Original Article

Assessment of Kidney Impairment and Related Risk Factors in Pregnant Women Attending the University Center for Public Health and Rango Health Centers in the Southern Province of Rwanda

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Abstract

Background

Pregnant women are susceptible to kidney function impairment due to physiological and metabolic changes induced by pregnancy. A series of studies suggested an overall progressive increase in glomerular filtration rate approximating 40-50% of the non-pregnant state.

Objective

To determine the prevalence of kidney impairment and related risk factors in pregnant women attending the University Center for Public Health and Rango health centers in Rwanda.

Methods

An analytical cross-sectional study that enrolled 139 consecutive pregnant women was conducted. Serum creatinine and qualitative urine protein and glucose determinations were carried out using standard laboratory methods to assess the integrity of kidney function.

Results

The prevalence of kidney impairment in pregnant women was 20.9% comprising mainly women in the 2nd trimester of pregnancy (60.4%). Among the women with kidney impairment, 2.9% had high blood pressure. Of the overall study participants, 8.6% had glycosuria whilst 5% had proteinuria. The majority had gravida of one. There was a significant association between hypertension, glucosuria, age and gravida with kidney impairment (P = 0.001).

Conclusions

Findings show that pregnancy with or without putative risk factors is associated with kidney impairment in apparently healthy women, as shown by the high prevalence of 20.9%. We therefore recommend routine screening of kidney dysfunction during pregnancy.

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Keywords: renal impairment, preeclampsia, proteinuria, glycosuria, gravida

Introduction

The kidneys are a paired organ system located retroperitoneally in the abdomen, on either side of the vertebral column. Functions of the kidney include excretion of mainly nitrogenous metabolic waste, water and electrolyte homeostasis and an endocrine function.[1] Kidney dysfunction is therefore characterised by such metabolic aberrations as, nitrogenous waste retention, dysregulation of electrolyte homeostasis, anaemia, bone disorders and metabolic acidosis, among others.[2]

In normal pregnancy there is plasma volume expansion that increases the glomerular filtration rate (GFR) by 40-65% whilst renal plasma flow increases by up to 80% as compared to the non-pregnant state. The underlying mechanisms remain unknown although nitric oxide and endothelin may play a role through renal vasodilation.[3] Tubular function is also altered, leading to mild proteinuria, hyponatraemia and glycosuria.[3] Kidney size increases owing to fluid retention that leads to physiologic hydronephrosis and urinary stasis which in turn increases the risk of pyelonephritis and asymptomatic bacteriuria. Both these are risk factors for kidney impairment.[4]

The increase in GFR leads to lower concentrations of serum urea and creatinine compared to the non-pregnant state. The decrease in serum urea is further exacerbated by the positive nitrogen balance associated with pregnancy. Serum urea and creatinine are routine biomarkers of kidney function thus, the pregnancy induced decrease in their concentrations diminishes their clinical utility in the diagnosis of kidney impairment.[5] Laboratory tests for renal function assessment in pregnancy must therefore be interpreted bearing in mind these changes in GFR since results that would be regarded as normal in the nonpregnant state, could actually indicate renal dysfunction during pregnancy. However, uniformly agreed diagnostic criteria of kidney impairment in pregnancy is non-existent thus, many cases may be missed in pregnancy.[6] Furthermore, the estimated GFR inconsistently underestimates renal function and should not be used for diagnosis during pregnancy. However, if serum creatinine levels exceed 0.8mg/dL at any stage during pregnancy, renal dysfunction should be suspected and further investigations carried out.[7]

Kidney disease during pregnancy presents as pre-existing disease diagnosed before conception, chronic kidney disease (CKD) with onset during pregnancy and renal disease that presents for the first time during pregnancy. Kidney impairment can occur acutely leading to acute kidney injury (AKI) often as a result of hypovolaemia, sepsis or due to the effects of a wide range of nephrotoxins.[8] Without intervention AKI, will progress to CKD that without intervention, leads to end stage renal disease. Both AKI and CKD are associated with adverse feto-maternal outcomes.[9] Pregnancy-related acute kidney injury (PR-AKI) commonly occurs in the third trimester, predominantly precipitated by hypertensive disorders and puerperal pathologies that include sepsis and haemorrhage.[9] PR-AKI also occurs due to fluid losses secondary to excessive vomiting, induced by hyperemesis gravidarum, blood loss from pregnancy-related complications such as antenatal bleeding or from obstetric complications such as septic abortion or abruptio placentae. Intrinsic renal disease during pregnancy occurs in pre-eclampsia and eclampsia.[10]

In Africa, PR-AKI is of major public health concern and is reported as the most common cause of severe AKI requiring dialysis in young women.[11] PR-AKI is the leading cause of maternal and foetal morbidity and mortality.[11] The pathophysiological basis of PR-AKI depends on local factors such as legality of abortion, exposure to infectious diseases such as malaria and HIV, adequacy of infrastructure for obstetric care, preeclampsia and local contact with nephrotoxins.[12] Racial/ethnic differences have been reported to exist in the incidence of PR-AKI with black women having over 40% higher risk compared to white women.[13]

Additional risk factors of PR-AKI include older age, history of pre-eclampsia, lower socioeconomic status and a history of diabetes mellitus.[12] Furthermore, PR-AKI has a profound impact on future health by increasing the risk of developing hypertension, CKD and cardiovascular diseases.[12] Monitoring renal function in pregnant women is therefore crucial in reducing the rate of adverse events, both in women with pre-existing kidney disease and those who develop kidney disease during pregnancy. Determining the incidence of PR-AKI has however, remained difficult because of lack of validated criteria. Furthermore, kidney function assessment is not routinely conducted during ante natal care in women considered to be at low risk of kidney function impairment.[12]

The incidence of PR-AKI in low- and middle-income countries (LMIC) is reported to be compared to high income countries (4%–26% versus 1%–2.8%, respectively).[14] The incidence of PR-AKI is however, declining in LMIC, due to improved antenatal care with such decreases reported in India and China where prevalences decreased from 15% in the 1980's to about 1.5% in 2010.[15] The incidence of PR-AKI in Africa is about 1:1000 deliveries, accounting for 5–27% of all cases of AKI among adults in Africa, but this prevalence is still 20–100-fold higher than in developed countries.[11] There is however, limited and fragmented data on the incidence of overall AKI in hospitalised patients in Africa with the incidence being estimated to be 0.3–1.9% but incidences as high as 17.2% have been reported in Malawi.[16] A study from Morocco, reported an incidence of 6.6 cases per 1000 deliveries with 16% requiring dialysis.[17] A study conducted in Rwanda in 2015 reported an overall AKI incidence of 2.8% and a mortality rate of 32% among patients admitted to tertiary care teaching hospitals in Rwanda.[18] However, there is paucity of data on the prevalence and risk factors of PR-AKI in in sub Saharan Africa including Rwanda. Furthermore, in Rwanda, pregnant women are not routinely evaluated for possible renal dysfunction and it is likely that cases of PR-AKI can develop insidiously leading to potential increases in adverse feto-maternal outcomes. This study assessed the prevalence of kidney impairment among pregnant Rwandan women aged 18 years or older and in their second and third trimester of pregnancy.

Methods

Study Design and Setting

An analytical cross sectional study to determine the prevalence of kidney impairment was carried out at the University Center for Public Health and Rango Health Centers, Huye district, Southern Province of Rwanda. The two health institutions have a large participant catchment area whose population demographics allowed for generalization to the rest of Rwanda. The catchment area also includes a mixture of rural and urban area dwelling patients.

Sample Size Calculation

The sample size of 139 was estimated using Cochran's formula for prevalence studies based on an expected prevalence of kidney impairment of 10% and a level of precision of 5%.[19]

Participant recruitment

A total of 139 consenting pregnant women aged 18years old and above and in their second and third trimesters of pregnancy were consecutively enrolled. The participant ages ranged from 18–44 years. Women who self-reported a history of pre-existing kidney diseases and diabetes mellitus were excluded.

Data Collection and Laboratory Procedures

After screening for fulfilment of inclusion criteria, each participant was asked to provide written informed consent. A structured questionnaire was administered to consenting participants to collect clinical and demographic characteristics and information on putative risk factors such as age, gestational period, gravida, self-reported history of kidney disease and diabetes mellitus. A total of 3 milliliters whole blood was drawn from each consenting participant.

The blood was allowed to clot at room temperature before centrifugation at 3000rpm for five minutes to harvest serum which was stored at -200C until the time of laboratory analysis. In addition, 20millilitres of random urine were also collected from each participant for immediate urinalysis.

Serum creatinine concentrations were measured on each participant based on the Jaffe reaction using the Humalyser semi-automated chemistry analyser 3500 (HUMAN Diagnostics, Wiesbaden, Germany). In this method, creatinine in the patient's specimen reacts with alkaline picrate to form the reddish-orange Janovsky complex whose absorbance was measured at 520nm and used to calculate the concentration. [20] Semi-quantitative protein and glucose analysis was carried out using urine "dipstix' manufactured by ACON Laboratories Inc, (San Diego USA). The 'dipstix' pad for glucose analysis incorporated glucose oxidase and iodine as reagents that react with glucose giving variations of brownish colour corresponding to the quantity of glucose present in the urine sample. Urine protein was detected using the 'protein error of indicators' principle that utilises tetrabromophenol blue buffered with citrate at pH3. The presence of protein gives variations of a green colour.[21]

All laboratory procedures were carried out in accordance with the principles of good clinical laboratory practice to ensure quality results.

The reference interval for serum creatinine used to define kidney dysfunction in the present study was 0.4–0.8mg/dL, [22] and urine protein excretion was considered abnormal when levels exceeded positive (++) which corresponds to 300mg/24hours. [23] Urine glucose was considered clinically significant when urine glucose levels were at least positive (++) corresponding 100mg/dL.[24,25]

Data Analysis

Categorical data were summarized as counts and proportion. Normally distributed continuous data was summarized as mean and standard deviation (SD) whilst non-normal continuous data were summarised as median and interquartile range (IQR). Data were also summarized in tables and histograms. Participant data were stratified according to the variations in clinicodemographic characteristics such as age categories, gravida, proteinuria, glucosuria and serum creatinine level. The Student's t-test was used for intergroup statistical comparisons of means whereas one-way analysis of variance (ANOVA) with post hoc Bonferroni correction was used to compare means of three groups or more. In all cases, α was set at 0.05.

Ethical considerations

Ethical clearance was granted by the University of Rwanda, College of Medicine and Health Sciences, Institutional Review Board (Ref: CMHS/IRB/440/2022) before conducting the study. Each consenting participant gave written informed consent prior to enrolment and participants were at liberty to opt out of the study at any stage without any penalties. Participant confidentiality was maintained by de-identifying participants through use of unique study code numbers. Participants' data were kept strictly confidential, with access restricted only to authorized study personnel. Participants with abnormal laboratory findings were referred for clinical management.

Results

Altogether 139 study participants aged 18-44years were enrolled. The gestation periods of these participants ranged from second to third trimester. The clinicodemographic characteristics of the study participants are presented in Table 1.

The median (IQR) age of the participants was 28 (24–33) years. The study participants were further stratified into three age categories; 15–25; 26–35 and over 35 years. The majority of the women 63 (45.3%) were in the 26–35 years category. The gravida of the study participants ranged from 1 to 10 with a median (IQR) of 2 (1–3). Out of the 139 pregnant women enrolled, the majority 84 (60.4%) were in the second trimester whilst 55 (39.6%) were in trimester three of pregnancy. The women were further grouped by blood pressure status and the majority 135 (97.1%) were normotensive.

Table1. The clinicodemographic characteristics of the study participants

Variable	n (%)
Trimester	
2nd	84(60.4)
3rd	55(39.6)
Age Category	
18-25 years	52(37.4)
26-35 years	63(45.3)
>35 years	24(17.3)
Hypertension Status	
Hypertensive	4(2.9)
Non-hypertensive	135(97.1)
Gravida	
≤5	126(90.7)
>5	13(9.4)

Laboratory evaluations were also done to determine the prevalence of kidney impairment among the study participants. Serum creatinine was measured and proteinuria and glycosuria were also assessed on random urine specimens collected from the study participants. Results are presented in Table 2.

Table 2. Prevalence of serum and urine indicators of kidney impairment in study participants

Variable	n (%)
Glycosuria	
Negative	127(91.4)
Positive(+) (up to 50mg/dL)	2(1.4)
Positive(++) (51–100mg/dL)	9(6.5)
Positive(+++) (≥300mg/dL)	1(0.7)
Proteinuria	
Negative	132(95.0)
Positive(+) (up to100mg/dL)	2(1.4)
Positive(++) (101–300mg/dL)	2(1.4)
Positive(+++) (≥500mg/dL)	32(2.2)
Serum Creatinine	
≤0.8mg/dl	110(79.1)
>0.8mg/dl	29(20.9)

Overall, 110 (79.1%) of the study participants had serum creatinine levels ≤ 0.8mg/dl whilst 29 (20.9%) had abnormally high serum creatinine levels indicating possible kidney function impairment. In terms of glycosuria, 127 (91.4%) did not have any detectable glucose in their urine whilst 12 (8.6%) had detectable glucose ranging from positive (+) to positive (+++). A total of 132 (95.0%) of the participants had no detectable proteins in urine whilst only 7 (5.0%) had detectable proteinuria ranging from positive (+) to positive (+++).

In order to determine possible risk factors for kidney impairment, we compared mean serum creatinine levels between women grouped according to the binary outcomes of gravida, trimester, hypertension status and the tri-level age groups. The groups based on urine glucose and protein were dichotomized to positive and negative for further statistical evaluation. For the binary outcomes, the Student's t-test was used to ascertain if there were statistically significant differences in serum creatinine. However, for the three age categories, the ANOVA test with Bonferroni correction was used to determine if there was any significant difference in serum creatinine by age. The level of significance was fixed at 0.05 in each case. The results are presented in Table 3.

Mean serum creatinine levels were significantly higher in women with glycosuria 1.07 (SD 0.14) mg/dl compared to those whose urine was free of detectable glucose 0.63 (SD 0.24) mg/dl ($P < 0.001$). Similarly, mean serum creatinine levels were significantly higher in women with proteinuria 1.18 (SD 0.21) mg/dl compared to those whose urine specimens lacked detectable protein 0.64 (SD 0.24) mg/dl ($P < 0.001$). Mean serum creatinine levels were also significantly higher by gravida and hypertension status (both $P < 0.001$). No overall significant difference was observed by age category but serum creatinine levels were significantly higher in older women (>35 years) compared to those aged 26-35 years and those aged 15-25years (both $P < 0.001$). However, there was no significant difference in creatinine results based on trimester.

Table 3. Association between mean serum creatinine and risk factors for kidney impairment

Variable	Mean Serum creatinine mg/dl	*P* value
Glycosuria		
Negative	0.63±0.24	**<0.001**
Positive	1.07±0.14	
Proteinuria		
Negative	0.64±0.24	**<0.001**
Positive	1.18±0.21	
Trimester		
Second	0.68±0.23	0.5591
Third	0.65±0.31	
Gravida		
≤5	0.64±0.24	**0.001**
>5	0.92±0.34	
Hypertension		
Yes	1.25±0.24	**<0.001**
No	0.65±0.25	
Age (years)		
15-25	0.60±0.21	0.151
26-35	0.64±0.25	
>35	0.90±0.29	

Discussion

Kidney function impairment during pregnancy is associated feto-maternal morbidity and mortality, yet kidney function assessment is not part of the routine battery of tests conducted during the antenatal assessments unless the woman has a prior diagnosis of kidney disease.[9] This study sought to assess the presence of kidney function impairment in pregnant women aged 18 years and above who were in the second and third trimesters of pregnancy. The study yielded some interesting findings and a surprisingly high prevalence of kidney impairment of 20.9%. This finding is a major cause of concern that should warrant a relook at clinical guidelines on the management of pregnant women in order to minimize feto-maternal complications. The findings of this study are similar to the study conducted in Egypt in which PR-AKI accounted for 14% of all patients who presented in the renal unit.[10] The results are also in concordance with the findings in a study which reported a high incidence of PR-AKI of between 4-26% in developing countries.[14] The same study found a low incidence of 1-2.8% in developed countries.[14] The difference in these findings could be attributed mainly to advanced prenatal and antenatal care service provision in developed countries compared to developing countries. Differences could also be due to social, cultural, economic and ethical variations. The results are also in agreement with findings from a systematic review including 41 studies in Sub-Saharan Africa which showed that obstetric cases presented 16% of all AKI causes.[11] The same study also revealed an incidence of PR-AKI in Africa accounting for 5-27% of all cases of AKI.[11] A study from Morocco, reported an incidence of 6.6 cases per 1000 deliveries with 16% requiring dialysis.[16]

The majority of the study participants were within the 26-35 years' age range which reflected the peak female reproductive age category in Rwanda. Data from the 2005, 2010 and 2015 Rwanda Demographic and Health Surveys reported a fertility transition which was also associated with changes in nuptial patterns with women getting married when they are older.[26] Only 2.9% of the study participants were hypertensive. This finding was much lower than the 11.3% reported in a study conducted at Ruhengeri Referral Hospital, in northern Rwanda in 2021.[27] The discordance in the findings with the present study could be attributed to differences in the underlying study population. In the present study only women in the second and third trimesters of pregnancy were enrolled whereas in the other study women in the first trimester were also enrolled. Furthermore 90.7% of the women in this study had a gravida ≤ 5 which is reflective of the observation reported in the 2019-2020 Rwanda demographic and health survey that women in Rwanda have an average of 4.1 children.[28] Mean serum creatinine levels were significantly higher in women with proteinuria. In a previous study, proteinuria was observed in 79% of the participants which was much higher than the findings of this study.[29]

The possible reasons for this discordance could be that the pregnant women that participated in that study were diagnosed with diabetic nephropathy accompanied with moderate-to-severe renal dysfunction.[29] Findings from the current study indicate that apparently healthy pregnant women have a low but significant risk of developing pregnancy induced kidney impairment.

Dysglycaemia had a low frequency among our study participants and was also associated with pregnancy induced kidney impairment in the current study. This finding is in concordance with the hypothesis stated in a previous study that reported the presence of glycosuria in normoglycemic pregnant women.[25] This glycosuria could be purely of renal origin given that the glomerular filtration is normally increased in pregnancy due to increased renal blood flow. When the glomerular filtration increases, the kidneys become less efficient at reabsorbing materials including glucose from the ultra-filtrate.[30] It is for this reason that pregnancy associated glycosuria cannot be attributed to frank diabetes mellitus and glucose intolerance.

The current study also found an association between gravida and kidney impairment. Mean serum creatinine levels were significantly higher as gravida increased but 65.46% of pregnant women in this study had normal serum creatinine level. Women with gravida ≥ 5 had higher serum creatinine levels which might have been due repetitive deterioration of kidney function caused by successive pregnancies over time. These findings are in concordance with findings from a previous study that also highlighted that hyperemesis gravidarum common in most pregnancies, is among the major causes of AKI in pregnant women in early pregnancy probably due to vomiting induced hypovolemia.[31]

The current study showed that 97.1% of the participants were normotensive with only 2.9% having high blood pressure. Hypertension is an established risk factor for kidney impairment and the mean serum creatinine levels were also significantly higher by hypertension status in the current study confirming the well-recognized association between hypertension and high creatinine levels hence kidney impairment in pregnant women.

In a study conducted in the USA, aggravation of hypertension was observed in 73% of pregnant women which was much higher than the findings from this study.[29] The basis for this difference could be that the pregnant women that participated in that study were diagnosed with diabetic nephropathy and mild-to-severe renal dysfunction prior to enrolment.[29] The researchers concluded that pregnancy had a > 40% probability of aggravating renal disease.[29] The findings from the current study indicate that hypertensive pregnant women had significantly higher serum creatinine levels implying a higher probability of developing overt kidney impairment.

There was no significant statistical difference in creatinine results by trimester as the study deliberately enrolled women in or above their midterm trimester of pregnancy based on reports from literature that kidney impairment and other metabolic disorders were likely to manifest after the first trimester of pregnancy.[3,31–34]
It was also observed in this study that serum creatinine levels were significantly different by age group. Serum creatinine generally increased as age increased. Kidney size diminishes with age accompanied by an age dependent decrease in the glomerular filtration rate (GFR). This age dependent reduction in GFR explains the significant difference in serum creatinine observed when study participants were stratified by age. Advancing age is therefore a risk factor for kidney impairment in pregnant women.

Strengths and Limitations

The major strength of the present study was the fairly large sample size and the measurement of serum creatinine using an established laboratory method. Our study however, also had some limitations. The first limitation was our inability to measure urine protein using quantitative method on timed urine specimens.

We also used the qualitative urine glucose test as a proxy for the assessment of dysglycaemia. Glucose is known to also appear in non-dysglycaemic states. Our study participants were derived from two health centers in close proximity. Findings from this study may therefore not be generalizable to the Rwandan population but still provide important baseline data to guide clinical practice. The cross sectional study design employed in the current study precludes the determination of the temporal relationship between pregnancy and kidney impairment. In addition, the scope of our study did not allow for stratification of the different types kidney disease and we only explored a limited number of putative risk factors of PR-AKI.

Lastly, our research and community engagement strategy aims to prioritize the need for credible scientific evidence on kidney impairment to support evidence based clinical practice.

Conclusion

Findings from this study show that pregnancy in patients with or without the putative risk factors is associated with kidney impairment in apparently healthy women. The apparently high prevalence of kidney impairment at 20.9% is alarming and should stimulate future preferably prospective studies to ascertain the temporal relationship between pregnancy and kidney impairment.

Accurate diagnosis, treatment and monitoring of associated pregnancy related kidney impairment is essential in order to promote feto-maternal wellbeing.

Conflict of interest

None

Authors' contribution

SM, FI, SM, AI, HTM all played a role in the conception, design, interpretation, and writing of the manuscript; D K T contributed with the conception and design of the manuscript; CM contributed with conception, data analysis, writing and editing the manuscript.

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