ORIGINAL ARTICLE

IGFBP-1 marker of cervical ripening and predictor of preterm birth

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ABSTRACT

Aim To establish a correlation between positive values of IGFBP-1 (>10 μg/L, Actim Partus Test, APT) and premature cervical ripening in imminent preterm labor.

Methods A prospective study was conducted in primary health care centers in Tuzla, Gynecology and Obstetrics Clinic of the University Clinical Centre in Tuzla and General Hospital Tešanj. The study included 50 women (singleton pregnancy, 28-37 week) with imminent preterm labor diagnosed by cervical biometry and modified Bishop score) (examinees) and 30 healthy pregnant women (control group). The presence of IGFBP-1 was tested in cervical secretion several times in weeks 28-37 until a positive test was shown.

Results IGFBP-1 was positive in 43 (86%) examinees and in six (20%) patients from the control group (p=0.001). In 31 (62%) examinees APT was positive in weeks 28-30, and in nine (18%) in weeks 31- 33, while three (6%) examinees had positive test in 34-37 week; in the control group, three (10%) were tested positive in weeks 31-33 and three (10%) in weeks 34-37. At first testing (28-30 weeks) APT was statistically significantly more frequently positive in the examined group (p<0.05). Later, tests did not find statistically significant difference in the frequency of positivity between the control and examined group (p=0.08).

Conclusion Elevated values of IGFBP -1 in cervical secretion were highly correlated with preterm labor. Screening for IGFBP could help in preventing preterm labor and its complications.

Key words: insulin-like growth factor binding proteins, premature birth, cervix mucus

INTRODUCTION

Preterm labor is one of the main problems of modern perinatology, neonatology and medicine in general due to potential consequences for future life of a child. Preterm birth complications are the leading cause of death among children under 5 years of age, responsible for nearly 1 million deaths in 2013 (1-4). According to recommendations of the World Health Organization preterm is defined as the birth of babies born alive before 37 weeks of pregnancy are completed (1). There are four sub-categories of preterm birth based on gestational age: late preterm (born between 34 and 36 weeks of pregnancy), moderately preterm (born between 32 and 34 weeks of pregnancy), very preterm (born at less than 32 weeks of pregnancy), and extremely preterm (born at or before 25 weeks of pregnancy) (1-3). Inequalities in survival rates around the world are expected. In low-income settings, half of the babies born at or below 32 weeks (2 months early) die due to a lack of feasible, cost-effective care, such as warmth, breastfeeding support, and basic care for infections and breathing difficulties. In high-income countries, almost all of these babies survive (4).

After 28 weeks of pregnancy it is possible to speed up maturation of fetal lungs using corticosteroid therapy whish increases chances for survival (5).

Often, the specific cause of premature birth is not clear. Many factors may increase the risk of premature birth including: having a previous premature birth, pregnancy with twins, triplets or other multiples, an interval of less than six months between pregnancies, conceiving through in vitro fertilization, problems with the uterus, cervix or placenta, smoking cigarettes or using illicit drugs, poor nutrition, not gaining enough weight during pregnancy, some infections (particularly of the amniotic fluid and lower genital tract), some chronic conditions (such as high blood pressure and diabetes), being underweight or overweight before pregnancy, stressful life events, such as the death of a loved one or domestic violence, multiple miscarriages or abortions, physical injury or trauma (3,4).

Every year, an estimated 15 million babies are born preterm (before 37 completed weeks of gestation), and this number is rising (1,4). Across 184 countries, the rate of preterm birth ranges from 5% to 18% of babies (4). Prematurity is the leading cause of death in children under the age of 5 (1-4, 6-8).

The best way for prevention of prematurity is early screening of pregnant women with high risk of preterm labor. Methods of selection of pregnant women at risk include clinical and biochemical markers for preterm labor. Clinical markers include changes of cervix, which could be detected by regular vaginal examinations and ultrasonography. Monitoring of occurrence of uterus contractions, vaginal bleeding and registering of epidemiological risk factors are also performed (4-7). Biochemical methods include monitoring of serum collagenase activity, cervicovaginal elastosis and determination of cervicovaginal fetal fibronectin and insulin-like growth factor binding protein (IGFBP-1) (9-11).

In the last decades numerous studies identified IGFBP-1 as a marker of cervical changes that are related to preterm labor (9-11). Unfortunately, there were just few reports from Bosnia and Herzegovina about the correlation between preterm labor and IGFBP-1 or other biochemical markers. This multi-centric study is designed to show that even if two regions are not within the same health administration, if detected on time, even in small healthcare center, prematurity treatment can be successfully performed in a nearest well equipped center.

The aim of this study was to establish a correlation between positive values of IGFBP-1 (>10 μg/L, Actim Partus test) and imminent preterm labor.

PATIENTS AND METHODS

Study design and examinees

The prospective study was conducted in obstetrics practice of primary health care centers in Tuzla, Gynecologic and Obstetrics Clinic of the University Clinical Centre in Tuzla and General Hospital Tešanj during the nine-month period between September 2013 and end of May 2014. The estimated population of the cities Tuzla and Tešanj is 400.000 inhabitants. More than one center was selected to provide sufficient number of relevant data. The selection of the medical institution of Tuzla Canton and neighboring Tešanj region was based on regional similarity of the

population within the area of 70 kilometers and a possibility for quick transport "*in utero*" from Tešanj to Tuzla for neonatal care.

Three (out of four) sub-categories of preterm birth (based on gestational age) (1-3) were tested: late preterm (born between 34 and 36 weeks of pregnancy), moderately preterm (born between 32 and 34 weeks of pregnancy), very preterm (born at less than 32 weeks of pregnancy). Extremely preterm (born at or before 25 weeks of pregnancy) was excluded due to poor prognosis and lack of prophylactic treatment for fetal lung maturation. The pregnancies after the 28th week from the groups of examinees (all other subgroups of preterm labor) with diagnosed preterm labor were on corticosteroid treatment. In order to avoid any differences between the tested groups caused by possible influence of corticosteroid therapy to final results on preterm labor, extremely preterm labor group was excluded from study.

A total number of 80 patients was included in study: an examined group of 50 pregnant women with imminent preterm labor and a control group of 30 healthy pregnant women.

Both groups included patients who had had no deliveries before, who had no diagnosed developmental anomaly of uterus or any other diseases that would be treated as a risk factor for preterm labor. The criteria for inclusion in the study (both groups) were: nulparity, absence of anomalies of genital tract, absence of other problems and surgery of the uterus, cervix, absence of complications with placenta, absence of multiple miscarriages or abortions, absence of physical injury or trauma, no smoking cigarettes or using illicit drugs, no chronic conditions (particularly high blood pressure and diabetes), not being underweight or overweight before pregnancy, no stressful life events (such as the death of a loved one or domestic violence), as well as absence of hard working conditions. All patients with uterine contraction were excluded.

The examined group included 50 healthy pregnant women with singleton pregnancy of the gestation age between the 28th and 37th week who were diagnosed with imminent preterm labor based on two main criteria: modified Bishop score and ultrasound biometry.

The control group comprised 30 healthy pregnant women with singleton pregnancy of the gestational age between the 28th and 37th week, who had no changes identified by ultrasound biometry and modified Bishop score that would indicate imminent preterm labor caused by cervical changes (Table 1).

Table 1. Assessment of the condition of cervix based of cervical length, dilatation, consistensy, position of cervical axis and position of fetal head

Parameters	Index			
	0	1	2	3
Dilatation of cervical channel (cm)	closed	1 – 2	3 - 4	5 and more
Cervical length (cm)	3	2	1	0
Position of fetal head (cm)	-3	-2	-1	1 +2
Cervical consistency	hard	middle	tempered	soft
Position of cervical axis	maximal back or front	slightly back	slightly front	centered

Approvals of the Ethics Committees of all institutions participating in the multicentric study were obtained (Healt Center Tuzla, GeneralHospitah Tešanj, University Clinical Ceter Tuzla).

Methods

The diagnosis of imminent preterm labor caused by cervical changes was determined by modified Bishop score and ultrasound biometry according to cervix condition. Measured parameters included: length of cervix, dilatation of cervical channel, cervical consistency, position of fetal head, and a position of cervical axis (Table 1).

The condition of uterus was further assessed by transvaginal and transabdominal ultrasound cervical length measurement and elements were monitored and scored according to cervical length measurement. Parameters measured included length of cervix, dilatation of cervical channel, and shape of internal ostium ("T" represented closed cervical ostium and channel, "Y" initial dilatation, and "U" advanced dilatation). Each parameter, dependently of measures, was marked from 1 (for slight changes) to 3 (for extreme changes). A sum of marks represented cervical score (CS) (Table 2).

Table 2. Assessment of the condition of cervix by transvaginal and transabdominal ultrasound based on the measurement of cervical length, dilatation and internal ostium shape

Parameters	Index		
	0	1	2
Cervical length (mm)	30 and more	20	less than 20
Dilatation of cervical channel (mm)	0	3 -5	more than 5
Shape of internal ostium	T	Y	U

T, closed cervical ostium and channel; Y, initial dilatation; U, advanced dilatation

Bishop score represents a sum of marks (index) from 1 to 3 for each of the parameters. Minimal changes in Bishop score had to be shown by Bishop score 2 and higher, or at least 2 minimally changed parameters, or one significantly changed parameter.

All patients were tested for the presence of IGFBP-1 in cervical secretion starting in gestational age of the 28th week (very preterm). The group of examinees had the test repeated in the period 31st - 33rd week (moderately preterm), 34th -37th week (late preterm) until the positive result occurred, and if the third test remained negative, the test was definitely recorded as negative. In order to determine the presence of IGFBP-1 in cervical secretion the Actim Partus test (APT) (Medix Biochemica, Finland) was used (one-step dipstick test for detecting the presence of phosphorylated IGFBP-1 in cervical secretions to observe the risk of preterm or imminent delivery when fetal membranes are intact). Values higher than 10 μg/L are considered to be positive and indicate the maturity of cervix, i.e. imminent preterm labor.

Statistical analysis

The χ^2 test, standard deviation, Fisher test, Student T test was used, as well as a relative risk was calculated. APT value, Bishop Score and Cervical Score were measured every two weeks and compared between the group of examinees and the control group in gestational age from 28 to 36 weeks. The significance level was p≤0.05.

RESULTS

The average age of patients in the examined group was 25.4 years; the youngest patient was 16 years old, eldest one was 30. In the control group the average age of pregnant women was 27; the youngest patient was 17, and the eldest was 33. The total of 62% examinees lived in town, 10% in a smaller town, 28% lived in rural areas. In the control group 66.6% of patients lived in town, 10% in a smaller town, and 23% lived in villages. Both groups included an equal number of employed and unemployed with statistically insignificant difference in professional qualifications. Everyday activities at home, either housekeeping or performing duties at work, exposed patients from both groups to equal physical effort or position (data are not shown).

Bishop score (BS) 2 was found in 23 (46%), BS 3 in 20 (40%), BS 4 in one (4%) of examinee. Most frequently diagnosed cervical changes were shortening, in 21 (42%), dilatation in 16 (32%) and softening in 10 (20%) patients.

Transvaginal cervical measurement showed changed values of cervical measurement score (CS). The highest number of the examinees (39) had changes of cervical score (CS) CS2 and CS3, which means that at least one parameter was highly expressed (mark 2 or 3) or two parameters were moderately expressed (marks 1 and 2), or three parameters were slightly expressed (mark 1). Most frequently diagnosed changes were found on the shape of internal orifice of the uterus, in 21 (42%), length in 16 (32%) and dilatation of cervical canal in 12 (24%) examinees.

Actim Partus test was positive in 43 (86%) examinees and six (20%) patients from the control group. The analysis of frequency of positive Actim Partus tests (APT) with regard to the examined group found a statistically significant difference, and the highest percentage of examinees from the examined group had it positive 43 (86%) (p=0.001).

In 31 (62%) examinees APT was positive in gestation weeks 28-30, in nine (18%) examinees it was positive at the second testing between weeks 31 and 33, while in three (6%) examinees the test was positive upon the third testing performed between gestation weeks 24 and 36. In patients from the control group three (10%) patients had the positive test in the period between 31st and 33rd week, while three (10%) patients had it positive in gestation weeks 34-37 (Figure 1).
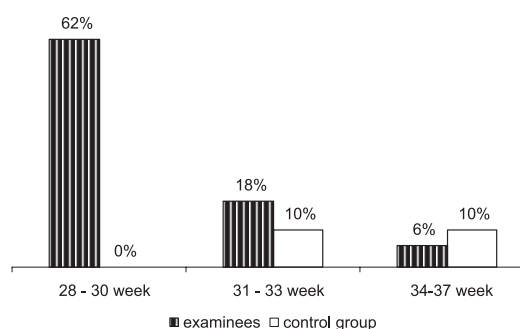

Figure 1. Occurrence of positive Actim Partus test in observed gestational periods

Already at first testing (28-30 weeks of gestation) APT was statistically significantly more often positive in the examined group in comparison

with the control group (p<0.05). During later measurements, nine (18%) and three (10%) patients in examined and control group, respectively had positive test during 31-33 week; three patients in each had positive test in examined (6%) and control group (10%), respectively in 34-34 week. There was no statistically significant difference in the frequency of positive tests between the control and examined group in periods 31-33 and 34-37 weeks (p=0.08).

Presence of infection in cervical chanel was detected in 35 (70%) examinees and in four (13%) patients from the control (p=0.001). Most frquent microbiological patogens found were: *Ureaplasma urealyticum* in seven (20%), *Mycoplasma hominis* in seven (20%), *E. coli* in five (14%), *Trichomonas vaginalis* in four (11%), *Chlamydia trichomatis* in three (9%) and other patogens in nine (26%) cases. Presence of ureaplasma and mycoplasma infections (40%) was statistically significant as compared to all other patogens (p=0.001).

Preterm labor occurred in 30 (60%) patients of the examined group, while 20 (40%) patients had term labor. In the control group all the patients had term labor. The highest number of the examinees with preterm labor was in the group of 34-36 weeks, i.e. in the group of late preterm prematurity, 19 (63%) examinees of all preterm deliveries among the examinees. Moderate prematurity occurred in nine (10%) examinees of all preterm labors in the examined group, while two (6%) examinees had very premature labor (Table 3).

Table 3. Term of labor in the examined group

	Preterm labor			Term labor	
Gestation week	28-31	32-33	34-36	37-40	Total
No (%) of examinees	2 (4)	9 (18)	19 (38)	20 (40)	50 (100)

In 29 (58%) examinees with preterm labor APT was positive, but it was also positive in 14 (28%) examinees with term labor (predicative value of 96% for preterm labors and 70% for term labors) (Table 4).

Table 4. Actim Partus test (APT) and pregnancy outcome

	No (%) of examinees		
Labor	APT positive	APT negative	Total
Preterm	29 (58)	1 (2)	30 (60)
Term	14 (28)	6 (12)	20 (40)

DISCUSSION

Being the most frequent complication of the second semester of pregnancy, preterm labor is a significant health problem in perinatology and medicine in general (1-3). Cervical changes are presented as shortening, softening and dilatation of the canal, which are thereafter followed by central position of cervix and descent of the presenting part of the fetus. This does not necessarily have to happen in the sequence stated above but it is most likely to occur in that sequence (7, 8, 11-16).

According to the first results of our survey, the highest number of examinees (46%) had the Bishop score 2, which means that at least one significant change was noted for one of the parameters or two smaller changes, while a lower number of examinees (40%) had the Bishop score 3, which indicates at least one larger change or a significant change of one parameter and/or several joined changes, i.e. several changed parameters. In 42% of examinees shortening of cervix was a leading parameter for the Bishop score, be it Bishop score 2, 3 or 4. It is followed by dilatation (32%) and softening (20%), while descent of the presenting part of the fetus (4%) and central cervical position (2%) were noted less frequently. Similar results were obtained by other researchers (14-16). Values of cervical length measurement were correlated with the Bishop scoring, tough the most frequent parameter registered by transvaginal cervical length measurement is the change of internal orifice of the uterus (42%), while shortening (32%) and dilatation of cervical canal (24%) are seen less frequently. These data correlate with data from the literature (13-16).

In 2011 the Society of Gynecologists and Obstetricians of Canada accepted recommendations of the Diagnostic Imaging Committee provided in the guidelines for transvaginal cervical length measurement in imminent preterm labor, and made recommendations for therapeutic procedure based on results of monitoring (17).

The APT was positive in 86% of examinees and 14% of patients from the control group. The evident statistically significant difference between the results obtained for the examined and control group correlates with data from the literature (15-16, 18-21). On a sample of 80 asymptomatic

pregnant women Balić et al. found the positive predicative test value of 44.4% and negative predicative test value of 98%, while the specificity of the Bishop score was 83.7%, and they concluded that in asymptomatic pregnant women the value of positive APT indicated the presence of imminent preterm labor (19).

Preterm delivery occurred in 60% examinees in present study, while in 40% of examinees the delivery was recorded as term labor. It is a statistically significant difference when compared with the control group where there was no record of any preterm labor. In 58% of examinees with preterm labor APT was positive. Reliability of the test for the prediction of preterm labor correlates with the data from the literature (18-23). However, the number of preterm deliveries would have been probably higher if the risk had not been noted on time and if other measures of preventing preterm labor had not been taken.

Timely identification of the problem and efficiency of the therapy are likely to be the reason for the fact that 63% of examinees in this study gave birth between the 34th and 36th week of gestation, i.e. in the gestation age of mild prematurity according to the gravity clinical presentation of prematurity. The screening for detection of elevated values of IGFBP-1 could set a diagnostic and therapeutic algorithm for monitoring the first and second trimester of pregnancy and ensure that measures are taken to prevent preterm labor and administer corticosteroid prophylaxis for lung maturity thus decreasing perinatal morbidity and mortality rate (7-8, 20-23).

In conclusion, IGFBP-1 is a valuable marker for preterm labor. It could be a useful part of diagnostic and therapeutic algorithm for monitoring during pregnancy and could be used to select patients who are in need of prophylactic administration of corticosteroid therapy for fetal lung maturation. Such an algorithm could be particularly important for small hospitals and obstetrics departments to prepare patients for transport "*in utero*" to centers with units for premature newborns care.

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IGFBP-1 marker cervikalnog sazrijevanja i prediktor prijevremenog porođaja

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SAŽETAK

Cilj Istražiti korelaciju između pozitivnih vrijednosti IGFBP-1 (>10 µg/l, Actim Partus Test, APT) i preranog sazrijevanja grlića kod prijetećeg prijevremenog poroda.

Metode Prospektivna studija, provedena u Domu zdravlja u Tuzli, Ginekološko-akušerskoj klinici Univerzitetskog kliničkog centra Tuzla i Općoj bolnici Tešanj, obuhvatila je 50 trudnica (ispitanice) (jedno čedo, 28-37 gestacijskih sedmica), kojima je dijagnosticiran prijeteći prijevremeni porod ultrazvučnom cerviometrijom i modificiranim Bishop-skorom, i 30 trudnica (kontrolna skupina) (jedno čedo, 28-37 gestacijskih sedmica) bez znakova prijetećeg prijevremenog poroda. Testirano je prisustvo IGFBP-1 u cervikalnom sekretu između 28. i 37. sedmice, sve dok test nije bio pozitivan.

Rezultati IGFBP-1>10 µg/L bio je pozitivan kod 43 (86%) ispitanice i 6 (20%) pacijentica iz kontrolne skupine (p=0.001). Kod 31 (62%) ispitanice APT je bio pozitivan u periodu 28-30. sedmice, kod 9 (18%) ispitanica drugo testiranje bilo je pozitivno u periodu 31-33. sedmice i kod 3 (6%) ispitanice treće testiranje je bilo pozitivno u periodu 34-37. sedmice. U kontrolnoj skupini kod 3 (10%) pacijentice test je bio pozitivan između 31-33. sedmice i kod 3 (10%) između 34-37. sedmice. Pri prvom testiranju (28-30. sedmica) APT je statistički signifikantno češće bio pozitivan kod ispitanica u odnosu na kontrolnu skupinu (p<0.05). Testiranjem u kasnijoj gestacijskoj dobi nije se statistički razlikovala učestalost pozitivnih nalaza između kontrolne i ispitivane skupine (p=0.08).

Zaključak Povećane razine IGFBP -1 u cervikalnom sekretu jako su povezane s prijevremenim porodom. Probir pomoću IGFBP mogao bi pomoći u preveniranju prijevremenog poroda i njegovih komplikacija.

Ključne riječi: insulinu slični proteini koji vezuju faktor rasta, prijevremeni porod, cervikalna sluz