status. The variables of interest were as follows: age (<25, 25-34, ≥35), race (Caucasian, African American, Hispanic, and other), median household income (quartiles), insurance type (Medicare, Medicaid, private, and other), and hospital type (rural, urban non-teaching, and urban teaching). We also considered obesity (obese [BMI 30-34.9kg/m^2], and morbidly obese [BMI 35+kg/m^2]) and smoking status (Yes/No). Weight at admission and smoking status were assessed using ICD-9 codes. Associated variables evaluated included urinary tract infection (ICD-9 codes 599.0, V13.03, 590.x), sepsis (995.91, 038.9), pyelonephritis (590.10), hydronephrosis and/or hydroureter (593.5, 591), and acute renal failure (584.9). Presenting symptoms that were compared in the two groups were as follows: flank pain (788.0, 789.0), hematuria (599.7x), fever (780.6x), dysuria (788.1), urination frequency/urgency (788.4x), and nausea and/or vomiting (787.01-787.02). The interventions / procedures evaluated were identified using the respective ICD-9 procedural codes including: ureteral catheterization (59.8), pyelography (87.4, 87.73, 87.75), cystoscopy (57.32), ureteroscopy (56.31), nephrotomy with or without fragmentation (55.01, 55.03, 55.04), nephrostomy (55.02), ultrasonic fragmentation of urinary calculi (98.51, 59.95), and imaging by computed tomography (CT scan) (88.38, 88.01). Conditional logistic regression models adjusting for baseline characteristics were created to estimate the adjusted effect of pregnancy on presenting symptoms, interventions, and length of hospital stay.

Since this study used only de-identified publicly available data, institutional review was not necessary per the 2010 Tri-Council Policy statement. All analyses were carried out using the statistical software package SAS Enterprise Guide 6.1 (Cary, NC, USA).

4.4 Results

The baseline characteristics of pregnant and non-pregnant women with urinary tract stones are summarized in Table 1. In both groups, Caucasians represented the majority of patients, with frequencies of 71.6% in the pregnant group and 70.5% in the non-pregnant group. Pregnant patients tended to have a higher median household income than their non-pregnant counterparts. This corresponds with pregnant patients also having higher rates of private insurance (55.4% vs 49.0%). Both groups had similar distributions in terms of treatment location, with the majority of treatments occurring in urban hospitals. Non-pregnant women were more likely to be obese and to smoke.

Clinical presentations differed between both groups. Overall, pregnant women were statistically less likely to experience symptoms associated with urinary tract stones than were non-pregnant women, as seen in Table 2. As shown in Table 3, pregnant women tended to have longer hospital stays than the non-pregnant group (OR 1.07, 95% Confidence interval 1.02-1.12).

Common comorbidities and associated diagnoses are presented in Table 4. Pregnant patients had lower risks of infectious conditions, such as urinary tract infections (OR 0.56, 95% CI 0.53-0.59), sepsis (OR 0.17, 95% CI 0.14-0.20), and pyelonephritis (OR 0.34, 95% CI 0.36-0.44) than non-pregnant patients. There was an indication that pregnant women may be more likely to experience hydronephrosis or hydroureter (OR 1.01, 95% CI 0.96-1.06); however, upon adjusting for baseline characteristics, statistical significance was lost. The pregnant group also had much lower risk of acute renal failure (OR 0.13, 95% CI 0.10-0.17).

Lastly, Table 5 shows the procedures received by each group. Pregnant women were less likely to receive any intervention for urolithiasis than non-pregnant women.

4.5 Discussion

The objective of this study was to evaluate the inpatient presentation and management of urolithiasis in pregnant patients compared with women whom were not pregnant at the time of disease. Using data from the HCUP-NIS database from 1999-2015, we conducted an age-matched cohort study to compare the clinical presentation, presence of comorbidities, inpatient procedure rates, and length of hospital stay of pregnant and non-pregnant women with urinary stones.

We observed that the baseline characteristics were fairly consistent between the two groups. Both pregnant and non-pregnant women had similar frequencies in relation to race and hospital type/location. Disparities between pregnant and non-pregnant women were observed in terms of income, insurance types, and obesity.   Specifically, pregnant patients tended to have higher household incomes, higher rates of Medicaid and private insurance, and were less likely to be obese or to smoke.

When comparing clinical presentations in our cohort, pregnant patients were less likely to present with the classic urinary calculi symptoms of flank pain and fever. Pregnant patients were also statistically less likely to present with symptoms of, dysuria, frequency/urgency of urination and nausea and/or vomiting. We hypothesize that pregnant women are more attuned to their symptoms, which leads them to seek prompt medical advice in order to avoid potential complications of pregnancy. Also, pregnant women regularly visit their obstetricians and/or family physicians for perinatal care, which would allow for quicker consultations, referrals, and admissions, when compared to non-pregnant women whom do not see their physicians as frequently. It is also likely that the threshold for admission to hospital is lower among pregnant women thereby explaining the overall milder symptomatology and lower intervention rate in the pregnant cohort compared with non-pregnant women. In turn, as urinary tract stones are usually treated in the outpatient setting, the non-pregnant women who require admission are likely to have a more severe disease.

Pregnant patients tend to have longer hospital stays compared to non-pregnant women. Pregnant patients were more likely to be admitted to the hospital for 3 days or more, whereas their non-pregnant counterparts were more commonly admitted for less than 3 days. Typically, uncomplicated urinary calculi are often treated in the outpatient setting. However, we hypothesize that due to their pregnant status, these women are required to undergo further observation to avoid complications to the pregnancy. Also, the prolonged hospital stay in the pregnant cohort can be due to pregnancy-related issues in some patients, such as induction, delivery, and post-partum complications not associated with their urinary calculi.

Similarly, our study results showed that pregnant patients were less likely to develop infectious conditions associated with their urolithiasis, such as urinary tract infections, sepsis, and pyelonephritis, than non-pregnant women. Also, the pregnant patients were much less likely to develop acute renal failure compared to their non-pregnant counterparts. As previously mentioned, earlier diagnosis in pregnant patients can lead to more prompt management of urinary tract stones, and thus, diminish the risk for complications.[10] Hydronephrosis and/or hydroureter, however, were more common in the pregnant group versus the non-pregnant group, although the adjusted association was not statistically significant. This latter association may in in part be explained by the physiologic effect of hydronephrosis and hydroureter seen in pregnancy given the effect of the gravid uterus / mass effect in the abdomen resulting in distal obstruction of the ureters. [11]

Overall, we observed that pregnant patients underwent less surgical interventions. These procedures, including ureteral catheterization, cystoscopy, pyelography and invasive surgical interventions, were most commonly conducted in the non-pregnant group. We were unable to identify any North American clinical practice guidelines for urolithiasis in pregnant patients, but observed multiple recommendations from previous publications. Based on our study results, we hypothesize that physicians attempted to abstain from such procedures in the pregnant population to avoid provoking complications to the pregnancy, including fetal loss, prematurity, and surgery-induced delivery.[12] We also stipulate that, considering the physiological ureteral dilation in pregnant patients, the reduction in surgical interventions can be caused by a higher rate of spontaneous passage of the stone.[13] However, Meria et al. theorized that this observed higher rate of spontaneous stone passage among pregnant women may be biased because surgeons would likely be reluctant to operate on pregnant women and instead, would recommend them for a trial of passage.[14] Furthermore, as already stated, prompt diagnosis and management should lead to a decreased risk of complications, and thus, a concomitant decreased need for surgical interventions.

Our study has some limitations. For instance, some variables of interest were not available as our study was retrospective in design and it was based on an established dataset. In particular, data regarding gestational age at the time of diagnosis with urinary tract stones in the pregnant group and long-term patient outcomes do not exist in the HCUP-NIS database. It would have been interesting to observe the relationship between gestational age at admission, length of hospital stay, frequencies of comorbidities, and procedural rates. Furthermore, the dataset lacks information regarding emergency room and outpatient consultations, which would have been important data to have since most cases of urinary stones are managed expectantly in an outpatient setting.[15] In the absence of such information, we must assume that the non-pregnant comparison group had reasonable cause for admission, and were thus already very sick. Additionally, information on stone composition was not available for study. It would have been interesting to compare with a study by Ross et al., which states that pregnant women are more likely to create hydroxyapatite/calcium phosphate stones.[16] Lastly, the potential over-documentation in pregnant patients may lead to an overestimation of the odds ratios presented in this study. However, since this study focuses solely on hospital admissions, it is less likely that symptoms would be recorded differentially between pregnant patients and non-pregnant patients. In spite of these limitations, our study possessed several strengths. To our knowledge, this is the first major population-based study comparing the disease course of urinary tract stones in age-matched pregnant and non-pregnant patients. It is also the largest comparative study on this very common medical condition to date. The large, population-based nature of the HCUP-NIS dataset renders our results generalizable to the greater North American population of individuals who have been admitted to the hospital for urolithiasis**.** The HCUP-NIS dataset also contained a vast amount of baseline demographic and clinical information; hence, allowing us to adjust models for potential confounding. Furthermore, the ICD-9 codes used to isolate patients with urolithiasis (592.X) is in concordance with other studies reporting on urinary tract stones in different subsets of patients, such as Abbott et al. [17]

4.6 Conclusion

Urinary tract stones are not uncommon in pregnancy, as the normal physiologic changes characteristic of pregnancy can be precipitating risk factors for stone formation. However, increased vigilance, heightened awareness of symptoms, as well as, frequent and regular medical consultations for perinatal care can allow for earlier diagnosis and prompt management of urinary calculi in pregnant patients. Hence, pregnant women with urolithiasis tend to have a milder disease course than their non-pregnant counterparts. We recommend maintaining current clinical standards in this patient population, such as increased trials of passage and heightened awareness of urolithiasis in pregnant patients.

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4.8 Tables

Table 1: Baseline Demographic and Patient Characteristics By Pregnancy Group		
Baseline Characteristics	Pregnant N=42,113 (%)	Not Pregnant N=42,113 (%)
Age*		
<25	33.22	33.22
25-34	54.66	54.66
35+	12.12	12.12
Race		
Caucasian	71.59	70.54
African American	6.21	8.39
Hispanic	16.41	16.02
Other	5.79	5.05
Income Quartile		
Q1	24.54	30.31
Q2	25.71	27.92
Q3	25.97	23.99
Q4	23.79	17.78
Insurance Type		
Medicare	0.85	3.58
Medicaid	37.31	28.11
Private	55.35	49.04
Other	6.49	19.27
Hospital Location/Teaching		
Rural	12.71	16.02
Urban Non-Teaching	40.33	42.55
Urban Teaching	46.96	41.43
Obesity		
Obese	1.72	5.72
Morbidly Obese	0.71	2.84
Smoker	7.67	18.36
Pregnant and non-pregnant patients were matched by age 1:1.		

Table 2: Presenting Symptoms by Pregnancy group

Symptoms of Urinary Calculi	Pregnant N=42,113 (%)	Not Pregnant N=42,113 (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	P-Value
Flank Pain	3.77	6.09	0.60 (0.57 –0.64)	0.63 (0.56 – 0.70)	<0.01
Hematuria	4.82	5.14	0.94 (0.88 –1.00)	0.99 (0.89 – 1.11)	NS
Fever	0.35	1.43	0.24 (0.20 – 0.29)	0.22 (0.16 – 0.30)	<0.01
Dysuria	0.23	0.34	0.67 (0.52 – 0.87)	0.55 (0.34 – 0.90)	<0.05
Frequency/Urgency	0.12	0.24	0.50 (0.36 – 0.71)	0.20 (0.08 – 0.51)	<0.01
Nausea and/or Vomiting	1.11	4.63	0.23 (0.21 – 0.26)	0.23 (0.19 – 0.28)	<0.01

*Adjusted for baseline characteristics: Race, income, insurance type, hospital location, weight class, and smoking status

Abbreviation: NS, not statistically significant

Table 3: Length of Hospital Stay by Pregnancy Group					
Length of stay	Pregnant N=42,113 (%)	Not Pregnant N=42,113 (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	p-value
Less than 3 days	58.46	60.04	1.0 (Ref.)	1.0 (Ref.)	< 0.01
3 days or more	41.54	39.96	1.07 (1.04 – 1.10)	1.07 (1.02 – 1.12)	

*Adjusted for baseline characteristics: Race, income, insurance type, hospital location, weight class, and smoking status

Table 4: Associated Conditions and Comorbidities by Pregnancy Group					
Comorbidities and associated diagnoses	Pregnant N=42,113 (%)	Not Pregnant N=42,113 (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	P-Value
Infectious conditions					
Urinary tract infection	27.67	39.23	0.59 (0.57 – 0.61)	0.56 (0.53 – 0.59)	<0.01
Sepsis	1.04	5.63	0.18 (0.16 – 0.19)	0.17 (0.14 – 0.20)	<0.01
Pyelonephritis	4.29	9.46	0.43 (0.41 – 0.46)	0.40 (0.36 – 0.44)	<0.01
Renal Pathology					
Hydronephrosis and/or hydroureter	38.70	36.44	1.10 (1.07 – 1.13)	1.01 (0.96 – 1.06)	NS
Acute renal failure	0.45	2.83	0.16 (0.13 – 0.18)	0.13 (0.10 – 0.17)	<0.01

*Adjusted for baseline characteristics: Race, income, insurance type, hospital location, weight class, and smoking status

Abbreviation: NS, not statistically significant

Table 5: Interventions and Procedures by Pregnancy Group					
Procedures	Pregnant N=42,113 (%)	Not Pregnant N=42,113 (%)	Unadjusted OR (95% CI)	Adjusted OR* (95%CI)	p-Value
Ureteral catheterization	16.08	36.86	0.33 (0.32 – 0.34)	0.31 (0.29 – 0.33)	<0.01
Pyelogram	6.72	23.66	0.23 (0.22 – 0.24)	0.22 (0.20 – 0.24)	<0.01
Cystoscopy	5.14	9.87	0.5 (0.47 – 0.52)	0.50 (0.45 – 0.55)	<0.01
Ureteroscopy	1.91	7.00	0.26 (0.24 – 0.28)	0.26 (0.23 – 0.30)	<0.01
Nephrotomy w/ or w/o fragmentation	1.97	5.85	0.32 (0.30 – 0.35)	0.33 (0.28 – 0.38)	<0.01
Nephrostomy	0.25	0.39	0.65 (0.51 – 0.83)	0.62 (0.38 – 1.01)	NS
Ultrasonic fragmentation of calculi	0.45	0.30	0.12 (0.10 – 0.14)	0.12 (0.09 – 0.16)	<0.01
CT scan	0 .42	3.11	0.13 (0.11 – 0.15)	0.13 (0.10 – 0.18)	<0.01

*Adjusted for baseline characteristics: Race, income, insurance type, hospital location, weight class, and smoking status

Abbreviations: CT scan, computerized tomography scan; NS, not statistically significant.

CHAPTER 5: PREFACE TO MANUSCRIPT II

The previous chapter aimed to investigate and analyze the differences in inpatient care of women with urolithiasis based on pregnancy status. The overall findings showed that pregnant women tend to have a milder disease course when compared to age-matched non-pregnant women. Heightened awareness of symptoms, regular consultations with a physician and increased vigilance allow for earlier diagnosis and management of urinary tract stones in the pregnant population, which in addition to preference for conservative management, lead to decreased rates of surgical interventions.

The next chapter aims to identify the incidence of urolithiasis in pregnancy, as well as compare maternal and neonatal outcomes of pregnancies complicated by urolithiasis with pregnancies not complicated by urolithiasis. Specifically, information on frequencies of adverse obstetrical outcomes, in addition to maternal and fetal morbidity and mortality, will be studied in this pregnancy cohort.

CHAPTER 6: MATERNAL AND FETAL OUTCOMES OF UROLITHIASIS: A RETROSPECTIVE COHORT STUDY

The following chapter present the methods and results of objective 2, which is to identify the incidence of urolithiasis in pregnancy, as well as to compare maternal and fetal outcomes of urinary tract stones with pregnancies not affected by urinary tract stones.

The topic presented in this manuscript will be introduced with some background information. The methods will cover comprehensive details on the study population and statistical methods used. Results are described in detail and a thorough discussion provides critical information as well as study limitations and future implications.

Maternal and Fetal Outcomes of Urolithiasis: A Retrospective Cohort Study

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6.1 Abstract

Background: Although urolithiasis is relatively common in the general population, there is limited information on this condition available in the pregnant population.

Objective: The objectives of this study are to identify the incidence of urolithiasis in pregnancy, as well as to compare maternal and fetal outcomes associated with urolithiasis in pregnancy.

Study Design: Using the United States' Healthcare Cost and Utilization Project-Nationwide Inpatient Sample database, a population-based retrospective cohort study consisting of pregnant women who delivered between 1999 and 2015 was conducted. ICD-9-CM code 592.X was used to identify pregnant women with urolithiasis within the cohort, with pregnant women without urolithiasis forming the comparison group. Unconditional logistic regression models were used to estimate the associations between urolithiasis in pregnancy and maternal and neonatal outcomes, while adjusting for baseline maternal characteristics.

Results: A cohort of 13,792,544 pregnant women was identified, of which 11,528 had a urolithiasis-related admission during pregnancy, for an overall incidence of 8.3 per 10,000 pregnancies. Women with urolithiasis had a greater risk of developing preeclampsia/eclampsia, OR 1.35(95% CI 1.24-1.47), gestational diabetes, 1.29(1.20-1.30), abruptio placenta, 1.41(1.22-1.64), placenta previa, 1.55(1.27-1.90), pyelonephritis, 88.87(81.69-96.69), venous thromboembolism, 1.65(1.23-2.22), and more likely to deliver by cesarean, 1.20(1.15-1.25). As well, maternal death was also more common among these women, 2.85 (1.07-7.60). Congenital anomalies, 2.84(2.43-3.31) and prematurity, 1.92(1.82-2.03) were more commonly found among babies born to women with urolithiasis.

Conclusion: Although the mechanism is unclear, women with urolithiasis in pregnancy have an increased risk of adverse pregnancy and newborn outcomes.

Keywords: Kidney stones; Urolithiasis; Nephrolithiasis; Renal Calculi; Peripartum; Pregnancy

6.2 Introduction

In a study spanning three decades, women of reproductive age, between the ages of 18 and 39 were found to have the highest rates of confirmed symptomatic urolithiasis. [1] Although there are discrepancies between studies, the current literature suggests a correlation between urolithiasis in pregnancy and maternal complications, most commonly gestational diabetes and preeclampsia.[2-4] Further, there are many inconsistencies in findings pertaining to associations between maternal urolithiasis and fetal outcomes. For instance, some studies have observed a relationship between maternal urolithiasis and preterm delivery,[3-10] other studies contradict this association.[2,8,11] Also, this study excluded anomalous gestations, which have been noted in other similar studies, such as Banhidy et al.[11] Overall, population-based data on maternal and fetal outcomes of pregnancies complicated by urolithiasis remains scarce. The objectives of this study are to evaluate the incidence of urolithiasis in pregnancy, as well as to examine the maternal and fetal outcomes of urolithiasis.

6.3 Materials and Methods

6.3.1 Data source

Data from the Healthcare Cost and Utility Project-National Inpatient Sample (HCUP-NIS) were used to conduct a retrospective cohort study. Per the 2010 Tri-Council Policy statement, institutional ethics approval was not necessary as only de-identified publicly available data was used for this study. The National Inpatient Sample (NIS), which is maintained by the Health Care and Utilization Project (HCUP), is a publicly accessible all-payer inpatient health care database set in the United States.[12] It contains approximately

20% of all inpatient admissions, excluding rehabilitations and long-term hospitalizations. HCUP adheres to the Health Insurance Portability and Accountability Act (HIPAA) privacy rule, which protects the health care information of Americans. The Clinical Classifications Software (CCS) is based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), which is a uniform and systematized coding system.

6.3.2 Study Population

Within the HCUP-NIS, we used the following ICD-9 codes for pregnancy and delivery to identify a cohort of women who delivered between 1999 and 2015: diagnosis codes V22.xx, V23.xx, V27.xx, 634.xx-679.xx, and procedure codes 72.xx-75.xx. Due to a change in the NIS coding system from ICD-9 to ICD-10 on October 1, 2015, data from October to December 2015 were excluded from this study. Then, in concordance with similar studies on urolithiasis, such as Abbott et al., the ICD-9 code for urolithiasis (592.X) was used to identify deliveries complicated by a urolithiasis admission.[13] The remaining delivery admissions, not complicated by urolithiasis, formed the comparison group.

6.3.3 Statistical analysis

Initially, the annual incidence of urolithiasis in pregnancy over the study period was calculated. For each group, we determined the frequencies of baseline maternal demographic characteristics (age, race, median household income (quartiles), insurance type, and hospital type) and risk factors for urolithiasis (pre-existing diabetes, hypertension, smoking status, and obesity). A priori, based on medical knowledge, it was decided to adjust models for the baseline maternal demographic characteristics and co-morbidities seen in Table 1, as they were considered potential confounders. Subsequently, we used unconditional logistic regression models to estimate the effect of urolithiasis in pregnancy and maternal and neonatal outcomes. Specifically, we evaluated the association on gestational hypertension (ICD-9 code 642.3), preeclampsia/eclampsia (642.4-642.6), gestational diabetes mellitus (648.8), preterm premature rupture of membranes (658.1), abruptio placentae (641.2), placenta previa (641.0, 641.1), chorioamnionitis (658.4), cesarean delivery (763.4), instrumental delivery (669.5, 763.2, 763.3), postpartum hemorrhage (666.xx, 641.x), pyelonephritis (590.1, 590.8, 590.9), venous thromboembolism (V12.51, 453.xx, 671.4), maternal death (761.6), congenital anomalies (740.xx-759.xx), intrauterine fetal growth restriction (ICD-9 code 764.9, 632), intrauterine fetal death (656.4), and preterm delivery (644.2). The associations are presented as adjusted odds ratios (ORs), with 95% confidence interval (CIs).

All analyses were achieved using the statistical software package SAS Enterprise Guide 6.1 (Cary, NC, USA).[14] P-values <0.05 were considered statistically significant.

6.4 Results

Our cohort consisted of 13,792,544 deliveries, of which 11,528 were complicated by urolithiasis. As shown in Figure 1, the incidence of urolithiasis admissions in pregnancy rose between 1999 and 2015. Specifically, the incidence increased from 5.3 per 10,000 deliveries in 1999 to 10.2 per 10,000 deliveries in 2015 ($p < 0.0001$), resulting in an overall incidence of urolithiasis related admissions in pregnancy of 8.3 per 10,000 deliveries during the study period.

The basic characteristics of the cohort are tabulated in Table 1. The majority of pregnant women admitted for urolithiasis were 25 years old of age or older (69.5%). They were most commonly Caucasian, privately insured, and treated in urban teaching hospitals. Both groups had similar disparities in income. The pregnant women admitted for urolithiasis were more likely to smoke and to be obese.

The results of the regression analyses of maternal complications of urolithiasis are summarized in Table 2. Pregnancies with urolithiasis were more likely to be associated with preeclampsia/eclampsia, gestational diabetes, abruptio placenta, and placenta previa. They were also more likely to undergo cesarean deliveries and, likewise, they were less likely to undergo instrumental deliveries. Pregnant women with urolithiasis were at greater risk of experiencing certain postpartum complications, such as pyelonephritis, venous thromboembolism, and maternal death.

Neonatal outcomes of maternal urolithiasis in pregnancy are listed in Table 3. Pregnancies complicated by urolithiasis were more commonly associated with congenital abnormalities and preterm birth when compared to pregnancies not complicated by stones. However, intrauterine fetal death was less common in pregnancies complicated by urolithiasis, when compared to those not complicated by urolithiasis.

6.5 Discussion

The objectives of this study were to evaluate the incidence and effects of urolithiasis in pregnant women. We aimed to explore temporal trends of urolithiasis diagnoses in this cohort, as well as to investigate potential maternal and neonatal outcomes related to this complication. Using the HCUP-NIS database, a cohort of 11,528 delivery admissions complicated by urolithiasis were identified. These admissions were subject to increased complications for both the mother and child.

The overall incidence of urolithiasis in our pregnancy cohort was 8.3 per 10,000 admissions, with the incidence of urolithiasis rising from 5.3 per 10,000 pregnancy admissions in 1999 to 10.2 per 10,000 pregnancy admissions in 2015. This two-fold increase in urolithiasis diagnoses in pregnancy is in concordance with similar studies that examined trends of urolithiasis in women over time. For instance, Edvardsson et al. observed an increase in urolithiasis incidence in Icelandic women of all ages from 8.0 to 11.2 per 10,000 over a 24-year time span.[15] They also observed similar trends in women of different age groups, however these were not quantified. Similarly, a U.S. study spanning 28 years observed a rise in urolithiasis diagnoses among women of different age groups, with the highest incidence rate rates of 1.28 and 1.33 among women aged 18-39 years and 40-59 years, respectively[1]. In the same study, a comparable rise was seen in the diagnoses of calcium oxalate monohydrate and calcium hydroxyapatite stones, the most commonly diagnosed urinary tract stone. The rising incidence of urolithiasis in these younger patients may be due to increasingly consumed diets of high intakes of salt, animal proteins, and sucrose,[16-18] which have all been linked to increased calcium excretion. [19-21]

When compared with pregnancies not complicated by urolithiasis, there were higher rates of adverse maternal outcomes in the pregnancies complicated by urolithiasis. Notably, women with urolithiasis had a statistically higher risk of developing gestational diabetes. Retrospective cohort studies by Tangren et al.[3] and Rosenberg et al. [2] also found higher frequencies of gestational diabetes in women with urolithiasis. It is hypothesized that insulin resistance can lead to acidification of urine, which in turn increases the risk of uric acid stone formation.[22] The dataset used for this current study, however, did not allow for investigation of stone composition.

Our results also demonstrated a statistically higher risk of preeclampsia/eclampsia in the pregnancies complicated by urolithiasis. A study by Filali Khattabi et al. observed a higher prevalence of chronic kidney disease among women diagnosed with preeclampsia.[23] While a study from Rule et al. showed that patients with urolithiasis are at a 50-67% higher risk of developing chronic kidney disease, and that previous undocumented stones may have lead to the diagnosis of chronic kidney disease before the first documented stone.[24] although the mechanism is unclear, it is possible that urolithiasis may result in some subclinical renal dysfunction that may lead to the development of hypertensive diseases of pregnancy and preeclampsia.

Pregnancies complicated by urolithiasis were also subject to increased risk of cesarean delivery, which is in concordance with other studies, such as Rosenberg et al.[2] and Ordon et al.[4] We propose various reasons for this observed greater likelihood of cesarean deliveries. First, we cannot exclude other pregnancy complications as potential causes for these cesarean deliveries, such as placenta previa and placental abruption, as the HCUP-NIS database does not provide the conditions that precipitated the cesarean deliveries.

Second, although pain control is a crucial initial step in managing a patient with urolithiasis, it can sometimes be delayed due to the personal preference of the patient. The increasing pain and stress can precipitate labor[25], which in certain women, may lead to the need for a cesarean delivery. Another hypothesis is that late-preterm or term women whom are in need of invasive treatment for symptomatic urolithiasis may decide to deliver before undergoing treatment in order to avoid potential complications to the fetus.

Obstructive urolithiasis is commonly associated with infection, namely pyelonephritis.[26] Urinary tact stones may cause a blockage in the ureter, leading to stasis and proximal infection.[27,28] This is in concordance with our study results showing that pregnant women with urolithiasis had an extremely high risk of pyelonephritis. Specifically, the risk of having or developing an upper urinary tract infection was almost 90-fold greater among those with urolithiasis when compared to those without urolithiasis. A 2014 study noted that urinary stasis, due to compression of the ureters by the gravid uterus, may induce infection of the upper urinary tract. In turn, this infection can increase urinary pH, potentially leading to stone formation.[26] Unfortunately, the HCUP-NIS dataset did not allow us to determine which condition came first, the infection or the stone. A 2019 review of literature on nephrolithiasis in the general population by Whitehurst et al. identified infection as the leading cause of mortality among patients with urolithiasis, with 9% of deaths caused by sepsis.[29] In our study, pregnant women with urolithiasis were also seen to have a significantly higher risk of developing thrombosis. As physiologic and anatomic changes in pregnancy already lead to a hypercoagulable state [30], incremental decreases in renal function can further increase the risk of arterial and venous thromboembolism, as stated in a 2016 publication by Ribic et al.[31]

Considering the significantly elevated risk of developing the previously stated pregnancy complications, women with urolithiasis were accordingly noted to be at a significantly higher risk of death. Unfortunately, we were not able to examine the causes of death, as the HCUP-NIS does not provide this data. Future studies should investigate this greater risk of death among pregnant women with urolithiasis.

We observed that urolithiasis during gestation was also associated with adverse fetal outcomes. In particular, neonatal anomalies were more commonly seen in the infants born to women with urolithiasis. Little research has examined the association of maternal urolithiasis and congenital anomalies. One such study conducted in Hungary by Bánhidy et al. found a higher frequency of congenital anomalies in the offspring of mothers with urolithiasis; although their regression analyses did not reach statistical significance, which may be a consequence of the small sample size of 216 mothers with urolithiasis.[11] Although underlying mechanism for this association is unclear, a potential mechanism may be first trimester exposure of non-steroidal anti-inflammatory drugs (NSAIDs) for pain control during which point these women may not have known that they were pregnant. NSAIDS have been associated with increased risks for gastroschisis, cleft palate, and hypospadias, among other congenital anomalies.[32] As well, the use of opioids in the first trimester has also been associated with congenital malformations including genitourinary, respiratory, and cardiac malformations .[33]

Moreover, pregnancies complicated by urolithiasis were shown to have higher rates of preterm birth and lower rates of intrauterine fetal demise. A small case series by Fligelstone et al. described renal colic as a precipitating factor for premature labor.[25] Another small case series published in 1982 reported cessation of premature labor with relief of renal colic or passage of the stone.[34] A more recent study by Clennon et al. also observed 30% greater odds of preterm delivery among women with urolithiasis.[35] We speculate that increased monitoring and earlier deliveries due to the enhanced risk of experiencing obstetrical complications, such as preeclampsia and abruptio placenta, may explain the greater frequency of preterm births among pregnancies complicated by urolithiasis. Although we lack information on the gestational ages of women at admission, we hypothesize that there exists a positive association between the observed increased rates of cesarean deliveries and preterm births. In addition, considering late deliveries are associated with higher rates of intrauterine fetal demise [36], the observed decreased risk of intrauterine fetal demise in this study population may be related to the increased rates of preterm birth and cesarean deliveries.

Like all studies, ours study had some notable limitations. This retrospective study was based on an existing dataset, which lacked certain variables of interest that would have been practical to our analysis. Notably, data on gestational ages at time of admission would have aided in anticipating the outcomes of the disease based on the timing of the pregnancy. This data would have allowed for the study of the effects of urolithiasis on early versus late-preterm deliveries, as well as the implications of early-gestation urinary tract stones on adverse fetal outcomes. Additionally, if models were adjusted for gestational age, it would have been possible to examine the impact of urolithiasis on maternal and fetal outcomes independent of gestational age. Also, data pertaining to long-term maternal and neonatal outcomes were not available for study. It would have been interesting to observe the long-term effects of urinary tract stones during gestation, however, access to this information would not have altered the study results. Although frequencies of cesarean sections were available, the dataset lacked information on the causal etiologies for cesarean deliveries. In addition, the receipt of pharmacologic pain management, including the specific drugs and the timing of this therapy, were not available within the HCUP-NIS database; hence, not allowing for detailed exploration of the association between drug intake and congenital anomalies. Furthermore, information on stone composition was not available. Nonetheless, this study also had several strengths. To our knowledge, this is the largest population-based study on maternal and neonatal outcomes of urolithiasis during pregnancy. Therefore, the findings in our study are generalizable to the larger North-American obstetric population. In addition, this large data sample provided us with the power to detect associations between maternal urolithiasis and various outcomes, if they indeed existed. Further, this study had data spanning 16 years, which permitted us to examine temporal trends in pregnancy-associated urolithiasis over a wide time interval. Lastly, as previously stated, the ICD-9 code 592.X was used to identify the subset of women whom were diagnosed with urolithiasis. This code has been similarly used by several other publications in order to identify urolithiasis [13, 37]; attesting to the validity of this ICD-9 code.

6.6 Conclusion

Although uncommon, the diagnosis of urolithiasis in pregnancy has increased significantly over the last two decades in the US. This rise in incidence, in conjunction with the adverse maternal and fetal outcomes associated with urolithiasis, highlight the need for prevention and early management of this condition in susceptible women. We conclude that pregnancies complicated by urolithiasis should be considered high risk, as this complication is associated with increased risk of death. Further, the findings of this study will allow obstetrical caregivers to more readily anticipate the greater risk of poor outcomes, with the ultimate goal of diminishing poor maternal and fetal outcomes.

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6.8 Tables and figures

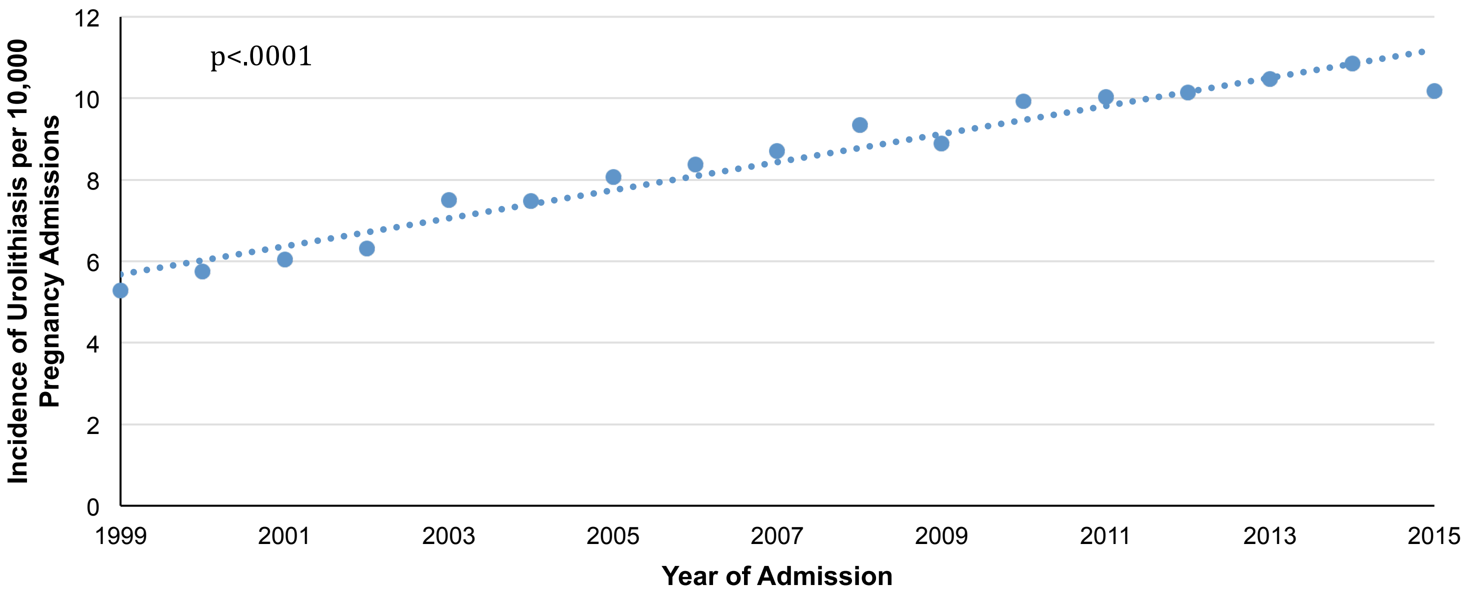

Figure 1: Incidence of urolithiasis in pregnant patients per year, 1999-2015

Table 1: Baseline demographic and patient characteristics for pregnant patients by urolithiasis status

Characteristic	Pregnant patients (n=13,792,544)	
	Urolithiasis N = 11,528 (%)	No Urolithiasis N = 13,781,016 (%)
Age (years), n (%)		
< 25	30.47	33.74
25-34	57.29	51.72
35+	12.24	14.54
Race, n (%)		
Caucasian	75.01	52.99
Black	4.84	13.70
Hispanic	14.20	22.84
Other	5.95	10.47
Insurance type, n (%)		
Medicare	0.72	0.54
Medicaid	35.79	40.66
Private	58.89	52.77
Other	4.59	6.02
Hospital type, n (%)		
Rural	12.55	11.57
Urban Non-teaching	38.77	41.10
Urban teaching	48.69	47.34
Income quartile, n (%)		
Q1	22.65	27.29
Q2	25.66	25.15
Q3	27.08	24.58
Q4	24.62	22.98
Risk factors, n (%)		
Preexisting Diabetes	0.82	0.88
Hypertension	0.82	1.59
Smoker	9.00	5.15
Obesity	3.05	1.81
Morbid Obesity	1.20	1.02

Table 2: Maternal outcomes in pregnancy by urolithiasis status

Maternal outcome	Pregnant patients (N=13,792,544) Urolithiasis N=11,528 (%)	Pregnant patients (N=13,792,544) No Urolithiasis N=13,781,016 (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	p-value
Antepartum					
Gestational HTN	3.73	3.20	1.17 (1.07 – 1.29)	1.10 (1.00 – 1.21)	NS
Preeclampsia/Eclampsia	4.65	3.55	1.32 (1.21 – 1.44)	1.35 (1.24 – 1.47)	<0.01
Gestational DM	6.75	5.27	1.30 (1.21 – 1.40)	1.29 (1.20 – 1.30)	<0.01
PPROM	0.63	0.60	1.06 (0.84 – 1.34)	1.05 (0.83 – 1.32)	NS
Abruptio placenta	1.51	1.07	1.42 (1.22 – 1.65)	1.41 (1.22 – 1.64)	<0.01
Placenta Previa	0.82	0.53	1.54 (1.26 – 1.88)	1.55 (1.27 – 1.90)	<0.01
Intrapartum					
Chorioamnionitis	1.78	1.83	0.97 (0.85 – 1.12)	1.04 (0.91 – 1.20)	NS
Cesarean delivery	35.03	30.23	1.23 (1.18 – 1.28)	1.20 (1.15 – 1.25)	<0.01
Instrumental delivery	4.95	6.07	0.87 (0.80 – 0.94)	0.88 (0.80 – 0.95)	<0.01
Post partum					
PPH	2.96	2.76	1.08 (0.97 – 1.20)	1.08 (0.97 – 1.20)	NS
Pyelonephritis	5.46	0.07	80.86 (74.44 – 87.84)	88.87 (81.69 – 96.69)	<0.01
VTE	0.38	0.20	1.89 (1.40 – 2.54)	1.65 (1.23 – 2.22)	<0.01
Maternal death	0.03	0.01	2.48 (0.93 – 6.60)	2.85 (1.07 – 7.60)	<0.05

* Adjusted for determinants of table 1: Age, race, income, insurance type, hospital location, smoking status, preexisting diabetes, preexisting hypertension, and weight class.

Abbreviations: HTN, hypertension; DM, diabetes mellitus; NS, not statistically significant

Table 3: Neonatal outcomes of pregnancy by urolithiasis status					
Neonatal Outcome	Pregnant patients (N=13,792,544)		Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	p-value
	Urolithiasis N=11,528 (%)	No Urolithiasis N=13,781,016 (%)			
Congenital anomalies, n (%)	1.43	0.43	3.35 (2.87 – 3.91)	2.84 (2.43 – 3.31)	<0.01
IUGR, n (%)	1.97	2.01	0.98 (0.86 – 1.12)	0.92 (0.81 – 1.05)	NS
IUFD, n (%)	0.37	0.67	0.56 (0.41 – 0.75)	0.60 (0.45 – 0.81)	<0.01
Preterm birth, n (%)	12.51	7.09	1.87 (1.77 – 1.98)	1.92 (1.82 – 2.03)	<0.01

Adjusted for determinants of table 1: Age, race, income, insurance type, hospital location, smoking status, preexisting diabetes, preexisting hypertension, and weight class.

Abbreviations: IUGR, Intrauterine growth restriction; IUFD, intrauterine fetal death; NS, not statistically significant

CHAPTER 7: GENERAL DISCUSSION

The results provided in the manuscripts included in this thesis reveal that pregnant women with urolithiasis have a milder disease course than do their non-pregnant counterparts. However, they have elevated risks of a multitude of adverse maternal and fetal outcomes when compared to pregnancies not complicated by urinary tract stones.

7.1 Findings and summary for the effect of pregnancy presentation and management of urinary tract stones

The main objective of this thesis was to further evaluate the effects of urinary tract stones during pregnancy. This objective was split into two separate steps. The first step was to conduct a matched retrospective cohort study comparing the clinical presentation and management of urinary calculi in women of childbearing age, based on their pregnancy status. This study was achieved using a nationwide American database, HCUP-NIS. A cohort of 42,113 pregnant patients with urolithiasis was identified and age-matched with 42,113 non-pregnant women with urolithiasis admissions. Conditional logistic regression models, adjusted for baseline characteristics, were used to estimate adjusted odds of presenting symptoms, length of hospital stay, complications, and management of urinary tract stones by pregnancy status. The observed results showed pregnant women to have a milder disease course than their non-pregnant equivalents, with lower rates of symptoms, complications, and invasive interventions.

Although many studies on the presentation and management of urinary tract stones in pregnancy exist [8,69,70,77,79,80], there is a paucity of comparative literature with non-pregnant women.

Urinary tract stones are most commonly treated in an outpatient setting[3], but their occurrence during gestation increases risks for pregnancy complications[80]. This may be a reason for the lack of comparative literature, as non-pregnant women have fewer grounds for admission. In concordance with this reasoning, the results of this manuscript showed that the non-pregnant women who warrant admission for urinary calculi tend to be sicker, and have a harsher disease course than those whom are pregnant.

While further studies are needed to expand and validate the results shown in this thesis, our study demonstrated that a high clinical suspicion of urinary tract stones in pregnant women can reduce the clinical impact of said stones on the patient, including less symptoms, lower risks for complications genitourinary complications, and decreased rates of invasive interventions.

7.2 Findings and summary of the effects of urinary tract stones on pregnancy outcomes

The second step of our objective was to conduct another retrospective cohort study, now comparing the outcomes of pregnancy based on urolithiasis status. The HCUP-NIS database was also used to achieve this step, allowing for identification of 11,528 pregnancies complicated by urinary tract stones and 13,781,016 pregnancies without urinary tract stones. The timespan of this database allowed for trends in urinary calculi incidence in this patient population. Multivariate logistic regression models, adjusted for baseline characteristics, were used to estimate adjusted odds of negative maternal and fetal outcomes. The observed results of this study proved that urinary calculi are a serious complication in pregnancy and pose risks to both maternal and fetal health.

While existing publications state different incidence values[7,65], our study showed that urinary tract stones affect 8.3 per 10,000 deliveries, with trends showing a rise in incidence over the 16-year timespan. Although there are no other existing studies focused on the rise of incidence of urolithiasis in pregnancy, there have been studies showing a rise in urinary tract stone incidence in women of reproductive age over time.[81,82]

This manuscript also detailed the increased risk of maternal and fetal complications of pregnancy in women with urolithiasis. These patients were at increased risk of hypertensive disorders of pregnancy, gestational diabetes, abruptio placentae, placenta previa, cesarean delivery, pyelonephritis, VTE and death. A 2018 retrospective observational study by Tangen et al. observed some similar results, with increased rates of preeclampsia and GDM in pregnancies complicated by urolithiasis.[73] Another study by Rosenberg et al. also saw elevated risks of hypertensive disorders, GDM, and cesarean deliveries in this patient group.[74]

It is well known that urinary tract stones are associated with urinary tract infections, namely pyelonephritis.[8] A 1982 study by Aubert et al. mentions that although pyelonephritis is often caused by a stone obstruction of the ureter, physiologic obstruction by the gravid uterus may also be a cause, and that proper etiological identification is important to prevent recurrence.[83] A study by Ribic et al. validated that urinary tract stones can increase the risk of VTEs by reducing renal function. [84]

Most of the present literature on neonatal outcomes in pregnancies complicated by stone formation note an increase in risk of prematurity. [7,73,85] The manuscript results presented in this thesis validate that stone-complicated pregnancies are in fact at a higher risk of premature delivery. Also, there are no statistically significant publications mentioning the association between mothers with urolithiasis and congenital anomalies in their offspring.[76] Additional research is necessary to support and detail the association noted in this thesis.

7.3 Strengths and limitations

There are several strengths and limitations of both studies included in this thesis. These studies were limited by the dataset used, which lacked some variables of interest that would have enhanced the analysis. These include gestational age at the time of admission and long-term maternal and neonatal outcomes of this pregnancy complication. Additionally, outpatient and emergency room data do not exist in this dataset, thus notably absent from our analyses. Stone composition and pharmacologic therapies would have also been interesting to study.

In spite of these limitations, the studies presented in this thesis had several strengths. The first manuscript is the first and largest major population-based study comparing urolithiasis admissions in age-matched women, based on pregnancy status. The second manuscript is the largest population-based study on maternal and neonatal outcomes of urinary tract stones during gestation. Hence, providing the study with the power to detect associations that existed. Further, the population-based nature of the dataset allows for the generalizability of study findings to the larger North-American obstetric population. Data regarding potential confounders allowed for the estimation of adjusted models. Moreover, the large time interval of the data, spanning 16 years, allowed for examination of temporal trends. The ICD-9 code used to identify admissions for urinary tract stones was in concordance with similar publications.[86,87]

Additional studies are required investigating the effect of pregnancy on the development of urinary tract stones, as well as the effect of urinary tract stone development on pregnancy outcomes.

7.4 Bias

The database used to conduct these studies, the Healthcare Cost and Utilization Project – National Inpatient Sample, encompasses 20% of all hospital admissions in the United States. Although the HCUP-NIS database is the largest publicly available all-payer inpatient healthcase databse, it lacks certain variables that may not allow researchers to control for potential biases in their studies. Due to its focus on inpatient care, the HCUP-NIS is deficient in outpatient data. For the context of this thesis, outpatient data would have been valuable, as uncomplicated urolithiasis in the general population is most commonly treated in an outpatient setting. Pregnancy is often a cause for admission for fetal monitoring, even in uncomplicated urolithiasis cases. The non-pregnant comparaison group must have probable cause for admission, thus are likely to be sicker. In a similar fashion, since pregnant patients are monitored more closely, their symptoms are possibly more likely to be documented, when compared to non-pregnant patients. However, since database utilized for this thesis solely emcompasses hospital admissions, it is less likely that symptoms would be recorded differentially between pregnant patients and non-pregnant patients; hence, limiting the possibility of diff.

Although the study population shows a primarily Caucasian distribution, this should not affect external validity of the study results, as the results of this study were adjusted for race.[2]

CHAPTER 8: CONCLUSION

Urinary tract stones are a rare complication of pregnancy, but rates of urolithiasis in this patient population have been rising in recent years.[65] Our study showed that pregnant women tend to have a milder disease course, with lower risks of renal or systemic complications and less indication for invasive management when compared to non-pregnant women. However, when compared to pregnancies not complicated by urinary tract stones, pregnancies complicated by stones are at higher risk of adverse obstetrical outcomes, as well as increased risk of congenital anomalies and preterm births. Although there is need for further validation, these findings prove that a high level of suspicion is crucial to ensure prompt diagnosis and care of these high-risk patients

CHAPTER 9: FUTURE RESEARCH DIRECTIONS

Although not a common occurrence in the pregnant population, additional research on urolithiasis in pregnant patients is warranted. Studies focusing on clinical presentation and management of urinary tract stones in this patient population can delve deeper into details about etiologies for certain complications and reasons for performing invasive procedures. This would validate the findings of this thesis, as well as aid in creating guidelines for prompt diagnosis and management of these women. A prospective study designed to observe pregnant women who develop urinary tract stones and compare them to pregnant women who do not develop urinary tract stones, with detailed a priori information on potential cofounders, should theoretically be the next step. Although this study would be costly and require an extensive study population due to the rare nature of this disease during pregnancy, it would offer a much stronger study design and robust results. Furthermore, research on neonatal abnormalities is imperative to detail the specific congenital anomalies occurring in neonates born to women with urolithiasis. This would aid in increasing awareness and monitoring of the fetal anatomy throughout the gestation in pregnancies complicated by urinary calculi.

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