Placental growth hormone (PGH), pituitary growth hormone (GH1), insulin-like growth factor (IGF-I) and ghrelin in pregnant women's blood serum

Hormon wzrostu łożyskowy, przysadkowy hormon wzrostu, insulinopodobny czynnik wzrostu oraz grelina w surowicy krwi kobiet ciężarnych

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Abstract

Objectives: *The aim of this work is to evaluate levels of placental growth hormone (PGH), pituitary growth hormone (GH1), insulin-like growth factor (IGF-I) and ghrelin in pregnant women's blood serum before, during and after delivery. Furthermore, the aim is to search for links and interdependence of GH1, PGH and IGF-I concentrations.*

Material and methods: *Seventy nine blood samples were taken one to two hours before, during and half an hour after expulsion of placenta. All proteins studied were determined by ELISA method, using ELISA Kit.*

Results: *The highest PGH concentration and IGF-I concentration in pregnant women's blood serum was observed before delivery, while GH1 concentration was lowest. During and after delivery PGH and IGF-I concentration decreased proportionately and pituitary growth hormone concentration increased accordingly. About half an hour after delivery of the placenta, GH1 concentration was highest.*

Conclusions: *In pregnant women's blood there is a metabolic interdependence between PGH and IGF-I. Their concentration increases proportionately during pregnancy, and decreases after delivery. It appears that labor and delivery releases GH1 blockade, which level rises three-fold during delivery. After parturition its role and concentration returns to levels before pregnancy.*

Key words: **pregnant women** / **PGH** / **GH1** / **IGF-I** / **ghrelin** / **blood serum** /

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Streszczenie

Cel pracy: *Celem pracy jest ocena stężenia hormonu wzrostu łożyskowego PGH), przysadkowego hormonu wzrostu (GH1), insulinopodobnego czynnika wzrostu (IGF-1) i greliny w surowicy krwi kobiet ciężarnych przed porodem, w czasie porodu i po porodzie, a więc po wydaleniu łożyska. Poza tym poszukiwano powiązań współzależności pomiędzy stężeniami GH1, PGH, IGF-I.*

Materiał i metody: *Zbadano próbki krwi od 79 kobiet. Krew pobierano 1-2. godzin przed porodem, w czasie porodu i po wydaleniu łożyska. Wszystkie badane białka były oznaczane metodą ELISA z wykorzystaniem zestawów ELISA Kit.*

Wyniki: *Najwyższe stężenie PGH w surowicy krwi ciężarnych obserwowano przed porodem, natomiast stężenie przysadkowego GH1 w tym samym czasie było najniższe. Stężenie IGF-I podobnie jak PGH było najwyższe. W trakcie porodu i po porodzie stężenie PGH i IGF-I proporcjonalnie malało a stężenie hormonu wzrostu przysadkowego odpowiednio powiększało się. Pół godziny po wydaleniu łożyska GH1 wykazywał najwyższe stężenie.*

Wnioski: *We krwi kobiet ciężarnych istnieje współzależność metaboliczna pomiędzy PGH i IGF-I. Ich stężenia narastają proporcjonalnie w czasie ciąży i obniżają się po porodzie. Poród wydaje się uwalniać blokadę GH1, którego koncentracja trzykrotnie rośnie w czasie porodu. Po porodzie jego rola i stężenie wracają do warunków przed ciążą.*

Słowa kluczowe: **kobiety ciężarne** / **(PGH)** / **GH1** / **IGF-I** / **grelina** / **surowica krwi** /

Introduction

Placental growth hormone (PGH) was discovered and described in 1985 by Hennen et al. [1, 2]. It shows a high degree of homology with pituitary growth hormone (GH1). The difference between placental growth hormone and pituitary growth hormone lies in 13 amino acids and N-glycosylation sites [1]. It is a product of GH-V gene, which belongs to the family of five growth hormone genes located on the long arm of chromosome 17 [3]. This hormone is synthesized and secreted by syncytiotrophoblast and extravillous cytotrophoblast [4, 5, 6].

Syncytiotrophoblast covers free villi and releases PGH into maternal bloodstream. This protein is detectable as early as five to eight weeks of gestation. Its concentration increases and reaches peak levels between 34 and 37 weeks of gestation. It is eliminated from the bloodstream after placental expulsion [4, 7]. It is described that during pregnancy PGH progressively displaces pituitary GH from maternal circulation, the values of which decrease as pregnancy progresses [4]. In the pituitary gland of pregnant women the number of somatotrophs decreases considerably to the advantage of PRL-synthesizing cells [8, 9]. Insulin-like growth factor and GH constitute key growth factor acting based on principle of feedback concentrations. This endocrine mechanism has been extensively researched in adults, however little is known about changes occurring during pregnancy.

Numerous authors draw attention to the link between ghrelin and growth hormone - ghrelin induces GH secretion from pituitary gland somatotrophs both in humans, also during fetal life, and in experimental animals [10]. In addition, ghrelin participates in the brain-intestine axis. Together with leptin, it creates a complementary system, which regulates and informs the central nervous system of energetic state of an organism [10, 11].

Aim of the study

The aim of the study is to evaluate protein concentrations in pregnant women's blood serum before, during and after delivery, that is after expulsion of the placenta. Furthermore, we look for links and interdependence of GH1, PGH and IGF-I concentrations.

Materials and Methods

Studies were conducted on blood samples collected from pregnant women. The samples were taken one to two hours before, during parturition and half an hour after the expulsion of placenta. Total of 79 blood samples collected from pregnant women were investigated. Most of the pregnant women were healthy and did not report any ailments. Eight pregnant women suffered from type I diabetes, six of them suffered from class G1DM, one from G2DM and one from class "C" diabetes. Three of the women delivered prematurely. The remaining pregnancies were full-term of which one was a twin pregnancy.

The following hormones were marked in blood samples of pregnant women:

- pituitary growth hormone (GH1)
- placental growth hormone (PGH)
- insulin-like growth factor (IGF-I)
- acylated ghrelin

All the proteins were marked using ELISA Kits. GH1 and IGF-I were assayed with R&D Systems ELISA Kits (R&D Systems, Minneapolis, USA), PGH protein with a Uscn life Science ELISA Kit (Uscn life Science, Wuhan, China) and ghrelin was assayed with a BioVendor ELISA Kit (BioVendor, Modrice, Czech Republic), all according to the manufacturers' recommendations.

Results

Table below shows that the highest concentration of placental growth hormone in pregnant women's blood serum was observed before delivery, while the concentration of the pituitary growth hormone was the lowest. The concentration of insulin-like growth factor, like that of PGH, was highest before labor and delivery. During and after delivery the PGH and IGF-I concentration decreased accordingly and the pituitary gland hormone increased accordingly. About half an hour after placental expulsion, PGH

Table I. Statistical analysis of results of hormone levels found in the peripheral circulation in women during peripartum period.

Hormone	Before parturition		During parturition		After parturition	
	Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)
PGH [pg/ml]	11427.3 (10582.4)	*6452,3 (5523.8-27280.6)	2701.7 (968.4)	*2819.1 (1006.7-4610.2)	586.3 (44.2)	*600.0 (495.4-644.4)
GH1 [pg/ml]	459.1 (239.4)	397.9 (240.4-800.0)	1534.9 (1691.6)	1062.5 (96.6-7771.3)	1775.7 (2177.89)	845.2 (152.1-6342.9)
IGF-I [ng/ml]	166.1 (87.7)	135.5 (101.6291.8)	230.4 (136.8)	177.7 (99.2-576.8)	193.5 (95.0)	165.6 (83.4-363.6)
Ghrelin [pg/ml]	51.2 (15.3)	54.5 (30.1-65.7)	43.3 (33.9)	33.9 (6.4-119.5)	37.5 (20.07)	33.0 (16.7-65.9)

*Kruskal-Wallis One Way Analysis of Variance on Ranks P<0.001

and IGF-I concentration was lowest, while GH1 concentration was highest after delivery. Statistically significant level of PGH difference was observed between studied groups ($p<0.001$). The remaining hormone levels did not demonstrate statistically significant differences (Table I). Ghrelin concentrations did not change significantly during the three studied stages.

Discussion

Our studies show a decrease in PGH concentration during delivery progression to very low levels after expulsion of the placenta. Chellakooty et al. [7] monitored PGH concentration in pregnant women's blood by collecting blood samples seven times during pregnancy and showed that the concentration of this hormone increased from fifth to 37th week of gestation, then its concentration gradually decreased. Its highest concentration is 22 ng/ml. There are attempts to use presence of high concentration of this hormone in blood serum during first trimester of pregnancy to estimate the risk of Down Syndrome [12]. Moreover, high concentration of PGH and GH1 was also described in preeclamptic patients [13, 14]. The main source of PGH is the placental trophoblast and for decades it was thought that this protein is located only in maternal circulation. It was only between 2007 and 2008 that the first works appeared, which also described the presence of the placental growth hormone in the umbilical blood of newborns and in the amniotic fluid [11, 15, 16]. In our earlier work in which we evaluated, among others, PGH and IGF-I levels in serum of umbilical blood, we showed a correlation between IGF-I and body mass of full-term newborns. Meanwhile, PGH concentration was higher in premature newborns and full-term, low-birth-weight infants than in normal pregnancies. We put forward a suggestion that higher PGH values in the blood of premature neonates and full-term, low-birth-weight newborns may be connected with activation of compensatory mechanisms - increased PGH secretion stimulates IGF-I in the placental tissue, thereby increasing its proliferation and increasing body mass of newborns. At the same time our studies showed a gradual decrease of PGH and IGF-I concentrations in the serum of maternal blood during delivery, until expulsion of placenta. Also, the behavior of both proteins studied suggests that the main place of their synthesis is the placenta. However, we wonder if PGH is exclusively synthesized by the trophoblast. If it is, then a question arises: how does it go into the fetal circulation?

The presence of m-RNA of GH-V gene coding PGH in hydatidiform mole, choriocarcinoma culture, adenoma of the pituitary gland, and testicular neoplasm was described in the literature, however their authors were unable to identify this hormone in blood serum of these patients [10, 17]. The problem is whether PGH, besides being synthesized by the trophoblast, is also synthesized by fetal cells - it is an open question and requires further in-depth studies. All our studies suggest that there is a metabolic relation between PGH and IGF-I in both, the fetal and maternal circulation. In circulation of pregnant women PGH plays a similar role as does the pituitary GH1 in an adult organism with the exception that it does not function in a pulsatile manner.

Placental growth hormone actively suppresses pituitary GH1 in pregnant women's bloodstream. Its concentration, as well as that of IGF-I, increases proportionately with advancement of pregnancy, while GH1 decreases to almost zero. Meanwhile, during labor and delivery the situation is opposite - PGH and IGF-I concentration decreases, while pituitary GH1 concentration increases. It is a well known the fact that during pregnancy the pituitary gland is restructured and enlarged, while the total number of somatotrophs decreases to the advantage of cells that synthesize PRL. Some also suggest that somatotrophs may transform into PRL-synthesizing cells [10, 17].

As far as ghrelin is concerned, its concentration in studied pregnant women's blood serum did not show any considerable changes. In blood serum ghrelin is found in two forms, the acylated form, which is endocrine-active, and the non-acylated from, which is endocrine-inactive. Ghrelin participates in the control of metabolic energy homeostasis, which regulates energy consumption by influencing appetite, modulation of immunological system, pituitary stimulation of the gonadal and adrenal axis, and many others [12].

Conclusions

To conclude, based on the results we obtained and the data presented in literature on this subject, it can be assumed that in pregnant woman's blood there is a metabolic interdependence of PGH and IGF-I. There is a statistically significant difference in PGH levels between studies ($p<0.001$). Its concentration increases proportionally during pregnancy until mechanisms of childbirth are activated. During last period of pregnancy its values distinctively decrease. Simultaneously parturition releases pituitary GH1 blockade and its concentration and role return to levels before pregnancy.

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