



## The role of insulin-like growth factor in prediction and prevention of preterm delivery

### Određivanje uloge faktora rasta sličnog insulinu u predviđanju i prevenciji prevremenog porođaja

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#### Abstract

**Background/Aim.** Prediction and prevention of preterm delivery remain great challenge. It is important to include in everyday medical practice determination of certain markers that could help identifying pregnant women with preterm delivery. Insulin-like growth factor (IGF) is involved in the control mechanism of fetal and placental growth and development. The aim of this study was to examine the presence of insulin-like growth factor binding protein 1 (IGFBP-1) in cervicovaginal secretion of pregnant women with symptoms of preterm labor, but with apparently intact fetal membranes and to point out a possible application of the strip test for detection of phIGFBP-1 in diagnosis of preterm premature rupture of total membranes (PPROM) in everyday medical practice. **Methods.** The study was performed at the Department for Obstetrics and Gynecology, Clinical Center of Vojvodina between October 2008 and May 2009. The study included 54 pregnant women between 20–35 weeks of gestation (WG), divided into two groups: the study group (16 pregnant women with symptoms of preterm delivery that gave birth before 37 WG) and the control group (38 pregnant women with the normal course of pregnancy that gave birth on term). In cervicovaginal secretion of the examined pregnant women the level of IGFBP-1 was determined by the immunochromatographic assay with monoclonal antibodies 6303 as a detecting antibody (Actim PROM test, Medix Biochemica, Kauniainen, Finland). **Results.** Gestational age (GA) at delivery in the study group was 32.6 WG and in the control group it was 38.4 WG. Weight of newborns in the study group was 2,021 g and in the control group 3,430 g. IGFBP test was positive in 15 women (93.75%) of the study group, while in the control group it was positive only in 1 woman (2.63%). **Conclusion.** Test on phIGFBP-1 in cervicovaginal mucus was positive in 93.75% women with preterm delivery, suggesting that this test could be used in diagnosis of silent rupture of fetal membranes and in prediction of preterm delivery.

#### Key words:

obstetric labor, premature; placenta; rupture; vaginal smears; insulin-like growth factor I.

#### Apstrakt

**Uvod/Cilj.** Predikcija i prevencija prevremenog porođaja predstavlja veliki izazov i zato bi bilo veoma važno da se u svakodnevnu praksu uvedu markeri koji bi pomogli u prepoznavanju ovih trudnica. Faktor rasta sličan insulinu (IGFBP-1) uključen je u kontrolni mehanizam fetuskog i placentalnog rasta i razvoja. Cilj rada bio je ispitivanje prisustva vezujućeg proteina-1 za faktor rasta sličan insulinu (IGFBP-1) u cervikovaginalnom sekretu žena sa simptomima prevremenog porođaja, ali sa naizgled intaktnim fetalnim membranama i ukazivanje na mogućnost primene testa na phIGFBP-1 u dijagnostici preterminske premturane rupture (PPROM) fetusnih membrana u svakodnevnoj praksi. **Metode.** Istraživanje je sprovedeno na Klinici za ginekologiju i akušerstvo Kliničkog centra Vojvodine u periodu od oktobra 2008. do maja 2009. godine. Istraživanjem su bile obuhvaćene 54 trudnice između 20 i 35 nedelja gestacije (NG), podeljene dve grupe: ispitivanu (16 trudnica sa simptomima prevremenog porođaja koje su se porodile pre 37 NG) i kontrolnu (38 trudnica sa urednim tokom trudnoće koje su porođene u terminu). U cervikovaginalnom sekretu ispitivanih trudnica određena je koncentracija phIGFBP-1 imunohromatografskom metodom sa monoklonalnim antitelima 6 303 koji vezuju phIGFBP-1. **Rezultati.** Pri porođaju gestacijska starost u ispitivanoj grupi bila je 32,6 NG, a u kontrolnoj 38,4 NG. Telesna masa novorođenčadi u ispitivanoj grupi iznosila je 2 021 g, dok je u kontrolnoj iznosila 3 430 g. Pozitivan phIGFBP-1 u ispitivanoj grupi imalo je 15 (93,75%) trudnica, a u kontrolnoj grupi jedna (2,63%). **Zaključak.** Kod 93,75% trudnica čija trudnoća se završila prevremenim porođajem, test na phIGFBP-1 u cervikovaginalnom mukusu bio je pozitivan, što ukazuje na mogućnost primene ovog testa u dijagnostikovanju prikrivenih ruptura plodovih ovojaka i u predviđanju prevremenog porođaja.

#### Ključne reči:

porođaj, prevremeni; placenta; ruptura; vaginalni brisevi; IGF1.

## Introduction

Prediction and prevention of preterm delivery remain great challenge in obstetrics. Therefore, it would be very important to point out a possible application in everyday medical practice of certain markers that could help in identifying pregnant women with a silent preterm premature rupture (PPROM) of fetal membranes, who have the highest risk of preterm delivery and who might benefit from timely admission and appropriate treatment.

The insulin-like growth factor (IGF) (including IGF-I and IGF-II, their receptors and the binding proteins) is involved in the control mechanism of fetal and placental growth and development. The insulin-like growth factor binding protein 1 (IGFBP-1) is mainly secreted by the fetal and adult liver. Its concentration in maternal plasma increases as pregnancy advances. It is a major constituent of amniotic fluid from the second trimester to term. Concentration of IGFBP-1 in amniotic fluid is 100–1,000 fold higher than in the serum. Amniotic fluid contains non-phosphorylated and less phosphorylated isoforms of IGFBP-1, whereas the decidua contains phosphorylated isoforms, including a highly phosphorylated isoform (phIGFBP-1) not present in amniotic fluid<sup>1-5</sup>. Because of this difference, the origin of IGFBP-1, decidua or amniotic fluid isoforms of IGFBP-1 can be identified through the use of monoclonal antibodies. The presence of amniotic fluid isoforms of IGFBP-1 in cervical samples has proved to be diagnostic as regards rupture of fetal membranes (Actim PROM test, Medix Biochemica, Kauniainen, Finland) and testing is currently in routine use<sup>1,6-10</sup>.

The aim of this study was to examine the presence of highly phosphorylated isoform (decidual) of the insulin-like

from 1975, which was revised in 1983, and approved by the Ethical Committee of Clinical Center of Vojvodina (Novi Sad). The investigation included 54 pregnant women between 20 and 35 weeks gestation (WG). Gestational age was based on the last menstrual period and was confirmed by early first trimester ultrasonography. A total of 16 women with symptoms of preterm delivery (presence of contractions or increased tonus of the uterus, but without cervical changes or an evident rupture of membranes) who delivered prematurely (before 37 WG) were enrolled into the study group. The control group (n = 38) included pregnant women without symptoms of preterm delivery, who delivered in term (37–40 WG). Anamnestic data were taken from all patients and obstetrical examination was performed. The concentration of phIGFBP-1 in cervicovaginal secretion of investigated pregnant women was measured by immunochromatographic assay with monoclonal antibodies 6 303 as a detecting antibody (Actim PROM test, Medix Biochemica, Kauniainen, Finland).

The pregnant women with positive results of Actim PROM test were treated with antibiotics from the cephalosporine or penicillin groups to prevent infection, and with dexametason (6 mg four times per day in duration of 48 h) for fetal lung maturation.

The Student's *t*-test was used for statistical analysis. Any *p*-value less than 0.05 was considered significant.

## Results and discussion

Table 1 shows maternal demographic characteristics (age, information about previous deliveries as well as spontaneous abortions and preterm deliveries) in both the study

**Table 1**  
Demographic characteristics of pregnant women

Characteristics	Study group	Control group
Age (years), $\bar{x} \pm SD$	29.75 $\pm$ 4.64	29.29 $\pm$ 3.59
Gravidy (n), $\bar{x} \pm SD$	2.13 $\pm$ 1.45	1.58 $\pm$ 0.64
Parity (n), $\bar{x} \pm SD$	1.75 $\pm$ 1.06	1.5 $\pm$ 0.6
Previous preterm deliveries (%)	6.25	5.26
Previous spontaneous abortions (%)	25	7.89

Study group – preterm delivery

Control group – term delivery

growth factor binding protein 1 (phIGFBP-1) in cervicovaginal secretion of pregnant women with symptoms of preterm labor, but with apparently intact fetal membranes, as well as to point out a possible application of the strip test for detection of phIGFBP-1 (Actim PROM test, Medix Biochemica, Kauniainen, Finland) in everyday medical practice for diagnosis of increased risk of preterm delivery.

## Methods

The study was performed at the Department of Obstetrics and Gynecology, Clinical Center of Vojvodina between October 2008 and May 2009. The protocol for this study was performed in compliance with the Declaration of Helsinki

and the control groups. Maternal age was between 20 and 38 years in both groups (approximately 29.8 years in the study group and 29.3 years in the control group). Previous preterm deliveries had 6.25% women from the study group and 5.26% women from the control group. Previous spontaneous abortions had 25% women from the study group and 7.89% from the control group.

Table 2 shows obstetric parameters in both investigated groups. The mean GA of pregnant women at the moment Actim PROM test was performed, was 28.2 WG in the study group and 30.3 WG in the control group, while cervical dilatation was 1.9 cm in the study group, and 1.0 cm in the control group. The mean GA at birth was 32.5 WG in the study group and 38.4 WG in the control group.

Table 2

Obstetric parameters in pregnant women

Obstetric parameters	Study group $\bar{x} \pm SD$	Control group $\bar{x} \pm SD$
Gestational age at admission (weeks)	28.19 ± 6.39	30.32 ± 4.81
Gestational age at delivery (weeks)	32.56 ± 2.53	38.38 ± 1.13
Cervix dilatation in the moment of hospitalization (cm)	1.88 ± 1.23	0.99 ± 0.84

Study group – preterm delivery

Control group – term delivery

The modus of delivery is shown in Figure 1. Vaginal delivery had 56.25% women from the study group and 81.58% women from the control group. Cesarean section was performed in 43.75% women in the study group, and in 18.42% women in the control group. No postpartum and postoperative complications were noted in the mothers of both groups.

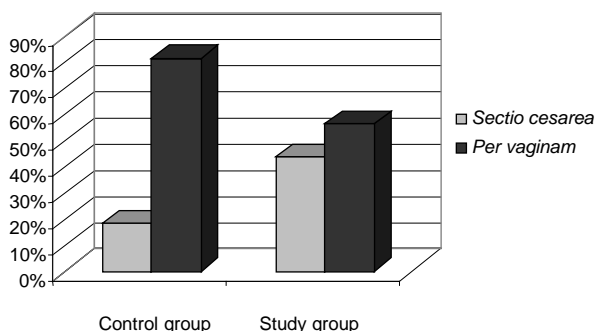


Fig. 1 – The way of the delivery termination

Control group – term delivery

Study group – preterm delivery

The results of Actim PROM test are presented in Figure 2. Positive test for phIGFBP-1 had 15 (93.75%) patients in the study group, and only 1 (2.63%) in the control group ( $p < 0.05$ ).

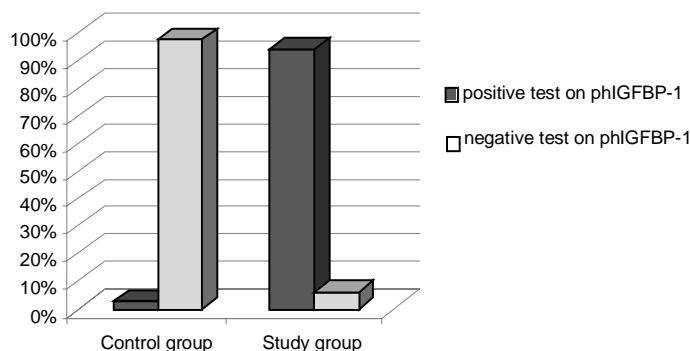


Fig. 2 – Test results on the presence of phIGFBP-1 in cervical mucus of pregnant women (study group – preterm delivery; control group – term delivery)

In both groups there were 53 live births and one stillbirth (in the study group). Average body weight of the infants in the study group was 2,021 g, and in the control group 3,430 g.

Preterm premature rupture of fetal membranes is very frequent diagnostic and therapeutic dilemma in obstetrics.

The tests previously used for diagnosis of PPRM (the use of litmus paper or nitrazine swabs for detection of vaginal pH, the vaginal prolactin test, tests for alpha-fetoprotein and vaginal fibronectin) are insufficient and frequently give false positive results because of the presence of blood or semen in cervical mucus and vagina.

The Actim PROM test is superior in comparison with the tests mentioned above because it does not react with mucus, blood or semen, and sensitivity of the test is so high that even micro ruptures of fetal membranes can be detected<sup>11-18</sup>.

The obtained results suggest that 93.75% pregnant women who delivered prematurely (the study group) also had preterm rupture of fetal membranes (positive test for phIGFBP-1 in cervical mucus). This indicates the possibility of using this test in diagnosis of micro ruptures of fetal membranes. Since the test is very simple and gives a result in a few minutes, it is possible to prescribe antibiotics and corticosteroid therapy for pregnant women in the nick time and to prolong their pregnancy, as well as to suppress infection and avoid respiratory distress in newborns.

Conclusion

Our results suggest that IGFBP-1 test could be used in diagnosis of silent rupture of fetal membranes and in prediction of preterm delivery.

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