

Hypertension in pregnancy: A future risk for chronic kidney disease in South Africa

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Background. Hypertension in pregnancy is a risk factor for end-stage chronic kidney disease (ESKD) and is particularly common in South Africa (SA). There are no data for the risk of developing chronic kidney disease (CKD).

Objectives. To conduct a study of all female patients who presented to the renal replacement programme at Groote Schuur Hospital, Cape Town, SA.

Methods. This was a retrospective study of female patients with ESKD who were presented to renal replacement meetings between 2007 and 2017. For each patient who was assessed, there was a comprehensive letter detailing patient demographics, as well as psychosocial and medical history, which served as the source data. Patients with a history of hypertension in pregnancy were identified as the case group and those without the condition were the control group. Patient demographics, causes of CKD, kidney function and outcome of the meeting were documented.

Results. Of the 415 female patients with ESKD, 70 (16.9%) had a history of hypertension in pregnancy. The ethnic breakdown was as follows: 132 (42.44%) black, 172 (55.3%) mixed ancestry and 7 (2.25%) white. Compared with the control group, the patients were younger, with a median age of 33 v. 41 years ($p < 0.001$), higher serum creatinine 1 045 v. 751 $\mu\text{mol/L}$ ($p = 0.017$) and lower estimated glomerular filtration rate (eGFR) 4.0 v. 5.1 mL/min ($p = 0.029$). Patients were more likely to abuse methamphetamine (5.7 v. 1.7%; $p = 0.049$), and less likely to be diabetic (1.4 v. 20.9%; $p < 0.001$) or HIV-positive (2.9 v. 12.5%; $p = 0.019$). There were no ethnic differences between patients and controls. Underlying causes of renal disease showed significant differences, as patients were more likely to have hypertensive nephropathy (57.1 v. 22.9%; $p < 0.0001$), and less likely to have diabetic kidney disease (1.4 v. 20.4%; $p < 0.001$), HIV-associated nephropathy (HIVAN) (1.4 v. 6.4%) or polycystic kidney disease (1.4 v. 7.0%). There was no difference in acceptance to the dialysis and transplant programme (53 v. 47%).

Conclusions. This study suggests an important link between hypertension in pregnancy and ESKD. The patients were significantly younger, presented later and were more likely to have hypertensive nephropathy. Methamphetamine abuse appears to be a risk factor. The study suggests that all women with hypertensive disorders during pregnancy need further evaluation and follow-up postpartum.

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Hypertensive disorders of pregnancy (HDP) is one of the most common medical complications of pregnancy, affecting ~8% of all pregnancies. Two hospital-based studies in sub-Saharan Africa put the prevalence of this disorder at 11.5% and 26.5%, respectively.^[1] It remains one of the most direct causes of maternal morbidity and mortality. HDP is classified into chronic hypertension, gestational hypertension, pre-eclampsia and eclampsia. Despite clinical remission in most instances (the exception being chronic hypertension), with blood pressure usually decreasing to normal within 6 weeks,^[2] there is no structured follow-up programme for these women in South Africa (SA).

It is now abundantly clear that healthy women who develop pre-eclampsia are more likely to develop hypertension at a younger age (30 - 40 v. 50 - 60 years), have an up to 4-fold increased risk of cardiovascular disease, and are more likely to develop stroke, myocardial infarction, atrial fibrillation and end-stage chronic kidney disease (ESKD).^[3-6]

The mechanism underlying this association remains unclear.^[7] There are two competing hypotheses. Firstly, HDP reflects an underlying genetic/environmental predisposition to hypertension that is uncovered during pregnancy and predicts future risk. This is akin to gestational diabetes and future diabetes where hormonal changes in pregnancy unmask this predisposition.

The second and possibly a more important hypothesis is that in women who have had pre-eclampsia there is consistent evidence of a residual degree of vascular dysfunction postpartum.^[8] This undermines future vascular and renal function, resulting in an excess of cardiovascular and renal disease. Mechanisms underlying residual vascular damage are complex and involve, e.g. endothelin, angiotensin II, oxidative stress and inflammation, which may also interact with traditional risk factors for vascular disease.

There are few data regarding the prevalence of ESKD in SA following HDP. With this in mind, we conducted a retrospective study of women presenting to the renal assessment meetings at Groote Schuur Hospital, Cape Town, SA, for long-term dialysis to determine the prevalence of HDP and compare these women with those without this history.

Methods

This was a retrospective study performed on female patients with stage 5 chronic kidney disease (CKD), who were presented to renal replacement meetings at Groote Schuur Hospital between 2007 and 2017. Patients returning to the renal replacement programme after a failed transplant were excluded. For each patient there was a comprehensive letter detailing demographics, psychosocial status, medical history and causes of CKD. This served as the source data. The

causes of kidney disease were divided into hypertensive nephropathy, chronic glomerulonephritis (CGN), autosomal dominant polycystic kidney disease (ADPKD), diabetic kidney disease, HIV-associated nephropathy and miscellaneous. This information was obtained from a detailed report by the referring doctor in consultation with the consulting nephrologist and a detailed psychosocial review by an experienced social worker. Patients whose report indicated a history of HDP were identified as the case group and those without such history were the control group. HDP was classified into chronic hypertension, gestational hypertension, pre-eclampsia, eclampsia, or undefined if there was insufficient information in the assessment letter. Acceptance into the programme was based on criteria developed by the Western Cape Provincial Government.^[9]

Results were analysed using basic statistical tests – Pearson's χ^2 , Fisher's exact (2-sided) and 2-sample Wilcoxon rank-sum (Mann-Whitney) tests.

Ethical approval

The study was approved by the Health Sciences Research Ethics Committee of the University of Cape Town (ref. no. 422/2017), and formed part of a student study module for 3rd-year medical students.

Results

Of the 415 female patients with ESKD, 70 (16.9%) had a history of hypertension in pregnancy. The causes of the latter were as follows: eclampsia ($n=1$; 1.4%), pre-eclampsia ($n=26$; 37.1%), gestational hypertension ($n=11$; 15.7%) and undefined ($n=32$; 45.7%).

Compared with the control group, the patients were younger, with a median age of 33 v. 41 years ($p<0.001$), higher serum creatinine of 1 045 v. 751 $\mu\text{mol/L}$ ($p=0.017$) and lower estimated glomerular filtration rate (eGFR) of 4 v. 5.1 mL/min ($p=0.029$) (Table 1). Patients were more likely to abuse methamphetamine (5.7 v. 1.7%; $p=0.049$), and less likely to be diabetic (1.4 v. 20.9%; $p<0.001$) or HIV-positive (2.9 v. 12.5%; $p=0.019$). Underlying causes of renal disease showed significant differences, as patients were more likely to have hypertensive nephropathy (57.1 v. 22.9%; $p<0.0001$), and less likely to have diabetic kidney disease (1.4 v. 20.3%; $p<0.0001$), HIV-associated nephropathy (HIVAN) (1.4 v. 6.4%) or polycystic kidney disease (1.4 v. 7.0%). Six renal biopsies were available in case groups – 4 in the CGN group showed focal segmental glomerulosclerosis, IgA nephropathy ($n=2$) and mesangial capillary glomerulonephritis; 2 in the hypertensive nephropathy group showed malignant hypertension, and 1 showed cortical necrosis. There was no difference in acceptance

to the dialysis and transplant programme between patients and controls, respectively (53 v. 47%).

Discussion

This small retrospective study is the first to examine the prevalence of HDP in female patients with ESKD in SA. The prevalence was found to be 16.9%, with a relative risk of 4.2 compared with patients without HDP. The patient demographics, medical histories and causes of ESKD were also significantly different from those of the controls. In summary, the patients were younger, more likely to present later, abuse methamphetamines and have hypertensive nephrosclerosis, but less likely to be HIV-positive or diabetic, and fewer had HIVAN, diabetic kidney disease or polycystic kidney disease as the underlying cause of their kidney disease.

This is in agreement with previous studies of HDP where pre-eclampsia during a first pregnancy was associated with a relative risk of ESKD of 4.7, but the absolute risk was small: 14.5 per 100 000 population in a study from Norway.^[4] In a study in the UK, the number of ESKD events in normotensive patients' first pregnancy was 3.9%, gestational hypertension 5.2% and pre-eclampsia 7.5%.^[3] However, these studies did not report the underlying cause of ESKD.

The current study suggests that there is a significant unmet need for women with HDP. As we only studied patients with ESKD, our figures represent the tip of the iceberg. Many women have a lesser degree of CKD and are at risk of progression of their kidney disease. As the underlying cause is hypertensive nephrosclerosis, it suggests that this form of ESKD is preventable with earlier intervention. This is especially important in SA, where >50% of these young women did not qualify for dialysis owing to lack of resources. We recommend that women with HDP should undergo regular follow-up postpartum for early detection and treatment of hypertension and CKD and screening for methamphetamine abuse. The association of methamphetamine and CKD has previously been documented by our group^[10] – a service to establish this association is being planned at our hospital.

Study limitations

One of the limitations of the study was that we were unable to classify the HDP in 45.7% of cases, and were therefore unable to determine the effects of gestational hypertension, pre-eclampsia and chronic hypertension on ESKD. However, a recent publication has shown that both gestational hypertension and pre-eclampsia are associated with ESKD.^[11] A second limitation was that we assessed only women

Table 1. Demographic data of patients and controls

	Patients ($n=70$)	Controls ($n=345$)	p -value
Median age, years	33 (IR 28 - 41)	41 (IR 31.5 - 48.0)	<0.001
Median creatinine, $\mu\text{mol/L}$	1 045 (IR 573 - 1 585)	751 (489 - 1 245)	0.017
Median eGFR, mL/min	4 (IR 2 - 7)	5.1 (3 - 9)	0.029
BMI, kg/m^2	25.8 (IR 23.0 - 31.1)	26 (IR 22.7 - 31.1)	0.261
Methamphetamine use, n (%)	4 (5.7)	2 (1.7)	0.049
Diabetic, n (%)	1 (1.4)	72 (20.9)	<0.002
HIV-positive, n (%)	2 (2.9)	43 (12.5)	0.019
HPT nephropathy, n (%)	40 (57.1)	79 (22.9)	<0.00001
CGN, n (%)	15 (21.4)	80 (23.2)	0.74
Diabetic kidney disease, n (%)	1 (1.4)	70 (20.3)	<0.0001
HIVAN, n (%)	1 (1.4)	22 (6.4)	0.1
ADPKD, n (%)	1 (1.4)	24 (7.0)	0.09

IR = interquartile range; eGFR = estimated glomerular filtration rate; BMI = body mass index; HPT = hypertensive; CGN = chronic glomerulonephritis; HIVAN = HIV-associated nephropathy; ADPKD = autosomal dominant polycystic kidney disease.

who were presented to the renal replacement meetings; those with outright exclusion criteria, such as age >60 years, were not included. A third limitation was the retrospective design, but all records of patients presented during this period were captured. Furthermore, a comprehensive medical and psychosocial assessment that included a formal report by an experienced social worker was undertaken in every case and it is unlikely that there are significant missing data.

Conclusions

This study suggests an important link between hypertension in pregnancy and CKD. These patients are significantly younger, present later and are more likely to have hypertensive nephropathy. Methamphetamine abuse appears to be a risk factor. Further investigation is warranted, but the study suggests that all women with HDP need further evaluation and should be followed up postpartum.

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