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Plasma and Urinary Uroguanylin in Preeclamptic and Healthy Pregnant Women and Their Fetuses

Stężenie uroguaniliny w surowicy krwi i w moczu u zdrowych kobiet ciężarnych, ciężarnych z preeklampsją oraz u ich płodów

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Abstract

Background. Preeclampsia is characterized by elevated blood pressure, proteinuria, and abnormal water-electrolyte metabolism. Uroguanylin (UG) is a member of a new family of natriuretic, diuretic, and kaliuretic peptides which may indirectly influence blood pressure.
Objectives. This study aimed to establish the pathophysiological role of uroguanylin in preeclamptic and healthy pregnant women and their fetuses.
Material and Methods. Uroguanylin was measured in cubital vein blood obtained from 11 non-pregnant women, 14 preeclamptic, and 13 healthy pregnant women some minutes before delivery and in amniotic fluid and umbilical cord blood of the fetuses. In addition, UG was assessed in the urine of pregnant women collected 1–3 days before delivery. Uroguanylin was measured using the RIA method.
Results. Preeclamptic women showed significantly lower UG plasma levels than healthy pregnant women and non-pregnant women (2.9 ± 0.6 vs. 5.6 ± 0.5 and 8.2 ± 1.0 fmol/ml, respectively). In preeclamptic women the UG level in umbilical cord blood was lower (although not significantly) than in healthy pregnant women (3.4 ± 0.6 vs. 5.1 ± 0.6 fmol/ml). Urinary UG excretion in non-pregnant women (72.4 ± 19.3 pmol/day) was not significantly higher than in healthy pregnant women (51.3 ± 11.3 pmol/d), but was significantly higher than in preeclamptic women (24.2 ± 4.6 pmol/d). Finally, the UG concentration in the amniotic fluid of the preeclamptic women was significantly reduced compared with that of healthy pregnant women (41.1 ± 8.2 vs. 68.6 ± 6.0 fmol/ml).
Conclusions. Abnormal UG secretion seems to be involved in the pathogenesis of the abnormal water-electrolyte homeostasis in preeclampsia (**Adv Clin Exp Med 2006, 15, 5, 789–795**).

Key words: preeclampsia, hypertension, uroguanylin.

Streszczenie

Wprowadzenie. Preeklampsja charakteryzuje się nadciśnieniem tętniczym, białkomoczem i zaburzeniami gospodarki wodno-elektrolitowej. Uroguanilina jest nowym członkiem rodziny peptydów działających natriuretycznie i kaliuretycznie, a więc związkiem potencjalnie wpływającym na ciśnienie tętnicze krwi.
Cel pracy. Określenie roli patofizjologicznej uroguaniliny u ciężarnych zdrowych i z preeklampsją oraz u ich płodów.
Materiał i metody. Uroguanilinę oznaczono we krwi żylnej pobranej z żyły łokciowej u 11 nieciężarnych kobiet, u 14 ciężarnych z preeklampsją i 13 zdrowych ciężarnych (kilka minut przed rozwiązaniem), w płynie owodniowym ciężarnych oraz we krwi pępowinowej ich płodów. Uroguanilinę oznaczono ponadto w moczu kobiet nieciężarnych i u ciężarnych (zebranym 1–3 dni przed rozwiązaniem).
Wyniki. U ciężarnych z preeklampsją stwierdzono istotnie mniejsze stężenie uroguaniliny w osoczu krwi niż u zdrowych ciężarnych (2,9 ± 0,6 *vs*. 5,6 ± 0,5 *vs*. 8,2 ± 1,0 fmol/ml). U kobiet z preeklampsją stwierdzono ponadto mniejsze (statystycznie nieistotne) stężenie uroguaniliny we krwi pępowinowej płodów niż u zdrowych ciężarnych (3,4 ± 0,6 *vs*. 5,1 ± 0,6 fmol/ml). U nieciężarnych kobiet dobowe wydalanie uroguaniliny z moczem było nieistotnie większe (72,4 ± 19,3 pmol/d) niż u zdrowych ciężarnych (51,3 ± 11,3 pmol/d), lecz znamiennie większe

niż u ciężarnych z preeklampsją (24,2 ± 4,6 pmol/d). Stężenie uroguaniliny w płynie owodniowym ciężarnych z preeklampsją było istotnie mniejsze niż u zdrowych ciężarnych (41,1 ± 8,2 *vs*. 68,6 ± 6 fmol/ml).
Wnioski. Udział nieprawidłowej sekrecji uroguaniliny w patogenezie zaburzeń gospodarki wodno-elektrolitowej u ciężarnych z preeklampsją jest prawdopodobny (**Adv Clin Exp Med 2006, 15, 5, 789–795**).

Słowa kluczowe: preeklampsja, nadciśnienie, uroguanilina.

The recent definition of preeclampsia involves mostly arterial hypertension and proteinuria and ignores severe edemata, although the last should not be omitted for clinical purposes [1]. Although the pathogenesis of preeclampsia seems to be very complex, abnormal interaction between fetal and maternal tissues seems to be the triggering mechanism of this syndrome [2]. Recent studies are consistent with the hypothesis that there seems to be both a maternally and a paternally transmitted genetic predisposition to preeclampsia [3]. The morphological hallmark of preeclampsia is abnormal endovascular invasion of the cytotrophoblast in the maternal spiral arteries with subsequent abnormal function of the fetal-uterus unit [4]. Among the many metabolic abnormalities induced by impaired trophoblast invasion, disturbances in the water-electrolyte balance are to be mentioned [5, 6]. As is well known, normal pregnancy is characterized by an increase in GFR and renal blood flow and by a significant expansion of maternal plasma volume, which is accompanied by a decrease in systemic vascular resistance [4, 5]. In preeclampsia, GFR and RBF are reduced. Simultaneously, plasma volume is contracted, although total sodium and water retention are of the some magnitude or even greater than in normal pregnancy. Thus a proportionally greater increase in the interstitial fluid space than in the vascular compartment is observed. The redistribution of body fluids seems to be due to complex regulatory factors leading to abnormal endothelial cell function and increasing capillary permeability [4, 5,7]. Excessive sodium and water retention is an important clinical symptom of preeclampsia. In spite of many studies, the pathogenesis of abnormal sodium and water retention in preeclampsia has not been completely clarified [for review, see: 4–6].

In recent years a new family of natriuretic peptides has been identified which comprises at least three hormones: guanylin [8], uroguanylin [9–10], and lymphoguanylin [11]. These natriuretic hormones seem to be involved in blood pressure regulation by influencing sodium excretion by the kidneys and sodium resorption by the gastrointestinal tract [12–15]. As uroguanylin shows a natriuretic and diuretic effect, it was of interest to study plasma uroguanylin and urinary excretion of this hormone in preeclamptic and healthy pregnant women, that is in pathophysiological settings characterized by excessive sodium and water retention.

Material and Methods

This study comprised 11 non-pregnant women (mean age: 28.9 ± 1.9 years), 13 healthy pregnant women (mean age: 25.1±1.0 years), and 14 preeclamptic women (mean age: 25.1 ± 1.0 years). The preeclamptic women were characterized by proteinuria (mean: 2.1 ± 0.27 g/day) and hypertension (MAP: 124.1 ± 3.3 mmHg). They also showed lower platelet counts in blood (167.4 ± 12.4 T/l) than non-pregnant (212.2 ± 2.3 T/l) and healthy pregnant women (236 ± 12.5 T/l). The mean gestosis index was 5.2 ± 1.2.

All the pregnant women were admitted to the hospital 1–3 days before the calculated time of delivery. Blood samples for measuring uroguanylin were obtained from the cubital vein in the fasting non-pregnant women, while in the pregnant women blood was taken some minutes before delivery as well as umbilical cord blood and amniotic fluid. The study protocol was accepted by the local ethics committee.

Uroguanylin was assessed by the RIA procedure according Kinoshita et al. [16, 17] with some modifications. In brief, the blood samples were collected in polypropylene tubes containing sodium EDTA (1 mg/ml of blood) and aprotinin (500 units/ml of blood) and centrifuged within 15 minutes at 3000 rpm at 4 C. Two ml of supernatant plasma was diluted by an equal volume of a 0.9% NaCl solution and applied to a Sep Pack C 18 cartridge (Waters Associates, Milford, MA, USA) which was previously equilibrated with 0.9% NaCl solution. Then the columns were washed with 5 ml of 0.9% saline and 5 ml of a 10% acetonitrile solution containing 0.1% trifluoroacetic acid (TFA). Desorption of the adsorbed uroguanylin was performed with 3 ml of 60% acetonitrile containing 0.1% TFA. The eluate was evaporated in a stream of air and the dry residue dissolved in 0.4 ml of 0.05 M phosphate buffer containing 0.25% albumin (BSA), 0.08M NaCl, 0.05% sodium azide, and 0.1% triton X-100. This solution was used for the RIA procedure.

A volume of 0.1 ml of the uroguanylin extract was incubated for 48 hrs at 4 C with antiuroguanylin antibodies (kindly supplied by Dr. Nakazato) (final dilution: 1 : 9600) and 0.1 ml of ^{125}I-labeled ligand (12,000–16,000 cpm). Separation of the free and bound ligand was done by adding 0.5 ml of 23% polyethylene glycol to the incubation mixture. The

^{125}I-labeled ligand was obtained by iodination of [Tyr^{o}]-uroguanylin by the chloramine T method [18]. Radio-labeled [Tyr^{o}]-uroguanylin was adsorbed on a Sep Pack cartridge and desorbed by 60% acetonitrile containing 0.1% TFA. A calibration curve was obtained using [Tyr^{o}]-uroguanylin as a standard. The inter- and intra-assay deviations were 10% and 7%, respectively. All samples were processed in duplicate.

Measurement of uroguanylin was done in urine specimens which were centrifuged at 3000 rpm for 15 minutes at 4 C. A volume of 0.5 ml of supernatant was diluted with 0.9% NaCl solution and applied to a Sep Pack C-18 cartridge. Then the cartridge was washed with 0.9% saline and 10% acetonitrile. The adsorbed uroguanylin was desorbed by 60% acetonitrile containing 0.1% TFA and the eluate evaporated. The dry residue was dissolved in 1 ml of phosphate buffer. 0.1 ml of this extract was further processed like the plasma extracts.

Data entry and statistical analysis were performed with Statistica 6.0 (Stat Soft). Descriptive data were expressed as the means and standard errors of means (*SEM*). Statistical evaluation of the results was performed using the Mann-Whitney U test for unpaired variables and the Student t test for paired variables. Correlation coefficients were calculated according the tau Kendall correlation test.

Results

The pregnant women of both the examined groups did not differ in gestational age or significantly from the ages of the non-pregnant women.

The preeclamptic women showed significantly elevated MAP (124.1 ± 3.3 mm Hg) compared with healthy pregnant women (97.1 ± 1.7 mm Hg) and non-pregnant women (96.2 ± 2.8 mm Hg). In preeclamptic women the blood pressure measured six months after delivery was systolic 123 ± 1.2, diastolic 74.7 ± 1.1, and MAP 90.9±1.1 mm Hg. The mean weight of the fetuses of the healthy pregnant women was 3362 ± 132 g and of the preeclamptic women 3469±183 g (difference statistically not significant). The mean weight of the placenta from the healthy pregnant women was higher (542 ± 24 g) than that from preeclamptic women (485 ± 24 g) (difference statistically not significant).

As can be seen in Figure 1, the pregnant women of both groups showed lower uroguanylin plasma levels than the non-pregnant women. This difference was statistically significant between non-pregnant and preeclamptic women (8.2 ± 1.0 vs. 2.9 ± 0.6 fmol/ml, $p = 0.0003$). The difference between the healthy pregnant and the preeclamptic women was also statistically significant (5.6 ± 0.5 *vs*. 2.9 ± 0.6, $p = 0.0013$). Uroguanylin plasma levels in umbilical cord blood of the preeclamptic women were lower (not significantly) than those of the healthy pregnant women (3.4 ± 0.6 *vs*. 5.1 ± 0.6 fmol/ml).

The uroguanylin concentration in the amniotic fluid of the preeclamptic women was significantly lower ($p = 0.01$) than in the healthy pregnant women (Fig. 2).

Urinary uroguanylin excretion was significantly lower in the preeclamptic women than in the healthy pregnant and the non-pregnant women

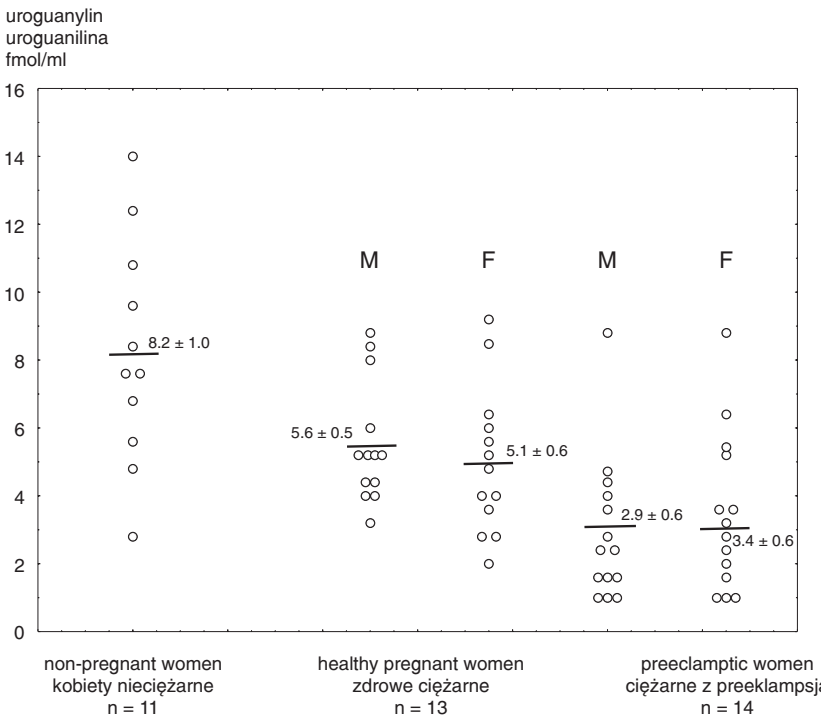

Fig. 1. Plasma levels of uroguanylin in non-pregnant women, healthy pregnant, and preeclamptic women.
M – mother cubital blood,
F – umbilical cord blood

Ryc. 1. Stężenie uroguaniliny w surowicy u niecięŜarnych kobiet oraz zdrowych ciężarnych i ciężarnych z preeklampsją.
M – krew z żyły łokciowej matki,
F – krew z żyły pępowinowej

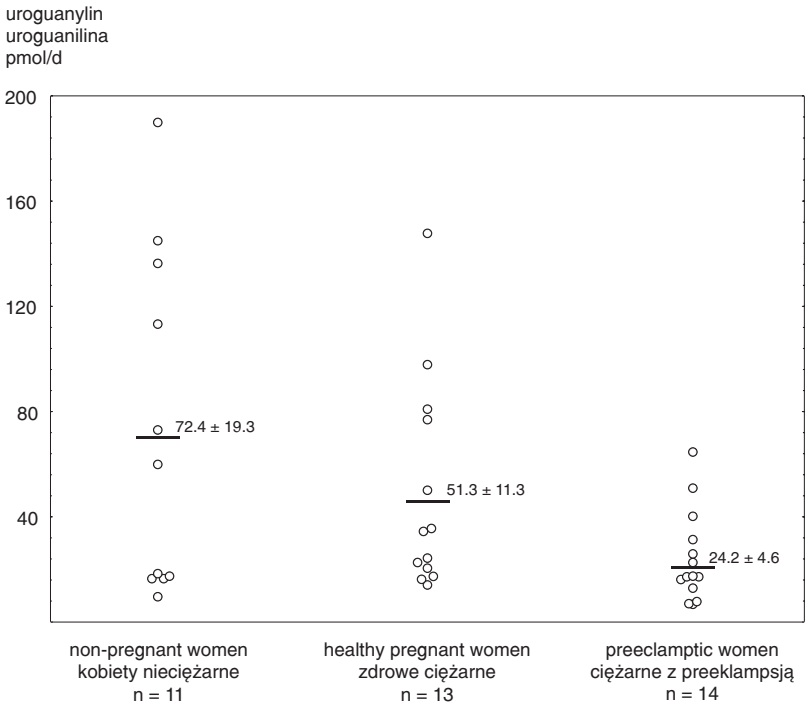

Fig. 2. Uroguanylin concentration in amniotic fluid of healthy pregnant and preeclamptic women

Ryc. 2. Stężenie uroguaniliny w płynie owodniowym zdrowych kobiet ciężarnych i ciężarnych z preeklampsją

(24.2 ± 4.6 *vs*. 51.3 ± 11.3 *vs*. 72.4 ± 19.3 pmol/d, $p = 0.045$ and $p = 0.012$, respectively). Although urinary uroguanylin in the healthy pregnant women was lower than in the non-pregnant ones (51.3 ± 11.3 *vs*. 72.4 ± 19.3), this difference was statistically not significant.

In the non-pregnant healthy women, a significant positive correlation was found between MAP and plasma uroguanylin level (tau = 0.56, $p = 0.017$) and between MAP and urinary uroguanylin excretion (tau = 0.46 $p = 0.05$). In the healthy pregnant women, a significant negative correlation was found between MAP and maternal urinary uroguanylin excretion (tau = –0.49, $p = 0.02$). Such a correlation was absent in the preeclamptic women.

Only in the preeclamptic women a significant positive correlation was found between plasma uroguanylin level in the maternal blood and umbilical cord blood (tau = 0.85, $p = 0.000021$). No significant correlation was noted between uroguanylin concentration in amniotic fluid and plasma uroguanylin level in maternal or fetal blood in both the examined groups of pregnant women.

Discussion

As shown in this study, pregnant women (both healthy and preeclamptic) have lower plasma levels of uroguanylin in maternal peripheral blood and reduced urinary uroguanylin excretion compared with healthy non-pregnant women. These differences between pregnant and non-pregnant women became statistically significant in the preeclamptic women. In addition, the preeclamptic women showed lower (but statistically not significant) uroguanylin plasma levels in umbilical cord blood, but significantly lower uroguanylin concentrations in amniotic fluid and uroguanylin excretion in urine than healthy pregnant women. Finally, preeclamptic women, in contrast to healthy pregnant ones, did not show any relationship between urinary uroguanylin excretions and MAP. In the light of these findings the question arises whether uroguanylin is of pathophysiological relevance in preeclampsia.

Uroguanylin is a polypeptide containing 16 amino acids [10, 19, 20]. It is a member of a new family of natriuretic peptides which comprises guanylin [8], uroguanylin [9, 10], and lymphoguanylin [11]. It shows structural homology with the heat-stable enterotoxins (STs) that cause traveler's diarrhea [11]. All guanylins and STs are ligands for the guanylate cyclase C (GC-C) receptor [13]. After activation of this receptor, cyclic GMP (cGMP) is generated, which is the intracellular messenger of guanylins actions [for review see: 21]. GC-C belongs to the family of guanylate cyclases which comprises guanylate cyclase A (GC-A) and guanylate cyclase B (GC-B). The ligands for GC-A are, in order of decreasing affinity, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP), while for GC-B they are CNP, ANP, and BNP, respectively [13, 22]. Uroguanylin is present not only in the gastrointestinal tract [23–30], but also in the pancreas [28, 31], heart[24], kidney [24, 29, 32, 33; for review see: 34, 35], brain [28], and other organs [28].

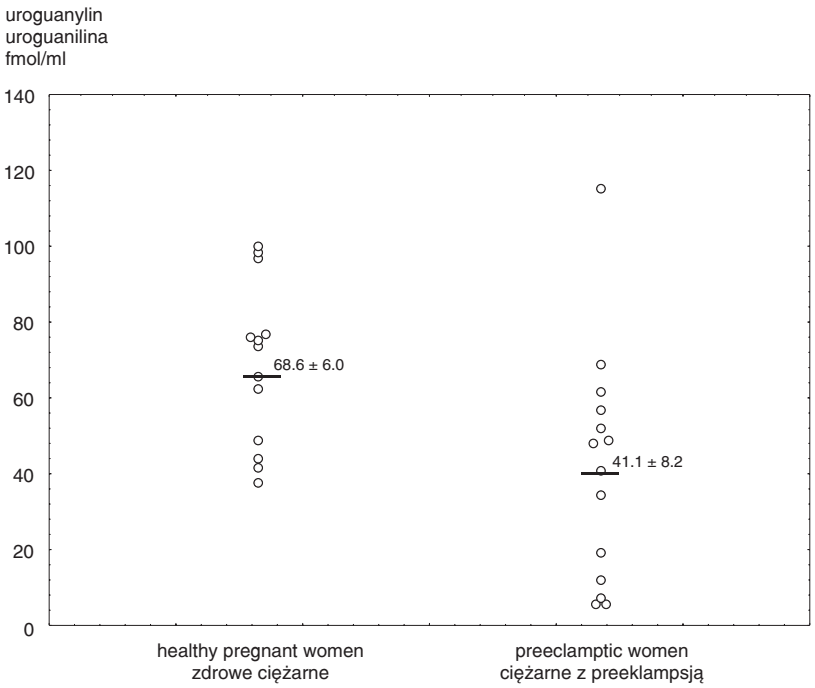

Fig. 3. Urinary uroguanylin excretion in non-pregnant, healthy pregnant, and preeclamptic women

Ryc. 3. Wydalanie uroguaniliny z moczem u niecięźarnych kobiet oraz zdrowych ciężarnych i ciężarnych z preeklampsją

It is generally presumed that guanylins are involved in the salt and water balance by influencing Cl^- and HCO_3^- secretion into the intestinal lumen [14, 36, 37] and water sodium, and potassium excretion by the kidneys [38]. This effect seems to be the result of guanylins' actions on membrane GC-C by an autocrine and or paracrine pathway mediated by cGMP [8, 39]. As uroguanylin and guanylin increase water sodium and potassium excretion even in GC-C-null mice, it seems that the mechanism(s) of their action may also be GC-C independent [40]. Quite recently the existence of two signaling pathways for guanylin peptides in principal cells of mouse cortical collecting duct were found [41]. One pathway is cGMP and protein kinase G (PKG) dependent but not mediated by guanylate cyclase C, while the second is a cGMP-independent signaling pathway for these peptides which apparently involves phospholipase A2 (PLA2) and arachidonic acid [41]. Intestinal guanylin and uroguanylin are secreted not only into the lumen of the gastrointestinal tract, but also into the circulatory blood, from where they are cleared by the kidneys [28, 33] and where they exert a natriuretic, diuretic, and kaliuretic effect [21, 38; for review see: 34, 35]. The guanylins seem to link the gastrointestinal tract and kidneys in a potential endocrine axis which participates in monitoring water-electrolyte homeostasis [for review see: 12, 34, 35, 42, 43].

Until now, only scarce reports on the clinical relevance of guanylins have been available. The intake of a high-salt diet is accompanied by a significant increase in urinary excretion of uroguanylin [16]. This increase shows a significant positive correlation with natriuresis, kaliuresis, and urinary cGMP excretion [16]. In patients with chronic renal failure, both plasma guanylin [44] and uroguanylin [16] are elevated and positively correlated with the severity of renal failure. Plasma levels of guanylin [44] and uroguanylin [45] are also significantly elevated in dialyzed patients with end-stage renal failure compared with healthy controls. Elevated uroguanylin plasma levels were also found in edematous nephritic patients [17] and patients with congestive heart failure [46]. In the latter, urinary uroguanylin was substantially increased [46]. The present authors found higher values of urinary uroguanylin in patients with essential hypertension than in normotensive subjects [47].

As shown in experimental studies in guinea pigs, pregnancy is characterized by a significant increase in myometrical cGMP production [48]. As shown by Buhimshi et al., this increase in cGMP production is due to an increased GC-A activity which is responsive to ANP [48]. These authors suggest that the enhanced production of cGMP in the pregnant myometrium is due to increased particulate GC-A activity induced by a natriuretic peptide in a paracrine manner [48]. As shown by Itoh et al., amniotic fluid obtained from pregnant women contains high concentrations of BNP [49]. This natriuretic peptide, by acting in a paracrine manner on myometrical GC-A, could be responsible for the high myometrical content of cGMP [49]. The relationship between amniotic uroguanylin and cGMP concentrations in pregnant myometrium has not been studied until now. As uroguanylin is present in human amniotic fluid, it seems likely that this hormone, acting on GC-C,

may contribute to increased cGMP concentration in the pregnant myometrium. This speculation is not consistent with studies reported by Buhimschi et al., in which no influence of uroguanylin on particulate GC-C in the myometrium was noted [48].

Taking into account the above-mentioned effects of uroguanylin on water-electrolyte homeostasis as well as the results presented in this paper (significantly lower uroguanylin levels in plasma and amniotic fluid, markedly reduction of uroguanylin excretion in urine, and lower uroguanylin plasma levels in umbilical cord blood in preeclamptic women compared with healthy pregnant ones), it seems likely that uroguanylin is involved in the pathogenesis of preeclampsia. Further studies are necessary to elucidate the role of this hormone in the pathogenesis of abnormal water-electrolyte metabolism in preeclampsia.

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