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 before 37 WG) and the control group (38 pregnant women with symptoms of preterm delivery, 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 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.

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.

Ključne reči: porodaj, prevremen; placenta; ruptura; vaginalni brisevi; IGF1.
Introduction

Prediction and prevention of preterm delivery remain a 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 (decidual) of the insulin-like growth factor binding protein 1 (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 (decidual) of the insulin-like growth factor binding protein 1 (IGFBP-1) not present in amniotic fluid. Antibody (Actim PROM test, Medix Biochemica, Kauniainen, Finland) directed against the amniotic fluid isotype of IGFBP-1 was validated by immunochromatographic assay with monoclonal antibodies and tested in routine use.

The aim of this study was to examine the presence of highly phosphorylated isoform (decidual) of the insulin-like growth factor binding protein 1 (phIGFBP-1) in cervicovaginal secretions of pregnant women with symptoms of preterm delivery, who delivered preterm (before 37 WG) and who had intact membranes, as well as spontaneous abortions and preterm deliveries in both the study and 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 7.89% women from the study group and 5.26% women from the control group. The Student’s t-test was used for statistical analysis. Any p-value less than 0.05 was considered significant.

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 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 secretions of pregnant women was measured by immunochromatographic assay with monoclonal antibodies 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 dexamethason (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 group and control group. The mean GA of pregnant women at the moment of labour, 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.

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 1: Characteristics of pregnant women

| Characteristics                  | Study group | Control group |
|----------------------------------|-------------|---------------|
| Age (years), x ± SD              | 29.75 ± 4.64| 29.29 ± 3.59  |
| Gravidy (n), x ± SD              | 2.13 ± 1.45 | 1.58 ± 0.64   |
| Parity (n), x ± SD               | 1.73 ± 1.06 | 1.5 ± 0.6     |
| Previous preterm deliveries (%)  | 6.25        | 5.26          |
| Previous spontaneous abortions (%)| 25          | 7.89          |

Study group – preterm delivery
Control group – term delivery

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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](image)

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](image)

Table 2

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

The tests previously used for diagnosis of PPROM (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 $^{11-18}$.

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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REFERENCES

1. Kekki M, Kurki T, Paavonen J, Ratanen E-M. Insulin-like growth factor binding protein-1 in cervix as a marker of infectious complications in pregnant women with bacterial vaginosis. Lancet 1999; 353: 1494.

2. Martina NA, Kim E, Chikara U, Wathen NC, Chard T, Giudice LC. Gestational age-dependent expression of insulin-like growth factor-binding protein-1 (IGF BP-1) phosphoisofoms in human extraembryonic cavities, maternal serum, and decidua during early pregnancy. J Clin Endocrinol Metab 1997; 82(6): 1894–8.

3. Jain K, Morris PG. A clinical study to evaluate the usefulness of the MAST test in diagnosing pre-labour rupture of membranes. J Obstet Gynaecol 1998; 18(1): 33–6.

4. Giudice LC, de Zegher F, Gargosky SE, Dsupin BA, de las Fuentes L, Crystal RA, et al. Insulin-like growth factors and their binding proteins in the term and preterm human fetus and neonate with normal and extremes of intrauterine growth. J Clin Endocrinol Metab 1995; 80(5): 1548–55.

5. Verhaeghe J, Van Herck E, Billen J, Moerman P, Van Asche V-A, Giudice LC. Regulation of insulin-like growth factor-I and insulin-like growth factor binding protein-1 concentrations in preterm fetuses. Am J Obstet Gynecol 2003;188(2): 485–91.

6. Lembet A, Eroglu D, Ergin T, Kuscu E, Zeyneloglu H, Batioglu S, et al. New rapid bedside test to predict preterm delivery: phosphorylated insulin-like growth factor binding protein-1 in cervical secretion as a predictor of preterm delivery. Am J Obstet Gynecol 2003;188(2): 485–91.

7. Kekki M, Kurki T, Karkkainen T, Hiilesmaa V, Paavonen J, Rutanen EM. Insulin-like growth factor binding protein-1 in cervical/vaginal secretions: comparison with the ROM-check Membrane Immunoassay in the diagnosis of ruptured fetal membranes. Clin Chim Acta 1993; 214(1): 73–81.

8. Bittar RE, da Fonseca EB, de Carvalho MH, Martinieli S, Zagoit M. Prediction of preterm delivery in asymptomatic patients with prior preterm delivery by measurement of cervical length and phosphorylated insulin-like growth factor-binding protein-1. Ultrasound Obstet Gynecol 2007; 29(5): 562–7.

9. Paternoster DM, Muresan D, Vitulo A, Serena A, Battaglini G, Dell’Avanzo M. Cervical phosphoIGFBP-1 in the evaluation of the risk of preterm delivery. Acta Obstet Gynecol Scand 2007; 86: 86–9.

10. Elizur SE, Yinon Y, Epstein GS, Suidman DS, Schif F, Sivan E. Insulin-like growth factor binding protein-1 detection in preterm labor: evaluation of a bedside test. Am J Obstet Gynecol 2005; 22: 305–9.

11. Darj E, Lyrenäs S. Insulin-like growth factor binding protein-1, a quick way to detect amniotic fluid. Acta Obstet Gynecol Scand 1998; 77: 295–7.

12. Westwood M, Gibson JM, Davies AJ, Young RJ, White A. The phosphorylation pattern of insulin-like growth factor-binding protein-1 in normal plasma is different from that in amniotic fluid and changes during pregnancy. J Clin Endocrinol Metab 1994; 79(6): 1735–41.

13. Halls EA, Gunn LK, Hardiman P, Thamaratnam S, Chard T. IGFBP-1 in the placenta, membranes and fetal circulation: levels at term and preterm delivery. Early Hum Dev 1996; 44: 71–6.

14. Erdemoglu E, Mungan T. Significance of detecting insulin-like growth factor binding protein-1 in cervicovaginal secretions: Comparison with nitrazine test and amniotic fluid volume assessment. Acta Obstet Gynecol Scand 2004; 83: 622–6.

15. Cvetković M, Ljubić A. Protocols of high risk pregnancies. Beograd: Medicina moderna; 2002.

16. Gibbs RS, Karlan BY, Haney AF, Nygaard IE. Danforth’s Obstetrics and Gynecology. Philadelphia, PA: Lippincott Williams and Wilkins; 2008.

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