The concentration of insulin-like growth factor-1 in pregnancies complicated by pregnancy-induced hypertension and/or intrauterine hypotrophy

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ABSTRACT

Objectives: The aim of the study was to compare Insulin-like Growth Factor-1 (IGF-1)concentration in pregnancies complicated by pregnancy-induced hypertension and/or intrauterine hypotrophy, and its correlation with maternal pressure and umbilical artery pulsatility and resistance indices.

Material and methods: 65 pairs pregnant-newborn were included to four groups: I — control, II — PIH, III — Hypotrophy, IV — PIH and Hypotrophy. In the study we analyzed cord blood IGF-1 concentration, newborns antropometry, umbilical artery pulsatility and resistance indices and maternal pressure before delivery.

Results: The concentration of IGF-1 was the lowest in IV group of hypotrophic newborns from pregnancies complicated by pregnancy-induced hypertension. In this group of patients there was strong negative correlation between IGF-1 concentration and maternal systolic and diastolic pressure.

Conclusions: There is a strong negative correlation between IGF-1 concentration and maternal systolic pressure in group of hypotrophic newborns from pregnancies complicated by pregnancy-induced hypertension.

Key words: intrauterine growth restriction; pregnancy-induced hypertension; insulin-like growth factor-1

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INTRODUCTION

Pregnancy induced hypertension (PIH) is one of the most serious complication of pregnancy significantly increasing the risk of stillbirth, prematurity, and perinatal death, both maternal and neonatal. Coexistence of pregnancy induced hypertension with intrauterine fetal hypotrophy increases these risks [1], but also has long-term negative impact on the further development of the children [2].

It is estimated that PIH occurs with varying intensity in 5–8% of all pregnancies [3], and their etiology is multifactorial and still unclear. It is believed that the basis for the development of this pathology are abnormal differentiation and invasion of extravillous trophoblast cells [4]. In healthy developing placentas, the extravillous trophoblast cells infiltrate spiral arteries, undergoing transformation from an epithelial to an endothelial phenotype. This leads to remodeling of their walls, conversion of muscles and

elastic tissue localized in tunica media to fibrinous tissue. This process consists of two phases and enables transformation of these high resistance arteries into high capacitance, easily responsive to increased blood flow utero-placental vessels. The first stage includes the migration of trophoblast cells into the decidua. In the second stage, lasting from the 15th to 20th week of gestation, trophoblast cells infiltrate the spiral arteries. Abnormalities of the second phase was histologicaly observed in placentas from pregnancies complicated by PIH, especially incomplete transformation of spiral arteries. This pathology can result in high resistance in placental vessels, significantly reducing placental blood flow. Impaired placental perfusion leads to fetal growth retardation, activation of inflammatory response cascade and damaging of endothelium [5, 6].

Intrauterine growth restriction occuring before the 32nd week of gestation (early onset IUGR) is more often associ-

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ated with serious structural and functional abnormalities of the placenta, increased resistance in the placental vessels, haemodynamic changes with circulatory redistribution, and in the most severe cases centralization of fetal circulation. This form of IUGR is in 35% associated with pregnancy-induced hypertension [7].

Umbilical arteries pulsatility and resistance indices are good parameters of fetal well-being status. Studies have also shown that screening doppler velocimetry between 20–24 weeks of gestation are good prognostic factors in assessing the risk of developing pregnancy-induced hypertension and intrauterine growth retardation [8].

Objectives

The aim of this study was a comparative analysis of IGF-1 concentrations in cord blood in three clinical situations: 1. In pregnancies complicated by pregnancy-induced hypertension (PIH) and intrauterine fetal hypotrophy. 2. In pregnancies complicated by PIH, with normal intrauterine growth of the fetus. 3. In pregnancies complicated by intrauterine fetal hypotrophy, without pregnancy-induced hypertension. An attempt was also made to assess the correlation between values of the pulsatility and resistance indices in umbilical arteries and maternal blood pressure on the concentration of insulin-like growth factor-1 in cord blood.

MATERIAL AND METHODS

In this study 65 pairs, pregnant-newborn, hospitalized in the Department of Gynecology and Obstetrics of the Specialist Hospital No. 2 in Bytom between 2015–2018 were assessed.

The pairs were included to one of four groups depending on the clinical situation:

- Control — eutrophic newborns from uncomplicated pregnancies;
- PIH — eutrophic newborns from pregnancies complicated by Pregnancy-Induced Hypertension;
- Hypo — Hypotrophic newborns from uncomplicated pregnancies;
- PIH+Hypo — hypotrophic newborns from pregnancies complicated by Pregnancy-Induced Hypertension. Exclusion criteria:
- prematurity < 32. weeks of gestation;
- multiple pregnancy;
- maternal diabetes;
- congenital diseases (including congenital defects, infections, persistent pulmonary hypertension);
- chronic maternal hypertension.

In all groups, the concentration of Insulin-like growth factor-1 (IGF-1) in the umbilical cord blood was tested by an immunoenzymatic method — ELISA with the use of Human IGF-1 Elisa Kit. The obtained results were analyzed

in relation to mean values of systolic and diastolic blood pressure evaluated in the last day before pregnancy termination, pulsation index value and resistance index in umbilical arteries, based on routine pre-natal ultrasound examination with Color Doppler option. Neonatal anthropometric parameters (body length, birth weight, head circumference, chest circumference) were also analyzed.

Statistical analysis of the collected research material was based on the STATISTIKA statistical package, version 9.4. Distribution of quantitative variables was characterized by the mean and median values, standard deviation and standard error. The conformity assessment of the distribution of quantitative variables with normal distribution was performed using the Shapiro-Wilk test. Statistical significance of differences in distributions of quantitative variables between research groups was carried out using analysis of variance (ANOVA), with the assumption of homogeneity variations, whereas in the case where the variable distribution deviate from the normal, or in case of failure assumption of homogeneity of variance, Kruskal-Wallis and non-parametric U Mann-Whitney test was applied. Simple analysis was summarized multivariate regression analyzes. Statistical inference is based on the criterion of statistical significance of $\alpha = 0.05$.

RESULTS

Based on the analysis, it was observed that the concentration of insulin-like growth factor-1 was the lowest in the group of hypotrophic newborns from pregnancies complicated by pregnancy-induced hypertension and was significantly lower compared to eutrophic newborns from normal pregnancies and pregnancies complicated by pregnancy-induced hypertension. In the groups with isolated hypotrophy or pregnancy-induced hypertension, IGF-1 concentrations were also lower than in healthy newborns, but without statistical significance (Fig. 1).
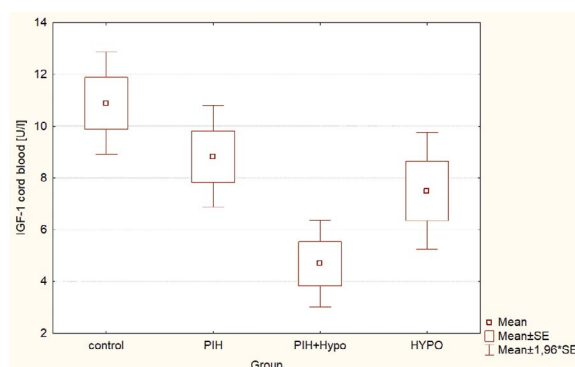

Figure 1. Comparative analysis of mean concentration of IGF-1 in cord blood in study groups with standard error and the 95% confidence interval

Table 1. Patients characteristics — median values with the lowest and the highest values and standard deviations in parentheses

	Control	PIH	Hypo	PIH + Hypo
N	25	14	16	10
Maternal age	30 (6)	34 (5)	34 (6)	33 (4)
Maternal BMI [kg/m^2]	28.8 (4.4)	35.3 (4.6)	29.5 (4.5)	30.3 (6.47)
Maternal Weight [kg]	78.5 (12.9)	95.2 (14.7)	77.4 (13.2)	86.7 (16)
Hbd	37 (34–41)	36 (32–41)	37 (34–40)	**34** $^{CTR, H}$ (32–41)
B.W. [g]	3190 (2170–4480; 492.5)	2870 (1960–3800; 580)	**2257** $^{CTR, P}$ (1600–2900; 352)	**1550** ^{CTR,P} (840–2920; 562)
Lenght [cm]	53.1 (47–60; 2.5)	52.5 (47–60; 4.0)	**49** ^{CTR} (43–54; 3)	**43.0** ^{CTR,P} (35–55; 5.2)
Head circ. [cm]	35 (31–38; 2)	34 (30–37; 2)	**32.0** ^{CTR} (30–34; 1)	**29.0** $^{CTR, P}$ (24–32; 2.2)
Chest circ.[cm]	33 (29–37; 2)	31 (27–34; 2)	**29.0** $^{CTR, P}$ (26–33; 2)	**25.0** $^{CTR, P}$ (20–32; 3.4)
PI in UA	0.86 (0.52–1.26; 0.17)	0.86 (0.55–1.18; 0.20)	0.90 (0.63–1.44; 0.24)	1.1 (0.81–1.9; 0.32)
RI in UA	0.57 (0.39–0.75; 0.08)	0.56 (0.40–0.68; 0.08)	0.59 (0.46–0.79; 0.09)	**0.70** ^{CTR} (0.55–1.00; 0.14)
Sys. Pressure	109 (82–132; 12)	139 (109–178; 24)	124 (105–145; 14)	**160** $^{CTR, P, H}$ (118–249; 36)
Dia. Pressure	68 (50–90; 9)	88 (72–103; 11)	76 (49–92; 11)	**98** $^{CTR, P, H}$ (70–149; 21)
IGF-1 (IU/l)	10.9 $^{P+H}$ (2.02–38.3; 6.4)	**7.50** $^{P+H}$ (3.28–16.81; 3.74)	5,9 (2.44–19.96; 4.62)	**3,4** $^{CTR, P}$ (2.28–11.21; 2.70)

^{P}; ^{H}; $^{P+H}$; ^{CTR} — statistical significance comparing to group (respectively): PIH, Hypo, PIH + Hypo and Control (p value < 0.05)

The groups also differed in the values of anthropometric measurements, birth weight, body length, head circumference and chest circumference. These parameters were, of course, significantly lower in hypotrophic neonatal groups with or without gestational-induced hypertension. There was also a tendency to lower values of these parameters in newborns from the PIH group relative to the control group but no statistical significance was found. It may indicate some risks in this group of patients in which pre-natally no intrauterine growth inhibition was observed. Regression analysis showed a strong negative correlation between systolic blood pressure and the concentration of insulin-like growth factor-1 in the hypotrophic neonatal population from pregnancies complicated by pregnancy-induced hypertension (Tab. 1). A similar tendency was observed in the group of eutrophic neonates from pregnancies with PIH, although without statistical significance. Interestingly, there seem to be differences between groups of newborns with pregnancies complicated by pregnancy-induced hypertension and isolated hypotrophy. In the group of isolated hypotrophy we observed possitive correlation between values of pulsatility and resistance indices and concentrations of IGF-1. We also observed surprisingly positive correlation between antropometric parameters and systolic and diastolic maternal pressure, but there was no correlation between the head circumference and body length and the concentration of insulin-like growth factor-1 in cord blood in this group of patients. In the remaining groups, lower concentrations of IGF-1 were observed with the increase of the pulsatility and resistance indices. In the PIH and PIH + Hypo groups, higher values of birth weight and body length, head and

Table 2. Correlation between the concentration of insulin-like growth factor-1 in cord blood and selected parameters in the tested and control groups

	Control	PIH	Hypo	PIH + HYPO
HBD	0	0.28	0	0.24
B.W [g]	0	0.44	–0.31	0.30
Lenght	–0.21	0.39	0	0.41
Head circ. [cm]	–0.21	0.16	0	0.18
Chest circ. [cm]	0	0.37	–0.43	0.35
Sys. Pressure [mm Hg]	0	–0.24	0	–0.81#
Dia. Pressure [mm Hg]	0	–0.20	0	–0.63
Mean UA PI	–0.27	–0.42	0.20	–0.47
Mean UA RI	–0.24	–0.32	0.27	–0.64

means statistical significance (p < 0.05)

chest circumference were observed with an increase in IGF-1 concentration (Tab. 2).

DISCUSSION

Insulin-like growth factors (IGF-1 and IGF-2) are peptides with structural similarity to proinsulin. The biological role of insulin-like growth factor-1 is omni-directional, with both aut-, para- and endocrine regulation. Its presence is already observed in the early stages of embryonic development and is one of the most important factors of growth, differentiation and maturation of tissues, affecting fetal growth processes. It also seems to be an extremely important factor, in addition to vascular endothelial growth factor (VEGF), Progesterone induced blocking factor (PIBF) and insulin-like

growth factor-2, which determines normal course of maturation, differentiation and invasion of extravillous trophoblast in spiral arteries, which process, if it goes wrong, is considered the main cause of pregnancy-induced hypertension [9]. The studies also demonstrated the regulatory effect of IGF-1 on endothelial function. It regulates and stimulates the migration of endometrial cells, stimulates neovascularization processes. There are also reports of IGF-1 vasodilatation function in in vivo studies [10]. In animal model studies, low concentrations of IGF-1 were found to be associated with higher blood pressure values due to impaired endothelium-dependent vascular relaxation via nitric oxide and increased expression of vasoconstrictor endothelin [11]. In vitro studies on endothelial cells of human umbilical veins showed a strong effect of insulin and IGF-1 on the synthesis of nitric oxide [12]. It is believed that one of the mechanisms of pregnancy-induced hypertension is the disturbed balance between vasodilators and vasoconstrictors. It is also known that insulin resistance is one of the important risk factor for pregnancy-induced hypertension.

In pregnancies complicated by preeclampsia, a lower IGF-1 concentration was observed as compared to pregnancies with normal maternal blood pressure [13, 14], and the severity of preeclampsia was inversely correlated with IGF-1 expression in the placenta and was in direct proportion to expression of Insulin-like growth factors binding protein-3 [15].

In the present study, similar results were also observed with lower IGF-1 concentrations in pregnancies complicated by pregnancy-induced hypotension and/or hypotrophy compared to the control group. Only in groups with pregnancy-induced hypertension concentration of IGF-1 was negatively correlated with maternal arterial pressure and resistance and pulsatility indices in umbilical arteries.

The limitation of this study was lower mean gestational age in groups of isolated PIH and PIH with hypotrophy compared with the other groups. It resulted from the necessity to terminate such a complicated pregnancy earlier, both due to the mother's condition (preeclampsia, placental abruption) and threatening fetal asphyxia, which was the most common cause.

However, in the statistical analysis, there was no significant relationship between IGF-1 concentration and gestational age. Similar results were published by S. Sifakis et al. [16]. They did not show statistically significant correlations between gestational age, pulsatility index values in the umbilical arteries and IGF-1 concentration.

The other limitation of this study was the lack of information about biochemical profiles and uterine artery flow in the first trimester. Other limitations included the presence of PIH and/or IUGR in previous pregnancies and the usage of acetylsalicylic acid as a prophylaxis of preeclampsia.

Incorrect placental formation leads to its insufficiency, inadequate supply of nutrients to the fetus and, as a result, to fetal growth restriction. These unfavorable intrauterine conditions result in limitations of cell divisions, changes in metabolic and signaling pathways, and even lead to epigenetic changes. This phenomenon was discribed as Barker's hypothesis [17].

An extremely important role in these processes plays reduced insulin secretion, as well as disturbances in the Growth Hormone/IGF-1 axis. The animal model studies have shown a reduction of pancreatic B-cells mass in growth restricted fetuses [18—20]. An animal model presented by Jones et al. in 1984 showed significant endocrine differences between eutrophic and hypotrophic fetuses. In smaller gestational age fetuses (SGA) they observed hypoglycaemia, hypoinsulinaemia, hypocortyzolemia and hypothyreosis, and they were negatively correlated with severity of growth restriction. In the SGA group there was also higher secretion of androstenedione and glucagon [21]. The studies also showed significantly lower insulin-like growth factor-1 secretion and increased insulin-like growth factor-2 secretion compared to normal growing fetuses [22].

SUMMARY

Pregnancy-induced hypertension is strongly associated with the risk of IUGR, and insulin-like growth factor-1 seems to be a common denominator in the pathomechanism of these pregnancy complications, both independently and coexisting. An extremely interesting issue is the increased risk of hypotrophy in the normotensive pregnancy of mothers with history of pregnancy-induced hypertension in previous pregnancies. This phenomenon has not been explained yet, but it has been confirmed in a large cohort study on the Swedish population, which may indicate a common molecular mechanism of both complications of pregnancy [23]. Based on this study it seems that in the case of pregnancy-induced hypertension, the concentrations of insulin-like growth factor-1 are lower with the higher values of maternal systolic and diastolic pressures and pulsatility and resistance indices in umbilical arteries. However, in the case of isolated hypotrophy, despite lower cord IGF-1 concentrations, there was no correlation between maternal blood pressure and IGF-1 concentration. Interestingly, during the study we observed that in the hypotrophy group the IGF-1 concentration was discretely higher at higher values of the umbilical artery resistance and pulsatility indices, which may suggest a completely different pathomechanism. Therefore, it is necessary to broaden the research in this field with the comparison of this two serious complications of pregnancy.

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