Urinary abnormalities and renal function in pregnant women with chronic hypertension

Avaliação de alterações urinárias e função renal em gestantes com hipertensão arterial crônica

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Abstract

Introduction: Renal involvement in pregnant women with chronic hypertension is not widely known. **Objectives:** 1- To describe the epidemiological profile of pregnant women with chronic hypertension; 2- To evaluate urinary abnormalities (by urinalysis), renal function (serum creatinine and cystatin C, and estimated glomerular filtration rate (eGFR); 3- To evaluate the pregnancy outcome in chronic hypertension. **Methods:** 103 pregnant women with chronic hypertension (blood pressure over 140/90 mmHg, detected previously to pregnancy or until the 20th week) were submitted to clinical and laboratorial evaluation. **Results:** Pregnant women were 21-45 (mean: 34) years-old. Protein/creatinine ratio in random urine was elevated in 5.2% (0.0-6.4g/g), serum creatinine in 19.6% and cystatin C in 14.7% of them. It was observed that characteristics of pregnant patients and their newborns (*vs.* frequencies of the cases with CKD-EPI cystatin C < 60 ml/min/1.73 m^2) were: 20.5% (33.3%) of preterm birth < 37 weeks, 17.5% (22.2%) of birth weight < 2500g and 17.5% (22.2%) of small for gestational age; superimposed preeclampsia-eclampsia occurred in 24.7% (22.2%) of the cases. **Conclusions:** Renal abnormalities were detected by proteinuria, determinations of serum creatinine and cystatin C in 5.2, 19.6 and 14.7% of the cases. The results suggest that the formulas CKD-EPI and MDRD can have applicability in assessing renal function in pregnant women. It was also shown a high frequency of preterm birth or with < 2500g at birth or small for gestational age, as well as of superimposed preeclampsia-eclampsia (24.7%) in pregnant women with chronic hypertension.

Keywords: creatinine; cystatin C; glomerular filtration rate; high-risk; hypertension; pregnancy; proteinuria.

Resumo

Introdução: O acometimento renal em gestantes portadoras de hipertensão arterial crônica (HAC) não é amplamente conhecido. **Objetivos:** 1- Descrever o perfil epidemiológico de pacientes com HAC; 2- Avaliar a ocorrência de alterações urinárias e de função renal (por meio de determinação sérica de creatinina, cistatina C e ritmo de filtração glomerular estimada - RFGe); 3- Avaliar o desfecho das gestações em HAC. **Métodos:** Foram submetidas a avaliações clínicas e laboratoriais 103 gestantes com HAC (pressão arterial acima de 140/90 mmHg, identificada previamente à gestação ou até a 20ª semana). **Resultados:** As gestantes tinham 21-45 (média: 34) anos; 12,6% eram primigestas, 64,1% tiveram múltiplas gestações. A relação proteinúria/creatininúria em amostra isolada estava alterada em 5,2% casos (0-6,44 g/g), creatinina sérica estava elevada em 19,6% e cistatina C em 14,7%. Na avaliação das características da gestação em pacientes com HAC e seus recém-nascidos (RN) (*vs.* frequências nos casos com CKD-EPI cistatina C < 60 ml/min/1,73 m^2), observou-se: 20,5% (33,3%) de nascidos pré-termo < 37 sem, 17,5% (22,2%) de RN com peso < 2500 g e 17,5% (22,2%) de RN pequeno para a idade gestacional (PIG); sobreposição de DHEG ocorreu em 24,7% (22,2%) dos casos. **Conclusão:** Alterações renais foram identificadas por proteinúria, creatinina e cistatina C séricas em 5,2%, 19,6 e 14,7% das gestantes. Os resultados sugerem que as fórmulas do CKD-EPI e MDRD também podem ter aplicabilidade nessa avaliação em gestantes. Detectou-se alta frequência de RN pré-termo ou com menos de 2500 g ao nascer ou PIG, assim como de sobreposição de DHEG (24,7%) em gestantes com HAC.

Palavras-chave: cistatina C; creatinina; gravidez de alto; hipertensão; proteinúria; taxa de filtração glomerular.

Introduction

One of the most common clinical complications during pregnancy, high blood pressure (BP) is estimated to affect between six and eight percent of pregnant women.[1] Increases in maternal and perinatal morbidity place hypertensive pregnant women at risk and under specific health care protocols.[2] According to the World Health Organization (WHO), the number of maternal deaths decreased by 45% between 1990 and 2013.

In 2013, approximately 790 women died each day of complications arising from pregnancy or delivery; most of these deaths were preventable and occurred in areas with few resources. The primary causes of death were hemorrhage, hypertension, infection, and indirect causes, most of which connected with the interaction between pre-existing comorbidities and gestation. In 2013, the rate of maternal mortality for each 100,000 live births in developing nations was 14 times greater than the rate observed in developed nations.[3] Pregnant women are diagnosed with hypertension when their systolic BP is 140 mmHg or greater and their diastolic BP is 90 mmHg or greater. In the roster of hypertensive syndromes affecting pregnant women, chronic hypertension concerns patients with hypertension before pregnancy and individuals diagnosed with hypertension for the first time during pregnancy (BP measured in two different occasions) before the 20th week of gestation extending to at least 12 weeks after delivery.[4]

The incidence of chronic hypertension, one of the many presentations of high blood pressure during pregnancy, has been estimated to affect between 30.0% and 61.5% of all patients with hypertension,[5,6] depending on the service at which the issue has been studied. According to a small number of population studies and papers published over 20 years ago,[7] chronic hypertension is a complication factor in 1% to 5% of pregnancies. The complicated forms of chronic hypertension may include renal and cardiac disorders and progression to eclampsia, a condition that often requires the termination of gestation as soon as the fetus is mature.[6] Preeclampsia is defined by hypertension diagnosed for the first time after the 20th week of gestation associated with 24-hour urinary protein levels of 0.3 g or greater.[4] A urine protein to creatinine ratio of 0.3 or greater may be used alternatively to the same end.[8]

Eclampsia occurs in cases in which, in addition to preeclampsia, the patient has seizures not attributable to other causes.[4] Preeclampsia accounts for 12% of maternal deaths in the world, and kills 50,000 to 60,000 women every year.[9]

Although some cases of asymptomatic renal disease and chronic hypertension are diagnosed only during pregnancy, it is up to nephrologists to warn others of the impact preexisting kidney disease and chronic hypertension have on pregnancy.[10] Although chronic hypertension is not an uncommon condition during pregnancy, renal involvement secondary to this condition has not been substantially explored in the literature. This study aims to assess the broader consequences of renal impairment in pregnant women with chronic hypertension.

Methods

Study groups

This prospective study enrolled 103 pregnant females diagnosed with chronic hypertension seen at the Outpatient Prenatal Care Clinic of the Department of Obstetrics (High-risk Pregnancies) at UNIFESP. Individuals with chronic hypertension were randomly selected according to the definitions set forth by the *National High Blood Pressure Education Program*.[11] Subjects aged 18 years or younger and patients diagnosed with preeclampsia, *diabetes mellitus* types 1 or 2, or urinary tract infection (UTI) based on urine culture findings were excluded.

The control group included 22 pregnant females with ages greater than 18 years, with no preexisting comorbidities or altered workup results.

Assessment

This is a quantitative, descriptive, observational, longitudinal, and predominantly prospective study. The individuals included in the study answered a questionnaire, had their BP measured, and underwent blood (creatinine and cystatin C levels) and/or urine tests (urinalysis and urine protein to creatinine ratio in isolated urine samples). BP measurements were carried out with a digital automatic Microlife BP3BTO-A blood pressure meter (calibrated every two years) approved by INMETRO and validated according to the British Hypertension Society protocol, with the patient on an empty bladder in a seated

position after resting for five minutes.[4] BP was measured only once, regardless of how far the patients were on their pregnancies, during a routine medical appointment. The patients were allowed to have a reasonable meal before having their BP measured.

Data on gestational adverse events, births, and neonates were collected from the patient charts of the individuals with chronic hypertension once they reached the end of pregnancy. The 27 pregnant females in the control group underwent the same workup procedures as the pregnant individuals with chronic hypertension.

Urine 1

Urinalysis was performed within two hours of urine collection and included the analysis of erythrocyte dysmorphism in cases of hematuria.

The study adopted the following references of normality: pH: 5.0-7.0; density: 1010-1030; glucose: < 4.0 mg/L; white blood cells: up to 10/high power field; red blood cells: up to 10/high power field (values above this threshold indicated significant hematuria). Only individuals with more than ten red blood cells per high power field were analyzed for erythrocyte dysmorphism; positive cases (present dysmorphism) had their test results shown with plus signs. Urine cultures were ordered for patients with more than ten white blood cells per high power field to rule out UTI.

Urine protein to creatinine ratio

Urine protein and creatinine levels were determined based on isolated urine samples. Urine protein levels were measured through the colorimetric pyrogallol red method on a Cobas Mira Plus - Roche device (Labtest); urine creatinine levels were measured through the alkaline picrate method on a Hitachi 912 - Roche device. The outcomes of these tests were used to calculate the urine protein to creatinine ratio in g/g. Values > 0.30 g/g were deemed altered.[4]

Serum creatinine

Serum creatinine levels were measured through the alkaline picrate method on a Hitachi 912 - Roche, in serum. Serum creatinine levels were expressed in mg/dL; values equal to or smaller than 0.6 mg/dL were deemed normal.[12,13]

Serum cystatin c

Cystatin C levels were measured from the serum of patients through an in-house developed method using the Luminex system (flow cytometry). Test results were expressed in mg/L and used as reference the standard curve produced with the C-PET cystatin C kit marketed by DAKO. The reference values for serum cystatin C levels were defined based on age ranges. The normal values for women with ages below 50 years range between 0.55 mg/L and 1.15 mg/L. Values above the upper limit of the range were deemed altered.

Estimated glomerular filtration rate

Lab test results and questionnaire answers were compiled to allow the calculation of the estimated glomerular filtration rate (GFR) using the formula presented by Cockcroft-Gault and in the Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI creatinine, CKD-EPI cystatin C, and CKD-EPI creatinine-cystatin C equations).[14-17]

Statistical analysis

Mean, minimum and maximum values and standard deviations were calculated for quantitative (numerical values) variables. The conclusions pertaining to the inferential analyses presented in this paper adopted a statistical significance level of 5%. Statistical analysis was performed on software *Statistical Package for the Social Sciences* (SPSS) version 15.0 for Windows and R-program version 2.11.0.

Results

The pregnant individuals with chronic hypertension enrolled in this study were aged between 21 and 45 years and had a mean age of 34 years. At the time of the interview, the gestational ages of the patients ranged from eight and 38 weeks, with a mean of 22 weeks. A significant number of individuals had prior gestations (64.1%) and deliveries (52%), while a smaller portion (12.6%) of the subjects were on their first pregnancy. Nineteen (86.4%) of the 22 patients with prior cases of pregnancy-induced hypertension (PIH) had preeclampsia and three (13.6%) had eclampsia. The patients enrolled in this study were diagnosed with hypertension during pregnancy in 14.9% of the cases,

and 20.0% of them had a history of PIH. Table 1 describes other characteristics of chronic hypertension. Some pregnant patients with chronic hypertension had a history of renal impairment, including chronic kidney disease progressing to renal transplantation (2), IgA nephropathy (1), minimal change glomerular disease (1), focal segmental glomerulosclerosis (1), acute kidney injury of unknown etiology (1), mild proteinuria (1) without indication of renal biopsy, and histological signs of pyelonephritis (1). Almost two thirds (62.5%) of the individuals with a history of nephropathy (7.8%) were 35 years old or younger.

The chronic hypertension and control groups had similar compositions in terms of ethnicity (p = 0.646), gestational age (p = 0.712), number of pregnancies (p = 0.128), history of miscarriage (p = 0.660), and BMI (p = 0.070); and similar results for the following workup tests: serum cystatin C levels (p = 0.071), urinalysis findings such as pH (p = 0.117), density (p = 0.230), presence of glucose (p > 0.999), white blood cells (p = 0.187), red blood cells (p = 0.192), erythrocyte dysmorphism (p > 0.999), and urine protein to creatinine ratio (p = 0.583). The group with chronic hypertension had more individuals aged 35 years or older (p = 0.002) than the control group.

Pregnancy findings

Workup results are shown in Table 2.

Serum creatinine levels ranged from 0.36 mg/dL to 2.8 mg/dL, with a median value of 0.51 mg/dL and a mean value of 0.56 ± 0.27 mg/dL. The cystatin C levels ranged from 0.54 to 3.14 mg/L, with a median value of 0.90 mg/L and a mean value of 0.97 ± 0.35 mg/L. The group with chronic hypertension had a greater share of individuals with altered serum creatinine levels (p = 0.023) when compared to the control group. The mean values for serum creatinine and cystatin C levels seen in the control group were similar to the levels observed in the subjects in the chronic hypertension group without a history of nephropathy (normal values for pregnant individuals); the mean values for the patients with chronic hypertension and a history of nephropathy were significantly higher.

The two groups had similar GFR results estimated by the CKD-EPI creatinine (p = 0.824), CKD-EPI creatinine-cystatin C (p = 0.203), MDRD (p = 0.244), and Cockcroft-Gault (p = 0.915) formulas. The group with chronic hypertension had a greater share of individuals with lower GFR estimated by the CKD-EPI cystatin C (p = 0.010) equation when compared to the control group. In the assessment of estimated GFR

Table 1 Characteristics of pregnant subjects with chronic hypertension

Characteristics		Values
Diagnosed with high BP during current gestation		14.9%
Time since diagnosed with high BP (years)	≤ 5a	60.4%
	> 5a and ≤ 10a	23.7%
	> 10a	15.9%
	total	100.0%
Prior nephropathy		7.8%
Drug therapy for high BP before gestation		79.6%
Number of antihypertensive drugs taken before pregnancy*	one	66.6%
	two	29.5%
	Three or more	3.9%
	total	100.0%
Pre-gestational BMI (kg/m²)*	< 25	24.2%
	25 to 29.9	29.3%
	> or = 30	46.5%
	total	100%
Family history of hypertension n/n total (%)		97/100 (97%)
Family history of preeclampsia-eclampsia n/n total (%)		7/97 (7.2%)
Systolic BP ≥ 140 mmHg**		24.3%
Diastolic BP ≥ 90 mmHg**		28.2%

BP- blood pressure; BMI- body mass index*Four cases were not able to provide information;** Checked once in only one appointment.

Table 2 Distribution of workup of pregnant patients with chronic hypertension and controls (n = 22)

		Chronic Hypertension		Controls		*p*
Serum creatinine	Normal	82	80.4%	22	100.0%	0.023[b]
	altered	20	19.6%	-	-	
	total	102	100%	22	100%	
Serum cystatin C	normal	87	85.3%	22	100.0%	0.071[b]
	altered	15	14.7%	-	-	
	total	102	100%	22	100%	
Urine I: pH	normal	93	95.9%	19	86.4%	0.117[b]
	altered	4	4.1%	3	13.6%	
	total	97	100%	22	100%	
Density	normal	94	96.9%	20	90.9%	0.230[b]
	altered	3	3.1%	2	9.1%	
	total	97	100%	22	100%	
Glucose	normal	94	96.9%	22	100.0%	> 0.999[b]
	altered	3	3.1%	-	-	
	total	97	100%	22	100%	
Leukocytes	normal	38	39.2%	12	54.5%	0.187[a]
	altered	59	60.8%	10	45.5%	
	total	97	100%	22	100%	
Red blood cells	normal	81	83.5%	21	95.5%	0.192[b]
	altered	16	16.5%	1	4.5%	
	total	97	100%	22	100%	
Erythrocyte dysmorphism	absent	93	95.9%	22	100.0%	> 0.999[b]
	present	4	4.1%	-	-	
	total	97	100%	22	100%	
Urine protein to creatinine ratio	normal	92	94.8%	22	100.0%	0.583[b]
	altered	5	5.2%	-	-	
	total	97	100%	22	100%	

[a]Pearson's chi-square test, [b]Fisher's exact test or extension.

of pregnant individuals with chronic hypertension, the CKD-EPI cystatin C equation detected levels < 60 ml/min in 9.0% of the cases. The Cockcroft-Gault, MDRD (not adjusted for body surface area), CKD-EPI creatinine, and CKD-EPI creatinine-cystatin C formulas yielded values lower than 60 ml/min for estimated GFR with similar frequencies among patients with chronic hypertension (2%, 2%, 2%, and 3%, respectively). A general assessment of the data revealed that 75% of the patients with chronic hypertension and a history of nephropathy had an estimated GFR ≥ 60 ml/min/1.73 m^2 by the Cockcroft-Gault, MDRD, CKD-EPI creatinine, and CKD-EPI creatinine-cystatin C formulas; however, according to the CKD-EPI cystatin C equation, 50% of them had an estimated GFR ≥ 60 ml/min/1.73 m^2. Significant hematuria was observed in 16.5% (16/97) of the subjects with chronic hypertension; 13.3% (12/90) did not have a history of nephropathy and most of the 57.1% (4/7) with a history of nephropathy were positive for dysmorphism. Three of the seven individuals (42.8%) with chronic hypertension and a history of nephropathy had altered urine protein to creatinine ratios, *versus* 2.1% (2/95) of the subjects with chronic hypertension without nephropathy. The presence or absence of a history of PIH was not associated with important workup alterations in either of the groups in terms of serum creatinine and cystatin C levels or urinary anomalies.

Birth and puerperium findings

Almost a fifth (19.5%) of the individuals with chronic hypertension were lost during follow-up. No cases of maternal or fetal death were recorded among the patients included in the postnatal follow-up protocol. Tables 3 and 4 show the obstetric data of the pregnant individuals with chronic hypertension at the end of gestation and data on their newborns.

The groups with and without overlapping PIH in the postnatal period had similar levels of GFR estimated by the CKD-EPI creatinine (p = 0.776), CKD-EPI cystatin C (p = 0.252), CKD-EPI creatinine-cystatin C (p = 0.376), MDRD (p = 0.426), and Cockcroft-Gault (p = 0.931) formulas. The comparison of pregnancy outcomes of individuals with chronic hypertension associated or not with history of nephropathy had similar profiles in terms of gestational age (p = 0.877), categorizations correlating weight and gestational age (p = 0.999), gestational diabetes (p 0.246), and overlapping PIH (p > 0.999). More than half (55.6%) of the nine pregnant individuals with chronic hypertension with a GFR estimated by the CKD-EPI cystatin C equation of less than 60 ml/min/1.73 m^2 had Cesarean sections, and 22.2% had overlapping PIH; a third (33.3%) of their neonates were born prematurely, 22.2% had birth weights of less than 2,500 g, and 22.2% were small for their gestational ages. More than a quarter (27.7%) of the pregnant patients with chronic hypertension and a history of PIH had new episodes of PIH at the end of their current pregnancies, and 24.2% of the individuals without a history of PIH had PIH by the end of the study. Table 5 describes the characteristics of the individuals with chronic hypertension who progressed to PIH by the end of the study. The incidence of preeclampsia among women who had never given birth (at the start of the study) was 20% (3/15).

Discussion

Maternal clinical findings (table 1)

Many women are choosing to become pregnant in later stages of their lives, and hypertension has evolved into a more common factor in pregnancy.[18] The patients with chronic hypertension enrolled in this study had a mean age of 34 years. Increased risk of chronic hypertension has been described in the pregnancies of individuals aged 30 years or older, and particular attention has been devoted to women above the age of 35 years.[19,20] Most of the individuals with chronic hypertension included in this study had prior gestations (64.1%) and deliveries (52%). The share of women pregnant for the first time (12.6%) was not far from the 18% reported by Sibai *et al.*[21] More than a fifth (21%) of the individuals enrolled in the study had a history of PIH. This is a very important finding, once patents with a history of preeclampsia have a threefold risk of having hypertension in the future.[22] History of renal disease was reported by 7.8% of the individuals in the group with chronic hypertension HAC, and 62.5% of the subjects in this subset of the studied population were 35 years old or younger. From the beginning of this study, the time of progression to hypertension was five year or less in 60.4% of the cases, *versus* 71.2% of the cases according to Ruiz *et al.*[23] Most of the patients were on one (63.4%) or two (28%) medications, showing their cases of hypertension were not difficult to manage.

Use of contraceptive drugs (23%) ranked high among the possible causes of hypertension, but illicit

Table 3 Distribution of obstetric characteristics of pregnant individuals with chronic hypertension after delivery and newborns

Characteristics		Values	
Type of delivery	normal n (%)	27	32.9%
	Cesarean section	55	67.1%
	Total	82	100.0%
Gestational diabetes	yes n (%)	10	12.0%
	no	73	88.0%
	Total	83	100.0%
Overlapping PIH	yes n (%)	21	24.7%
	no	64	75.3%
	Total	85	100.0%

PIH- pregnancy-induced hypertension (preeclampsia or eclampsia).

Table 4 Distribution of obstetric characteristics of pregnant individuals with chronic hypertension after delivery and newborns

Characteristics		Values	
Gestational age (weeks)	n	83	
	mean	37.1	
	median	38.0	
	minimum-maximum	26.0-41.9	
	standard deviation	3.0	
Categorization by gestational age	Full-term birth n (%)	66	79.5%
	Preterm birth	17	20.5%
	Total	83	100.0%
Weight (grams)	n	80	
	mean	2863.3	
	median	2922.5	
	minimum-maximum	500.0-4165.0	
	standard deviation	696.0	
Weight at birth (category 1)*	adequate weight n (%)	34	42.5%
	insufficient weight	32	40%
	low weight	9	11.2%
	very low weight	2	2.5%
	extremely low weight	3	3.8%
Weight at birth (category 2)*	< 2500g n (%)	14	17.5%
	> or = 2500g	66	82.5%
Categorization by weight *vs.* gestational weight*	SGA n (%)	14	17.5%
	AGA	63	78.8%
	LGA	3	3.7%
	Total	80	100.0%

AGA- appropriate for gestational age; LGA- large for gestational age; SGA- small for gestational age. * Data from 80 pregnant individuals.

drugs and alcohol were not common findings. Five patients had taken illicit drugs (four cases of cocaine and one of marijuana), but all claimed to have stopped taking drugs before their pregnancies. Almost three quarters (72%) of the patients with chronic hypertension had a pre-gestational BMI greater than 25 kg/m^2, and a significant portion of them (44.7%) were obese. Confirming the trend described above, the control group also had a significant portion of individuals with a BMI greater than 25 kg/m^2. A retrospective study carried out at the São Paulo Hospital (1985-86) reported found that 17% of the pregnant women with chronic hypertension were obese.[2] A significant increase has been observed in the number of overweight people in Brazil, and the issue has now become a public health concern.[24]

Family history of hypertension is a relevant predictor for the development of high blood pressure[25]; in this study, 97% of the cases had a family history of hypertension. Family history of preeclampsia has been significantly correlated with the occurrence of gestational hypertensive syndromes[26]; in this study, 7.2% of the cases had a family history of PIH (preeclampsia or eclampsia).

Maternal workup (table 2)

a) Estimation of the GFR from serum creatinine and cystatin C levels

Although the equations used to estimate the GFR were designed for non-pregnant subjects and their use with pregnant individuals requires further validation, they were applied to the women enrolled in this study. The

Table 5 Distribution of characteristics of pregnant individuals progressing to overlapping PIH (preeclampsia or eclampsia) and chronic hypertension

Ethnicity n (%)	n = 21
Black	1 (4.8)
White	4 (19.0)
Brown	16 (76.2)
Age (years)	
Mean and standard deviation	35 ± 4.86
Age > 35 years n (%)	12 (57.1)
Pre-gestational BMI (kg/m^2) n (%)	n = 19
< 25	2 (10.5)
25 to 29.9	8 (42.1)
≥ 30	9 (47.4)
Nulliparous n (%)	3 (14.2)
Smoking n (%)	2 (10.0)
Time with high BP n (%)	n = 20
≤ 10 years	15 (75.0)
> 10 years	5 (25.0)
History of PIH n (%)	5 (23.8)
Familial PIH n (%)	1 (5.0)
Preterm birth in current pregnancy n (%)	10 (52.6)
Low birth weight (< 2499 g) n (%)	6 (35.2)
SGA in current pregnancy n (%)	4 (23.5)
Serum creatinine > 0.6 mg/dL n (%)	4 (19.0)
Serum cystatin C (> 1.15 mg/L) n (%)	3 (15.0)
High UPC > 0.3 n (%)	2 (10.0)

BMI- Body mass index; PIH- pregnancy-induced hypertension; SGA- small for gestational age; UPC- urine protein to creatinine ratio in isolated urine sample.

results varied substantially depending on the equation used in the estimation. Decreased renal function is a relevant finding during gestation. Renal disease alone and regardless of other factors substantially increases the risk of an unfavorable outcome both for mothers and their newborns.[27] Renal function tests revealed increased levels of serum creatinine and cystatin C in 19.6% and 14.7% of the studied individuals, respectively. Serum cystatin C is a useful marker of glomerular filtration for not suffering from the interferences commonly seen with serum creatinine, for example. The latter may vary because of gender, age, muscle mass, and interferences in the analyte dosage process, to name a few.[28] The GFR of the pregnant individuals with chronic hypertension was estimated with a number of formulas, and the CKD-EPI cystatin C equation yielded values below 60 ml/min in 9% of the cases, a much higher frequency than with the other formulas. The CKD-EPI cystatin C equation may be more sensitive to detect loss of renal function in this group, but only a comparison against a gold-standard marker, which was not performed in this study, might confirm this hypothesis.

According to some authors, the equations based on serum cystatin C are more reliable and accurate in estimating the GFR and predicting chronic kidney disease and GFR below 60 ml/min/1.73m^2.[29] However, there still are no accurate formulas to estimate the GFR in pregnant individuals with or without chronic kidney disease.[30] Cystatin C may be an interesting alternative to assess renal function in pregnant subjects. In this study, the estimation of the GFR by the CKD-EPI cystatin C equation distinguished between patients with chronic hypertension and controls. Babay *et al*.[31] described a strong positive correlation between serum cystatin C and creatinine levels and a negative correlation between estimated GFR and cystatin C in healthy pregnant women, thus leading the authors to consider cystatin C as a good marker of early changes in renal function during gestation. However, there is no consensus over the use of cystatin C in the renal function assessment of pregnant individuals.[31,32] When compared to the GFR estimated for patients with chronic hypertension (with or without associated nephropathy) and controls, it is clear that the GFR is lower among patients with chronic hypertension than in controls and in subjects with nephropathy than in individuals without nephropathy. These differences became more apparent with the CKD-EPI and MDRD equations. These findings suggest that the two formulas may possibly be applied in the assessment of pregnant subjects, pending confirmation by other authors and large prospective studies designed with this specific end using a gold-standard method (inulin clearance, for example) to compare between the different equations. Inulin clearance has been used with pregnant individuals in other studies. This is a controversial matter, as when inulin clearance was compared to the MDRD formula in a group of pregnant subjects (including healthy individuals, subjects with altered renal function, and patients with preeclampsia), the authors found that the MDRD equation underestimated the GFR during gestation and should not be used in clinical practice.[33]

B) urine protein to creatinine ratio

High urine protein/creatinine ratios were observed in 5.2% of the patients with chronic hypertension at the time of assessment. This finding is a known reason for concern and a trigger for further investigation in any context.[34] Ten to twenty percent of the patients with gestational hypertensive syndrome have proteinuria as one of their symptoms,[35] particularly women with preexisting hypertension, prior preeclampsia, and *diabetes mellitus*.[36]

C) urine test

In addition to proteinuria, leukocyturia was found in the tests of 61% of the pregnant individuals. UTI was rarely found in these cases, as mentioned before. In some cases, leukocyturia was attributed to sample contamination by containers holding urine specimens with vulvovaginitis without UTI; minor leukocyturia may also be detected as a consequence of poor asepsis during urine collection. Nonetheless, urine cultures were ordered for these patients to check for UTI.

No significant changes were seen in urine pH or glycosuria. Hematuria was found in 16.5% of the cases with chronic hypertension, and erythrocyte dysmorphism in a quarter of them. These values are close to the maximum levels described for the general population.[37] Renal involvement shown by the presence of hematuria was also a more evident finding in the group with chronic hypertension and prior nephropathy (50%), as was proteinuria (increased urine protein to creatinine ratio in 42.8% of the subjects with nephropathy *vs*. 2.1% of the individuals without nephropathy).

Pregnancies, births, and newborns of individuals with chronic hypertension (tables 3 and 4)

A significant portion (67.1%) of the patients in our series had Cesarean sections; other studies have reported rates of 29% to 60% of C-sections among patients with chronic hypertension.[38,39] No cases of stillbirth or perinatal death were reported for the 83 patients with postpartum data, despite the higher incidence of these outcomes in the pregnancies of hypertensive women with preeclampsia.[40,41] Pregnant individuals with chronic hypertension and higher blood pressure levels are at a greater risk of placental abruption and preterm birth.[42] In our series, only one patient had placental abruption and 20.5% of the cases had preterm births. Preterm birth rates in some prospective studies enrolling pregnant women with chronic hypertension ranged from 34% to 70%.[39,43] The prevalence of preterm births among pregnant women with chronic hypertension at the São Paulo Hospital in 1985-1986 was 30%.[2] In our series, 17.5% of the patients had newborns weighing less than 2,500 g, as similarly reported by other authors with 21% and 22%.[23,44] More than a sixth (17.5%) of the babies born to women with chronic hypertension were small for their gestational ages. The risk of adverse events such as a newborns small for their gestational ages is higher among pregnant women with hypertensive disease during gestation[40] and grows even further the higher the blood pressure levels are in pregnant women with chronic hypertension.[35] The incidence of newborns small for their gestational ages born to women with chronic hypertension ranges from 15% to 43%.[39,41,43] The prevalence of newborns small for their gestational ages born to mothers with chronic hypertension at the São Paulo Hospital in 1985-1986 was 20%,[2] a value close to what this study found.

Patients with overlapping PIH and chronic hypertension (table 4)

Patients with a history of PIH had normal urine protein/creatinine ratios and renal function, as also reported by Mangos *et al*.[45] No significant differences were seen between having or not having a history of PIH in regards to serum creatinine and cystatin C levels or the presence of urinary alterations. Sibai *et al*.[21] found that pregnant women with chronic hypertension and proteinuria were three times more likely to have preterm neonates (gestational age of less than 35 weeks) than patients without proteinuria. In our study, the urinalysis findings of patients with chronic hypertension and full-term or preterm births were similar. Likewise, the estimated glomerular filtration rates did not indicate loss of renal function correlated with greater risk of preterm birth among pregnant individuals with chronic hypertension. In our study, 12% of the patients with chronic hypertension had gestational diabetes. Pre-gestational obesity was the most relevant factor for hypertensive disease in patients treated for gestational diabetes.[46] Overlapping PIH and chronic hypertension was observed in 24.7% of the cases, a value characteristically seen in other prospective studies.[39,47] Five of eighteen (27.7%) individuals with a history of PIH had PIH again at the

end of gestation, as also described by Sibai *et al.*,[21] in a study in which the authors found overlapping PIH and chronic hypertension in 32% of their patients.

The incidence of old age in our study was much higher than the 26% reported by Sibai *et al.*,[21] who also failed to find a correlation between old age and increased incidence of preeclampsia. Liu and Zhang[20] observed that patients aged 35 years or older were at a higher risk not only of having preeclampsia, but also gestational diabetes, Cesarean sections, preterm births, low birth weight newborns, and perinatal death. An elevated BMI, and obesity in particular, are risk factors for preeclampsia.[47,48] In our series, 47.3% of the patients progressing to preeclampsia were obese before pregnancy. When pregnant individuals with a BMI greater than 25 kg/m^2 are added to this number, the share of individuals in this group shoots up to 89.5%. Nearly half (45%) of the pregnant women with overlapping PIH and chronic hypertension had a history of high blood pressure for over five years. Other studies have found that patients with chronic hypertension suffering from high blood pressure for over four years had a greater chance of having preeclampsia in future pregnancies.[21,41] In our series, preterm births occurred in 52.6% of the patients with PIH, *versus* 10.9% of the patients with chronic hypertension without PIH, as similarly reported by Chapell *et al.*,[47] in 51% and 15% of their patients, respectively. Twenty-three percent of the newborns of individuals diagnosed with preeclampsia were small for their gestational ages. Sibai *et al.*,[21] found 13% of newborns in this situation. Only two of our patients (9.5%) with a history of nephropathy had overlapping PIH. Regardless of having chronic hypertension, pregnant women with kidney disease and their newborns are at a greater risk of having adverse events and spend more resources than pregnant women without renal disease.[49] Pregnant women with renal disease are implicitly at a greater risk of having preeclampsia.[47,49] Fischer *et al.*[27] enrolled 37 patients with moderate or severe kidney disease and observed progression to preeclampsia in 58% and 64% of the included individuals, respectively. It should be noted that when the tests were performed there was no proteinuria in 90% of the cases to suggest the presence of PIH. Proteinuria is a useful marker in the treatment of patients with preeclampsia. The test result, even when derived from a test strip, is a good predictor for risk of adverse events.[50] However, Sibai *et al.*[21] failed to find a correlation between proteinuria (> 0.3 g/24h) and increased incidence of preeclampsia.

Although the patients with chronic hypertension enrolled in our study were being treated with antihypertensive medication, they had decreases ranging between 15% and 20% in their glomerular filtration rates estimated based on several markers, the more evident of which being serum creatinine and the CKD-EPI cystatin C equation.

This group is known for having a high rate of overlapping PIH, preterm births, and newborns weighing < 2,500g or small for their gestational ages, a finding made more evident in the group of pregnant women with chronic hypertension and decreased GFR by the CKD-EPI cystatin C equation.

Study limitations

The lack of a gold-standard test to assess the GFR, as discussed above, is a limitation in the current study for the comparison between the results derived from the equations used to estimate the GFR.

The analysis of the data was also affected by the loss of some of the patients during postpartum follow-up.

Conclusion

This study draws attention to the situation of pregnant women with chronic hypertension and the risks this condition introduces to mothers and their newborns. Renal function assessment in a broader sense, including urinary alterations such as proteinuria and the glomerular filtration rate, has to be further studied in pregnant populations. And to make matters worse, even though the risks connected with poor progression are known, pregnant patients with hypertensive disease often quit the follow-up protocol after their babies are born to remain exposed to complications such as sustained high blood pressure and progression to chronic kidney disease, conditions often asymptomatic until they become severe.

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