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RISK OF ACUTE KIDNEY INJURY AND CHRONIC KIDNEY DISEASE IN PRE-ECLAMPSIA

Hanadi M. Alhozali MBBS, FRCPC, ABIM Department of Medicine, Faculty of Medicine, King Abdulaziz University Jeddah, Saudi Arabia

Samera F. Albasri MBBS, FRCPC, ABIM Department of Medicine, Faculty of Medicine, King Abdulaziz University Jeddah, Saudi Arabia

Aisha A. Alzabedi MBBS, FRCPC, ABIM Department of Medicine, Faculty of Medicine, King Abdulaziz University Jeddah, Saudi Arabia

Hisham A. Makki MBBS, FRCPC, ABIM Department of Medicine, Faculty of Medicine, King Abdulaziz University Jeddah, Saudi Arabia

Hanin A. Alsini MBBS, FRCPC, ABIM Department of Medicine, Faculty of Medicine, King Abdulaziz University Jeddah, Saudi Arabia

ABSTRACT Background: Pre-eclampsia is new-onset hypertension with proteinuria in pregnancy. Some patients may develop acute kidney injury (AKI) due to pre-eclampsia. However, very few studies link the risk of developing chronic kidney disease (CKD) due hypertension in pregnancy. This study aims to determine the prevalence of AKI and the association between pre-eclampsia and future risk for CKD. Methods: This single-center retrospective study was conducted in the western region of Saudi Arabia on patients diagnosed with pre-eclampsia between 2010 and 2015. The records of each patient were taken into consideration and the data were statistically analyzed. The binary logistic regression model was used for the independent variable 'pre-eclampsia with AKI' and the dependent variable 'CKD'. Results: A total of 568 patients were included. Pre-eclampsia together with AKI strongly influenced the risk for CKD. The prevalence of AKI was similar to those reported in studies conducted in developed countries. Conclusion: Patients with AKI and pre-eclampsia have a greater risk of developing CKD. However, the association between CKD and AKI needs to be studied further. Additionally, patients with pre-eclampsia should have regular follow-up, be given adequate information on the disease, and be treated and informed of the risk of cardiovascular disease.

KEY WORDS : Chronic kidney disease; pre-eclampsia; epidemiology; risk factors; Saudi Arabia; acute kidney injury

Introduction

Pregnancy is marked by various physiological changes. Hypertensive disorders in pregnancy are major causes of fetal mortality and morbidity. Hypertension affects close to 5-10% of all pregnancies [1-2]. These disorders include gestational hypertension and pre-eclampsia [3]. Gestational hypertension and pre-eclampsia differ in the sense that the former is new-onset hypertension (> 140/90 mm Hg) without proteinuria after 20 weeks of gestation, whereas the latter is new-onset hypertension with proteinuria after 20 weeks of gestation. In pre-eclampsia proteinuria, a 24-hour urine sample contains 300 mg of protein after 20 weeks of gestation. Evidence shows that gestational hypertension progresses to pre-eclampsia in 10-20% of pregnant women [4]. First pregnancy, family history of pre-eclampsia, pre-existing hypertension, renal disease, advanced maternal age, multiple gestation, and diabetes mellitus are risk factors associated with pre-eclampsia [5]. There is also an increased risk for cardiovascular disease in pregnant women with hypertensive disorders [6-15]. These disorders also alter renal function and morphology during pregnancy. Previous literature suggests that microalbuminuria is markedly increased in pregnant women with hypertensive disorders [16-17]. A study also demonstrated an association between renal diseases and a history of pre-eclampsia [18]. In this regard, there is a paucity of studies on the causal relationship between kidney injury in pre-eclampsia and chronic kidney disease (CKD) [19]. An analysis of data from the birth and death registries of Norway revealed that women with first trimester pre-eclampsia generally had a higher risk (more than 3.2 times) to progress to CKD [19].

Acute kidney injury (AKI) in pregnancy is common in developing nations [20-21], contrary to developed nations, which have relatively few cases due to better antenatal care [20,22-25]. Developed countries also have lower rates of septic abortion because of its legalization. In underdeveloped countries, poverty, poor obstetrics care, lack of proper healthcare facilities and awareness of AKI during pregnancy and delayed referral process, multiparty, and the increasing population [20-21] contribute to AKI in pregnancy.

In the late trimester, hypertensive disorders of pregnancy were reported to be the most common cause of AKI [22,26-29]. Acute kidney injury in the presence of pre-eclampsia is rare and is often associated with a mild increase in serum creatinine. The mechanism underlying the development of AKI in pre-eclampsia is attributed to pathognomonic glomerular endotheliosis and injury. Acute kidney injury is more common in cases of severe pre-eclampsia and pre-eclampsia accompanied by HELLP syndrome—a severe variant of pre-eclampsia in which hemolysis, low platelet count, and elevated liver enzymes are present [30-31]. The aim of this study is to determine the prevalence of AKI in pre-eclamptic patients and to identify patients who are at risk of developing CKD.

Materials and methodology

This single-centre retrospective study was performed on women admitted with a diagnosis pre-eclampsia between 2010 and 2015 at King Abdulaziz University Hospital (KAUH), Jeddah, Kingdom of Saudi Arabia. Patients were included provided they had a diagnosis of pre-eclampsia with a follow-up period of two to five years. Approval to conduct this study was obtained from the Institutional Review Board of KAUH.

***Corresponding Author** Samera F. Albasri

MBBS, FRCPC, ABIM Department of Medicine, Faculty of Medicine, King Abdulaziz University Jeddah, Saudi Arabia 2Saalbasri@kau.edu.sa

The data were analyzed using the Statistical Package for the Social Sciences (IBM SPSS, Armonk, NY, US), version 20.0. Descriptive statistics such as frequency distribution and central tendency were calculated for the demographic details of patients. Binary logistic regression analysis was used to determine the factors associated with CKD, and the association between AKI and CKD was determined by the chi-square test. The tests were run with an alpha level of 0.01 and 0.05.

The estimated glomerular filtration rate (eGFR) was used to determine kidney function. We used the CKD-EPI formula to estimate the GFR.

Regarding the eGFR rates, the kidney function of patients was categorized as follows: Normal (> 90 mL/min/1.73 m2), stage 1 kidney disease (90 mL/min/1.73 m2), stage 2 kidney disease (60-89 mL/min/1.73 m2), stage 3 kidney disease (30 - 59 mL/ min/1.73 m2), stage 4 (15 - 29 mL/ min/1.73 m2), and stage 5 (<15 mL/ min/1.73 m2).

Results:

A total of 568 patients were included in this study. The majority of patients (43%) were in the 21–30-year age group (Table 1). Approximately 70% of the patients were non-Saudis, who originated from different regions of the kingdom. Abortion and infertility were documented as follows: most patients did not have a history of pre-eclampsia, infertility, or abortion whereas 2% of patients had a history of pre-eclampsia, 26% had a history of abortion, and 1% had a history of infertility. Only a small proportion of the sample had co-morbidities such as diabetes mellitus, hypertension, or heart failure.

Table 1. Demographic details of the patients (n=568)

Demographic details	Frequency (n)	Percent (%)
Age group (years)		
< 20	55	9.7
21-30	246	43.3
31-40	220	38.7
> 41	47	8.3
Nationality		
Saudi	167	29.4
Non-Saudi	396	69.7
Missing	5	.9
Previous Pre-eclampsia		
Absent	518	91.2
Present	12	2.1
Missing	38	6.7
Previous Abortion		
No	411	72.4
Yes	147	25.9
Missing	10	1.8
Previous Infertility		
No	526	92.6
Yes	3	.5
Missing	39	6.9
Co-morbidity		
Diabetes mellitus	2	0.4
Hypertension	14	2.5
Heart failure	4	0.7

Table 2 compares the patients' laboratory results at presentation and during the last follow-up. Hemoglobin, neutrophil count, platelets count, blood urea nitrogen, serum creatinine, and estimated glomerular filtration rate were highly variable at presentation and last follow-up ($p < 0.01$). In addition, pre-eclamptic patients had a high level of hemoglobin, neutrophil count, blood urea nitrogen, serum creatinine, and estimated glomerular filtration rate at presentation compared with the last follow-up. White blood cell (WBC) counts also slightly differed at presentation compared with the levels at the last follow-up ($p < 0.05$). However, there were no significant differences in the levels of HbA1C, fasting blood glucose, serum albumin, serum total cholesterol, serum LDL-C, and serum triglyceride at presentation and during the last follow-up.

Table 2. Comparison between biochemical levels at presentation and last follow-up of pre-eclamptic patients

Bio-chemical variables	At presentation (Mean ± SD)	Last follow-up (Mean ± SD)	p-value
Hemoglobin (mg/dL)	11.26 ± 1.71	10.32 ± 1.76	0.001**
Neutrophil count (x109/L)	60.15 ± 29.10	56.66 ± 28.59	0.001**
Platelets count (x109/L)	220.73 ± 90.79	275 ± 108.77	0.001**
WBC (x109/L)	13.98 ± 30.27	11.02 ± 4.93	0.027*
HbA1C level (%)	10.34 ± 12.40	9.80 ± 9.39	0.511
Fasting blood glucose (mmol/L)	6.52 ± 4.56	5.69 ± 1.68	0.164
Blood urea nitrogen (mmol/L)	3.98 ± 2.58	3.55 ± 2.69	0.001**
Serum creatinine (umol/L)	71.08 ± 38.63	64.84 ± 54.51	0.001**
Estimated glomerular filtration rate (mL/min/1.73 m2)	124.36 ± 49.33	114.38 ± 62.98	0.001**
Serum albumin (g/dL)	22.32 ± 4.95	22.82 ± 6.85	0.107
Serum total cholesterol (mmol/L)	4.61 ± 1.74	4.58 ± 1.10	0.957
Serum LDL-C (mmol/L)	3.29 ± 1.15	3.45 ± 1.19	0.411
Serum triglyceride (mmol/L)	2.17 ± 1.02	1.94 ± 1.29	0.406

Abbreviations: HbA1C, glycated hemoglobin; LDL-C, low-density liproprotein cholesterol; SD, standard deviation; WBC, white blood cell.

Approximately 95% of the patients had a normal GFR at presentation (Table 3). However, only 83.6% of the patients had a normal level GFR at the last visit. Further, 5.0% of the patients had pre-eclampsia with kidney disease at presentation, but only 2.0% of the patients had kidney disease during the last check up.

Table 3. Stages of kidney disease among pre-eclampsia patients at presentation and last follow-up

Kidney disease stage	At presentation n (%)	Last follow-up n (%)
Normal (> 90 mL/min/1.73 m2)	539 (94.9)	475 (83.6)
Missing	5 (0.9)	81 (14.3)
Abnormal kidney function	24 (4.22)	12 (2.11)
Stage 1 (90 mL/min/1.73 m2)	3 (0.5)	-
Stage 2 (60-89 mL/min/1.73 m2)	21 (3.7)	11 (1.9)
Stage 3 (30 - 59 mL/ min/1.73 m2)	-	1 (0.2)
Stage 4 (15 - 29 mL/ min/1.73 m2)	-	-

Stage 5 (< 15 mL/ min/1.73 m2)	-	-

Of the 568 pre-eclamptic patients, 42 developed diabetes mellitus during pregnancy, followed by 39 patients who had intrauterine fetal deaths. Other reported incidents are shown in Table 4. An emergency cesarean section was the most common mode of delivery (56.80%) followed by spontaneous vaginal delivery (31.10%).

Table 4. Morbidity of the pre-eclampsia patients during pregnancy

Variables	n (%)
Maternal morbidity	
Developed diabetes mellitus	42 (7.40)
Developed antepartum hemorrhage	9 (1.60)
Developed cardiovascular disease	3 (0.50)
Developed intrauterine fetal death	39 (6.90)
Admitted to intensive care unit	5 (0.90)
Mode of delivery	
Emergency cesarean section	323 (56.80)
Spontaneous vaginal delivery	177 (31.10)
Ventouse delivery	13 (2.30)
Elective cesarean section	5 (0.90)
Assisted breech	5 (0.90)
Forceps delivery	2 (0.40)
Emergency cesarean section and assisted breech	1 (0.20)
Ventouse delivery and spontaneous vaginal delivery	1 (0.20)
Emergency cesarean section and spontaneous vaginal delivery	1 (0.20)
Missing	41 (7.20)

The prevalence of AKI among pre-eclampsia patients was 4.2% (Table 5). A large proportion of pre-eclamptic patients (94%) had a normal GFR (without kidney disease) at presentation and the last follow-up visit while 3.3% of the patients had a normal GFR at the last follow-up, but they had kidney disease at presentation. Likewise, four patients had kidney disease at last follow-up, but they had a normal level of GRF at presentation. Finally, eight patients had pre-eclampsia with kidney disease at presentation and last follow-up. A significant association was found between patients' results at presentation and the last follow-up visit (p-value < 0.05).

Table 5. Prevalence of Acute Kidney Injury

	Frequency (n)	Percent (%)
No AKI	539	94.9
AKI	24	4.2
Missing	5	0.9
Total	568	100.0

Abbreviations: AKI, acute kidney injury.

Table 6 presents the binary logistic regression model for the independent variable 'pre-eclampsia with AKI' and the dependent variable 'CKD.' The findings strongly suggest that pre-eclampsia together with AKI significantly influence CKD (p < 0.01). In addition, pre-eclamptic patients with AKI possess a higher risk of CKD (OR > 1).

Table 6. Risk of Chornic kidney disease among the pre-eclampsia with acute kidney injury

Independent variable	p-value	Odds ratio	95% Confidence interval
Acute kidney injury	<0.001	668.750	155.928-2868.161
Constant	<0.001	0.007	

Dependent variable: Chronic kidney disease

Summary of the Findings

In this study, only a small proportion of the patients had co-morbidities such as diabetes mellitus, hypertension, and heart failure. The patients' hemoglobin, neutrophil count, platelet count, WBC count, BUN, serum creatinine and GFR levels varied at presentation compared with those at the last follow-up visit. However, there was no variation in the levels of HbA1C, fasting blood sugar, serum albumin, serum total cholesterol, LDL-C and triglyceride at presentation and the last follow-up visit. Based on eGFRe, a small proportion of the patients had CKD. Similarly, only 4% of the patients had AKI. Further, pre-eclampsia together with AKI increased the risk for CKD.

Discussion:

The prevalance of AKI in patients with pre-eclampsia who were followed up at our institution was 4.2%. However, we cannot compare our findings with those of other authors given that an estimation of the prevalence of AKI in pre-eclampsia is complicated by differences in the criteria used to define AKI among studies. Furthermore, previous reports state that the prevalence of AKI in women with pre-eclamsia is not well known [24-31] , and epidemiological studies have mainly reported the incidence of AKI in pre-eclamptic women [22-31]. According to a previous hospital-based study conducted in Turkey [32], approximately 8.9% of women with severe pre-eclampsia developed AKI. In another study conducted at a teaching hospital in Turkey [33], approximately 15% of women with pre-eclampsia/eclampsia had AKI. Data from other Gulf countries, notably from Saudi Arabia, are nonexistent. While studies from individual centers show that obstetric AKI is prevalent in Saudi Arabia [34-35], the lack of a meta-analysis on obstetric AKI compounds the issue of estimating the actual prevalence and incidence of AKI in pre-eclampsia in our region.

The pathogenesis of future renal disease in pre-eclampsia is not completely understood. However, it is believed that several mechanisms are involved in the development of renal disease in patients with pre-eclampsia. It has been suggested that similar factors cause kidney disease and pre-eclampsia. For example, factors such as insulin dysregulation, high blood pressure, and obesity have been linked to both kidney disease and pre-eclampsia [36-38]. In patients who develop pre-eclampsia, it is believed that the initial phase is characterized by abnormal placentation, probably due to ischemia. There is increased placental release of soluble antiangiogenic factors, including soluble Flt-1 and soluble endoglin, which enter the maternal blood circulation, triggerring endothelial dysfunction and the clinical syndrome [39]. Glomerular endothelial cells and possibly other fenestrated endothelial cells are deprived of necessary growth factors due to the presence of antiangiogenic substances in the circulation [40].

Our data suggest that pre-eclampsia per se does not increase the risk of CKD contrary to the report of Vikse et al [19], who suggested that pre-eclampsia was a clinical marker for an increased risk to develop end-stage renal disease. Furthermore, the authors found that the risk of CKD was greater if pre-eclamptic women had a low birth weight or preterm neonate or if the patient had pre-eclampsia in two or more pregnancies. We found that for patients with pre-eclampsia, where the risk for AKI is generally low, the risk for CKD was higher in patients who also had AKI during pregnancy, suggesting that pregnant women with pre-eclampsia and AKI were at a higher risk for CKD.

While it has been reported that chronic endothelial injury occurs in patients with severe pre-eclampsia, it has not yet been established whether pre-eclampsia causes chronic vascular injury over the course of time. Laboratory studies have demonstrated that episodes of AKI have a deleterious effect on the pathogenesis and course of CKD [41-42]. In one study [41], it was found that repetitive nephrotoxic insults resulted in high CKD in rates. In another study [42], the authors reported persistent alterations at the gene transcription in the kidneys of rats who are exposed to ischemia, even after they recovered and their creatinine levels were similar to those of untreated controls. These data support the association

between repetitive AKI and progressive kidney disease. In a more recent study, Bydash and Ishani [43] reported AKI as a strong marker of future episodes of AKI and end-stage renal disease and further suggested classifying a whole subset of CKD caused by AKI.

Limitations of the study

The main limitation of this study is that normal pregnancy (without pre-eclampsia) was not included. Another limitation is that the follow-up period after pregnancy was relatively short to measure the risk for CKD regardless of the presence or absence of AKI. Future multi-center, prospective studies should include normal pregnancies for comparison and a longer follow-up period.

Conclusion

This study shows that patients have a higher risk for CKD if they have AKI and pre-eclampsia. Patients with pre-eclampsia and AKI should have regular follow-up since they have an increased risk of CKD. Healthcare personnel should provide adequate education and monitor these patients for other cardiovascular risk factors.

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