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The Pharma Innovation

ISSN: 2277- 7695
TPI 2015; 4(2): 04-06

www.thepharmajournal.com
Received: 03-02-2015
Accepted: 15-03-2015

Pertseva T. O.
State Establishment "Dnipropetrovsk Medical Academy of Health Ministry of Ukraine", Department of Therapy and Endocrinology, Ukraine, Dniepropetrovsk, 49000, 13, Batumskaya str.

Kireyeva T. V.
State Establishment "Dnipropetrovsk Medical Academy of Health Ministry of Ukraine", Department of Therapy and Endocrinology, Ukraine, Dniepropetrovsk, 49000, 13, Batumskaya str.

Kravchenko N. K.
State Establishment "Dnipropetrovsk Medical Academy of Health Ministry of Ukraine", Department of Therapy and Endocrinology, Ukraine, Dniepropetrovsk, 49000, 13, Batumskaya str.

Correspondence:
Kravchenko N. K.
State Establishment "Dnipropetrovsk Medical Academy of Health Ministry of Ukraine", Department of Therapy and Endocrinology, Ukraine, Dniepropetrovsk, 49000, 13, Batumskaya str.

CAP in pregnant: the connection between inflammatory biomarkers and efficacy of antibacterial treatment

Pertseva T. O., Kireyeva T. V., Kravchenko N. K.

Abstract
Over the past three decades, the number of drugs used during pregnancy increased by 60%. Cluster analysis of COPSAC 2010 study showed that antibiotics were prescribed to 21% of included pregnant women to treat lower respiratory tract infections (LTRI). The most dangerous for both mother and fetus, but although the most rare is community-acquired pneumonia (CAP). However, no antibiotic prescribed for CAP applies to category "A" according to FDA classification, which means none of them is safe for use in the gestational period.
Aim. to study changes in PCT level and leukocyte count (Lc) in terms of evaluating the efficacy of antibiotic therapy (ABT) in pregnant with CAP.
Materials and methods. The study included 35 women with a diagnosis of CAP (Group A) and a control group of 15 healthy pregnant (Group B). Quantitative determination of the PCT level in the serum was performed by chemiluminescence method. In Group A PCT and Lc were measured on admission and on the 5th day of therapy.
Results. The study showed that PCT level measured on admission, unlike the Lc, was higher than in Group B ((Med [25–75%]) 0,18 [0,11–0,25] ng/ml vs 0,047 [0,036 – 0,071], p=0,000). And decreased on the background of ABT to 0,06 [0,04-0,08] ng/ml (p=0,000).
Conclusions. Revealed changes in the PCT levels in respond to antibiotic therapy in pregnant with CAP can be used as an objective method to evaluate the efficacy of treatment. This can reduce the duration of therapy and thus reduce possible negative influence on fetus.

Keywords: community-acquired pneumonia, pregnancy, procalcitonin, leukocyte count, antibiotics.

1. Introduction
Over the past three decades, the number drugs used during pregnancy increased by 60%, and this figure does not take into account the use of vitamins and mineral complexes. These data were obtained by A. A. Mitchell *et al.*, 2011 from the cluster analysis of questioning of more than 30 thousand pregnant during the period from 1976 to 2008 [1].
At the same, time the Copenhagen Prospective Study on Asthma in Childhood (COPSAC 2010) J. Stokholm *et al*. showed that antibiotics were prescribed to 21% (148) of the 706 pregnant women included in the study because of the lower respiratory tract infections (LTRI).
It should be noted that of all LTRI the most dangerous for both mother and fetus, but although the most rare is community-acquired pneumonia is (CAP).
Moreover, unlike the more prevalent acute bronchitis, CAP is an absolute indication for antibiotics use either as monotherapy or in combination. The usual course of treatment lasts from seven to ten days. However, no antibiotic applies to category "A" according to FDA classification, which means none of them is safe for use in the gestational period [2].
Therefore, prescribing medications, and in particular antibiotics, in pregnancy is a difficult medical problem because it is necessary not only to fight the infection, but also to minimize the possible adverse effects on the fetus.
One of the most effective methods to reduce frequency of antibiotic prescription and duration of treatment is by using procalcitonin (PCT), as an objective indicatior of presence and severity of bacterial inflammation.
In 2012, Nilam J. Soni *et al*. had analyzed 18 clinical trials that compared the efficacy of procalcitonin-guided initiation and / or discontinuation of antibiotics in different groups, including patients with respiratory tract infections, to standard therapy.
Analysis showed that the use of PCT in patients with LTRI as in patients from ICU had the strongest evidence base. PCT-guided therapy in above-mentioned groups of patients reduced

Frequency of prescription and duration of antibiotic use in comparison to standard clinical guidelines [3].
At the same time, authors noted that pregnancy was one of the excluding criteria in all of the analyzed studies. Which makes impossible to use the obtained data in pregnant patients with LTRI and determines the need of further research [4].
Recently a number of articles containing the results of PCT study in pregnancy have been published. They were dedicated to determination of PCT levels in uncomplicated pregnancy and to the possibility of its use in preeclampsia and urinary tract infections [5, 6].
For example, Pacolat C *et al.*, 2011 in their study of PCT at different stages of uncomplicated pregnancy showed that the levels of this marker in I, II and III trimester did not exceed the reference values for non-pregnant women of childbearing age [7]. This indicates the fact that it is possible to develop criteria for antibiotic initiation and/or discontinuation in pregnant with LTRI based on PCT level.

Aim: to study changes in PCT level and leukocyte count (Lc) in terms of evaluating the efficacy of antibiotic therapy (ABT) in pregnant with CAP.

2. Materials and methods. The study included 35 women with a diagnosis of CAP (Group A) and a control group of 15 healthy pregnant (Group B). All CAP patients were admitted to specialized obstetrical department in the period from October 2013 to November 2014. Both groups were comparable by age and gestational terms (Table 1).

Table 1:

Groups	Age Med [25–75%] (years)	Gestational terms Med [25–75%] (weeks)	p
A	25 [19–30]	30 [27–33]	<0,05
B	31 [25–37]	35 [34–37]	

In all patients from Group A, the diagnosis of CAP was confirmed by chest X-rey and assessed as not severe CAP according to the Order of Ministry of Health of Ukraine № 128. Ten women had a history of upper respiratory tract infection prior to the CAP development. None of the pregnant included in the study received antibiotics before hospital admission.
Quantitative determination of the PCT level in the serum was performed by chemiluminescence method. In Group A PCT and Lc were measured on admission (PCT-1, Lc- 1) and on the 5th day of therapy (PCT-2, Lc-2).
All women were informed about the purpose and methodology of the study and signed an informed consent.
Statistical analysis was performed using STATISTICA version 6.0 [7].

3. Results and discussion
The study showed that PCT level measured on admission to clinic was (Med [25–75%]) 0,18 [0,11–0,25] ng/ml. That did not exceed 0,25 ng/ml – the threshold for prescribing antibiotics developed in previous studies, which excluded pregnant.
This result may be due to physiological immunosuppression that develops in pregnancy, as well as to a small area of the lung tissue involved in inflammatory process observed in all patients of the study group.
In addition, it is important to take into account that all women were admitted on early stages of the disease development due to high alertness of doctors towards pregnant women with symptoms of LTRI. This, combined with the use of highly sensitive methods of quantitative determination of PCT, can be another reason for the low values of studied marker we have obtained.
If the upper-mentioned low levels of PCT were identified in non-pregnant women, the decision on initiation of antibiotic therapy would be delayed. Since the PCT level below 0,25 ng/ml in the general population indicates a self-limiting infection that does not require antibiotics [8].
But in pregnancy even a small focus of bacterial inflammation can lead to complications such as infection of the amniotic fluid and preterm delivery, thus the initiation of antibacterial therapy was based on standard clinical criteria, according to the Order of Ministry of Health of Ukraine № 128 [9].
Data on PCT and Lc changes in group A and their comparison to Group B are shown in Table 2.

Table 2:

Groups	PCT-1 Med [25–75%] ng/ml	PCT-2 Med [25–75%] ng/ml	Lc-1 Med [25–75%] $*10^9$ /l	Lc-2 Med [25–75%] $*10^9$ /l
A	0,18 [0,11 0,25]*∧	0,06 [0,04-0,08]	11,0 [8,2 – 14,0]#∨	8,6 [6,8 – 10,0]
B	0,047 [0,036 – 0,071]		9,8 [7,8 – 11,7]	

Notes: * - p<0,05 between visits by Wilcoxon
∧ - p<0,05 between groups by Mann-Whitney
- p <0,05 between visits by Wilcoxon
∨ - p<0,05 between groups by Mann-Whitney

Only PCT, unlike leucocyte count, showed statistically significant difference both in comparison between groups and visits.
The credibility of the detected changes in PCT levels shows that this marker reflects the response of pregnant with CAP to antibiotic therapy. Which indicates that PCT can be used as an objective indicator to regulate the duration of antibiotic therapy in women during pregnancy.

4. Conclusions
1. A lower level of PCT in pregnant women, compared to the criteria developed for the general population, does not exclude the presence of the CAP. It can indicate the small area of the lung tissue involved in inflammatory process and early stage of the disease.
2. The possibility of using PCT as an objective indicator for antibiotic therapy initiation in pregnant women with CAP requires further investigation.
3. Revealed changes in the PCT levels in respond to antibiotic therapy in pregnant with CAP can be used as an objective method to evaluate the efficacy of treatment. This can reduce the duration of therapy and thus reduce possible negative influence on fetus.

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