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Research Article

IGF-2 and IGFBP-3 in Pregnancies Complicated by PIH and IUGR

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Abstract

Objectives: Around 15% of pregnant women develop pregnancy associated complications that increase the risk of maternal and fetal morbidity and mortality. The most common pregnancy complications are: pregnancy induced hypertension (PIH) and intrauterine growth restriction (IUGR). Insulin-like growth factors (IGFs) were proven to play an essential role in placenta growth, fetus development and modifications of their metabolism. The aim of this study was to compare the concentration of IGF-2 and IGF binding protein-3 (IGFBP-3) in pregnancies complicated by PIH, IUGR and pregnacies complicated by both PIH and IUGR. Methods: 84 pairs of pregnant women and their newborns were divided into four cohorts: eutrophic newborns from pregnancies complicated by PIH, newborns who met the criteria for IUGR, newborns from pregnancies complicated by both PIH and IUGR and control group. IGF-2 and IGFBP-3 serum levels in umbilical cord blood were measured in each group by immunoenzymatic method. The obtain date were analised statistically using STATISCTICA statistical package. **Results:** IGF-2 serum levels per body surface area were found to be higher in neonates with IUGR (in both subgroups of pregnancies: complicated and uncomplicated by PIH). On the other hand, no differences in IGFBP-3 concentration between cohorts was found. **Conclusion:** Futher studies are essential to investigate whether changes in growth hormone secretion are the cause or the reasult of the ongoing adaptation to adverse conditions of intrauterine environment.

Keywords: IGF binding protein-3; Insulin-like growth factor; Intrauterine growth restriction; Pregnancy-induced hypertension

Introduction

Pregnancy-induced hypertension (PIH) remains a great challange in the field of medicine. It is estimated that PIH complicates nearly one in ten pregnancies and becames a great danger for developing fetuses. PIH is also associated with high maternal mortality. The multifactorial pathomechanism of this condition remains unclear. Despite the numerous studies conducted in this field, it is still difficult to define risk groups and therefore it is impossible to guarantee proper prophylaxis to those patient. The risk factors that are well documented are: PIH in family history and pre-existing obesity [1,2].

The spectrum of PIH includes preeclampsia (PE), a multiorgan disorder, that affects both fetus and mother. The condition is usually diagnosed by maternal hypertension followed by proteinuria and if the condition is left untreated may lead to maternal multi-organ failure, coagulopathy and seizures [3]. Moreover, preeclampsia is associated with an increased risk of cardiovascular diseases in later life. Althought the numerous studies were performed, the data concerning the alternation of hormonal balance in preeclamptic pregnancies are still conflicting [4].

However, it is already proven that the reason for developing PIH is impaired placenta development and abnormal invasion of trophoblast cells during uterine spiral artery transformation. During the pregnancy, trophoblast cells infiltrate the uterine spiral arteries

and lead to their remodeling and transformation into high-flow and low-resistance vessels. Incomplete remodelling of those spiral arteries results in developing high-resistance blood vessels that are unable to meet the demands of developing fetus. In properly developed placenta microvilli are able to ensure 12-14m^2 maternal-fetus surface of gas exchange [5]. Between the second and third trimesters of pregnancy, this area increases sharply by approximately 10 times, which is a response to the growing needs of a properly developing and growing fetus. Placental hormones are secreted into maternal circulation and modify maternal metabolism which is crucial for futher development of the fetus. On the other hand, fetus' metabolism is also regulated by placental growth factors. The mechanism regulating these interactions has not yet been fully elucidated. Epigenetic mechanisms related to imprinted genes are believed to play a major role in regulating these processes. The gene encoding insulin-like growth factor-2 is a tissue-specific stigma gene and is paterally expressed in the placenta. On the basis of experimental studies, a hypothesis was put forward about the important role of gene imprinting, including the IGF-2 gene polymorphism, in the direct regulation of nutrient transport to the fetus [6].

The studies show that insulin-like growth factors play an essential role in trophoblast infiltration, placenta growth, fetus development and modification of its metabolism [7,8]. Insulin-like growth factor I (IGF-1) is known as a key regulator of fetus growth and organs' development. Nearly 80% of IGF-1 bounds to IGF binding protein-3 (IGFBP-3) and therefore produce effect in target cells. The main effector of IGF-1 is central nervous system but its serum concentration is associated with proper function of various organs [9]. Partial deletion of the IGF-1 also results in severe fetal growth restriction (FGR) [7]. On the other hand, insulin-like growth factor II (IGF-2) is known as a factor which modulates placenta growth. The low level of IGF-2 leads to reduced placenta growth and is followed by FGR [6]. What is more, there is an evidence for positive correlation between maternal IGF-2 levels and preeclamsia.

Therefore, it seems to be obvious that the complications related to the abnormal development of the placenta are not a simple indicator of ischemia and insufficient supply of nutrients, but a multifaceted effect related to such a wide range of impacts of the placenta on the mother and fetus and futher studies are essential.

Objectives

The aim of this study was to compare the concentrations of IGF-2 and IGFBP-3 in pregnancies complicated only with intrauterine growth restriction, pregnancy-induced hypertension and in situation where pregnancy-induced hypertension was accompanied by intrauterine growth restriction. The obtained data were also compared with a group of healthy newborns from uncomplicated pregnancies. Moreover, the correlation between maternal arterial pressure, umbilical artery resistance and pulsatility index and the concentration of IGF-2 and IGFBP-3 was assessed.

Material and Method

Material

84 pairs of pregnant-newborn were enrolled in the study.

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

1. Control– eutrophic newborns from uncomplicated pregnancies

2. PIH – eutrophic newborns from pregnancies complicated by Pregnancy-Induced Hypertension

3. IUGR – fetal growth restriction, newborns weight below 10th percentile

4. PIH+IUGR –pregnancies complicated by Pregnancy-Induced Hypertension and fetal growth restriction with newborns weight below 10th percentile.

All participants signed informed maternal consent form.

Exclusion criteria were:

- multiple pregnancy

- congenital defect and infections

Patients characteristics are presented in the (Table 1)

	Control	IUGR	PIH	PIH+IUGR
N	32	17	24	11
Diabetic	0	4	6	2
Hbd	37 (32-41)	35 (27-42)	**37** $^{P+I}$ (28-40)	**33** $^{CTR, P}$ (27-41)
B.W. [g]	3190 (1700-4080; 669)	**2040** $^{CTR, P}$ (590-2940; 780)	3065 (1280-4050; 692)	**1700** $^{CTR, P}$ (460-3330; 757)
B.W pc [%]	58,6 (22,8-97,1; 22,4)	**10,1** ^{CTR,P} (0,2-58,9; 18)	55,7 (23,1-92,5; 21)	**14,1** ^{CTR,P} (0,2-38,8)
Lenght [cm]	53 (44-59; 3)	**47** $^{CTR, P}$ (32-55; 7,0)	53 (41-59; 5)	**44** $^{CTR, P}$ (31-56; 6,4)
Lenght pc. [%]	92,6 (57,2-99,9; 11,3)	**44,3** $^{CTR, P}$ (0,9-98,8; 36,8)	94,1 (30,6-99,9; 19)	**43,1** $^{CTR, P}$ (4,2-95,3; 29)
Head circ. [cm]	34 (31-39; 2)	**30,6** ^{CTR} (0,1-84,9; 27)	**64,3** ^{CTR} (19,8-97,6; 23,7)	**35** ^{CTR} (0,3-90,0; 30)
Head circ. Pc. [%]	77,7 (21-99,8; 21,8)	**30,6** ^{CTR} (0,1-84,9; 27)	**64,3** ^{CTR} (19,8-97,6; 23,7)	**35** ^{CTR} (0,3-90,0; 30)
Chest circ.[cm]	33 (27-37; 2)	**29** $^{CTR, P}$ (18,5-33; 4)	32 (23-36; 3)	**26** $^{CTR, P}$ (18-34; 4)
BSA [m^2]	0,22 (0,14-0,26; 0,03)	**0,16** $^{CTR, P}$ (0,07-0,21; 0,04)	0,21 (0,12-0,25; 0,03)	**0,15** $^{CTR, P}$ (0,06-0,23; 0,04)
PI in UA	0,93 (0,59-1,16; 0,17)	**1,10** $^{CTR, P}$ (0,58-1,72; 0,30)	0,89 (0,65-1,14; 0,16)	**1,25** $^{CTR, P}$ (0,96-1,68; 0,26)
RI in UA	0,59 (0,43-0,71; 0,08)	**0,68** $^{CTR, P}$ (0,43-0,85; 0,11)	0,58 (0,46-0,71; 0,08)	**0,72** ^{CTR,P} (0,61-0,87; 0,09)
Sys. Pressure	110 (82-126; 10)	110 (100-134; 11)	**140** $^{CTR, I}$ (120-170; 14)	**150** $^{CTR, I}$ (130-168; 14)
Dia. Pressure	70 (50-82; 8)	70 (60-100; 12)	**87** $^{CTR, I}$ (70-115; 12)	**90** $^{CTR, I}$ (80-100; 9)

Table 1: Patients characteristics - median values with the lowest and the highest values and standard deviasions in parentheses; $^{P; I; P+I; CTR}$ - Statistical significance comparing to group (respectively): PIH, IUGR, PIH+IUGR and Control (p value < 0.05)

Method

Insulin-like growth factor-2 (IGF-2) and Insulin-like Growth Factors Binding Protein-3 (IGFBP-3) concentrations were tested by immunoenzymatic method – ELISA with the use of Human IGF-2 Elisa Kit and Human IGFBP-3 Elisa Kit (Mediagnost Kit). The obtained results were analyzed in relation to mean values of systolic and diastolic blood pressure evaluated in the last day before delivery, umbilical artery pulsatility and resistance indices, based on routine prenatal ultrasound examination with Color Doppler option. Neonatal anthropometric parameters (body length, birth weight, head circumference, chest circumference) were also analyzed. Due to large differences in the values of birth weight, indexed values of IGF-2 and IGFBP-3 concentrations, related to the body surface area were also analyzed. Body surface area was calculated based on the Neo-BSA rule.

Statistical analysis of the collected research material was based on the STATISTIKA statistical package, version 8.0 by StatSoft Inc.. Distribution of quantitative variables was characterized by the mean and median values, standard deviation and standard error. Statistical significance of differences in distributions of quantitative variables between cohorts 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 was based on the criterion of statistical significance of $\alpha = 0.05$.

Results

The difference between birth weights of newborns in the cohorts (the lowest birth weight was 460 gram and the highest birth weight was 4080 gram) was the reason to adopt indexed values of IGF-2 and IGFBP-3 (IGFBP-3 ind.) that were calculated per body surface area. In contrast to the distribution of the absolute values of IGFBP-3 that were the lowest in the cohort with IUGR newborns and the cohort PIH+IUGR, IGFBP-3 values per body surface area were higher in those cohorts but the difference was not statistically significant (Table 2) (Figure 1).

	Control	IUGR	PIH	PIH+IUGR
N	32	17	24	11
IGF-2 (ng/ml)	167 (89-258; 41)	185 (89-305; 62)	177 (99-301; 51)	126 (99-265; 57)
IGFBP-3 (ng/ml)	2223 (1148-4967; 865)	1967 (537-3903; 977)	2668 (516-4451; 1028)	**1939** *CTR* (944-2709; 596)
IGF-2 ind. [ng/ml/m^2]	783,53 (379-1386; 254)	**1111** *CTR, P* (622-2757; 642)	868 (454-2024; 356)	**931** *CTR* (537-2001; 581)
IGFBP-3 ind. [ng/ml/m^2]	11170 (5372-22244; 4617)	16633 (2818-45298; 10637)	11905 (2317-23606; 5506)	14577 (6209-24222; 5492)

Table 2: IGF-2 and IGFBP-3 concentrations and indexed values (related to the body surface area) - median values with the lowest and the highest values and standard deviasions in parentheses; $^{P; I; P+I; CTR}$ - Statistical significance comparing to group (respectively): PIH, IUGR, PIH+IUGR and Control (p value < 0.05).

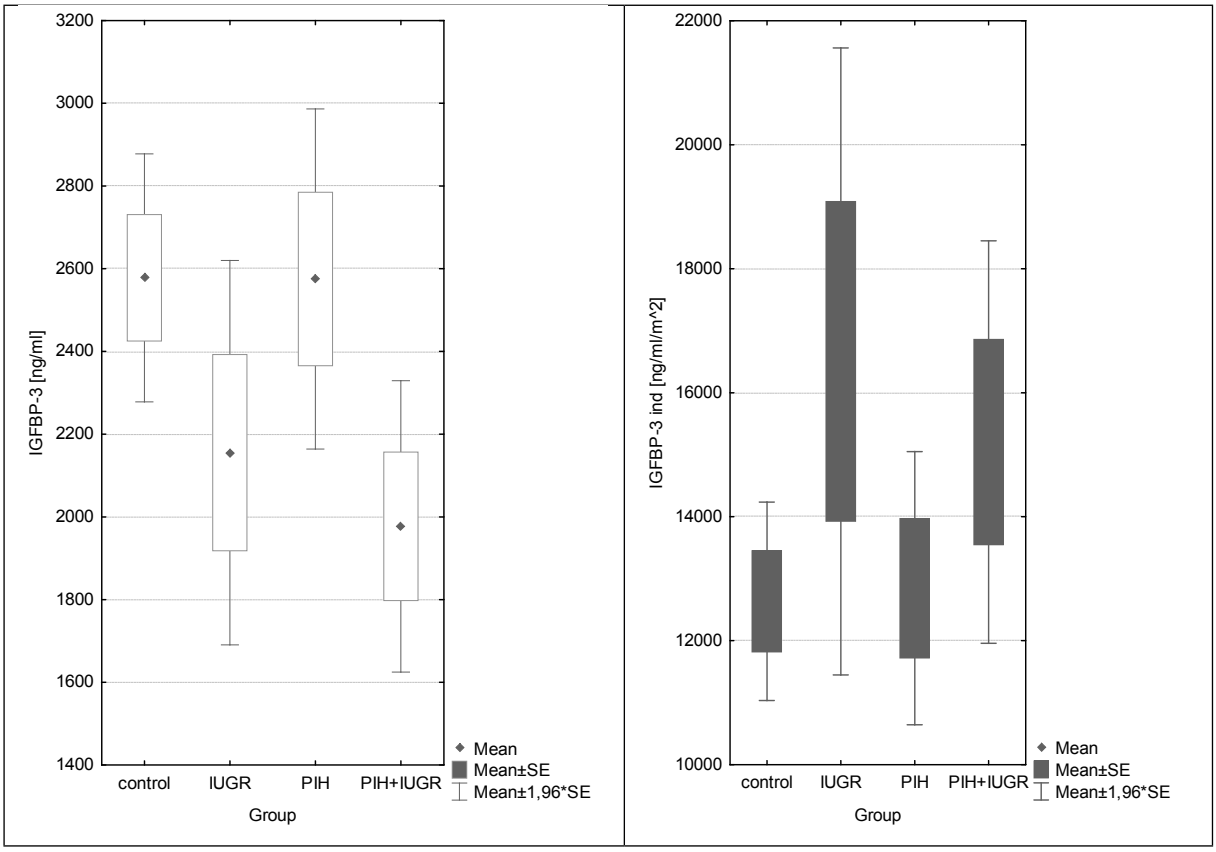

Figure 1: Comparative analysis of mean concentration of IGFBP-3 and IGFBP-3 ind. in cord blood in study groups with standard error and the 95% confidence interval

The absolute values of IGF-2 were not statistically significant higher in cohorts IUGR and PIH but IGF-2 values per body surface area occured to be higher in all cohorts in comparison to the control group. The diffrences in cohorts IUGR and PIH+IUGR were not statistically significant (Figure 2). Although no correlation was observed in individual groups between IGF-2 concentrations and fetal welfare parameters (UA PI and RI), the distribution of IGF-2 concentrations in the entire analyzed population as a function of the pulsatility index and the resistance index in the umbilical artery shows that the concentrations of IGF-2 ind. is higher with disturbed placental circulation (Table 3) (Figure 4). Moreover, the study showed a strong negative correlation between IGF-2 levels and neonatal body length in the PIH + IUGR group.

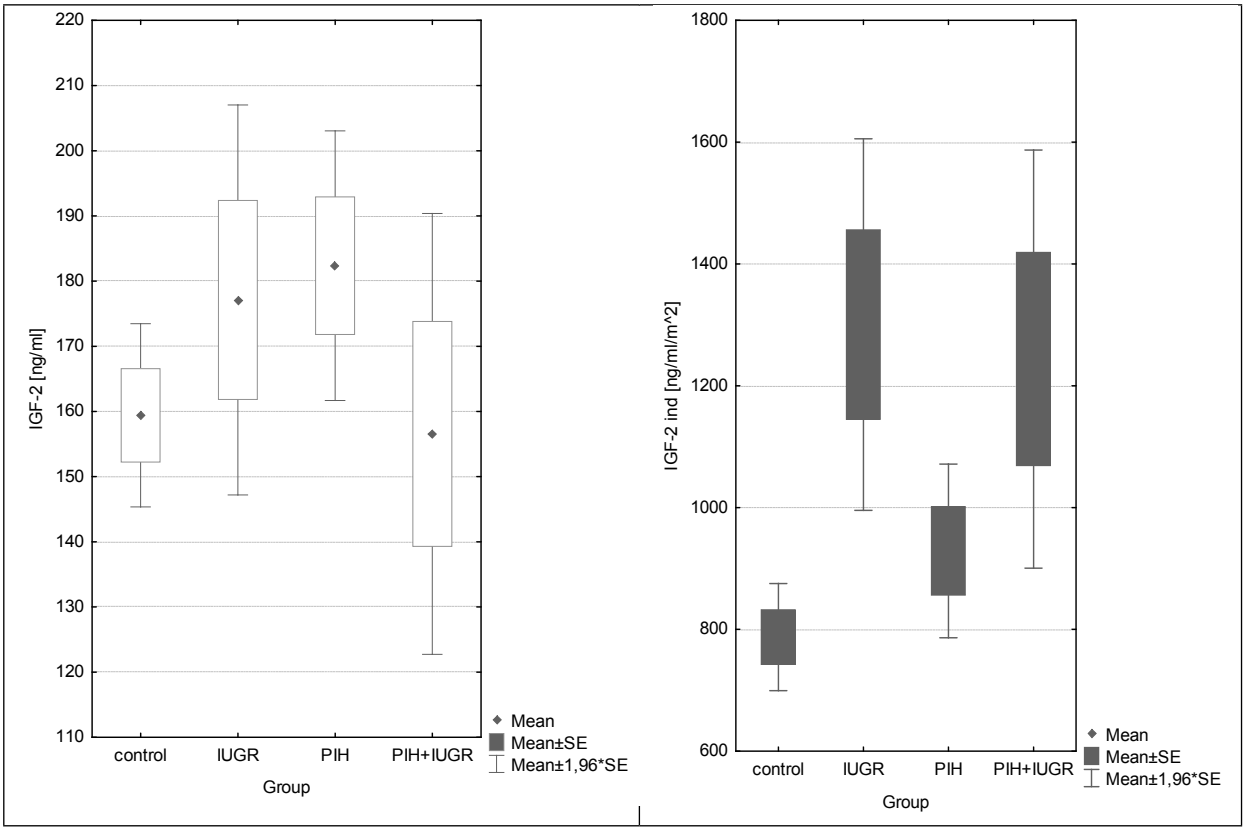

Figure 2: Comparative analysis of mean concentration of IGF-2 in cord blood in study groups with standard error and the 95% confidence interval

	Control		IUGR		PIH		PIH+IUGR
	IGF-2	IGFBP-3	IGF-2	IGFBP-3	IGF-2	IGFBP-3	IGF-2
HBD	0	0	0,21	0	0	0,29	0
B.W [g]	0	0	0	-0,20	0	0,27	0
B.W. pc.	0	0	-0,25	0	0	0	0
Lenght	0	0	0	-0,34	0	0,23	-0,31
Lenght pc.	-0,29	0	0	-0,31	0	0	**-0,67#**
Head circ.[cm]	0	0	0,20	0	-0,23	0,23	-0,22
Head circ. pc	0	0	0	0	0	0	-0,48
BSA	0	0	0	-0,26	0	0,26	0
Chest circ.[cm]	0	0	0	0	0	0,38	0

Sys. Pressure [mmHg]	0	0	0	0,31	0	0,21	-0,20
Dia. Pressure [mmHg]	0	0	0	0,36	0	0,34	0,39
Mean UA PI	0	0	0	-0,27	0,41	-0,37	0
Mean UA RI	0	0	0	0	0,29	-0,32	0

Table 3: Correlation between the concentration of IGF-2 and IGFBP-3 in cord blood and selected parameters in the tested and control groups. # means statistical significance ($p<0.05$).

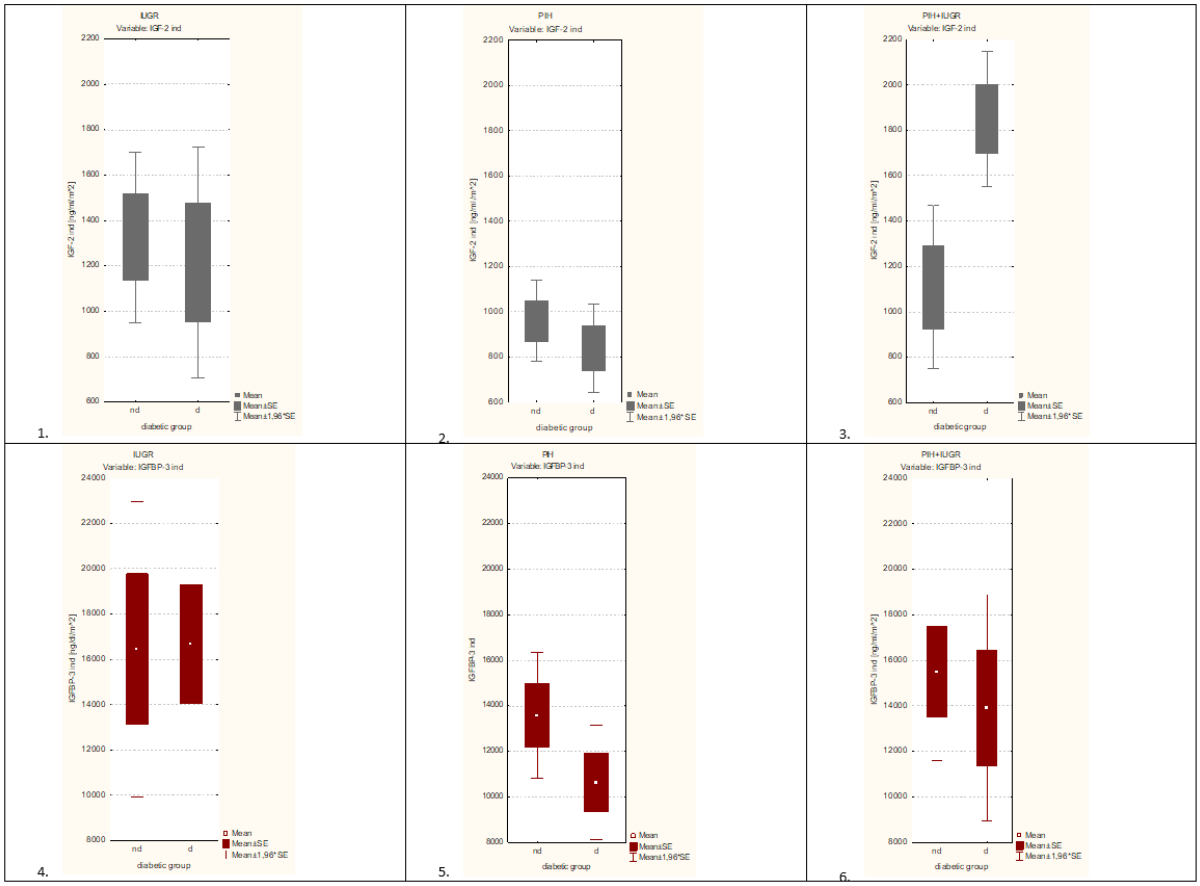

Figure 3: Comparative analysis of IGF-2 ind. and IGFBP-3 ind. in the study groups differentiated on „diabetic" and „non-diabetic" subgroups.

The mean gestational age was different in all cohorts.The lowest gestational age was noticed in cohort PIH+IUGR what is a result of the fact that pregnancies comlicated by PIH and IUGR are often terminated earlier due to deterioration of mother and fetus condition. There was no correlation between IGF-2 in cord blood and gestational age. The study shows that there is a correlation between IGFBP-3 values and gestational age in the cohorts PIH and IUGR but the correlation is not statistically significant. What is more, there is a strong negative statistically significant relationship between IGFBP-3 concentrations and the umbilical arteries pulsatility and resistance, which may indicate that in the most severely complicated pregnancies, these concentrations are lower, and abnormal flows in the umbilical vessels, deterioration of fetal well-being are often an indication for premature termination of pregnancy. Therefore, the observed positive correlation between IGFBP-3 concentrations and gestational age in the PIH + IUGR group may be more due to the

reasons why this pregnancy had to be completed earlier, than the actual tendency to increase IGFBP-3 secretion in the following weeks of pregnancy, which may confirm no such relationship in the control group.

In our study maternal diabetes was not an exclusion criterion because of the fact that diabetes and insulin resistance may be significant factors that influence the hormonal balance of the fetus and axis of growth hormone and insulin-like growth factors. However, the comparative analysis of the results in the cohorts has been performed, every cohort has been divided into subgroups ”diabetic” (pregnancies complicated by diabetes of mothers) and ”non-diabetic” (mothers who did not developed diabetes during the pregnancy). The results were comparable in cohorts IUGR and PIH but there was a significant difference in the cohort with pregnancies complicated by PIH and IUGR. In this cohort (PIH + IUGR) mean concentration of IGF-2 was significantly higher in the subgroup ”diabetic” in comparison to the subgroup ”non-diabetic”. The comparison of the results in other cohorts was different. The comparison of mean concentration of IGF-2 in all cohorts’ subgroups without diabetes revealed the lowest concentration of IGF-2 in the cohort with PIH + IUGR but the diffrence was not statistically significant. On the other hand, the comparison of mean concentration of IGF-2 in cohorts’ subgroups with diabetes in mothers showed that mean concentration of IGF-2 is not statistically significant higher in cohort with PIH + IUGR. However, the limitation of this study was low number of pregnancies complicated by diabetes in cohorts and no pregnancies complicated by diabetes in control group. Therefore, the analysis is incomplete. The study may indicate some kind of trend that should be taken into consideration in futher studies. The results are presented in the diagrams (Figure 3). There was no significant diffrences in mean concentration of IGFBP-3.

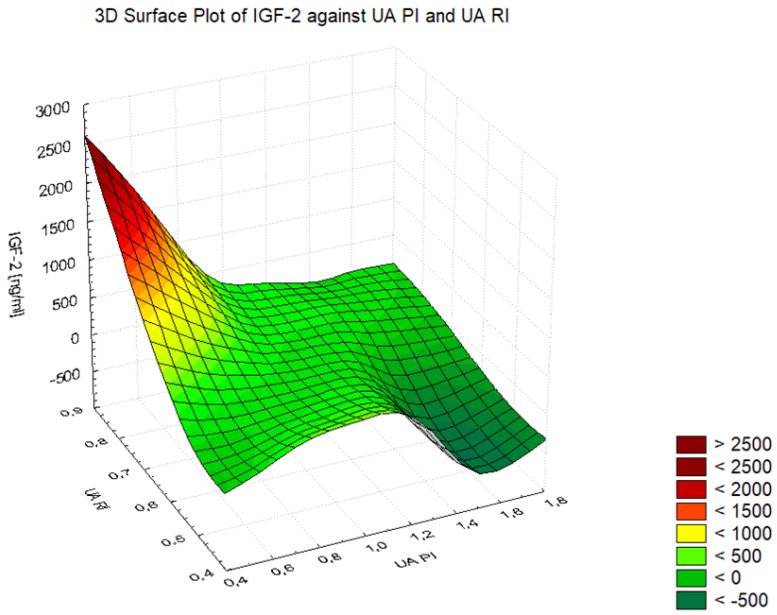

Figure 4: 3D Surface Plot of IGF-2 against UA PI and UA RI.

Discussion

Around 15 % of pregnant women develop pregnancy associated complications that increase the risk of maternal and fetal morbidity and mortality. The most common pregnancy complications are fetal growth restriction (FGR), also known as intrauterine growth restriction (IUGR), pregnancy induced hypertension (PIH), preterm delivery (PTD), gestational diabetes mellitus [10,11]. Despite the numerous studies, the etiopathogenesis of those conditions remains unclear and therefore futher studies assessing the effective methods of diagnosis, prevention and treatment are essential [12].

Intrauterine growth restriction (IUGR) is decribed as growth of fetus below its in-utero growth potential and is associated with numerous complication [13] like obesity, type 2 diabetes mellitus and hypertension [14]. Insulin-like growth factors 1 and 2 (IGF-

1 and IGF-2) and their binding proteins (IGFBPs) are known to regulate fetal growth [15]. It has been reported that serum levels of IGF-1 and IGFBP3 were significantly decreased in IUGR in comparision with normal neonates [16]. Less conclusive are the results of studies on IGF-2 concentrations in such complicated pregnancies. Tzschoppe et al. analyzed IGF-2 concentrations in the umbilical cord blood of 64 newborns (16 IUGR, 8 SGA, 40 AGA). In this study, it was shown that IGF-2 concentrations were significantly lower in the IUGR group compared to the AGA group, but interestingly they were also lower in relation to SGA newborns [17]. Much more often, however, the authors document higher placental expression of IGF-2 in pregnancies complicated by intrauterine growth restriction [18].

Adverse conditions of the intrauterine environment also lead to epigenetic changes, which, according to some authors, is a link between complications of the prenatal period and diseases of adulthood, such as hypertension, diabetes mellitus, obesity, affecting the increased risk of cardiovascular events, which is consistent with Barker's hypothesis. This phenomenon was first described by Heijmans et al. They showed a relationship between maternal malnutrition with low birth weight and hypomethylation of IGF-2 DMR [19], in turn, lower levels of IGF-2 DMR methylation are associated with higher serum concentrations of IGF-2 [20]. However, Tabano et al. did not show differences in the level of IGF-2 DMR methylation in umbilical cord blood in the SGA *vs* AGA group, which could indicate a completely different pathomechanism and hormonal relationships in SGA and in hypotrophy resulting from intrauterine growth restriction [21].

Insignificantly statistically lower IGF-2 values were observed in the PIH + IUGR group compared to the other groups, even in the group of hypotrophic neonates from normotensive pregnancies, what is more, in the IUGR group IGF-2 values were even higher compared to the group of healthy newborns from normotensive pregnancies. We also observed higher concentrations of IGF-2 per body surface area in the cord blood of neonates with fetal growth restriction in both groups complicated and uncomplicated by PIH. Interestingly, this trend was also visible in the cohort of AGA newborns from pregnancies complicated by pregnancy-induced hypertension.

These results may support previous observations that IGF-2 expression may be higher in pregnancy complications associated with abnormal placental function, i.e. not only in IUGR newborns, but also in eutrophic newborns from pregnancies complicated by pregnancy-induced hypertension, especially since in this study higher concentrations of IGF-2 were observed with worse ultrasound parameters of placental circulation. The limitation of this work, however, is the lack of full analysis of fetal hemodynamic status.

Pregnancy induced hypertension (PIH) is a serious complication of pregnancy that increases the risk of stillbirth, prematurity, maternal and neonatal perinatal death [22]. Preeclampsia (PE), part of the spectrum of pregnancy induced hypertension, affects about 2-8% of pregnancies, and is associated with high risk for metabolic diseases in the later life of the infants. Previous studies have shown that preeclampsia may influence the expression of IGFs and IGFBPs, what is particularly well noticed in the early-onset or sever PE [23]. Low expression of IGF-1 and high expression of IGF-2 and IGFBP-3 in the placental tissue depending on preeclamsia severity were detected. It is important to notice that the most visible changes were found in preeclamsia associated with intrauterine growth restriction [21]. However, no significant correlation between IGFs levels and PIH was noticed [20]. It also seems that in pregnancies complicated by pregnancy-induced hypertension, the pattern of regulatory effect of IGF-2 on fetal growth processes is disturbed. In normal, uncomplicated pregnancies, the degree of methylation of IGF-2 DMR negatively correlates with birth weight, which, however, is not observed in pregnancies complicated by pregnancy-induced hypertension [16].

Growth in the pre- and postnatal period is therefore subject to epigenetic variability. It is believed that methylation of the IGFBP-3 promoter gene may also be important in the pathogenesis of IUGR [24].

A study conducted by Baker Méio MD et al. in 2009 showed lower concentrations of IGFBP-3 in SGA compared to AGA newborns [25]. similar results were obtained by Ozkan et al. in 1999, with lower concentrations of IGFBP-3 observed in a group of newborns with intrauterine growth inhibition, in whom the normal phenomenon of catch-up growth was not observed in the follow-up process [26].

In this study, no differences in IGFBP-3 concentrations were shown, either in absolute values or indexed values per body surface area. According to previously documented observations, it appears that pregnancy complications associated with abnormal placental function may significantly affect IGF-2 secretion, which may be an important element linking fetal adaptation to the harsh conditions of the intrauterine environment, with distant sequelae and an increased risk of adult diseases. Further research is essential to determine whether changes in growth hormone secretion in pregnancies complicated by abnormal placental function are its cause or are a long-term result of the ongoing adaptation to adverse conditions of the intrauterine environment. Determining the right risk group is extremely important in the possible prevention of civilization diseases. According to the results of this study, such group may consist not only of newborns whose growth has been restricted intrauterinely, but also appropriate for gestation newborns, exposed to maternal pregnancy-induced hypertension.

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None declared.

Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests

Authors state no conflict of interest.

Informed consent

Informed consent was obtained from all individuals included in this study.

Ethical approval

The local Bioethics Commission accepted the study (KNW/0022/KB1/13/II/16/17).

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