Kidney Function After a Hypertensive Disorder of Pregnancy: A Longitudinal Study

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Background: Registry-based studies report an increased risk for end-stage kidney disease after hypertensive disorders of pregnancy (HDPs). It is unclear whether HDPs lead to an increased incidence of chronic kidney disease (CKD) and/or progression of kidney function decline.

Study Design: Subanalysis of the Prevention of Renal and Vascular Endstage Disease (PREVEND) Study, a Dutch population-based cohort with follow-up of 5 visits approximately 3 years apart.

Setting & Participants: Women without and with patient-reported HDPs (non-HDP, n = 1,805; HDP, n = 977) were identified. Mean age was 50 years at baseline and median follow-up was 11 years.

Factor: An HDP.

Outcomes: (1) The incidence of CKD using Cox regression and (2) the course of kidney function (estimated glomerular filtration rate [eGFR] and 24-hour albuminuria) over 5 visits using generalized estimating equation analysis adjusted for age, mean arterial pressure, and renin-angiotensin system (RAS) blockade. CKD was defined as eGFR < 60 mL/min/1.73 m^2 and/or 24-hour albuminuria with albumin excretion > 30 mg, and end-stage kidney disease was defined as receiving dialysis or kidney transplantation.

Results: During follow-up, none of the women developed end-stage renal disease and the incidence of CKD during follow-up was similar across HDP groups (HR, 1.04; 95% CI, 0.79-1.37; $P = 0.8$). Use of RAS blockade was higher after HDP at all visits. During a median of 11 years, we observed a decrease in eGFR in both groups, with a slightly steeper decline in the HDP group (98 ± 15 to 88 ± 16 vs 99 ± 17 to 91 ± 15 mL/min/1.73 m^2; $P_{group} < 0.01$, $P_{group*visit} < 0.05$). The group effect remained significant after adjusting for mean arterial pressure, but disappeared after adjusting for RAS blockade. The 24-hour albuminuria did not differ between groups.

Limitations: No obstetric records available. HDPs defined by patient report rather than health records.

Conclusions: HDPs did not detectably increase the incidence of CKD. During follow-up, we observed no differences in albuminuria, but observed a marginally lower eGFR after HDP that was no longer statistically significant after adjusting for the use of RAS blockers. In this population, we were unable to identify a significant risk for kidney function decline after patient-reported HDP.

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Hypertensive disorders of pregnancy (HDPs) occur in up to 10% of all pregnancies and are a major cause of maternal morbidity and mortality worldwide.[1,2] The spectrum of HDP ranges from the mild form of gestational hypertension to the more severe form of preeclampsia, which is clinically characterized by the presence of hypertension in combination with proteinuria, other organ disturbances, and/or intrauterine growth restriction in the second half of pregnancy.[3]

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In past decades, it has been shown that women with a history of HDP have an increased risk for developing end-stage kidney disease. Vikse et al[4] showed that women who had preeclampsia have a relative risk of 4.7 for developing end-stage kidney disease during a mean follow-up of 17 years. They also observed that risk tripled in women with a history of recurrent preeclampsia and in women after a pregnancy complicated by low birth weight or premature delivery.[4] Later, 2 Taiwanese cohort studies (with overlap) found hazard ratios (HRs) of 10.6 to 14 for developing end-stage kidney disease after preeclampsia.[5,6] One of the Taiwanese cohort studies found that not only women with a history of preeclampsia, but also women with a history of gestational hypertension have increased risk for developing end-stage kidney disease (HR 5.8).[5]

Due to the limited number of longitudinal follow-up studies with kidney assessment in women with a history of HDP, it is currently unknown whether the increased incidence of end-stage kidney disease represents a progressive kidney function decline after HDP. Only 2 studies have assessed whether a history of HDP increases the risk for developing chronic kidney disease (CKD) later in life, of which one found a lower incidence of CKD[7] whereas the other estimated increased risk for CKD after HDP.[6] In addition, only a few studies have assessed kidney function, mostly shortly after HDP, and reported either subtle alterations or no differences in kidney function and kidney hemodynamics.[7-11] With regard to moderately increased albuminuria after HDP, conflicting results are reported in the literature; a meta-analysis of a few small studies reports increased risk for albuminuria after preeclampsia,[8] whereas other smaller studies did not observe an increase.[7,9,12]

To evaluate the incidence of CKD and end-stage kidney disease and the course of kidney function after HDP in a longitudinal setting, we used data from the Prevention of Renal and Vascular End-stage Disease (PREVEND) Study, which is a population-based observational cohort study of the Dutch population with prospective data for kidney function and albuminuria.[13]

Methods

PREVEND Study

The PREVEND Study is a prospective investigation of kidney function, albuminuria, kidney disease, and cardiovascular disease in a large cohort drawn from the general population. Details of the cohort are described elsewhere.[14,15] In summary, 6,000 individuals with urinary albumin excretion ≥ 10 mg/L and 2,592 individuals with urinary albumin excretion < 10 mg/L from the population of Groningen, the Netherlands, aged 28 to 75 years were enrolled. From the period 1997 to 2012, five screening assessments took place about every 3 years. The PREVEND Study was approved by the Medical Ethics Committee of the University Medical Center Groningen (#96/01/22 on February 22, 1996). Written informed consent was obtained from all participants.

Selection of Participants

In this study we included 2,782 of 4,301 women participating in the PREVEND cohort who answered the question regarding hypertension during pregnancy at the first visit (n = 4,267; Fig 1, flow chart). First, we excluded women who answered "never been pregnant" (n = 1,096) and "don't know" (n = 389). Then we classified women who answered "no" on the question of whether they experienced hypertension during their pregnancy as "women with no patient-reported hypertensive pregnancy disorder" (non-HDP; n = 1,805) and women who answered "yes, allowed to do anything" or "yes, had to keep bed rest" as "women with a patient-reported hypertensive pregnancy disorder" (HDP; n = 977).

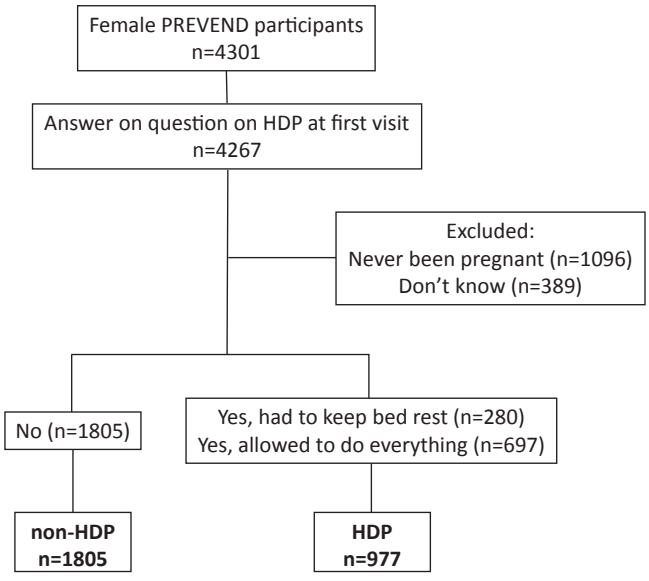

Figure 1. Flow chart of patient selection for the Prevention of Renal and Vascular Endstage Disease (PREVEND) cohort. Abbreviations: HDP, hypertensive disorder of pregnancy; n, number of participants.

Data Collection

Data collection, entry, and validation of the PREVEND Study was coordinated by the Trial Coordination Center of the University Medical Center Groningen. The date of the first PREVEND visit was taken as time point 0, after which median follow-up time at each visit was calculated (4, 6, 9, and 12 years). The questionnaire at the first visit provided information for birth date, race, employment, cardiovascular risk factors, cardiovascular comorbid conditions, and end-stage kidney disease at baseline. Cardiovascular comorbid conditions were defined as chronic heart disease or history of cerebrovascular accident. Alcohol use was defined as 2 to 7 glasses a day or more. At all visits, body mass index, systolic blood pressure, and diastolic blood pressure were measured and blood and urine were collected. The 24-hour urine was collected on 2 consecutive days and the mean of 2 albuminuria levels was calculated after using the formula: urinary albumin concentration (mg/L) × urinary volume (L) over 24 hours. Estimated glomerular filtration rate (eGFR) was calculated with the CKD-EPI (CKD Epidemiology Collaboration) creatinine–cystatin C equations, using serum creatinine and serum cystatin C values.[16] The presence of CKD was calculated for each visit and defined as eGFR < 60 mL/min/1.73 m^2 and/or 24-hour albuminuria with albumin excretion > 30 mg.[17] End-stage kidney disease during follow-up was assessed by linkage of the PREVEND cohort to our national database for dialysis and kidney transplantation. Measurements of urinary albumin, serum creatinine, serum cystatin C, cholesterol, uric acid, triglycerides, glucose, and insulin were determined from blood samples as described.[17-19] Homeostatic model assessment index was calculated using the formula (glucose × insulin)/22.5. To calculate the percentage of women using antihypertensive medication, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), lipid-lowering medication, and antidiabetic medication during follow-up, prescription data from pharmacies were collected. Oral contraceptive use was based on patient reporting.

Assessment Validity of Questionnaire

To assess the validity of patient-reported hypertension during pregnancy, we obtained medical records of 204 women by linking the PREVEND database to the registry of obstetric departments from 2 hospitals in the city of Groningen (the University Medical Centre Groningen and the Martini Hospital Groningen). We classified those women into 3 groups based on criteria for gestational