

P R A C E O R Y G I N A L N E
położnictwo

Contribution of maternal-fetal adrenomedullin polymorphism to gestational hypertension and preeclampsia – gene-gene interaction pilot study

Udział matczyngo i płodowego polimorfizmu adrenomedulliny w nadciśnieniu ciążowym oraz stanie przedrzucawkowym – badanie wstępne interakcji gen-gen

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Summary

Introduction: Adrenomedullin (ADM), a peptide with vasodilatory, natriuretic and diuretic properties, is secreted in many tissues and shows multidirectional activity. ADM activity may play an important role in the pathophysiology of gestational hypertension (GH) and preeclampsia (PE) by involvement in compensation of failed utero-placental unit circulation.

Aim of the study: The aim of the study was to evaluate the association of –1984A>G ADM gene polymorphism with the development of GH and PE in maternal-fetal dyads.

Materials and methods: The study group consisted of 46 hypertensive pregnant subjects (further divided into two subgroups: 20 pregnant women with GH and 26 women with PE). 43 healthy pregnant women constituted the control group. The study and the control groups as well as the newborns were genotyped for –1984A>G ADM gene polymorphism using PCR/RLFP procedures.

Results: Minor –1984G allele was found to be higher in both, the GH (15.00%, OR=3.62, p=0.05), and the PE groups (9.62, OR=2.18, p=ns) when compared with controls (4.65%). A tendency for higher frequency of minor –1984G allele (12.50 vs. 6.98% in controls, OR=1.91, p=ns) was observed in the newborns from the GH group. It was also noteworthy that coexistence of both heterozygous genotypes of maternal-fetal dyads (–1984AG mother/–1984AG fetus) was overrepresented in the GH group (15.00 vs. 6.98%, OR=2.35, p=ns) and in the PE group (11.54 vs. 6.98%, OR=1.74, p=ns) when compared to controls.

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Conclusions: The observed tendency for overrepresentation of minor -1984G ADM allele in the GH and PE women and their newborns, despite lack of statistical significance, suggests participation of this genetic variant in the pathogenesis of the mentioned conditions. Additionally, the obtained results could indicate that maternal-fetal gene-gene interaction may be a potential source of adverse perinatal outcomes.

Key words: **preeclampsia / gestational hypertension / adrenomedullin / genetic polymorphism /**

Streszczenie

Wstęp: Adrenomedullina (ADM), białko o właściwościach wazodylatacyjnych, natriuretycznych i diuretycznych, wydzielana jest przez wiele tkanek i wykazuje wielokierunkowe działanie. ADM może odgrywać ważną rolę w patofizjologii nadciśnienia ciążowego (GH - gestational hypertension) oraz stanu przedrzucawkowego (PE - preeclampsia) poprzez wpływ na zaburzoną kompensację w krążeniu maciczno-łożyskowym.

Cel badań: ocena związku polimorfizmu -1984A>G genu ADM z rozwojem GH oraz PE w parach matka- płód.

Materiał i metody: Grupa badana 46 kobiet ciężarnych z nadciśnieniem podzielona została na dwie podgrupy: 20 ciężarnych z GH oraz 26 ciężarnych z PE. Grupę kontrolną stanowiły 43 zdrowe kobiety ciężarne. Oznaczanie częstości genotypów polimorfizmu -1984A>G genu ADM u wszystkich kobiet i ich noworodków przeprowadzono z zastosowaniem metody PCR/RLFP.

Wyniki: Obserwowano tendencję do częstszego występowania zmutowanego allele -1984G w obydwu grupach GH (15,00%, OR=3,62, p=0,05), oraz w grupie PE (9,62%, OR=2,18, p=ns) w porównaniu do grupy kontrolnej (4,65%). U noworodków z grupy GH odnotowano tendencję do częstszego występowania zmutowanego allele -1984G (12,50 vs. 6,98%, OR=1,91, p=ns). Warto również zauważyć, że współwystępowanie obydwu heterozygotycznych genotypów w parach matka-dziecko (-1984AG matka/-1984AG płód) było znacznie wyższe w grupie GH (15,00 vs. 6,98%, OR=2,35, p=ns), jak również w grupie PE (11,54 vs. 6,98%, OR=1,74, p=ns) w porównaniu do grupy kontrolnej.

Wnioski: Tendencja do częstszego występowania zmutowanego allele -1984G ADM u kobiet z GH oraz PE i ich noworodków, mimo braku istotności statystycznej, sugeruje udział tego wariantu genetycznego w patogenezie powyższych powikłań. Dodatkowo, otrzymane rezultaty wskazują, że matczyno-płodowe interakcje gen-gen mogą być potencjalnie przyczyną wystąpienia powikłań w przebiegu ciąży.

Słowa kluczowe: **stan przedrzucawkowy / nadciśnienie ciążowe / adrenomedullina / polimorfizm genetyczny /**

Introduction

Adrenomedullin (ADM), a peptide with vasodilatory, natriuretic and diuretic properties, is secreted in many tissues and shows multidirectional activity. Multifunctional biological activity of ADM in circulatory, respiratory, neuroendocrine and immunological systems suggests its contribution in many pathophysiological processes. Numerous studies investigate potential possibilities of ADM and its clinical application. ADM synthesis in the endothelial cells and its participation in the vascular tone and arterial blood pressure regulation by different mechanisms deserve particular attention [1, 2]. The main ADM effects are inhibition of proliferation of vascular smooth muscle cells and stimulation of NO synthesis [3]. Decreased sensitivity of blood vessels to vasoconstrictor factors leads to reduction of blood pressure value [2, 4]. It seems that ADM concentration changes play an important role in these processes.

ADM level increases in the course of physiological pregnancy, what is an evidence of an active role of ADM in the process of adaptation of maternal circulatory system during pregnancy [5, 6]. Moreover, ADM concentration is modulated by single nucleotide polymorphisms [7]. Nowadays, ADM gene expression and its polymorphic variants are being investigated as probable risk factors of cardiovascular diseases and, in case of pregnant women, as the component of preeclampsia and gestational hypertension development [8, 9, 10]. In numerous

researches ADM concentration was significantly increased in the serum of preeclamptic women, such as the amniotic fluid and the umbilical blood [6, 11, 12]. Only few investigations indicated a decreased or the same ADM concentration in preeclamptic women in comparison to healthy pregnant patients [12, 13]. Despite such divergent results, ADM is thought to play an important role in the pathophysiology of gestational hypertension and preeclampsia by its involvement in compensation of failed utero-placental unit circulation [9, 14].

The ADM encoding gene is located on chromosome 11. Recently, much attention has been paid to ADM gene polymorphisms, which may modulate ADM activity and might be involved in the etiology of different diseases. One of the studied polymorphisms is -1984A>G variant in the promoter region of the ADM gene, which probably enhances adrenomedullin transcription and, in consequence, increases ADM concentration [15].

In numerous investigations of perinatal diseases, only the maternal genotype effects have been evaluated. At present, it is postulated that even fetal genotype could influence the perinatal outcome, either on its own or by interacting with maternal genes. Since preeclampsia could result from maternal-fetal incompatibility, the influence of genetic variants in maternal-fetal dyads should also be taken into consideration. In this area several polymorphisms in different genes have been investigated.

Aim

The aim of this study was to evaluate the association of $-1984A>G$ ADM gene polymorphism with the development of GH and PE in maternal-fetal dyads.

Material and methods

Patients: The research involved two groups of women: 46 hypertensive pregnant patients (mean age 30.4 ± 4.2 years, mean systolic blood pressure 156.4 ± 20.3 mmHg, mean gestational age at delivery 35.7 ± 4.0 week of pregnancy) and 43 healthy pregnant controls (mean age 29.7 ± 5.8 years, mean systolic blood pressure 112.2 ± 11.3 mmHg, mean gestational age at delivery 39.0 ± 1.3 week of pregnancy) (Table I). The patients were enrolled into the study at the Perinatology and Women's Diseases Division, Poznan University of Medical Sciences, between January 2008 and May 2009. All women gave their informed written consent to participate in research. The Bioethical Committee of Poznan University of Medical Sciences approved the study (03/08). All patients were Caucasian, of Polish nationality, residents of the Wielkopolska region. In each case gestational age was calculated using the date of the last menstruation and confirmed by an ultrasound investigation.

The study group of hypertensive pregnant women ($n=46$, singleton pregnancy) was further divided into two subgroups: patients with gestational hypertension ($n=20$, GH group; mean age 30.3 ± 2.8 years, mean systolic blood pressure 148.8 ± 7.1 mmHg, mean gestational age at delivery 38.6 ± 2.1 week of pregnancy) and patients with preeclampsia ($n=26$, PE group; mean age 30.5 ± 4.9 years, mean systolic blood pressure 162.3 ± 21.2 mmHg, mean gestational age at delivery 34.0 ± 8.5 week of pregnancy) (Table I). Gestational hypertension and preeclampsia were recognized according to the ACOG (*American College of Obstetricians and Gynecologists*) criteria (blood pressure $\geq 140/90$ mmHg, and, in PE cases, the presence of proteinuria ≥ 300 mg/24 h). Women with multifetal pregnancies, preterm rupture of amniotic membranes, intraamniotic infection, diabetes mellitus, chronic hypertension, other cardio-vascular and renal diseases, as well as cigarette smokers were excluded from the study.

The control group consisted of 43 healthy pregnant women. The inclusion criteria to the control group were: singleton pregnancy, blood pressure $< 140/90$ mmHg, lack of proteinuria, absence of internal diseases and uncomplicated course of pregnancy.

Genetic analysis: In both groups of patients and their newborns (umbilical blood) the frequency of genotypes and alleles of $-1984A>G$ ADM gene polymorphism were evaluated. From each woman 3-4 mL venous blood samples were collected. The venous umbilical blood samples were collected immediately after the delivery of the placenta. Both samples were stored at -20°C until the DNA isolation was performed.

Genomic DNA was extracted from blood leucocytes using the QIAamp DNA Blood Mini Kit (QIAGEN Inc., Germany). Genotyping was performed using polymerase chain reaction (PCR) and restriction length fragment polymorphism (RLFP) procedures. 2 starters were used for amplification: F-CAA GTG GAA GCT GGC GAC AAG, R-CGG ACC TGA ATT CCA TCT GAG G (Tib MolBiol, Poland). PCR reaction was performed in Dyad DNA Engine Thermocycler (MJ Research Inc., USA). The initial denaturation was performed at 95°C for 3 min., then through 30 cycles the following conditions were used: denaturation at 94°C for 30 s, annealing at 63°C for 30 s, and elongation at 72°C for 60 s. The final elongation was performed at 72°C for 10 min. PCR products (377 bp) were hydrolyzed with restriction enzyme *TaaI* (*Tsp4CI*) (Fermentas, Lithuania). Analysis of the digested fragments was conducted with agarose gel by electrophoresis (2.5 % agarose gel). Products of the electrophoresis were stained with ethidium bromide and visualized under UV light for evaluation, using the system of documentation (KS 4000i/ImagePC, Syngen Biotech, USA). The AA genotype was identified by the presence of 377 bp long band, heterozygous AG genotype by 377 bp, 241 bp, and 136 bp bands and homozygous GG genotype by 241 bp and 136 bp bands.

Statistical analysis: Statistical analysis was performed by SPSS 15.0. *p* value lower than 0.05 was considered statistically significant. Frequencies of genotypes were compared by chi-square test. Expected genotype frequencies were calculated from allele frequencies using the Hardy-Weinberg equation.

Table I. Description of the mothers from the investigated groups of hypertensive pregnant women and controls.

		GH + PE	GH	PE	Control group
Number of dyads		46	20	26	43
Age (years)	<i>mean</i> ± <i>SD</i>	30.4±4.2	30.3±2.8	30.5±4.9	29.7±5.8
	<i>range</i>	230-400	25.0-38.0	23.0-40.0	17.0-39.0
	<i>median</i>	30.0	30.0	30.5	30.5
Gestational age at delivery (weeks)	<i>mean</i> ± <i>SD</i>	35.7±4.0	38.6±2.1	34.0±8.5	39.0±1.3
	<i>range</i>	25.0-42.0	36.0-42.0	25.0-40.0	37.0-42.0
	<i>median</i>	36.5	38.5	33.0	39.0
Systolic blood pressure (mmHg)	<i>mean</i> ± <i>SD</i>	156.4±20.3	148.8±7.1	162.3±21.2	112.2±11.3
	<i>range</i>	110.0-200.0	110.0-180.0	120.0-200.0	90.0-135.0
	<i>median</i>	160.0	155.0	160.0	110.0
Diastolic blood pressure (mmHg)	<i>mean</i> ± <i>SD</i>	98.2±13.5	93.5± 0.0	101.7±0.0	71.4±7.7
	<i>range</i>	60.0-130.0	60.0-110.0	70.0-130.0	60.0-85.0
	<i>median</i>	100.0	100.0	100.0	70.0

GH – gestational hypertension, PE – preeclampsia

Results

Analysis of newborn clinical data

Statistically significant lower birth weight was observed in the group of newborns from hypertensive women 2553.1 vs. 3501.7 g in controls ($p < 0.0001$). Lower Apgar score values at first (7.3 vs. 9.7 in controls, $p = ns$) and fifth minute (8.7 vs. 10.0 in controls, $p = ns$), mean values of arterial (7.22 vs. 7.23 in controls, $p = ns$) and venous (7.27 vs. 7.32 in controls, $p = ns$) pH, and lower placenta weight (498.6 vs. 632.3 g in controls, $p = ns$) were also observed in that group (Table II).

Frequency of genotypes and alleles of $-1984A > G$ ADM gene polymorphism in mothers

A tendency for higher frequency of heterozygotic $-1984AG$ and homozygotic $-1984GG$ genotypes (21.74 vs. 9.30% in the control group, $OR = 2.71$, $p = ns$) and higher frequency of $-1984G$ allele (11.96 vs. 4.65% in the control group $OR = 2.78$, $p = 0.07$)

were observed in the whole study group ($n = 46$) when comparing to controls ($n = 43$). Similarly, when we compared the GH and PE groups separately to the control group, overrepresentation of heterozygotic $-1984AG$ and homozygotic $-1984GG$ genotypes in the GH patients, just as heterozygotic $-1984AG$ genotype in the PE group, was also observed (respectively, 25.00% in the GH group, $OR = 3.25$, $p = ns$ and 19.23% in the PE group, $OR = 2.32$, $p = ns$ vs. 9.30% in controls). A tendency for higher frequency of $-1984G$ allele in both studied groups in comparison to the control group was noted (in the GH group 15.00 vs. 4.65% in controls, $OR = 3.62$, $p = 0.05$, and in the PE group 9.62 vs. 4.65% in the control group, $OR = 2.18$, $p = ns$) (Table III).

Frequency of genotypes and alleles of $-1984A > G$ ADM gene polymorphism in newborns

In newborns of hypertensive women slight higher frequency of heterozygotic $-1984AG$ genotype and $-1984G$ allele was

Table II. Description of the newborns from the investigated groups of hypertensive pregnant women and controls.

		Hypertensive pregnant	Control group	p
Number of dyads		46	43	
Birth weight (g)	mean±SD	2553,1±1167.2	3501.7±528.4	<0,0001
	range	620.0-4580.0	2430.0-4610.0	
	median	2540.0	3430.0	
Ap 1	mean±SD	7.3± 3.1	9.7±0.6	p=ns
	range	1.0-10.0	8.0-10.0	
	median	9.0	10.0	
Ap 5	mean±SD	8.7±1.8	10.0±0.0	p=ns
	range	3.0-10.0	10.0-10.0	
	median	10.0	10.0	
pH venous	mean±SD	7.27±0.10	7.32±0.08	p=ns
	range	7.01-7.45	7.14-7.48	
	median	7.28	7.34	
pH arterial	mean±SD	7.22±0.11	7.23±0.08	p=ns
	range	6.95-7.43	7.04-7.41	
	median	7.23	7.24	
Placental weight (g)	mean±SD	498.6±224.6	632.3±123.9	p=ns
	range	160.0-1200.0	420.0-900.0	
	median	470.0	605.0	

Table III. Frequency of ADM genotypes and alleles in mothers in the hypertensive pregnant women group and the controls.

ADM	Hypertensive pregnant n=46		GH n=20		PE n=26		Control group n=43	
	observed value n (%)	expected value n (%)	observed value (%)	expected value (%)	observed value n (%)	expected value (%)	observed value n (%)	expected value (%)
Genotypes								
AA	36 (78.26)	77.51	15 (75.00)	72.25	21 (80.77)	81.69	39 (90.70)	90.91
AG	9 (19.56)	21.06	4 (20.00)	25.50	5 (19.23)	17.39	4 (9.30)	8.87
GG	1 (2.18)	1.43	1 (5.00)	2.25	0 (0.00)	0.92	0 (0.00)	0.22
Total	46 (100.00)	100.00	20 (100.00)	100.00	26 (100.00)	100.00	43 (100.00)	100.00
Alleles								
A	81 (88.04)	-	34 (85.00)	-	47 (90.38)	-	82 (95.35)	-
G	11 (11.96)	-	6 (15.00)	-	5 (9.62)	-	4 (4.65)	-
Total	92 (100.00)	-	40 (100.00)	-	52 (100.00)	-	86 (100.00)	-

observed when compared to controls (respectively, 19.57 vs. 13.95%, OR=1.50, $p=ns$ and 9.78 vs. 6.98%, OR=1.44, $p=ns$). The frequency of heterozygotic *-1984AG* genotype (15.38 vs. 13.95% in controls OR=1.12, $p=ns$) and *-1984G* allele (7.69 vs. 6.98%, OR=1.11, $p=ns$) was similar in the PE and the control group. However, almost a two-fold higher frequency of *-1984AG* genotype (25.00%) in comparison to the control group (13.95%, OR=2.06, $p=ns$) was noted in the newborns from the GH group. The same observation was connected with mutated *-1984G* allele. The frequency of this variant was also almost two-fold higher in the newborns from the GH group when compared to controls (12.50 vs. 6.98%, OR=1.91, $p=ns$). All the observed values were in accordance with Hardy-Weinberg equilibrium (Table IV).

Co-occurrence of genotypes in maternal-fetal dyads

Finally, we compared the co-occurrence of investigated genotypes in mothers and fetuses from the study groups.

Interestingly, an overrepresentation of coexistence of both heterozygous genotypes in maternal-fetal dyads (*-1984AG mother/-1984AG fetus*) was observed in the entire group of hypertensive women (GH + PE): 13.04 vs. 6.98% in controls, OR=2.00, $p=ns$) (Table V).

The fact that the coexistence of both heterozygous genotypes in the maternal-fetal dyads (*-1984AG mother/-1984AG fetus*) in the GH group (15.00 vs. 6.98%, OR=2.35, $p=ns$) and in the PE group (11.54 vs. 6.98%, OR=1.74, $p=ns$) was overrepresented when compared to the control group seems noteworthy. (Table V).

Discussion

Recent studies showed that physiological course of pregnancy depends on the proper "cooperation" between the mother and the fetus. Disturbances of balance in the maternal-fetal dyads are one of the mechanisms involved in the development of perinatal diseases. Fetal genome has been suggested to have an influence on

Table IV. Frequency of ADM genotypes and alleles in newborns from the hypertensive pregnant women group and the controls.

ADM	Hypertensive pregnant n=46		GH n=20		PE n=26		Control group n=43	
	observed value n (%)	expected value n (%)	observed value (%)	expected value (%)	observed value n (%)	expected value (%)	observed value n (%)	expected value (%)
Genotypes								
AA	37 (80.43)	81.4	15 (75.00)	76.56	22(84.62)	85.21	37 (86.05)	86.53
AG	9 (19.57)	17.65	5 (25.00)	21.88	4(15.38)	14.20	6 (13.95)	12.98
GG	0 (0.00)	0.95	0 (0.00)	1.56	0 (0.00)	0.59	0 (0.00)	0.49
Total	46 (100.00)	100.00	20 (100.00)	100.00	26 (100.00)	100.00	43 (100.00)	100.00
Alleles								
A	83 (90.22)	-	35 (87.50)	-	48(92.31)	-	80 (93.02)	-
G	9 (9.78)	-	5 (12.50)	-	4 (7.69)	-	6 (6.98)	-
Total	92 (100.00)	-	40 (100.00)	-	52 (100.00)	-	86 (100.00)	-

Table V. Co-occurrence of ADM gene polymorphism genotypes in maternal-fetal dyads in the studied groups.

<i>-1984A>G</i> ADM		Mother			Total	
		AA	AG	GG		
Hypertensive pregnant (n=46)	Newborn	AA	34 (73.91)	3 (6.52)	0 (0.00)	37 (80.43)
		AG	2 (4.35)	6 (13.04)	1 (2.17)	9 (19.56)
		GG	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		Total	36 (78.26)	9 (19.56)	1 (2.17)	46 (100.00)
GH	Newborn	AA	14 (70.00)	1 (5.00)	0 (0.00)	15 (75.00)
		AG	1 (5.00)	3 (15.00)	1 (5.00)	5 (25.00)
		GG	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		Total	15 (75.00)	4 (20.00)	1 (5.00)	20 (100.00)
PE	Newborn	AA	20 (76.92)	2 (7.69)	0 (0.00)	22 (84.61)
		AG	1 (3.85)	3 (11.54)	0 (0.00)	4 (15.39)
		GG	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		Total	21 (80.77)	5 (19.23)	0 (0.00)	26 (100.00)
Control group (n=43)	Newborn	AA	36 (83.72)	1 (2.32)	0 (0.00)	37 (86.04)
		AG	3 (6.98)	3 (6.98)	0 (0.00)	6 (13.96)
		GG	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		Total	39 (90.70)	4 (9.30)	0 (0.00)	43 (100.00)

the pregnancy course, among others by interacting with maternal genes. An investigation of adverse perinatal effects should consider both, maternal and fetal genetic conditions and, indeed, in some current studies the correlation between hypertensive disorders in pregnant women and gene polymorphisms at maternal-fetal interactivity has been reported [16, 17, 18, 19]. Therefore, identification of candidate genes involved in PE pathogenesis, and especially research connected with imbalance in maternal-fetal dyads, may offer new and important insight into its prevention and treatment.

There are only few studies focused on genetic variants of hypertensive disorders including maternal-fetal dyads genotyping. A study analyzing a correlation between polymorphisms of transforming growth factor beta 3 (TGF-beta 3) gene and PE/GH risk was performed in a group of 136 subjects and 169 controls. Four single nucleotide polymorphisms (SNPs) in TGF-beta 3 gene (rs3917200, rs114664142, rs2268624, rs2205181) were genotyped. The most interesting results were connected with rs114664142 polymorphism (occurred genotypes: *CC*, *CT*, *TT*). The mothers with minor *T* allele were not inclined to develop either GH or PE. On the other hand, fetuses with at least one copy of the minor allele for rs114664142 polymorphism were delivered more frequently in the group of hypertensive women (23% vs. 16% in controls) and the risk of developing GH/PE was lower among mother-fetus dyads when the fetus was carrying one or two copies of *T* allele in comparison to fetuses with no *T* allele. None of the other polymorphisms were associated with an increased risk of hypertensive disorders in the course of pregnancy [20].

Furthermore, an interesting study was performed by Hill et al., who investigated the association between catechol-O-methyltransferase (COMT) haplotypes, methylenetetrahydrofolate reductase (MTHFR) 677C>T polymorphism and PE risk (1103 maternal-fetal dyads). Four SNPs of COMT gene (rs6269, rs4633, rs4680, and rs4818) were shown to be connected with the enzyme activity. The study revealed that maternal *ACCG* COMT haplotype was correlated with a reduced risk of PE ($p=0.004$). Fetal *ATCA* COMT haplotype and the presence of fetal MTHFR minor 677T allele increased PE risk ($p=0.022$) [21].

To the best of our knowledge, this is the first research concerning at the same time maternal and fetal $-1984A>G$ ADM gene polymorphism and its correlation to hypertensive disorders during pregnancy. Despite lack of statistically significant differences, we have observed high overrepresentation of the mutated $-1984G$ allele in the whole hypertensive group (OR=2.78), as well as in the GH and PE groups. However, the analysis of maternal-fetal dyads frequency and their influence on GH/PE development in pregnant women was the most important fact. Our study evaluated genotypes and allele frequencies in pregnant women with PE and GH, as well as in the umbilical blood of their newborns, demonstrate a possible role of both maternal and fetal genotype in increasing the risk of PE. Moreover, the overrepresentation of coexistence of both heterozygous genotypes in the maternal-fetal dyads ($-1984AG$ mother/ $-1984AG$ fetus) in the whole group of hypertensive women (GH + PE) (OR=2.0), the GH group (OR=2.35) and the PE group (OR=1.74) was observed. These exciting results could suggest a participation of minor *G* allele in the pathogenesis of PE and GH and, additionally, highlight the importance of maternal-fetal dyads analysis.

Unfortunately, there are some limitations to our research. First of all, PE and GH etiology is most probably multifactorial. Thus, it is incorrect to assume that genetic variability alone is a risk factor of hypertensive disorders in pregnancy [22, 23]. However, we eliminated known risk factors of PE and GH. Women with multifetal pregnancies, preterm rupture of amniotic membranes, intraamniotic infection, diabetes mellitus, chronic hypertension, other cardio-vascular and renal diseases, as well as cigarette smokers, were excluded from the study. Secondly, a relatively small group of investigated maternal-fetal dyads might have adversely influenced the accuracy of the obtained results. Finally, our study was conducted on Caucasian patients, of Polish origin. Genotypes and allele frequencies vary among different races and populations. Thus, it is necessary to emphasize the fact that further analysis, with involvement of more comprehensive data, is needed. Due to the fact that studies concerning the involvement of ADM in the etiology of GH and PE are scarce, the obtained results are difficult to interpret. There is a need to continue studies confirming the participation of ADM in the pathogenesis of various diseases, as well as research confirming its clinical usefulness and application.

Probably only a complex analysis of the processes involved in the modulation of ADM gene transcription factors and studies concerning polymorphic variants of ADM gene, ADM receptor/receptor gene, will allow us to figure out the actual role of this peptide in the etiology of hypertensive disorders during pregnancy [24, 25].

Conclusions

The observed tendency for overrepresentation of minor $-1984G$ ADM allele in the GH and PE women and their newborns, despite lack of statistical significance, suggests a participation of this genetic variant in the pathogenesis of these two conditions. Additionally, the obtained results could indicate that maternal-fetal gene-gene interaction may be a potential source of adverse perinatal outcome. To the best of our knowledge, this is the first study dealing with maternal and fetal $-1984A>G$ ADM gene polymorphism and its correlation to hypertensive disorders during pregnancy, thus further analysis is essential.

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