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The Influence of Clinical and Anthropometric Parameters on the Serum Levels of the Endothelin-1 in Pregnant Women and their Newborns

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A B S T R A C T

Pregnancy induced hypertension (PIH) is major contributor to maternal death in developing countries. Endothelin-1 (ET-1) is the most potent vasoconstriction agent known and its serum levels are increased in PIH. Therefore it is important to elucidate maternal and neonatal factors which influence endothelin-1 serum levels. 100 pathological pregnancies and 88 controls were analyzed for blood endothelin-1 and their anthropometric and clinical data were collected. In maternal blood ET-1 levels were strongly predicted by diagnosis, therapy and BMI, while umbilical cord ET-1 levels were strongly predicted by gestational age, therapy and delivery termination. Positive correlation between BMI and ET-1 levels suggest that obese pregnant women have increased risk for cardiovascular diseases. Inverse relationship between Apgar and umbilical ET-1 indicates that ET-1 could be considered as a prognostic marker in cases of neonatal asphyxia.

Key words: *endothelin-1, pregnancy induced hypertension, anthropometry, apgar*

Introduction

Hypertensive disorders are major contributors to maternal deaths in developing countries. These data should inform evidence-based reproductive health-care policies and programs at regional and national levels[1].

Pregnancy induced hypertension (PIH) affect up to 8–16% of pregnancies and has a significant portion of the enhancement of perinatal and neonatal mortality and morbidity. Some of those pregnancies often end in fetal loss, neonatal asphyxia, intrauterine growth retardation or premature birth, which carries a risk of serious neonatal complications[2–4]. PIH represents a spectrum of disease, whereby pregnant women suffer from newly onset of hypertension, usually after the 20 weeks of gestation. It could be manifested in several clinical entities, among which the most significant are preeclampsia (PE) and eclampsia, gestational hypertension, superimposed hypertension and according to some authors HELLP syndrome (hemolysis, elevated liver enzymes, low platelets)[2]. Last two decade recent literature has given the most acceptable pathophysiological model of PE.

By definition, PE represent systemic syndrome of pregnancy characterized by hypertension and proteinuria[5]. Mostly, PE could be associated with some degree of intrauterine growth restriction (IUGR). IUGR is a common diagnosis in obstetrics and represents second leading cause of perinatal mortality and morbidity, followed only by prematurity[6,7]. Most acceptable definition of IUGR is failure of the fetus to reach its own growth potential. In the cases of PE growing potential of fetus could be interrupted by shallow nutritional support from mother mediated by placenta. Pregnancies with PE may appear in two forms: most of them with restricted fetal growth

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and normal fetal growth. PE with restricted fetal growth is followed by »ischemic pathophysiology model«.

Current evidence suggests that pregnancy disorders such as PIH and IUGR seems to follow the same events in placental milieu and fetal/maternal circulation[8]. However, it is important to stress that the exact pathological sequence of these is mainly hypothetical. Although numerous factors including genetic, immunologic, behavioral and environmental influences have been implicated in the pathogenesis of PIH, mainly PE, the focus of recent studies is on link of endothelial dysfunction and hypertension. Advanced in understanding about the pathophysiology of these disorders put the new highlight on molecular basis of these.

Fetal growth and development during pregnancy and neonatal outcome depends primarily on protective, metabolic and endocrine function of the placenta. Fetal-maternal relations in the placenta are clearly determined by a range of vasoactive factors on the uteroplacental blood flow. Research over the past decade indicate that vascular disorders related to the placenta are the basic pathophysiological mechanism in hypertensive pregnancies and pregnancies with IUGR[2,5,8–10].

Despite all knowledge vascular etiology of these diseases are still controversial and unclear. It seems that endothelial cell activation is a center-piece in pathogenesis[10]. Till now, different reports showed that vasospasm and vascular endothelial injury are two major pathological conditions in previous disorders[8–10].

Unknown factors provoke activation and dysfunction of vascular endothelium in placental, maternal and fetal site.

During normal pregnancy, there is decreases in peripheral vascular resistance and arterial blood pressure, increases in cardiac output and vascular compliance, so called endothelium – dependent vasodilatation[10]. In PE there is significant hemodynamic changes; widespread vasoconstriction, increased vascular resistance and decrease cardiac output and vascular compliance. Till now there's no relevant studies that support the role of angiogenic factors in placenta and maternal endothelium in other PIH such as gestational hypertension and superimposed hypertension.

Some studies have suggested that obesity is associated with hypertensive pregnancy disorders[11–13]. Increasing body mass index (BMI) was significantly associated with severity of PIH[11]. Cardiac output may be higher in PE patient before the onset of clinical signs of disease, which is found in pregnant women with higher BMI (14). Further, some studies claimed that SGA rates are reduced in obese mothers, but not as causative factor[14–16]. Otherwise some multiple regression analysis suggesting a causal link between high BMI and IUGR[13,15]. Increasing BMI was significantly associated with severity of PIH[11,14]. In systematic review of 13 cohort study searchers found that risk of PE doubled increase in pregnancy BMI[17]. Clinical signs of these are suddenly weight gain demonstrated by visible or invisible edema. It could be speculated that »volume stroke« in these women could be additional cause of damaged endothelial cells which in turn secrete substances in maternal and fetal circulation that promote and increase sensitivity to vasopressors: prostaglandins, nitric oxide, angiogenic factors and endothelins, especially endothelin-1 (ET1). The main source of endothelin is vascular endothelial cells. ET-1 is known as the most potent endogenous vasoconstrictor and is well known for its role and effect on endothelial cell dysfunction. Endothelial dysfunction includes vasoconstriction, inflammation, thrombosis and microvascular obstruction. Mechanism of action of endothelin is fully understood by ET-1, which binds to two receptors: ET-A on the smooth muscles of blood vessels with the effect of vasoconstriction and ET-B, located on the plasma membrane of epithelial cells where it stimulates production of nitric oxide and prostaglandins from endothelial cells resulting in vasodilatation[18].

The main physical stimulus for ET1 synthesis is hypoxia[19]. It is known as specifically marker in only in hypertensive disorders of pregnancy, particularly PE[20–22].

ET-1 causes potent vasoconstriction and prolonged elevation of blood pressure in experimental models. But relationship between plasma levels of ET-1 and grade of hypertension is inconsistent in humans[21]. Elevated ET-1 has been detected in the amniotic fluid and blood of pregnant women with premature rupture of membranes, in the newborns with neonatal asphyxia and in the pregnancy with IUGR[23–27]. The main consequence of endothelial dysfunction is the nutritional deficit and metabolic imbalance that occurs when significant percentage of placental endothelial cells is affected during the pregnancy. In that way ET1 could be partly responsible for intrauterine fetal growth restriction. Placental ischemia stimulates endothelin production from blood vessels on both sides of placenta (maternal/fetal) consequently leading to placental vessel vasoconstriction and hypertensive/hypoxic placental and maternal environment. This cascade of events reflects on fetal and finally neonatal state.

Preclinical studies conducted in experimental animal models demonstrated the importance of ET1 as the main mediator in the pathophysiology of intrauterine growth retardation due to ischemic reperfusion injury. The limited of these studies is distinction of animal and specific nature of human pregnancies.

The trend is increasing scientific knowledge about the influence of vasoactive endothelial factors in obstetric and neonatal studies of physiological processes and pathogenetic disorders in pregnancy and neonatal period. Most of the previous reports reflect association of in vitro experiments, animal studies and observation in born infants from hypertensive disorders or/and IUGR rather than an undoubtful causal relationship. Also there are conflicting results of influence of maternal anthropometric or other clinic characteristic on previous disorders.

The aim of this study was to explore the influence of anthropometric and clinical parameters on ET-1 levels in pregnant women and neonates. This is important since

ET-1 levels are concerned as potential maternal or neonatal screening marker in pathological pregnancies related to increased blood pressure.

Subjects and Methods

Ethic approval

This study was approved by the ethic committee of School of Medicine of Rijeka and Rijeka University Hospital Center. All participants were given a complete description of the study, and provided written informed consent.

Subjects

A cross-sectional study was performed on pathological pregnancies and newborn children of women with: PIH, IUGR and PIH with IUGR. The examined women delivered newborns at the Department of Gynecology and obstetrics of the Rijeka University Hospital Center (Croatia) in a 3 years period (January 2009 – December 2011). The pre-existing hypertension, gestational diabetes and other pregnancies such as twin pregnancy or infants with congenital malformations were excluded. Maternal, obstetric and neonatal records were reviewed. The control group consisted of 88 healthy pregnant women and their newborns.

PIH was diagnosed by increased blood pressure during pregnancy (>140mmHg systolic and 90 mmHg diastolic), >20 weeks of gestation, with or without proteinuria (=300 mg protein/24 hours?. Pathological pregnancies were classified as: 1-PIH, 2-IUGR and 3-PIH with IUGR.

The infant birth weight below the 10th percentile for gestational age was classified as IUGR. Gestational age was determined from date of last menstrual period or early dating ultrasound. If the discrepancy was greater than 7 days, early dating scan was chosen. Gestational age was confirmed by the neonatologist's experience on basis of the New Ballard score. Gestational age was classified as: 1 – (<30 week), 2 – (31–36 week), 3 – (= 37 week).

We tested the blood for ET-1 levels from mothers during third trimester of pregnancy and 4th day after delivery, when was also taken venous blood of doubly clamped umbilical cord, which reflected the fetal status.

Therapy was classified as: 1 – women under anti-hypertension therapy and 2 – women with no therapy. Delivery termination was classified as: 1 – vaginal, 2 – vacuum extraction and 3 – caesarean section. Parity was classified as: 1 – primiparous and 2 – multiparous. Urine proteins were classified as: 1 – present, 2 – absent. Apgar score made by neonatologist to examine the newborns breathing effort, heart rate, muscle tone, reflexes and skin color. 5 minute Apgar score was classified from 1 to 10.

Methods

ELISA – 8 milliliters of blood were taken and centrifuged at 500xg. Serums were frozen at –20°C until the analysis. Serum endothelin-1 levels were determined by use of a sandwich Elisa assay according to the manufac-

TABLE 1
CHARACTERISTICS OF STUDY SUBJECTS

Characteristics	Normal pregnancy (N=88)	Pathological pregnancy (N=100)	p value
Women			
Age (years)	30.5±3.6	30±4.2	0.39
Body weight (kg)	83.6±7.9	89.1±17.5	<0.05
Body height (cm)	164.8±5.4	166.9±6.2	<0.05
Body mass index (kg/m^2)	30.8±2.9	31.9±5.7	0.08
Systolic pressure 2nd	115±6.1	151±18.4	<0.001
Diastolic pressure 2nd	74.3±4.6	98.3±13.5	<0.001
Systolic pressure 3rd	118.3±7.1	143.5±16.6	<0.001
Diastolic pressure 3rd	78.6±5.7	93.6±11.2	<0.001
Weight gain (kg)	12.5±5	12.8±6.2	0.73
3rd Endothelin-1 (fg/mL)	0.64±0.4	3.92±2	<0.001
P Endothelin-1(fg/mL)	0.58±0.4	3.75±1.9	<0.001
Neonates			
Body weight (kg)	3.58±0.4	2.58±1.2	<0.001
Length (cm)	52.3±1.8	46.3±6.6	<0.001
Head circumference (cm)	35.4±1	32.2±4.2	<0.001
UC Endothelin-1 (fg/mL)	0.82±0.4	4.53±2.1	<0.001

2nd – second trimenon, 3rd – third trimenon, UC – umbilical cord, P – (postpartum, 4th day after birth)

turer's instructions (Biomedica Gruppe, Wien, Austria). Endothelin-1 levels were measured in range from 0 to10 fmol/mL.

Statistical analysis

After normal distribution of results, parametric tests were used in statistical analysis. Descriptive analysis as well as differences between independent groups was performed by use of the Student t-test. Multiple regression analysis was employed to determine the influence of maternal parameters on ET-1 levels (Model 1) as well as influence of neonatal parameters on ET-1 levels (Model 2). Statistica 8.0 (Stat Soft Inc, Tulsa, United States) was employed and results were considered significant at $p<0.05$.

Results

Age, anthropometric and clinical parameters are presented at the Table 1.

Both regression models significantly predicted ET-1 levels in pathological pregnancies or controls. Only statistically significant influences of single predictors on ET-1 levels are presented at Tables 2-4.

Discussion

Results revealed that endothelin-1 serum levels are significantly predicted by maternal and neonatal parameters (Tables 2-4).

TABLE 2
MULTIPLE REGRESSION ANALYSIS OF 3RD TRIMENON ET-1 ON »MATERNAL« AND »NEONATAL« PARAMETERS

Model	R	R^2	F	p
1 (a)	0.80	0.63	9.66	0.000
2 (c)	0.40	0.15	3.74	0.007
(d)	0.44	0.19	4.51	0.001

a Pathological pregnancies predictors: diagnosis, therapy, parity, age, body height, body weight, body mass index, systolic blood pressure 2nd trimenon, diastolic blood pressure 2nd trimenon, systolic blood pressure 3rd trimenon, diastolic blood pressure 3rd trimenon, weight gain, urine proteins, gestation age, delivery termination

c,d Pathological and healthy neonatal predictors: body weight, body length, head circumference, Apgar score

Model	β	r	p
1 (a) Diagnosis	0.82	0.41	0.000
Therapy	–0.82	–0.28	0.009
Body mass index (kg/m²)	0.71	0.29	0.006
Body weight (kg)	–0.22	–0.26	0.015
Body height (cm)	0.26	0.25	0.020
2 (c) Apgar score	–0.53	–0.42	0.000
(d) Body weight (kg)	–0.66	–0.25	0.019
Apgar score	–0.18	–0.32	0.002

TABLE 3
MULTIPLE REGRESSION ANALYSIS OF 4TH POSTPARTAL DAY ET-1 ON »MATERNAL« AND »NEONATAL« PARAMETERS

Model	R	R^2	F	p
1 (a)	0.81	0.65	10.41	0.000
(b)	0.65	0.42	5.05	0.000
2 (c)	0.45	0.20	4.84	0.001
(d)	0.33	0.11	2.47	0.051

a,b Pathological and healthy pregnancies predictors: diagnosis, therapy, parity, age, body height, body weight, body mass index, systolic blood pressure 2nd trimenon, diastolic blood pressure 2nd trimenon, systolic blood pressure 3rd trimenon, diastolic blood pressure 3rd trimenon, weight gain, urine proteins, gestation age, delivery termination

c,d Pathological and healthy neonatal predictors: body weight, body length, head circumference, Apgar score

Model	β	r	p
1 (a) Diagnosis	0.85	0.43	0.000
Therapy	–0.80	–0.28	0.009
Body mass index (kg/m²)	0.71	0.30	0.005
Body height (cm)	0.26	0.26	0.016
Body weight (kg)	–0.22	–0.27	0.011
(b) Body mass index (kg/m²)	0.19	0.24	0.031
2 (c) Apgar score	–0.54	–0.43	0.000
(d) Body weight (kg)	–0.57	–0.23	0.036
Apgar score	–0.13	–0.24	0.024

TABLE 4
MULTIPLE REGRESSION ANALYSIS OF UMBILICAL CORD ET-1 ON »MATERNAL« AND »NEONATAL« PARAMETERS

Model	R	R^2	F	p
1 (a)	0.82	0.67	11.15	0.000
(b)	0.69	0.47	6.21	0.000
2 (c)	0.42	0.17	3.91	0.003
(d)	0.32	0.10	2.36	0.050

a,b Pathological and healthy pregnancies predictors: diagnosis, therapy, parity, age, body height, body weight, body mass index, systolic blood pressure 2nd trimenon, diastolic blood pressure 2nd trimenon, systolic blood pressure 3rd trimenon, diastolic blood pressure 3rd trimenon, weight gain, urine proteins, gestation age, delivery termination

c,d Pathological and healthy neonatal predictors: body weight, body length, head circumference, Apgar score

Model	β	r	p
1 (a) Gestation age (week)	1.61	0.60	0.000
Therapy	1.21	0.39	0.000
Delivery	–0.48	–0.26	0.014
Age (years)	0.09	0.24	0.028
(b) Body mass index (kg/m²)	0.18	0.23	0.046
2 (c) Apgar score	–0.54	–0.39	0.000
(d) Body weight (kg)	–0.69	–0.25	0.022
Apgar score	–0.13	–0.21	0.048

ET-1 levels and maternal predictors

In maternal blood ET-1 levels were strongly predicted by diagnosis, therapy and BMI, while umbilical cord ET-1 levels were strongly predicted by gestational age, therapy and delivery termination.

Our results showed proportional relationship between pregnancy induced diseases (PIH, IUGR) and maternal ET-1. The highest levels of the maternal ET-1 were found in subgroup PIH with IUGR, which corresponds to majority of similar studies[22,26]. Anti-hypertensive therapy negatively predicted maternal ET-1 (Tables 2 and 3), which indicates good compliance and possibility for vascular endothelial cell recovery. Opposite to maternal is positive correlation between umbilical ET-1 and therapy (Table 4), which argues for week neonatal compliance and strong vasoconstriction due to chronic hypoxia[27]. According to the theory of the vascular damage, clinical manifestations of hypertension are usually seen in third pregnancy trimester, but molecular mechanisms seem to start earlier. Positive correlation between umbilical ET-1 and gestational age is probably compensatory, due to neonatal response in state of chronic hypoxia[23–27]. Contrary to findings of Laforgia et al. who found higher ET-1 levels in neonates delivered by caesarean section, our results however, speak for lower ET-1 levels, which could be referred to a large number of elective caesarean section.

Recent literature data relates pregnancies with BMI higher than 30 to hypertensive disorders such as PIH, particularly preeclampsia[11–13]. Our findings of the positive correlation between BMI and ET-1 levels in pathological pregnancies are expected and evidence based, but the same finding in controls suggest that obese pregnant women have increased risk for cardiovascular diseases.

ET-1 levels and neonatal predictors

In pathological pregnancies, ET-1 levels were strongly predicted by Apgar score. Expected, Apgar score inversely correlated to maternal and neonatal ET-1 levels, which is similar to Laforgia et al.[24]. Except for inverse correlation between ET-1 levels and Apgar score in controls, direct correlation between ET-1 and neonatal weight is found to be expected, since healthy newborns did not suffer from compromised circulation due to hypoxia (Tables 2-4).

Conclusion

Numerous studies have been conducted in past decade as to better understand mechanisms underlying vascular pathology in hypertensive pregnancies. The role of vasoconstrictive endothelins is undoubtful, but except for increased blood pressure, little is known about other influences of endothelin-1. In this study different clinical and anthropometric factors were engaged and amongst others, BMI appeared as important predictor of ET-1 serum levels.

Neonatal 5 minute Apgar score is often based on subjective neonatologist estimation. Therefore, inverse relationship between Apgar and umbilical ET-1, indicates that ET-1 could be understood as a good prognostic marker in cases of neonatal asphyxia.

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UTJECAJ KLINIČKIH I ANTROPOMETRIJSKIH PARAMETARA NA SERUMSKU KONCENTRACIJU ENDOTELINA – 1 U TRUDNICA I NJIHOVE NOVOROĐENČADI

S A Ž E T A K

Hipertenzija u trudnoći, glavni je razlog smrti majki u zemljama u razvoju. Endotelin – 1 je najjači poznati vazokonstriktorni čimbenik, a njegova serumska koncentracija je povišena u hipertenzivnim trudnoćama. Stoga je važno utvrditi čimbenike majke i novorođenčeta, koji utječu na serumsku koncentraciju ET-1. U 100 hipertenzivnih trudnoća i 88 kontrola, krvi su analizirane za serumski ET-1 te su prikupljeni antropometrijski i klinički parametri majki i novorođenčadi. Utvrđeni su značajni utjecaji dijagnoze, terapije i indeksa tjelesne mase (ITM) na majčine vrijednosti ET-1. Također je utvrđen značajan utjecaj gestacijske dobi, terapije i načina dovršenja poroda na umbilikalne vrijednosti ET-1. Upravo razmjeran odnos između indeksa tjelesne mase i koncentracije ET-1 sugerira da trudnice s velikim ITM imaju povećan rizik za kardiovaskularne bolesti. Obrnuto razmjeran odnos Abgara i ET-1 upućuje da bi ET-1 mogao biti važan prognostički marker u slučaju neonatalne asfiksije.