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Influence of Selected Polymorphisms of the Renin-Angiotensin System on the Regulation of Blood Pressure during Pregnancy

Abstract

Hypertension during pregnancy is a heterogeneous group of disorders with elevated blood pressure with or without proteinuria. The blood pressure regulation is a complex issue, and research on this issue have been present in the world literature for many years. The study was designed to evaluate the impact of the ACE I/D, AGT-235, AGT-174 polymorphisms on the regulation of blood pressure.

It is a case-control study. The study included 104 women with uncomplicated pregnancies in the control group and 75 pregnant women with hypertension disorders in the study group, hospitalized in the Perinatology and Obstetrics Department of the University Hospital in Cracow. Genomic DNA was extracted from peripheral blood leukocytes and polymorphisms were genotyped from all the patients. We analyzed the genotypes distribution and its association to blood pressure values, the time of hypertension occurrence, the medications needed to control it and the time postpartum till the blood pressure normalization in all the groups. A p-value <0.05 was considered as significant.

Clinical evaluation included many standard anthropometric measures like weight and height for the calculation of the BMI in the beginning of the pregnancy and blood pressure values. It may be concluded that there is no influence of studied polymorphisms not only on the regulation of blood pressure during pregnancy, but also on the time of the onset or pharmacological treatment of hypertension during pregnancy and the time after delivery needed to normalization of blood pressure values. Further studies on larger groups are needed.

Keywords: Gestational hypertension; Preeclampsia; Blood pressure regulation; Polymorphism; ACE I/D; AGT-235; AGT-174

Research Article

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Abbreviations: RAS: Rennin-Angiotensin System; ACE I/D: Angiotensin-Converting Enzyme Insertion / Deletion; AGT: Angiotensynogen; DNA: Deoxyribonucleic Acid; EDTA: Ethylene Diamine Tetra Acetic Acid; PCR: Polymerase Chain Reaction; NHBPEP-WG: National High Blood Pressure Education Program Working Group; BMI: Body Mass Index; MAP: Mean Arterial Pressure

Introduction

The blood pressure regulation is a complex issue and research on this issue have been present in the world literature for many years. Some studies suggested that the renin-angiotensin system (RAS), not only takes part in regulating blood pressure and fluid and electrolyte balance [1], but also have an impact on the "physiological remodeling" of spiral arteries throughout pregnancy [2]. During normal pregnancy the RAS is stimulated including plasma renin activity or angiotensinogen, angiotensin II and aldosterone levels elevation [3].

ACE and the angiotensinogen (AGT) genes sequences have identified a variety of polymorphisms which may contribute to many kinds of hypertension [4-6]. Plasma levels of ACE have been associated with the insertion/deletion (I/D) polymorphism in intron 16 of the ACE gene. As the ACE I/D polymorphism was accounted for 47% of total phenotypic variance of serum ACE, so it is one of the most important polymorphism which contributes to the variability of the ACE level and consequently to angiotensin II levels [7]. The AGT is also a major component of RAS. The AGT-235 (M235T) polymorphism of the AGT gene is associated with increased plasma levels of AGT [8]. Still, not many studies have been conducted upon the AGT-174 polymorphism.

The aim of this study was to evaluate the probable impact of the ACE I/D, AGT-235 and the AGT-174 polymorphisms on the blood pressure regulation during the pregnancy and additional clinical aspects of the disease as the time of its occurrence, pharmacological treatment and the time of blood pressure normalization.

Material and Methods

179 pregnant patients were randomly enrolled for the study out of the women hospitalized in the Perinatology and Obstetrics Department of the University Hospital in Cracow (Poland). It is a case-controlled study. Hypertension and proteinuria were defined according to NHBPEP-WG [9]. The hypertensive patients were divided into smaller groups depending on the final diagnosis of preeclampsia, gestational hypertension or chronic hypertension in number of 29, 35 and 11 patients respectively. The hypertensiveness was considered if the systolic/diastolic blood pressure was ≥ 140/90 mmHg in two separated measurements.

If the proteinuria occurred with the hypertension at the end of the 20th week of pregnancy we diagnosed the preeclampsia. The exclusion criteria included: multiple pregnancy, stillbirth, fetal anomalies, patients with renal, liver or heart diseases as well as the withdrawal of patient's consent.

104 normotensive pregnant women were enrolled as a control group aged from 18 to 39 years old. Written informed consent was obtained from all the patients enrolled in this study and this study was approved by Ethic Committee of Jagiellonian University. Each patient was interviewed and detailed medical history like gravidity, parity, week of gestation was taken. Clinical evaluation included standard anthropometric measures like weight and height for the calculation of the BMI in the beginning and in the end of the pregnancy, blood pressure (systolic, diastolic and MAP), time and a method of the delivery and the birth weight with a percentile. Samples of venous blood from all the patients were collected into EDTA tubes while performing standard medical procedures during hospitalization. The blood samples were kept at –80°C till all of the samples were gathered and analyzed at the same time.

The genomic DNA was extracted from peripheral blood leukocytes. The DNA extraction was performed with Kit High Pure PCR Template Preparation Kit. The DNA quality and quantity were assessed on a spectrophotometer NanoDrop ND-1000. Genotyping was performed by investigators blinded to clinical status using the standardized protocols [10-12]. The characteristics of study groups were compared according to by the Kruskal-Wallis test, Mann-Whitney test, Fisher's exact test, chi-square test, Classical analysis of variance and the post-hoc Tuckey test. The distributions of the genotype variants among studied subjects were compared by the chi-squared analysis and test Fisher's exact. The odds ratios were calculated as a measure of the association between the genotypes and clinical phenotypes. For each odds ratio, p values and 95% confidence intervals were calculated. A p value of <0.05 was considered as statistically significant. The results were analyzed IBM SPSS Statistics v.20.

Results and Discussion

The anthropometric characteristics of the studied populations are presented in Table 1. Pregnant women with hypertension and normotensive pregnant patients were homogeneous for the gestational history and place of living (data not shown), but significant differences were found in the age and weight measurements.

Table 1: The anthropometric characteristics.

	Chronic hypertension	Gestational hypertension	Preeclampsia	Control group	p
Height (cm)					
mean [SD] min - max	n=10 165.3 ±6.6 [155-174]	n=34 165.9 ±6.1 [150-176]	n=27 163.1 ±6.2 [150-175]	n=85 165.8 ±6.5 [150-186]	p^{A}=0.249
Body weight before pregnancy (kg)					
mean [SD] min - max	n=10 83.1 ±23.0 [54-117]	n=31 69.2 ±12.3 [48-104]	n=25 61.1 ±13.8 [45-93]	n=77 62.7 ±9.8 [42-86]	p^{KW}=0.001 1
BMI before pregnancy (kg/m2)					
mean [SD] min - max	n=10 30.3 ±7.8 [21.6-41.5]	n=31 25.3 ±5.1 [17.9-41.7]	n=25 22.8 ±4.2 [17.2-32.2]	n=77 22.8 ±3.4 [16.8-31.6]	p^{KW}=0.002 2
Weight gain during pregnancy (kg)					
mean [SD] min - max	n=10 9.7 ±9.2 [-15 – 18]	n=31 15.2 ±6.2 [6-30]	n=25 16.0 ±7.1 [6-36]	n=78 14.9 ±5.1 [5-32]	p^{KW}=0.271
Maternal age (years)					
mean [SD] min - max	34.9 ± 3.8 [28-39]	30.6 ± 6.2 [21-44]	30.5 ± 4.3 [25-39]	29.1 ±4.4 [18-39]	p^{MW}=0.004 3

A: analysis of variance (ANOVA) for single classifications; KW -Kruskal-Wallis test, MW-Mann-Whitney test

1. post-hoc Tuckey test chronic hypertension group vs. gestational hypertension p = 0.012; chronic hypertension vs. preeclampsia p <0.001; chronic hypertension vs. control group, p <0.001, other pairwise comparisons p> 0.05
2. post-hoc Tuckey test chronic hypertension vs. gestational hypertension p=0,011; chronic hypertension vs preeclampsia p<0,001; chronic hypertension vs. control group p<0,001; gestational hypertension vs. control group p=0,028; other pairwise comparisons p>0,05
3. post-hoc Tuckey test: chronic hypertension group vs. gestational hypertension p = 0.045; chronic hypertension vs. preeclampsia p = 0.044; chronic hypertension vs. the control group, p = 0.001; other pairwise comparisons p> 0.05

Women with chronic hypertension presented a higher body weight and BMI before the pregnancy, than those with gestational hypertension and preeclampsia. Women with chronic hypertension also showed a higher body weight and BMI than the control group. There were no statistically significant differences between pregnant women in height and weight gain during pregnancy. The similar differences were seen when comparing the age of patients, as patients with chronic hypertension were older than patients in the rest of the groups with statistical importance.

The study analyzed the relationship of polymorphisms of the renin-angiotensin with values of the blood pressure in pregnant women. When comparing the average and the maximum values of systolic, diastolic and mean (MAP mean artery pressure) pressure based on the distribution of the genotypes of the polymorphisms tested, there were no statistically significant differences. However, a closer examination of the results show a trend consistent with the literature. The ACE I/D, AGT-235, AGT-174 polymorphisms were in the Hardy-Weinberg equilibrium.

The average pressure values were highly comparable between the groups, while the maximum pressure values were the lowest in the homozygous deletion (DD) group, with no statistical significance (Table 2). When comparing the average and maximum values of systolic and diastolic pressure, higher values were observed for genotype homozygous for a mutant variant of the T AGT-174, although with no significant differences (Table 3). The analysis of the distribution of values of blood pressure based on the genotype AGT-235 did not show a statistically significant difference. Only observed higher values of maximum systolic, diastolic and MAP in the group AGT-235 heterozygotes CT compared to homozygous CC, TT (Table 4).

When analyzing the week of pregnancy in which the hypertension occurred depending on the genotype of the ACE, AGT-174 and AGT-235 genes no statistically important conclusions can be made. Hypertension occurred nearly five weeks earlier in the DD patients of the ACE gene compared to patients II. Similarly, in the patients homozygous CC of AGT-174 polymorphism hypertension was diagnosed four weeks earlier than in the heterozygotes CT (Table 5), with no statistical significance. The detailed analysis of the number of medications needed to control the hypertension and time of blood pressure normalization after delivery showed no statistically important differences between the group depending on genotypes (data not shown).

Table 2: Average and maximum values of blood pressure in pregnant depending on the genotype of the ACE gene.

ACE	**DD n=44**	**ID n=86**	**II n=46**	
The average systolic blood pressure [mmHg]				
mean [SD] min - max	124.3± 17.6 [100-162]	123.7± 15.7 [90-164]	126.2± 16.1 [100-179]	p^A=0.702
The average diastolic blood pressure [mmHg]				
mean [SD] min - max	77.8± 10.9 [60-98]	77.3± 10.7 [60-105]	78.6± 10.6 [60-101]	p^A=0.807
The average MAP [mmHg]				
mean [SD] min - max	93.3± 12.5 [73.3-115.0]	92.8 ± 12.0 [70-122.3]	94.5± 12.0 [76.7-127.0]	p^A=0.750
ACE	**DD n=23**	**ID n=38**	**II n=21**	
The maximal systolic pressure [mmHg]				
mean [SD] min - max	156.5± 24.9 [110-230]	168.5± 19.8 [130-210]	163.8± 21.7 [120-200]	p^A=0.120
The maximal diastolic pressure [mmHg]				
mean [SD] min - max	98.3± 11.6 [70-120]	104.5± 12.6 [80-140]	102.3± 15.7 [70-140]	p^A=0.210
The maximal MAP [mmHg]				
mean [SD] min - max	117.7± 15.5 [87-157]	125.8± 14.1 [97-157]	122.8± 16.1 [87-157]	p^A=0.127

A: Classical Analysis Of Variance; MAP: Mean Arterial Pressure

Table 3: Average and maximum values of blood pressure in pregnant depending on the genotype of the AGT-174 gene.

AGT-174	**CC n=117**	**CT n=55**	**TT n=4**	
The average systolic blood pressure [mmHg]				
mean [SD] min - max	125.0± 15.5 [100-164]	123.0± 17.7 [90-179]	129.0± 16.5 [110-150]	p^{A}=0.646
The average diastolic blood pressure [mmHg]				
mean [SD] min - max	78.2± 10.6 [60-102]	76.8± 11.3 [60-105]	81.5± 2.4 [80-85]	p^{A}=0.569
The average MAP [mmHg]				
mean [SD] min - max	93.8± 11.8 [73.3-122.0]	92.2± 13.0 [70.0-127.0]	97.3±6.9 [90.0-106.7]	p^{A}=0.581
AGT-174	**CC n=61**	**CT n=19**	**TT n=2**	
The maximal systolic pressure [mmHg]				
mean [SD] min - max	163.6± 23.0 [110-230]	163.8± 20.8 [120-200]	175.0± 7.1 [170-180]	p^{A}=0.778
The maximal diastolic pressure [mmHg]				
mean [SD] min - max	101.8± 13.6 [70-140]	103.0± 13.2 [70-120]	105.0±7.1 [100-110]	p^{A}=0.905
The maximal MAP [mmHg]				
mean [SD] min - max	122.4± 15.6 [87-157]	123.3± 14.9 [87-140]	128.3± 2.4 [127-130]	p^{A}=0.856

A: Classical analysis of variance; MAP: Mean Arterial Pressure

Table 4: Average and maximum values of blood pressure in pregnant depending on the genotype of the AGT-235 gene.

AGT-235	**TT n=43**	**CT n=117**	**CC n=16**	
The average systolic blood pressure [mmHg]				
mean [SD] min - max	124.8 ± 16.0 [100-160]	124.5± 17.0 [90-179]	123.8± 11.3 [106-141]	p^{A}=0.975
The average diastolic blood pressure [mmHg]				
mean [SD] min - max	77.9± 10.0 [60-102]	77.5± 11.4 [60-105]	79.2± 6.4 [67-88]	p^{KW}=0.425
The average MAP [mmHg]				
mean [SD] min - max	93.6± 11.6 [73.3-120.0]	93.2± 12.8 [70.0-127.0]	94.0± 7.6 [81.0-105.3]	p^{A}=0.958
AGT-235	**TT n=21**	**CT n=51**	**CC n=10**	
The maximal systolic pressure [mmHg]				
mean [SD] min - max	157.2 ± 22.5 [110-200]	167.7± 21.6 [120-230]	159.0± 22.3 [130-190]	p^{A}=0.143
The maximal diastolic pressure [mmHg]				
mean [SD] min - max	98.2± 12.1 [70-115]	104.2± 12.7 [70-140]	100.5± 17.4 [80-140]	p^{A}=0.205
The maximal MAP [mmHg]				
mean [SD] min - max	117.9± 14.8 [87-140]	125.3± 14.5 [87-157]	120.0± 18.1 [97-157]	p^{A}=0.138

A: Classical analysis of variance; MAP: Mean Arterial Pressure

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Table 5: Week of pregnancy in which the hypertension occurred depending on the genotype of the ACE. AGT-174 and AGT-235 genes.

ACE	**DD n=18**	**ID n=32**	**II n=17**	
week of pregnancy mean [SD] min - max	26.3±11.2 [6-39]	28.2±9.8 [4-39]	31.7 ± 4.6 [21-39]	p^{KW}=0.532
AGT-174	**CC n=50**	**CT n=16**	**TT n=1**	
week of pregnancy mean [SD] min - max	27.6±9.3 [5-39]	31.7± 9.1 [4-39]	24.0± [--] [24-24]	p^{A}=0.285
AGT-235	**TT n=18**	**CT n=42**	**CC n=7**	
week of pregnancy mean [SD] min - max	29.4± 8.4 [5-39]	28.0± 10.1 [4-39]	29.9 ± 7.1 [23-39]	p^{A}=0.793

A: Classical Analysis Of Variance; KW: Kruskal-Wallis Test

Available results show evidence of the influence of body weight and ACE genotype on the appearance of hypertension. Although the study was conducted on a group of non-pregnant patients, the increased risk of hypertension in carriers of the D allele with obesity have been showed [13]. A closer analysis of I / D polymorphism of the ACE gene showed significant differences according not only to height and weight but also to gender and age, when tested for the systolic blood pressure and diastolic blood pressure between the homozygous (DD, II) and heterozygous (ID) [14], It points at a numerous relationships between changes in multi-phenotype and genotype, hindering direct comparisons between the study groups. Such conclusions also result from this work. The ID heterozygotes have higher values of maximum pressure, both systolic, diastolic and MAP, but without reaching statistical significance threshold. Other studies contradict the possible impact of the ACE gene mutation on the incidence of hypertension [15] and blood pressure regulation [16], but these studies have not been conducted in a group of pregnant women.

The AGT-174 (T174M) polymorphism of AGT gene appears to play a role in the regulation of blood pressure. It has been shown that homozygous carriers of the variant 174T, or C allele according to the new nomenclature, have lower systolic, diastolic, and mean arterial pressure, than heterozygotes or homozygotes the 174M variant (allele T according to the new nomenclature) [17]. These results are consistent with the results of this work, though due to the small sample size, no statistical significance was obtained. Another study on a group of men, but not on a group of women, confirmed the role of the AGT-174 polymorphism in the regulation of blood pressure and demonstrated the highest systolic blood pressure in carriers of the mutant allele T [18]. However, in other studies on large groups without distinction of pregnancy, there was no effect of this polymorphism on the regulation of blood pressure [19,20]. The contribution of this polymorphism in the pathophysiology of hypertension requires further study in a group of pregnant women.

Analysis of gene AGT-235 polymorphism in many studies did not show its' impact on the regulation of blood pressure, without distinguishing between pregnant women [11,16,20] which is consistent with the present study. When examining the current literature the authors have found no studies about associations between genotypes on pharmacotherapy of hypertension in pregnancy and postpartum period needed for blood pressure normalization.

Conclusion

On the basis of the collected material, the role of the ACE I/D, AGT-235, AGT-174 polymorphisms in the regulation of blood pressure was not shown. It may be concluded that there is no influence of these polymorphisms not only on the regulation of blood pressure during pregnancy, but also on the time of the onset or pharmacological treatment of hypertension during pregnancy and the time after delivery needed to normalization of blood pressure values. Researches on a larger study groups are needed.

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