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Evaluation of C-reactive protein (CRP) plasma concentration among women during labour and in early puerperium

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Abstract

Objectives: Calculation and analysis of CRP plasma concentration among women during labour and in the second day of puerperium in various clinical situations.

Material and methods: 317 participants about estimated due date (EDD) were included to the study and then divided into four groups:

1. Women with labour onset after previous rupture of membranes and spontaneous vaginal delivery – PROM (n= 97)

2. Women with labour onset at intact membranes and spontaneous vaginal delivery – non - PROM (n= 133)

3. Women who delivered by caesarean section for elective indications – ELCS (n= 58)

4. Women who delivered by caesarean section for emergency indications – EMCS (n= 29)

Venous blood sampling for CRP plasma concentration evaluation was done in the course of labour or strictly before elective caesarean section and then, subsequently, on the second day of puerperium.

Results: In all groups postdelivery CRP plasma level was significantly higher than in the course of labour ($p < 0,001$). CRP plasma concentration during labour in women who finally delivered vaginally was significantly higher in case of amniotic fluid leakage before the onset of labour, in comparison with this found in women with intact membranes (PROM = 6,30 mg/L vs non-PROM = 2,50 mg/L, $p < 0,05$).

There was a significant difference between groups who gave birth by caesarean section. CRP level was lower in women who had elective caesarean section (EMCS 6,30 mg/L vs ELCS 4,15 mg/L, $p < 0,05$).

In our study we found significantly higher puerperal CRP plasma level among women after caesarean section, as well for emergency as for elective indications, than in women after vaginal delivery, independently from ruptured or intact foetal membranes ($p < 0.001$).

There was no difference in the CRP concentration on the 2nd of puerperium between two groups of women who gave birth vaginally, with or without membranes rupture before labour onset (PROM vs non-PROM, NS), same as between those who had caesarean delivery (ELCS vs EMCS, NS).

Conclusions:

1. The increase of CRP plasma concentration follows the parturition and it is significantly higher after caesarean than after vaginal delivery
2. Intrapartum CRP level is higher in women with amniotic fluid leakage before the onset of labour, than in those with intact foetal membranes, what can suggest the participation of inflammatory response in the labour beginning with membranes rupture
3. CRP concentration on the second day of puerperium is similar in women after elective and emergency caesarean section
4. The assessment of CRP concentration as the only test in early puerperium is not useful for the decision making about antibiotic therapy

5. Because of early discharge of women from the hospital, as well after vaginal as caesarean delivery, the usefulness of CRP concentration assessment in early puerperium decreases progressively

Key words: acute phase reaction, C-reactive protein, caesarean section, delivery, labour, early puerperium

Introduction

The factors like bacterial or viral infection, mechanical or thermal trauma, neoplastic tumour growth or tissue ischemia leading to its necrosis, cause early non-specific reaction called acute phase response. It is accompanied with sharp increase in production of some plasma protein. These are mainly glycoproteins, synthetized in the liver, which are called acute phase proteins. They work to restore homeostasis of the system via different mechanisms, like inhibition of proteinases activity, blood coagulation controlling, binding and neutralization of pathogens or transport of different metabolites [1]. The criterion to include any protein to acute phase group is its plasma concentration change by at least 25% in the course of acute phase response.

One of cardinal acute phase proteins is C-reactive protein (CRP). It was first described in 1930 in patients suffering from pneumococcal pneumonia. CRP is a glycoprotein containing 206 amino acids. It is synthetized mainly in hepatocytes in response to cytokine action. Normal CRP plasma concentration in human does not exceed 10 mg/L. Its increase is one of the most sensitive acute phase parameters in tissue injury or inflammation [2]. CRP level begins to rise 6 – 8 hours after the stimulus, reaching its maximum within 24 – 72 hours. Short half-life of the CRP molecule makes its concentration reduction quick right after the factor of causation cease [3]. CRP is nonspecific marker of inflammation not only caused by different microbes, but also in connective tissue systemic diseases, tissue injury, combustion, neoplasm diseases and myocardial infarction.

Material and methods

The study participants were 317 women who gave birth in Department of Obstetrics and Gynaecology of Pomeranian Medical University from November 2014 to November 2016. The consent of the bioethics commission for the research was obtained and the project was approved by a resolution KB-0012/111/14.

The participants were divided into four groups, described in Table 1.

Table 1. Clinical material

Group symbol	Group size (n)	Group characteristics
PROM	97	women about EDD, with labour onset after membranes rupture and spontaneous vaginal delivery
non-PROM	133	women about EDD, with labour onset at intact membranes and spontaneous vaginal delivery
ELCS	58	women about EDD, who delivered by caesarean section for elective indications
EMCS	29	women about EDD, who delivered by caesarean section for emergency indications

Venous blood sampling for CRP plasma concentration calculation was done in the course of labour or strictly before elective caesarean section and, subsequently, on the second day of puerperium.

CRP plasma level concentration was measured with COBAS INTEGRA 800 C-Reactive Protein test (Latex CRPLX). The test works as an immunoenzymatic latex-enhanced method, in which human CRP agglutinates with latex particles covered with monoclonal anti-myoglobin antibodies. The precipitate is assessed with immunoturbidimetric method with the length of the light wave 552 nm. Normal plasma CRP concentration in pregnant women is below 10 mg/L.

Statistical differences analysis between groups was made with U Mann-Whitney test. The result was considered significant at $p < 0,05$. Results at $p < 0,01$ were considered very significant and those at $p <0,001$ – highly significant. Statistical analysis was made with dedicated programme STATA 11.

Results

Intrapartum CRP plasma level was significantly higher among women from PROM group than in those from non-PROM and ELCS groups (p , 0,05), and similar among women from EMCS group. Significantly higher level of this parameter was noticed in EMCS than in ELCS group

(p < 0,05). CRP intrapartum plasma level in non-PROM group did not differ significantly from those in ELCS and EMCS (Tab. 2).

Table 2. Comparison of intrapartum CRP plasma levels between groups

Group	n	CRP 1 (mg/L)				
		Minimum	Maximum	Q1	Median	Q3
PROM	97	0,70	141,90	3,20	6,30	11,47
non-PROM	133	0,40	37,10	2,50	4,50	8,60
ELCS	58	0,20	98,90	2,50	4,15	6,30
EMCS	29	1,10	46,10	4,10	6,30	9,00

PROM vs non-PROM: **p<0,05** PROM vs ELCS: **p<0,05** PROM vs EMCS: NS

non-PROM vs ELCS: NS non-PROM vs EMCS: NS ELCS vs EMCS: **p<0,05**

Puerperal CRP plasma concentration was significantly lower in women from PROM group in comparison with those from ELCS and EMCS (p < 0,001), and similar with non-PROM. There was also highly significant difference of CRP levels between non-PROM and ELCS and EMCS groups (p < 0,001). In both groups after caesarian delivery CRP level was higher, while there was no significant difference between ELCS and EMCS (Tab. 3).

Table 3. Comparison of puerperal CRP plasma level between groups

Group	n	CRP 2 (mg/L)				
		Minimum	Maximum	Q1	Median	Q3
PROM	97	7,36	96,11	13,10	24,60	39,50
non-PROM	133	3,50	94,90	17,95	27,30	39,50
ELCS	58	16,70	152,30	50,60	76,20	92,70
EMCS	29	20,10	244,00	67,00	93,80	110,40

PROM vs non-PROM: NS PROM vs ELCS: **p<0,001** PROM vs EMCS: **p<0,001**

non-PROM vs ELCS: **p<0,001** non-PROM vs EMCS: **p<0,001** ELCS vs EMCS: NS

Puerperal CRP plasma concentration significantly exceeded the intrapartum values of this parameter in all groups ($p < 0,001$) (Tab. 4).

Table 4. Comparison of intrapartum and postpartum CRP plasma level between groups

Group	n	CRP 2 (mg/L)		CRP 1 (mg/L)		CRP 2 – CRP 1 (mg/L)		p
		Mean	SD	Mean	SD	Mean	SD	
PROM	97	28,71	18,42	9,87	15,74	18,84	20,68	< 0,001
non-PROM	133	31,68	18,72	6,44	6,03	25,25	17,25	< 0,001
ELCS	58	76,85	30,68	8,23	14,51	68,62	34,28	< 0,001
EMCS	29	96,11	51,20	8,69	9,00	87,42	50,80	< 0,001

Discussion

In all groups puerperal CRP plasma concentration was significantly higher than this during labour. The increase in CRP plasma level strictly after delivery, no matter operational or vaginal, it was also noticed by other researchers [4, 5]. It shows that acute phase response follows not only caesarean section but also natural delivery [6]. In practice, postdelivery rise of C-reactive protein level as isolated parameter, particularly reaching three-digit value, especially after caesarean section, is often misinterpreted as a proof of infection and then the indication to antibiotic therapy. According to Bolz et al. the assessment of plasma CRP level as the only diagnostic test cannot be the reason for therapeutic decisions in puerperal patients [6].

The increase in CRP plasma concentration in the pregnant depends on various mechanisms in each stage of gestation, like interleukin 6 (IL-6) production in monocytes and macrophages, some changes caused by the blastocyst implantation, necrotic changes in maturing placenta, and increasing production of oestrogens. Meeus et al. showed that right after the onset of labour, which they find analogic to surgical procedure, maternal CRP level was significantly higher than in the non-pregnant. They also described several-fold increase in CRP concentration on the 3rd day of puerperium [7]. Cicarelli et al. found CRP plasma level in women 24 and 60 hours postpartum, as well after vaginal as caesarean delivery, significantly higher than the intrapartum and before the onset of labour [8]. In the authors' opinion, the acute phase response protects maternal system from the consequences of injuries during labour and C-reactive protein itself enhances phagocytosis of bacteria and supports dead cells removal from the organism. The

prospective observation of Deballon et al in Dijon Hospital in France showed that CRP level on the 2nd and 4th post operational day can be useful predictor of septic complications. The cut-off point was 125 mg/L with sensitivity 81,8% and negative predictive value 95,8% [9]. Chilesche calculated CRP plasma level in 240 women on the 2nd and 4th day after caesarean delivery, finding it higher than 100 mg/L in more than 64%, and independent from patient's age, parity, presence of HIV infection and antiretroviral therapy, urgency of caesarean section, complications during surgery and antibiotic prophylaxis [10]. The author claims that isolated CRP level exceeding 100 mg/L on the 2nd day after caesarean delivery is not related to the infection, but the increase in this parameter after the 3rd puerperal day suggests the development of infective complications. Because of it, the author proposes to evaluate CRP on the 4th day postdelivery.

According to Baez et al., increased CRP plasma level can work as an easy and cheap test to diagnose infections and postoperative inflammatory complications [11]. Yet, the study by Cole et al. in the United Kingdom showed that isolated CRP plasma level is insufficient as a tool for detection of early postoperative complications during the first three days after the procedure, because the value of the parameter rises in response to surgical tissue injury, which makes the result interpretation difficult [12]. The conclusion is to use CRP for diagnostics of infection beyond 3rd day after surgery. The research by Coulter and White showed the postoperative increase of CRP level in patients having had different operations, beginning after 4-6 hours and reaching 25 – 35 mg/L as its maximum within 48 – 72 hours [13, 14]. Further increase of the parameter value can suggest the infection {15, 16]. Keski-Nisula et al. found CRP concentration higher than 90 mg/L beyond 3rd day after surgery only in 5% women after elective caesarean section [17]. Today most of puerperal patients, having had vaginal or caesarean delivery, is discharged from obstetrics department on the 2nd postpartum day. Therefore the usefulness CRP level as a diagnostic tool in early puerperium decreases.

In the literature there is very few reports on CRP assessment in women during labour on or about estimated due date. Our research showed that intrapartum plasma CRP value during vaginal labour is significantly higher among women who experienced amniotic fluid leakage before the onset of labour than in those with intact membranes (PROM vs non-PROM). Similar was the observation by Wiser et al., who noticed increased CRP level few days before the onset of labour in more than 66% of women who began their parturition from the rupture of membranes. This finding suggests the inflammation to participate in the mechanism of labour [18].

In our research intrapartum CRP concertation in women after preterm membranes rupture exceeded this among women whose blood was sampled before elective caesarean section (PROM vs ELCS). A significant difference was also found between both groups who gave birth by caesarean delivery (ELSC vs EMCS). CRP was lower in group of elective caesarean section which yields from lacking acute phase response stimulation. Keski-Nisula et al. obtained similar results (17).

Our study showed significantly higher CRP plasma concentration on the 2nd day postpartum in women who had caesarean section, as well as for emergency indications (EMCS) as for the elective ones (ELCS), compared with those who delivered vaginally, with (PROM) or without the rupture of membranes before the onset of labour (non-PROM). There is not many reports in the literature on the comparison of CRP level depending on the mode of delivery.

There is no doubt that tissue injury is more severe in caesarean than in vaginal delivery. It confirms the observation of higher CRP plasma level in the parturient who experienced more extensive tissue damage, even in the absence of any infection. It was showed that after vaginal delivery CRP concentration reaches its maximum on the 1st day of puerperium, while on the 2nd day after caesarean section. Another observation was about 2,5 folds higher CRP level after non-complicated caesarean delivery than after vaginal one [17, 19]. Higher CRP level was correlated with longer duration of surgical procedure or vaginal labour and delivery, and also with vacuum extinctor use, which should be explained as a result of extensive and lasting tissue trauma [19]. However Erkaya et al. did not find significant difference between CRP levels in women who delivered by caesarean section and those who gave birth vaginally, but yet they took the blood samples as early postdelivery as six hours [20]. Adler et al., calculating CRP plasma concentration on the 3rd day of puerperium, found three-fold increase in the parameter in women who delivered vaginally and even forty-fold CRP rise in those after caesarean section, compared with the late 3rd trimester level [5]. Cicarelli et al. found significantly higher CRP concentration in women having had caesarean delivery both after 24 and 60 hours, compared with those who gave birth vaginally [8]. Meus et al. in test conducted 24 hours postpartum noticed the CRP increase to 60 mg/L, with following decrease to 25 mg/L after 48 hours in women who delivered vaginally, while the participants after caesarean section demonstrated constant increase in CRP value up to 150 mg/L within 2 days after the procedure [7].

In our research we did not found significant difference on the 2nd day of puerperium CRP level between women who gave birth vaginally with or without previous rupture of membranes (PROM vs non-PROM), as well as between those after caesarean birth giving (EMCS vs ELCS). Keski-Nisula et al. obtained different results, finding significantly lower 2nd day

postpartum CRP level in participants after elective caesarean delivery, compared with those who had emergency surgical delivery indicated during vaginal labour, independently from present or absent predelivery amniotic fluid leakage. The authors claim this finding to be the result of subclinical infection accompanying the labour. This applies especially to women with amniotic fluid leakage, those with prolonged delivery, and having multiple vaginal examination during their labour.

Conclusions

1. The increase of CRP plasma concentration follows the parturition and it is significantly higher after caesarean than after vaginal delivery
2. Intrapartum CRP level is higher in women with amniotic fluid leakage before the onset of labour, than in those with intact foetal membranes, what can suggest the participation of inflammatory response in the labour beginning with membranes rupture
3. CRP concentration on the second day of puerperium is similar in women after elective and emergency caesarean section
4. The assessment of CRP concentration as the only test in early puerperium is not useful for the decision making about antibiotic therapy
5. Because of early discharge of women from the hospital, as well after vaginal as caesarean delivery, the usefulness of CRP concentration assessment in early puerperium decreases progressively

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