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ORIGINAL ARTICLE

C-reactive protein as a predictor of threatening preterm delivery

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Abstract

OBJECTIVES: Preterm deliveries represent still one of the most important problems in contemporary obstetrics. They are associated with prematurity and higher rate of perinatal mortality and morbidity. During the last few years, the role of C-reactive protein (CRP) in prediction of threatening preterm delivery was emphasized. CRP is produced mainly inside the liver as a response to acute and chronic inflammatory processes.

AIM: The aim of this study was to assess relations between C-reactive protein, oxytocinase, izooxytocinase and vaginal culture in prediction of preterm delivery.

METHODS: This study was performed in the years 2000–2004 in the Department of Septic Obstetrics and Gynecology of Collegium Medicum of the Jagiellonian University. Some 389 patients hospitalized because of threatening preterm delivery or preterm delivery *in tractu* were enrolled into the trial.

CONCLUSION*:* C-reactive protein is a useful marker of threatening preterm delivery, overtaking the results of vaginal culture. CAP1 and CAP2 are effective biochemical markers in pregnancy monitoring.

Introduction

Preterm deliveries still belong to one of the most important problems in contemporary obstetrics. Prevalence of preterm deliveries in Poland ranges from 7.4 to 8.2% [17]. They are associated with prematurity and higher rate of perinatal mortality and morbidity. Management of the preterm delivery generally is based on the following schedule [10, 17, 21]:

1) inhibition of the contractile activity of the uterus,
2) choice of the mode of delivery,
3) intrauterine stimulation of maturation of the lungs of fetus by steroids,
4) cooperation between obstetricians and pediatrics in care of prematurely delivered infant.

Infections of vagina, cervix and urinary tract play significant role in etiology of preterm delivery [4, 6, 17, 18]. According to Divers M. and Lilford R., infections can cause up to 40 % of preterm deliveries [2].

There are some biochemical markers, which when elevated, may indicate an inflammatory process (fetal fibronectin, interleukin 6, interleukin 8, tumor necrosis factor or C-reactive protein) [3, 8, 17].

During the last few years, the role of C-reactive protein (CRP) in prediction of threatening preterm delivery was emphasized [1, 13, 15, 20]. CRP is produced mainly inside the liver as a response to acute and chronic inflammatory processes [15]. This is a part of nonspecific immunological response of human body. Production of CRP is induced by interleukin 1 (IL-1), interleukin 6 (IL-6) and tumor necrosis factor (TNF) [19]. It takes part in opsonization of microbes, classical activation of the complement and has influence on many human cells: macrophages, granulocytes, lymphocytes and platelets [19, 20].

During infection, there is increase of CRP within 2 to 5 hours before clinical symptoms of infection [13].

It is difficult to define the correct value of CRP in blood sample of pregnant women. Beck K. et al. concluded in their review that most authors choose the upper limit of CRP at 8–20 mg/l in normal pregnancy [1].

According to contemporary trends, the role of assessment of CRP in pregnant women with preterm contractile activity of the uterus becomes more significant in monitoring of the threatening preterm delivery. Hvilson H. et al. observed, that CRP level over 9.9 mg/l has positive predictive value in respect of higher risk of the preterm delivery [7].

Aim

The aim of this study was to assess relations between C-reactive protein, oxytocinase, izooxytocinase and vaginal culture in prediction of preterm delivery.

Material and methods

This study was performed in the years 2000–2004 in the Department of Septic Obstetrics and Gynecology of Collegium Medicum of the Jagiellonian University. Some 389 patients hospitalized because of threatening preterm delivery or preterm delivery *in tractu* were enrolled into the trial. Information about patients was collected retrospectively from information cards. Following factors were analyzed:

1) age,
2) parity,
3) gestational age at the time of hospitalization,
4) way of delivery, if patients delivered,
5) C-reactive protein (CRP) value in maternal blood sample (positive result was considered over 7ng/l),
6) results of microbiological examination of discharge from the vagina, if it was taken,
7) premature rupture of membranes,
8) using of steroids for the stimulation of fetal lung maturation,
9) level of oxytocinase and izooxytocinase if it was measured,
10) antibiotics treatment,
11) Apgar score of delivered infant at first minute.

Results of this study are presented in tables and graphs.

Results

The mean age of general population (N=389) was 27.52 ± 6.12 (range: 15–46); 49.87% patients were primagravidae. Gestational age during hospitalization was 29.63 ± 4.3 weeks (range: 23–36). Preterm rupture of membranes occurred in 45 patients (11.57). Positive results of CRP test were obtained for 162 women (41.65%). Antibiotics treatment was administrated to 203 pregnant women (52.19%). The most common antibiotics were penicillin and cefalosporyn (graph.1). Dexaven was used in 122 patients (31.36%). Summary about general population is presented in Table 1.

Preterm delivery occurred in 169 patients [n2] (43.44%) at 30.85 ± 4.34 gestational weeks (range: 22–36). 106 (62.72%) of patients underwent vaginal delivery and 63 (37.28%) cesarean section (Table 2). General condition of neonates at first minute after delivery according to Apgar score was 6.93 ± 3.06 points (Table 2). Positive value of CRP was in 96 women (56.80%). Patients who delivered preterm underwent therapy with steroids in 57 cases (33.73%). The mean value of oxytocinase was 5,6 ± 3,6 (range: 1,8–13,6) and izooxytocinase 4,6 ± 3,4 (range: 2,2–11,2). Antibiotics were administrated in 127 patients (75.15%). Preterm rupture of membranes occurred in 42 cases (24.85%). In 107 (63.31%) patients discharge from the vagina was cultured – 75 (70.09%) positive results. Escherichia coli were the most common microbe (graph.2).

The rest of 220 patients [n1] (56.56%) were hospitalized at 28.7 ± 4.03 of gestational weeks (range: 22–36). Inside this group positive results of CRP were obtained for 66 pregnant women (30%). Culture of discharge from the vagina was performed in 212 cases (96.36%) – 98 (46.23) positive results were collected. *Candida albicans* was the most common infectious factor (13.2%) (graph.3). Preterm rupture of membranes occurred in 3 cases (1.36%). 76 (34.55%) of pregnant women underwent antibiotics therapy; 65 (29.55%) steroids therapy. The mean value of oxytocinase was 4,4 ± 2,4 (range: 1,4–11,2) and 4 ± 1,8 (range: 1,8–8) of izooxytocinase.

Relation between patients with threatening preterm delivery [n1=220] and patients who delivered prematurely [n2=169] are shown in Table 3.

Comments

This study has shown that the elevated level of CRP is associated with an increased risk of preterm delivery (56.80% vs 30%). The similar indications were

presented by Mazor et al. These authors reported results from women in preterm delivery and found that the mean CRP level in a subgroup of women with a CRP level above 8mg/l was higher in women delivering preterm than in women delivering at term [13]. They also suggested that the mean gestational age on admission and the mean gestational age at delivery were significantly lower in women with increased CRP levels than in women with low CRP levels [13]. In our groups there were no difference in average age on admission and at delivery. According to Ghezzi F. et al. amniotic fluid CRP concentration over 110 ng/ml has a sensitivity of 80% and a specificity of 70% in prediction of spontaneous preterm delivery below 34 gestational weeks [5]. This study confirms the theory that subclinical intrauterine inflammatory process in gestation may be important for the occurrence of preterm delivery [5].

We observed that inside the second group, the antibiotics therapy was administrated more often than in the first one (75.15% vs 34.55%). It's probably related to the fact, that inside the second group preterm rupture of membranes occurred more often (24.85% vs 1.36%). There were not observed any differences in gestational age (28.7 weeks vs 30.85 weeks) and using of steroids between groups (29.55% vs 33.73).

One of the most useful biochemical markers in monitoring pregnancy is oxytocinase (CAP1) and izooxytocinase (CAP2). The first descriptions of oxitocin-oxytocinase axis and oxitocin-izooxitocinase axis were presented in 60's by Klimek R. [9]. These aminopeptidase's can regulate many physiological processes and inhibit contractile effect of oxytocine. Placenta is mainly responsible for their production [11]. According to Klimek R. and Klimek M. increasing level of CAP1 and CAP2 grants proper development of

Table 1. Basic information about general population (N=389).

Variables	Value
Patient age (years)	27,52±6,12 (15 – 46)*
Gestational age (weeks)	29,63±4,3 (22 – 36)*
Primagravida	194 (49,87%) **
Multigravida	195 (50,13%)**
PROM	45 (11,57%)**
Antibiotics therapy	203 (52,19%)**
Steroids therapy	122 (31,36%)**
Positive CRP	162 (41,65%)**
Preterm delivery	169 (43,44%)**

* mean value ± standard deviation (maximal value – minimal value)
** number of patients

Table 2. Patient's who preterm delivered (n2–169).

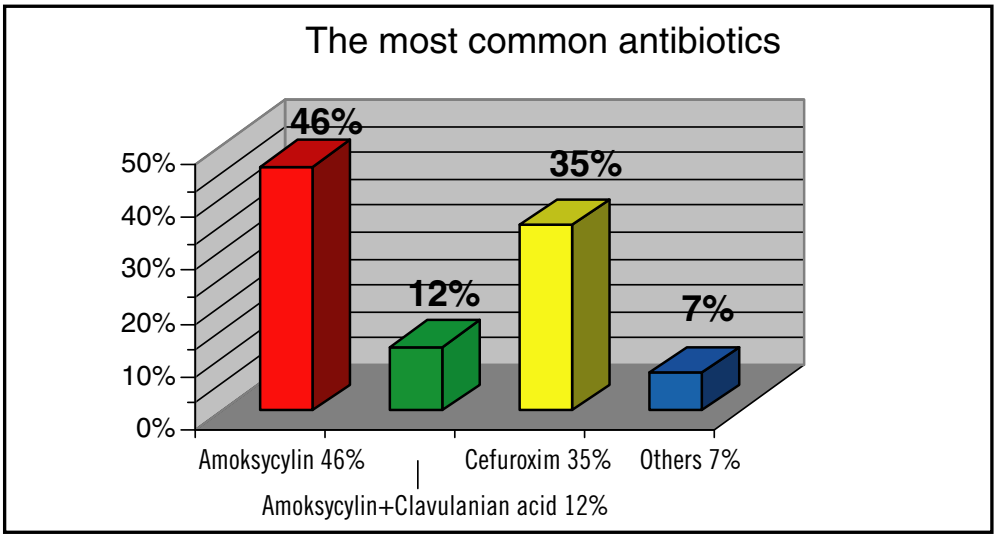
Variables	Value
Gestational age (weeks)	30,85±4,34 (22–36)*
Cesaream section	63 (37,28%)**
Vaginal delivery	106 (62,72%)**
Condition of neonates (Apgar score)	6,93±3,06 (0–10)*

* mean value ± standard deviation (maximal value – minimal value)
** number of patients

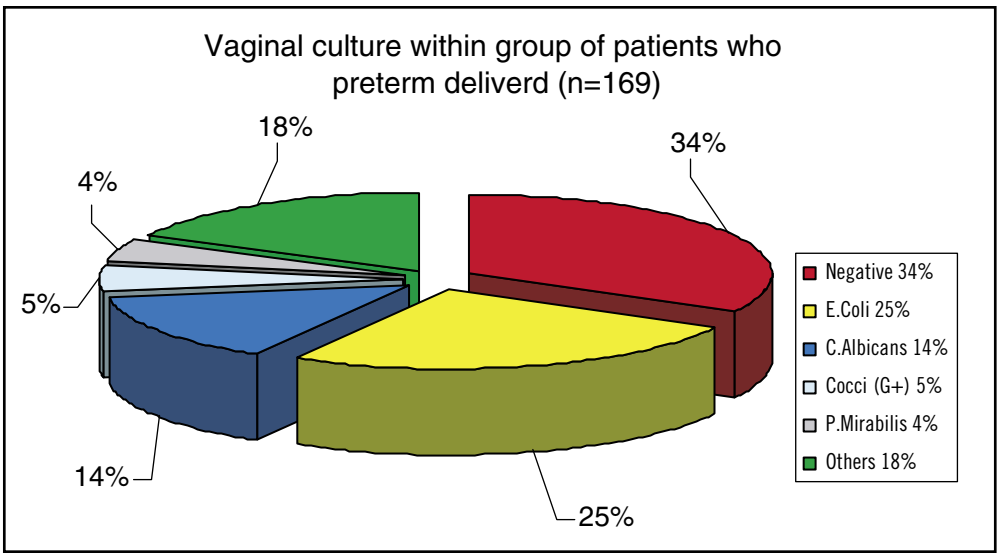
Table 3. Relation between patients with threatening preterm delivery (n1) and patients who preterm delivered (n2).

Variables	Value	
	n1	**n2**
Number	220 (56,56%)**	169 (43,44%)**
Gestational age (weeks)	28,7±4,03 (22–36)*	30,85±4,34 (22–36)*
Positive CRP	66 (30%)**	96 (56,80%)**
PROM	3 (1,36%)**	42 (24,85%)**
Positive vaginal culture	98/212 (46,23%)**	75/107 (70,09%)**
The most common pathogen	*Candida albicans*	*Escherichia coli*
Antibiotics therapy	76 (34,55%)**	127 (75,15%)**
Steroids therapy	65 (29,55%)**	57 (33,73%)**
Oxytocinase (CAP1)	4,4±2,4 (1,4–11,2)*	5,6±3,6 (1,8–13,6)*
Izooxytocinase (CAP2)	4±1,8 (1,8–8)*	4,6±3,4 (2,2–11,2)*

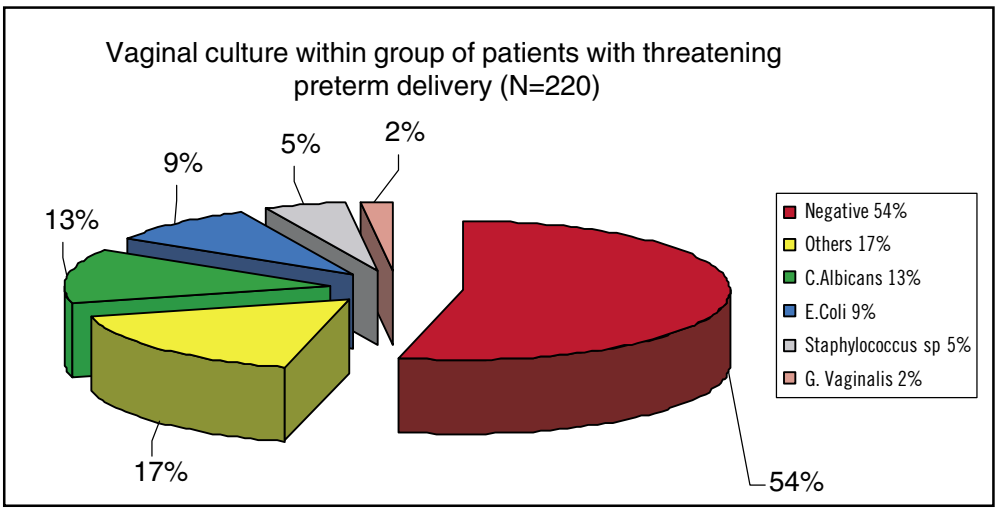
* mean value ± standard deviation (maximal value – minimal value)
** number of patients



Graph 1. The most common used antibiotics.



Graph 2. Vaginal culture within group of patients who preterm delivered (169)



Graph.3. Vaginal culture within group of patients with threatening of preterm delivery (220).

the pregnancy, while decreasing level allow to predict possibility of preterm delivery [11, 12]. The role of these two biochemical markers in pregnancy monitoring is unquestionable also in some obstetrics complication such as: pregnancy induced hypertension or gestational diabetes mellitus [9]. In our study there was no significant differences of CAP1 and CAP2 between groups. It indicates that the infectious factor played the most important role in induction of preterm delivery – 70.09% positive vaginal culture in patients who preterm delivered. Contractile activity of the uterus was not related to oxitocine but to inflammatory mediators such as: prostaglandins, leukotriens, tumor necrosis factor, interleukins and tromboxans. We claimed that positive CRP overtake positive vaginal culture and allow to administrate antibiotics therapy quicker than normal. It prevents from dissemination of infectious factor and obstetrical complications.

Effectiveness of assessment C-reactive protein in pregnancy monitoring is confirmed by many authors in different ways. Redman et al. postulated that CRP concentration is higher in patients in whom preeclampsia subsequently develop than in those patients who had uncomplicated pregnancy [16]. Minakami H. et al. showed relation between CRP level, white blood cell count and cerclage. They concluded, that preoperative concentration of CRP below 4 mg/ml, white blood cell count below 14000/ml and dilation of the cervix below 4 cm prolong pregnancy after cerclage [14]. Hvilson G. et al. claimed, that a high CRP level at the beginning of a pregnancy is associated with nearly twofold increased risk of preterm delivery, however the clinical value at this point is still limited [7].

The role of CRP in prediction of preterm delivery is unquestionable, specially when infectious factor is responsible for induction of preterm contractile activity of uterus. Assessment of CRP should be joined with CAP1 and CAP2 to increase the quality of prenatal care.

Conclusions

1) C-reactive protein is a useful marker of threatening preterm delivery, overtaking the significance of vaginal culture.
2) CAP1 and CAP2 are effective biochemical markers in pregnancy monitoring.

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