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Maternal and Fetal Prognosis in Pregnant Women with Renal Disease Associating Urinary Tract Infection

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ABSTRACT

Background: *Pregnancy related acute renal injury is a challenging diagnosis, mainly due to, among other factors, the physiological decrease in blood nitrogen retention parameters. As a consequence, the criteria required to establish the diagnosis may be first met as a result of the complications that appear, especially hypertension. The maternal and fetal complications which may occur in pregnancies with renal failure can be worsened by the relative immunodeficiency during pregnancy, which represents an elusive mechanism that is associated with a high risk of urinary tract infection (UTI). Therefore, the risk for intensive care unit admission, or developing sepsis, or preterm birth can increase.*

Objectives: *The present study aims to investigate whether the superimposition of UTI over an altered renal function leads to a worsened maternal and fetal prognosis.*

Patients and methods: *We performed an observational retrospective study that included pregnant women with increased serum creatinine levels, both with and without UTI. Thus, we analyzed 47 pregnant women who delivered in our unit between 1 January 2021 and 1 September 2023. Patients were divided into three groups: an acute renal injury (AKI) group (n=16), a chronic kidney disease (CKD) group (n=8) and a control group (n=23) which included patients with serum creatinine levels between 0.80-1 mg/dL. We evaluated the maternal and fetal complications in all three groups, taking into consideration the comparison between maternal and fetal parameters in women with UTI.*

Results: *Our study highlighted an important difference between fetal weight at delivery by patients with AKI associating UTI and the two remaining groups (1395 ± 992.50 grams compared to 2340 grams in the CKD group and 3103.33±83.86 grams in the control group, respectively). There was no statistically significant difference regarding preterm birth, intrauterine grow restriction, stillbirth or neonatal intensive care unit (NICU) admission. Preterm birth had a higher incidence in all patients with AKI (87.5% compared to 50% and 34.78%, respectively).*

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Conclusion: *Neonatal complications are important in pregnant women with AKI and CKD, irrespective of the UTI diagnosis. Most fetal complications occurred in patients diagnosed with AKI. The correlations highlighted by us should be studied further.*

Keywords: urinary tract infection, acute renal injury, chronic renal disease, fetal weight, one-minute Apgar score, neonatal intensive care unit.

INTRODUCTION

Urinary tract infection (UTI) during pregnancy, the most frequent bacterial infection in pregnancy, is associated with an increase in maternal and neonatal morbidity and mortality. It complicates almost 20% of all pregnancies (1, 2). Risk factors of UTI include urologic anomalies, diabetes mellitus, HIV or *Chlamydia trachomatis* infection (3, 4). Untreated symptomatic or asymptomatic bacteriuria is associated with a risk of developing acute pyelonephritis of up to 30%, a pathology which, in turn, increases the risk for developing preeclampsia, intrauterine growth restriction or preterm birth (1, 5).

The most common bacteria involved in UTI during pregnancy include *Escherichia coli* (76%-81%), followed by *Klebsiella*, *Proteus* or *Enterobacter* (10%) and group B *Streptococcus* (10%) (4, 6-8).

Studies show that the pathogenic correlation between maternal and fetal complications and the presence of urinary tract infection in pregnancy involves an excessive activation of the systemic inflammatory response (2).

Although there are numerous etiologies for AKI during pregnancy, most of them being related to pregnancy complications, some of them are not related to this condition. For example, pyelonephritis, an intra-renal cause of acute renal injury, has an incidence that significantly decreases with early treatment from 20% to 2% (6, 9).

Taking into consideration the maternal outcomes in chronic renal disease, it is stipulated that recurrent UTI is an individual factor, along with maternal hypertension, which lead to a poor pregnancy outcome. Recurrent UTIs are frequent complications of primary glomerulonephritis and vesicoureteral reflux nephropathy, among all renal pathologies which determine renal impairment (10-16).

Acute renal injury or chronic kidney disease (CKD) constitutes a public health issue, which is associated with an increased rate in maternal and fetal morbidity and mortality (4). While the diagnosis of chronic renal injury is established prior to pregnancy *via* renal biopsy, the diagnosis of AKI is more difficult to establish due to a lower baseline of serum creatinine (17, 18). A higher incidence of stillbirth, lower mean gestational age at delivery, lower birth weight and intensive care admissions were proven to be more frequent in women with pregnancy related AKI (19). ❑

MATERIAL AND METHODS

We performed an observational retrospective study aimed at evaluating maternal and fetal outcomes in pregnancies associated with renal disease and overlapping UTI. The study included 47 female patients who delivered in the Department of Obstetrics and Gynecology of Bucharest University Emergency Hospital between January 1st 2021 and September 31st 2023.

Study participants were divided into three groups: an AKI group (n=16), a CKD group (n=8) and a control group (n=23) which included patients with serum creatinine levels between 0.80-1 mg/dL.

Data regarding the maternal and fetal parameters was collected from the Database System of Bucharest University Emergency Hospital and from hospitalization sheets.

We included all cases of pregnant women with acute or chronic renal failure, regardless of their underlying pathology. The value of serum creatinine in the control group (0.8-1 mg/dL) was established taking into consideration the physiological reduction in serum creatinine level during normal pregnancies, which made it difficult to establish certain criteria for diagnosis. All included patients signed an informed consent regarding their participation to our study. The exclusion criteria were as follows: age under 18 years, lack of informed consent and twin

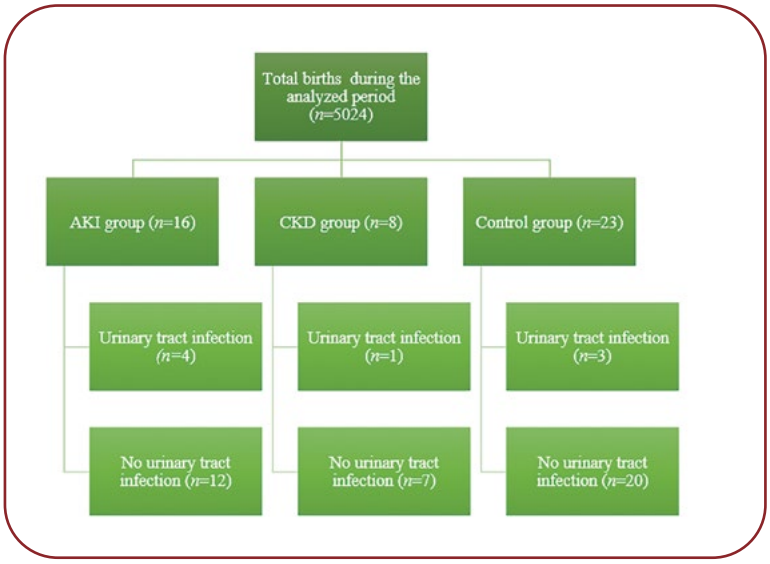

FIGURE 1. Distribution of study patients

pregnancy. Moreover, pregnancies below 24 weeks of gestation or displaying a fetal weight of less than 500 grams were considered abortions and not included in the present study.

Our study was approved by the Ethical Committee of Bucharest University Emergency Hospital (Np. 26407/17.05.2021).

The data was analyzed using the SPSS 26.0 Software. The statistically significant results had a p value lower than 0.05. The interdependence between nominal variables was established using the chi-square test. The impact of serum creatinine level on fetal parameters (gestational age at delivery, Apgar score, fetal weight) was determined using the Pearson correlation test. Figure 1 illustrates patient selection and distribution. ❑

RESULTS

We analyzed 24 pregnant women with renal injury compared to a group of 23 women with serum creatinine levels between 0.80-1 mg/dL. The incidence of acute renal injury was 3.18%, while in the chronic renal group the incidence was 1.59%.

The cases were stratified by maternal features, such as age, body mass index (BMI) category, history of genito-urinary infections or renal underlying pathologies and by fetal characteristics, including birth weight, 1-minute Apgar score and neonatal intensive care unit (NICU) admission (Table 1).

TABLE 1. Description of study participants

	AKI group	CKD group	Control group	p-Value
Maternal data				
Maternal age, years (mean ± SD)	29.68 ± 7.16	33.25 ± 5.36	32.08 ± 5.64	0.316
BMI (mean ± SD)	23.03 ± 4.03	26.48 ± 3.99	23.35 ± 5.07	0.560
Parity				0.534
Primiparous (n, %)	10, 62.5%	5, 62.5%	16, 69.57%	
Multiparous (n, %)	6, 37.5%	3, 37.5%	7, 30.43%	
Investigated pregnancy (n, %)	22, 95.65%	6, 75%	11, 68.75%	0.011
Urinary tract infection (n, %)	4, 25%	1, 12.5%	3, 13.04%	0.495
Genital tract infection (n, %)	0	1, 12.5%	6, 26.09%	0.057
History of renal pathology (n, %)	3, 18.75%	8, 100%	2, 8.7%	0.008
Viral infection (n, %)	3, 18.75%	1, 12.5%	1, 4.35%	0.186
Mode of delivery (n, %)				0.164
Cesarean section	14, 87.5%	8, 100%	22, 95.65%	
Spontaneous birth	2, 12.5%	0	1, 4.35%	
Days of hospitalization (mean ± SD)	13.06 ± 9.81	11.37 ± 10.57	6.69 ± 4.16	0.007
Serum creatinine at admission, mg/dL (mean ± SD)	1.94 ± 1.54	3.27 ± 3.14	0.85 ± 0.03	0.002
Serum creatinine at discharge (mean ± SD)	1.52 ±0.91	2.9.2 ± 2.56	0.72 ± 0.1	0.003
Serum urea at admission (mean ± SD)	53.06 ± 32.29	72.06 ± 47.97	28.83 ± 8.43	<.001
Serum urea at discharge (mean ± SD)	56.25 ± 31.06	87.97 ± 66.74	33.01 ± 11.48	0.002
Proteinuria, mg/L (mean ± SD)	100.31 ± 86.38	139.37 ±103.38	57.60 ± 67.33	0.035
eGFR, mL/min/1.73 m^2 (mean ± SD)	53.06 ± 25.14	54.62 ± 51.16	90 ± 14.12	<.001
Need of dialysis (n, %)				<.001
Short term	6, 37.5%	0	0	
Continuous	0	4, 50%	0	
Maternal death (n, %)	4, 25%	0	0	0.043
Neonatal outcomes				
Gestational age (weeks) (mean ± SD)	32 ± 5.13	35.62 ± 2.38	36.17 ± 3.72	0.023
Birth weight (grams) (mean ± SD)	1702.19 ± 940.8	2245 ± 455.38	2576.96 ± 872.91	0.015
Preterm birth (n, %)	14, 87.5%	4, 50%	8, 34.78%	0.029
Intrauterine growth restriction (n, %)	3, 23.07%	7, 87.5%	8, 38.09%	0.090
Stillbirth (n, %)	3, 18.75%	0	2, 8.69%	0.328
1-minute Apgar score (mean ± SD)	5.46 ± 2.63	8.12 ± 1.12	7.90 ± 1.48	0.009
NICU admission (n, %)	12, 92.30%	6, 75%	9, 42.85%	0.009

AKI=acute kidney injury; CKD=renal chronic disease; BMI=body mass index; NICU=Neonatal Intensive Care Unit; eGFR=glomerular filtration rate

	Urinary tract infection		
	AKI group	CKD group	Control group
Birth weight (grams) (mean ± SD)	1395 ± 992.50	2340	3103.33 ± 83.86
1-minute Apgar score (mean ± SD)	5.33 ± 3.21	7	9
Preterm birth (n, %)	2, 66.67%	1, 100%	0
Intrauterine growth restriction (n, %)	1, 33.33%	1, 100%	0
Stillbirth	1	0	0
NICU admission (n, %)	2, 66.67%	1, 100%	0
	No urinary tract infection		
	AKI group	CKD group	Control group
Birth weight (grams) (mean ± SD)	1773.08 ± 955.61	2231.43 ± 490.12	2498 ± 911.72
1-minute Apgar score (mean ± SD)	5.5 ± 2.63	8.28 ± 1.11	7.79 ± 1.51
Preterm birth (n, %)	11, 84.61%	3, 42.85%	8, 40%
Intrauterine growth restriction (n, %)	9, 69.23%	6, 85.71%	9, 50%
Stillbirth	2	0	2
NICU admission (n, %)	11, 84.61%	5, 71.42%	9, 50%

AKI=acute kidney injury; CKD=renal chronic disease; NICU=Neonatal Intensive Care Unit

TABLE 2. Description of the fetal complications in patients with urinary tract infection

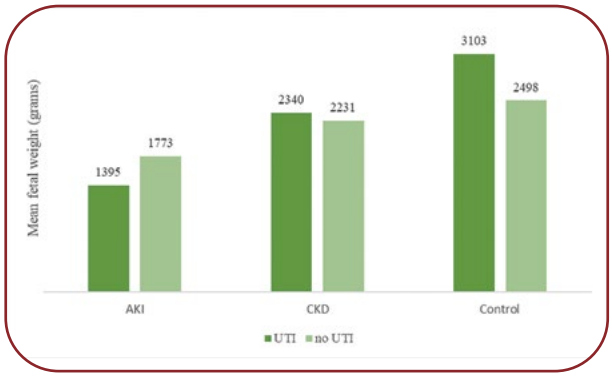

FIGURE 2. Fetal weight distribution in every group

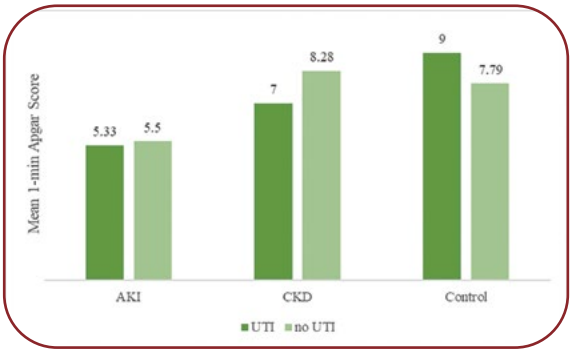

FIGURE 3. 1-minute Apgar score distribution in the study groups

Table 2 illustrates newborn outcomes in pregnant women who developed UTIs during pregnancy. Fetal birth weight is significantly lower in patients with acute kidney disease.

Our study findings showed a slight difference between fetal weight at birth in the AKI-associated pregnancy group with UTI, compared to the group without UTI (1395 ± 992.50 grams *vs* 1773.08 ± 955.61 grams). In the CKD and control groups, the presence of UTI was not associated with a low fetal weight at birth (Figure 2).

The 1-minute Apgar score in the AKI group was not influenced by the presence or absence of UTI; in the CKD group, the Apgar score was higher in the subgroup with no UTI, while this pathology had no significance in the control group (Figure 3).

Admission to NICU and intrauterine growth restriction risk was not influenced by the presence of UTI, given that a higher percentage of newborns from pregnancies with no urinary tract infections needed intensive care support.

Pre-eclampsia is the leading indication of caesarean section taking into consideration all study participants. Regarding the pregnant women with UTIs, urinary sepsis was a major indication of birth, among hypertensive complications (Figure 4).

Considering maternal outcomes, we underscored an inverse correlation between serum creatinine levels at admission and presence of UTI (1.41 ± 1.13 in the subgroup with UTI *vs* 1.67 ± 1.85 in the group without UTI). Furthermore, the serum creatinine level was 2.95 ± 2.85 in the AKI subgroup with UTI and 2.77 ± 2.59 in the AKI subgroup with no UTI, while in the CKD group the difference was significantly higher (1.53 *vs* 1.17 ± 0.54). In the control group, the

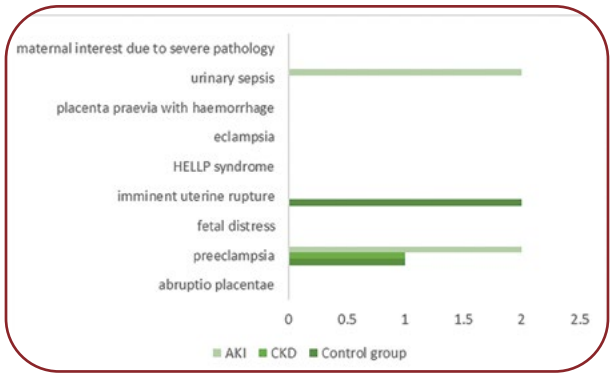

FIGURE 4. Distribution of caesarean section indication in cases with UTI

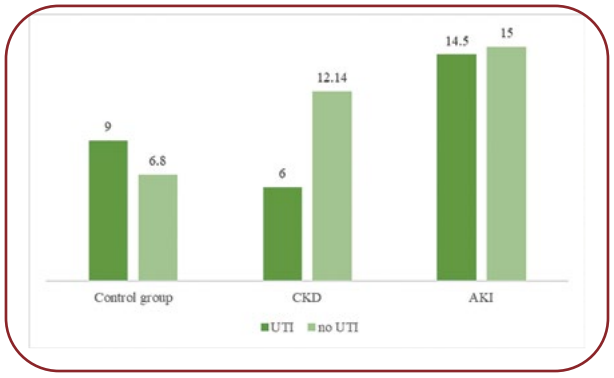

FIGURE 5. Distribution of hospitalization days in all groups

creatinine level was similar. In the AKI group, serum urea level was significantly higher in patients with UTI *versus* those with no UTI (75.7 ± 52.24 *vs* 47.83 ± 26.29).

Taking into account the hospitalization period, the number of days between admission and discharge was similar in both subgroups of the AKI group (15 ± 5.27 days *vs* 14.5 ± 3.09 among patients without and with UTI, respectively). In the control group, our study revealed a smaller number of days of hospitalization in the subgroup without UTI (6.8 ± 4.31 *vs* 9 ± 3.60) (Figure 5).

We found that 75% of pregnant women who developed acute renal injury based on an underlying renal pathology had UTIs, while in the CKD group, only one patient developed urinary tract infection caused by *Proteus*. We observed that *Escherichia coli* was involved in only 40% of cases, a lower ratio than that reported in the literature, while in the remaining cases UTI was caused by *Klebsiella*, *Enterococcus* and *Proteus* in equal percentages (20%). In the control group, all UTI cases involved the presence of *Escherichia coli*. None of the patients in the control group diagnosed with gestational diabetes had UTI. ❑

DISCUSSIONS

Acute renal injury affects 1 in 20.000 pregnancies, while chronic renal disease is estimated to affect 3% of pregnant women (20-22). The incidence of CKD depends on demographic characteristics, such as an increasing maternal age and obesity, while the incidence of AKI in pregnancy is shown to be continuously increasing despite the intensive therapeutic management of hypertensive complication during pregnancy, which is the main triggering factor (22). In pregnancy, loss of kidney function is not associated with certain criteria of diagnosis; furthermore, serum creatinine levels between 0.7-0.9 mg/dL were suggested to represent a significant increase from baseline, leading to either severe complications during pregnancy or a missed diagnosis of a prior renal pathology (20). In our study, the incidence of pregnancy-related AKI was 3.18%, which was in accordance with Trakarnvanich *et al*, who reported an incidence of 4.11% in developing countries (23). On the other hand, the incidence of chronic renal failure during pregnancies was 1.59% in our study.

Taking into consideration the physiological changes of the renal system during pregnancy, a meta-analysis performed by Wiles *et al* showed that a serum creatinine lever higher than 0.87 mg/dL was suggestive of acute renal injury or a preexisting and undiagnosed chronic renal pathology (24, 25). Despite this, the American College of Obstetrician and Gynecologists formulated the definition of pregnancy-related acute renal injury relative to a serum creatine level of 1.1 mg/dL (26).

In a meta-analysis, Salari *et al* found that the prevalence of UTI was 23.9% among the 30.641 pregnant female participants (27), with 70-80% of urine samples collected from patients being positive for *Escherichia coli* (27,28). Untreated bacteriuria during pregnancy may be associated with a higher risk for preterm birth, low birth weight and increased perinatal mortality (29). The increased incidence of UTIs in pregnancy was associated with maternal age between 26-35 years, primiparity (53.85% *vs* 46.15% in

multiparous women) and gestational age (higher frequency in third trimester), as revealed in a review performed by Obeagu *et al* (30-32). In our study, the average maternal age in UTI patients was significantly lower (25.75 ± 5.39 *vs* 32.02 ± 5.76). Moreover, primiparity among pregnant women who developed UTIs was 75%, higher than the percentage reported in the above-mentioned study.

Renal impairment is associated with poor maternal and fetal outcome, such as lower gestational age at delivery or a lower birth weight and prolonged ICU admission. In our study, the average gestational age at delivery was 32 ± 5.13 weeks in the AKI group, with a difference of almost four weeks in the control group. This difference was higher than that reported by Szczsepanski *et al*, who found a difference of 0.7 weeks between similar groups (33). The average weight at birth was 1702.19 ± 940.8 grams, similar with that reported by the above-mentioned study (-700 grams). Our study shows that the presence of UTI has an impact only over the fetal weight at delivery, with no significant impact on the 1-minute Apgar score or the risk of preterm birth.

When addressing management strategies for pregnancy-related AKI, the foremost priority is identifying the underlying cause of kidney impairment. Intravenous fluid resuscitation should be promptly administered and dialysis initiated if necessary. Additionally, timely delivery of the fetus is crucial if deemed necessary (18). In our study, six cases required short-term dialysis and emergency cesarean section. Among these, complications of pregnancy-induced hypertension were the primary cause in four cases, followed by one case with SARS-CoV-2 infection and another one with severe hemorrhage due to placenta previa. In the remaining cases, renal function was restored after delivery solely through active intravenous fluid resuscitation. Among cases with CKD, all patients received low molecular weight heparin treatment, but only four of them, who had a significantly reduced glomerular filtration rate, required dialysis. In cases where applicable, it is essential to administer specific treatment for the underlying pathology, such as lupus nephritis, membranous glomerulonephritis or polycystic kidney disease. In instances associated with urinary tract infection, antibiotic treatment is imperative.

Limitation of the study

The present study has various limitations that should be taken into account for further research. For more accurate results, a large-scale study regarding UTIs in pregnant women diagnosed with renal impairment should be performed, considering that our study is based on a small sample size. Moreover, since renal function parameters before pregnancy were not available, AKI cases could have a misdiagnosed chronic renal pathology. ❑

CONCLUSION

Urinary tract infection during pregnancy represents a risk factor for neonatal complications. In the present study we found that most neonatal complications occurred in patients with AKI. Therefore, the association of UTI with renal impairment can cause critical outcomes for both the newborn and mother. It is imperious to develop a diagnosis and therapeutical protocol regarding pregnant women with acute or chronic renal injury, considering the higher risk for developing maternal and fetal complications in these pregnancies. ❑

Authors' contributions: All authors had equal contributions to the present article. They have read and agreed to the published version of the manuscript.

Institutional Review Board: The present study was approved by the local Ethical Committee of Bucharest University Emergency Hospital (No. 26407/17.05.2021).

Informed consent: Informed consent was obtained from all patients involved in the present study.

Data availability: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest: none declared.

Financial support: none declared.

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