THE LOCAL IMMUNE PROFILE OF THE WOMAN AND DIFFERENT SCENARIOS OF PRETERM DELIVERY

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Preterm delivery (PD) is one of the central challenges faced by contemporary obstetrics. There has been growing evidence of the role of the innate immune response in triggering infection-associated preterm labor. Our study aimed to investigate the local immune status of women in different PD scenarios. The study enrolled 77 pregnant women; 25 of them constituted the control group (delivery at term). The experimental group was divided into two subgroups based on the PD type: Subgroup 1A included 28 women with spontaneous premature rupture of membranes in the absence of active labor, and Subgroup 1B included 24 women who went into genuine preterm labor. Cervical scrape specimens were collected from all patients to determine the level of expression of the following innate immunity genes: *IL1B*, *IL10*, *IL18*, *TNFa*, *TLR4*, *GATA3*, *CD68*, and *B2M*. The tests were performed using the ImmunoQuantex assay by DNA-Technology, Russia. Compared to the genuinely preterm women from Subgroup 1B and the controls, the women with premature rupture of membranes demonstrated statistically significant reduction in the expression of *TLR4* and *GATA3* and a higher inflammatory index (Me = 99.5 %, $p < 0.01$). No significant differences in these parameters were observed between Subgroup 1B and the controls. The revealed differences in the local immunity profiles of women indicate that pathways leading to the scenarios of premature labor studied in this work are not the same.

Keywords: preterm delivery, local immune status, innate immunity, systemic inflammatory response syndrome, cytokines

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СОСТОЯНИЕ ЛОКАЛЬНОГО ИММУННОГО СТАТУСА ПРИ РАЗЛИЧНЫХ ВАРИАНТАХ ПРЕЖДЕВРЕМЕННЫХ РОДОВ

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Преждевременные роды (ПР) — одна из наиболее актуальных проблем современного акушерства. Появляется все больше данных о роли элементов врожденного иммунитета в развитии преждевременных родов инфекционного генеза. Целью нашего исследования являлось изучение особенностей состояния локального иммунного статуса при различных вариантах ПР. В исследовании приняли участие 77 беременных женщин, из которых 25 составили контрольную группу (своевременные роды). Основная группа была разделена на две подгруппы по типу ПР: 28 рожениц с преждевременным излитием вод при отсутствии регулярной родовой деятельности (подгруппа 1А) и 24 роженицы с истинными преждевременными родами (подгруппа 1Б). У всех пациенток определяли уровень экспрессии генов врожденного иммунитета: *IL1B*, *IL10*, *IL18*, *TNFa*, *TLR4*, *GATA3*, *CD68*, *B2M*. Биоматериал — соскоб из цервикального канала — анализировали с помощью тест-системы «ИммуноКвантэкс» («НПО ДНК-Технология», Россия). Выявили достоверное снижение экспрессии генов *TLR4* и *GATA3*, а также более высокий индекс воспаления (Me = 99,5 %, $p < 0,01$) у женщин с преждевременным разрывом плодных оболочек при недоношенной беременности в сравнении с женщинами из подгруппы 1Б с истинными ПР и контрольной группы. Достоверных различий по этим показателям между подгруппой 1Б и контрольной группой не обнаружили. Выявленные нами различия в состоянии локального иммунного статуса при двух вариантах ПР свидетельствуют о разных механизмах их развития.

Ключевые слова: преждевременные роды, локальный иммунный статус, врожденный иммунитет, синдром системного воспалительного ответа, цитокины

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One of the biggest concerns of contemporary obstetrics is preterm delivery [1]. Its medical and social significance cannot be overestimated. PD is a major cause of neonatal morbidity and mortality, accounting for 60–70 % of early neonatal deaths and for up to 50 % of neurological complications; stillbirths are 8–13 times more common among preterm babies than among full-term neonates [2, 3].

In spite of improvements in medical care, preterm birth rates are not going down; moreover, some countries are reporting their increase. According to WHO, 15 million children are born preterm (before 37 completed weeks of gestation) annually [4]. Globally preterm birth rates range from 5 to 18 %. In Russia they are 6 to 15 %, depending on the region [5].

The majority of all PD cases (70 to 80 %) are spontaneous; others are due to induction necessitated by health conditions in either a woman or a fetus [6, 7]. Women at risk of spontaneous delivery can go into genuine active labor with their amniotic sac intact (genuine preterm labor accounts for 40 to 50 % of all cases of spontaneous PD) or suffer from premature rupture of membranes in the absence of active labor [8, 9].

According to the literature, about 40 % of all PD cases are associated with infection-related factors [7, 8, 10]. The nonspecific systemic inflammatory response (SIR) to infection is thought to be the leading mechanism in the pathogenesis of PD. In patients with SIR, local tissue damage in the area of pathogen invasion triggers a cascade of systemic reactions. This process is associated with the dysfunction of the innate and adaptive immunities and is manifested as an imbalance between pro- and anti-inflammatory cytokines. Currently the role of cytokines in PD is actively studied [11]. There is evidence indicating the connection between the elevated levels of pro-inflammatory cytokines in the cervical canal and a possible risk of PD [12]. Information about the local immunity status of a patient can elucidate molecular and biological pathways to PD.

This study aimed to describe the local immune status of the endocervix in women with different types of premature delivery.

METHODS

Our study was conducted at the facilities of Dzerzhinsk Center for Perinatology (Nizhny Novgorod Region) and enrolled 77 parturients admitted to the Center over the period from 2016 to 2017. The patients were distributed into two groups. The main group included 52 women with spontaneous preterm labor (22–36 completed weeks of gestation). The second group included 25 controls who delivered fullterm. The main group was subdivided into two subgroups depending on the PD scenario. Subgroup 1A included 28 pregnant females with premature rupture of membranes (PROM) in the absence of active labor; Subgroup 1B included 24 parturients who went into active labor with their amniotic sac intact. The age of the participants ranged from 19 to 41 (mean age was 29.8 ± 5.0 years). No significant difference between the groups was detected regarding age ($p > 0.05$).

The inclusion criterion applied to both groups was singleton pregnancy. Among the exclusion criteria were multiple pregnancy and severe congenital anomalies of the fetus.

We analyzed the socioeconomic status of the patients, their obstetric and gynecologic history and medical background in general, including the episodes of acute infection during pregnancy; patients' height and weight were measured, and the body mass index was calculated.

To evaluate the local immune status of the participants, endocervical scrapes were collected using sterile disposable scrapers. The specimens were placed into 1.5ml plastic tubes containing 500 µl RNA-stabilizing medium. Total nucleic acids were extracted using Proba NK reagent kit (DNA-Technology, Russia). DNA/RNA extraction was followed by reverse transcription (ImmunoQuantex, DNA-Technology, Russia) to synthesize complementary DNA from a messenger RNA template and subsequently amplify it by polymerase chain reaction (PCR). Then levels of mRNA expression were computed for innate immunity genes, namely *IL1B*, *IL10*, *IL18*, *TNFa*, *TLR4*, *GATA3*, *CD68*, and *B2M*. Inflammation or the lack of thereof was inferred from the inflammation index (II) value calculated from the results of the gene expression analysis. II>60 % indicated inflammation; II<50 % indicated the absence of inflammatory response. II values between 50 and 60 % were considered a grey area meaning that the possibility of inflammation could not be ruled out.

Data were statistically analyzed using Microsoft Excel 2010 (the AtteStat add-on) and Statistica v10 (StatSoft, USA). Quantitative data (expression of genes) were presented as a median (Me) and an interquartile range (the upper (0.25) and lower (0.75) quartiles). To compare differences between the groups, the Mann-Whitney U test was applied. Qualitative characteristics were evaluated using Pearson's chi-squared test with Yates' correction. For <5 frequencies a two-tailed Fisher's exact test was used (p). To evaluate associations between the studied factors and preterm delivery, we calculated the odds ratio (OR) with a 0.5 % confidence interval. Difference was considered significant at $p < 0.05$.

The study was approved by the Ethics Committee of Nizhny Novgorod State Medical Academy (Protocol No. 12 dated October 5, 2015). All participants gave written informed consent.

RESULTS

The analysis of the socioeconomic status of the participants revealed that there were more patients with no more than a high school education (65.4 %; $\chi^2 = 6.3$; $p = 0.012$) and single women (17.3 %; $p = 0.02$) in the main group than among the controls.

The body mass index (BMI) calculated from weight and height measurements was significantly higher in the main group (an average of 25.4 ± 5.2 kg/m^2) than in the controls (an average of 22.5 ± 2.3 kg/m^2; $p = 0.009$). No statistically significant differences between the groups were found regarding height ($p > 0.05$).

Obstetric and gynecologic histories showed that previous PD had been experienced only by the women who constituted the main group (15.4 %, $p = 0.048$; OR = 9.7 [0.5–175.9]). Also, previous curettage (two or more episodes) was more common in the main group than in the controls (34.6 %, $p = 0.013$; OR = 6.1 [1.3–28.8]).

We discovered a few distinct patterns in the obstetric and gynecologic history of patients with different types of preterm labor. For example, first-time pregnancies were statistically more common in subgroup 1B (genuine PD; 45.8 %; $p = 0.038$) than in subgroup 1A. Patients from subgroup 1B also reported having their first sexual experience at an earlier age (an average of 15.6 ± 1.3 years; $p = 0.009$). Besides, the proportion of women with episodes of pelvic inflammation before pregnancy was bigger (37.5 %) in this subgroup than in subgroup 1A ($p = 0.045$).

The analysis of patients' medical backgrounds revealed that there were more women with chronic nicotine addiction

(34.6 %, p = 0.013; OR = 6.0 [1.29–28.8]) and chronic infection (chronic hepatitis C, chronic hepatitis B, HIV) (13.5 %, p = 0.047; OR = 8.4 [0.5–153.3]) in the main group than among the controls.

The most common pregnancy complication in the main group was a threatened miscarriage affecting 44.2 % of patients. Notably, only 12 % of the controls were at a similar risk, accounting for a statistically smaller proportion, in comparison with the main group (p = 0.017; OR = 4.9 [1.3–18.7]). Isthmic-cervical incompetence (ICI) developed in the second trimester was observed in 19.2 % of patients with PD; no ICI was observed in the controls (p = 0.025; OR = 12.6 [0.7–224.3]).

Patients included in the main group were found to have had acute infections (ARVI, genitourinary infection, exacerbated pyelonephritis) during pregnancy more often than the controls (36.5 %, p = 0.032; OR = 4.2 [1.1–16.0]). Of note, pregnant women with PROM (subgroup 1A) had been diagnosed with acute infection during pregnancy more often than women with genuine preterm labor (subgroup 1B) (46.4 %, p = 0.044). Signs of chronic placental insufficiency, including intrauterine growth restriction, were observed only in the group of patients with preterm delivery (13.5 %, OR of 8.4 [0.5–153.3]). This pregnancy complication was more common among patients in subgroup 1B (25 %, p = 0.04).

Very interesting results were obtained regarding expression profiles of *IL1B*, *IL10*, *IL18*, *TNFa*, *TLR4*, *GATA3*, *CD68* and *B2M* genes in the endocervical scrapes. Using the ImmunoQuantex® kit, we discovered that measuring the expression of single genes involved in the local immune response was of no prognostic value for preterm delivery. We observed no significant differences in the levels of expression of *IL1B*, *TNFa*, *CD68* and *B2M* between the groups, within the main group and between its subgroups (p > 0.05). Still, patients with PROM and no signs of active labor (subgroup A) were found to have significantly lower levels of *TLR4* expression than women who went into genuine preterm labor (subgroup B) (p = 0.037). The highest levels of *TLR4* expression were observed in the controls, differing significantly from those in subgroup 1A (p = 0.021). No significant difference was found in *TLR4* expression between the controls and subgroup 1B (p = 0.408).

Expression of the *GATA3* transcription factor was different between the groups. It reached its minimum in subgroup 1A and its maximum in subgroup 1B (p = 0.012). However, no significant difference was observed regarding this parameter between subgroup 1B and the controls (p > 0.05).

Expression of *IL10* and *IL18* was found to be significantly lower in subgroup 1A, compared to subgroup 1B (p = 0.021 and p = 0.025, respectively).

To sum up, increased or reduced expression of genes encoding pro- and anti-inflammatory proteins does not give a full picture of the changes in the mucosal immunity. Nevertheless, inflammation or the lack of thereof can be inferred based on the comparative analysis of expression of different genes and the inflammation index calculated from the results of this analysis. The II values (see the Table) differed between the main group and the controls and within the main group. The highest II was observed in subgroup 1A (PROM): 99.5 % vs. 27.2 % (p < 0.01) in subgroup B and 13.1 % (p < 0.01) in the control group. The II values in subgroup B and the controls were comparable (p > 0.05).

DISCUSSION

A lot of effort has been made to understand the causes of preterm delivery and elaborate strategies for its prevention [1, 7, 11, 13]. However, in spite of the advances in this field, there still are many questions that need to be elucidated. Among the risk factors for preterm delivery are previous medical abortions, assisted pregnancy, late miscarriages, conization of the cervix, cervical or vaginal infection, infection of the genitourinary tract, severe comorbidities, nicotine addiction, low quality of life, and stress [14]. Our findings are consistent with those of other researchers. Our work demonstrated that patients with PD had a higher body mass index than the controls, who delivered fullterm (p = 0.009). Previous preterm labor, two or more curettage episodes, smoking, impaired fat metabolism, acute and chronic infections were identified as risk factors for PD in our study.

Recently, PD has been associated with the imbalance between pro- and anti-inflammatory cytokines in the maternal organism. In patients with PD accompanied by premature rupture of membranes, the inflammation index is more likely to be high (p < 0.01). According to a number of researchers, infection of the lower pole of the amniotic sac is the leading cause of PROM [9, 15]. Once the pathogen has entered the body, the first line of immune defense is activated represented by the components of the innate immunity. Primary inflammatory response to pathogens is mediated by Toll-like receptors (TLRs) activated upon contact with the microbial cell wall, which boosts production of pro-inflammatory cytokines, chemokines and prostaglandins. It is known that increased cytokine synthesis in the cervix is a cause of leukocyte infiltration and

Levels of gene expression in the subgroups of patients with preterm delivery and the controls (data are presented as a median and an interquartile range)

Gene	Main group (PD. n = 52)		p[1]	Control group (n = 25)	p[2]	p[3]
	Subgroup 1A. n = 28	Subgroup 1Б. n = 24				
IL1b	5.55 (5.05–6.1)	5.75 (5.35–6.2)	0.435	5.9 (5.5–6.3)	0.148	0.406
IL10	2.55 (2.1–3.05)	3.1 (2.85–3.4)	**0.021**	2.9 (2.25–3.3)	0.205	0.477
IL18	4.6 (3.7–4.9)	5.1 (4.65–5.55)	**0.025**	4.9 (4.1–5.35)	0.088	0.464
TNFa	3.85 (3.4–4.25)	4.1 (3.7–4.5)	0.061	4.0 (3.5–4.3)	0.570	0.714
TLR4	3.5 (3.2–3.7)	3.9 (3.4–4.25)	**0.037**	4.1 (3.5–4.3)	**0.021**	0.408
GATA3	3.6 (2.95–3.9)	4.2 (3.6–4.45)	**0.012**	4.05 (3.45–4.5)	**0.038**	0.618
CD68	4.5 (4.15–4.7)	4.85 (4.4–5.15)	0.057	4.7 (4.45–4.95)	0.169	0.589
B2M	5.6 (5.25–5.85)	5.7 (5.3–6.1)	0.904	5.9 (5.4–6.16)	0.117	0.668
II (%)	99.5 (95.3–99.9)	27.2 (12.8–58.9)	< 0.01	13.1 (10.5–17.7)	**< 0.01**	**> 0.05**

Note. p[1] — indicates differences between subgroups 1A and 1B; p[2] — indicates differences between subgroup 1A and the controls; p[3] — indicates differences between subgroup 1B and the controls.

cervical dilation. Increased protease activity that accompanies this process can have a destabilizing effect on fetal membranes and lead to their premature rupture [16]. The role of TLRs in preterm delivery has been confirmed by many researchers [17]. For example, Tutunnikov et al. [13] have demonstrated a significant reduction in *TLR4* expression in women going into preterm labor; it should be noted though that those women had vaginal dysbiosis.

According to other authors [18, 19], patients at risk of preterm delivery have elevated levels of *TLR4* and *TLR2* products in the cervical canal mucosa and placenta right before the onset of labor. Increased expression of TLR-encoding genes entails massive production of pro-inflammatory cytokines that enter the blood streams of the mother and the fetus and induce premature activation of corticotropin-releasing hormone, as well as a cascade of reactions in the placenta and the adrenal gland resulting in the uterine hypertonicity and a risk of PD.

In the course of our study, we did not observe any significant differences between the main group and the controls regarding the expression of the majority of the studied genes ($p > 0.05$). It is known that cytokines have a regulatory role in the onset of labor in healthy pregnancies. The onset is preceded by the infiltration of the placenta and the surrounding maternal tissues by different cytokines regardless of the presence of infection. In turn, prostaglandins and pro-inflammatory cytokines, such as IL-1, IL-6, IL-8, and TNF, stimulate uterine contractions [20].

We found no significant differences between the main and the control groups regarding *TLR4* expression ($p > 0.05$), which may be explained by the diversity of PD scenarios. However, the levels of *TLR4* and *GATA3* expression differed between the subgroups, depending on the type of PD scenario. In subgroup A *TLR4* expression was significantly lower ($p = 0.037$) than in subgroup B (genuine PD) and the controls ($p = 0.021$). Differences in *TLR4* expression between subgroup 1B and the controls were insignificant ($p > 0.05$). A similar tendency was observed for *GATA3* expression: it reached its lowest level in subgroup 1A ($p < 0.05$ when comparing the results with subgroup 1B). Here, differences between the subgroups and the controls were insignificant ($p > 0.05$).

So far, we have not found any research works on the role of the inflammation index in the PD onset. In our study the index value was significantly higher ($p < 0.01$) in women with PROM (99.5 %, subgroup 1A) than in subgroup 1B (27.2 %).

Apparently, the balance between the levels of *TLR4* and *GATA3* expression and the inflammation index itself can serve as markers indicating the onset of preterm labor. If pro-inflammatory molecules outnumber anti-inflammatory cytokines, a cascade of reaction is triggered leading to systemic inflammatory response and consequently to premature rupture of fetal membranes. A pathway to genuine preterm labor seems to be different, and its study is continuing.

CONCLUSIONS

The ImmunoQuantex reagent kit provides valuable data on the local immune status of patients with spontaneous preterm labor and helps to predict its scenario. Interpretation of the results should be based on the comparative analysis of expression of pro- and anti-inflammatory factors and on the value of the inflammation index.

We have demonstrated that different local immunity profiles correspond to different PD scenarios. For example, in women with PD and premature rupture of membranes, inflammatory response is mainly manifested by inflammation with reduced expression of *TLR4* and *GATA3*. Such patients have a higher inflammation index than women with genuine PD and those who deliver at full term. Therefore, it can be concluded that local inflammatory response leads to preterm delivery with premature rupture of membranes; here, the contribution of anti-inflammatory factors to the condition decreases, while the contribution of pro-inflammatory factors does not increase. We have not found any significant differences in the local immunity profiles of parturients who went into genuine preterm labor and healthy women who delivered at full term, which means that a pathway to delivery is the same in both cases.

Further research is necessary to explore the feasibility of using the ImmunoQuantex reagent kit to assess the risk of spontaneous PD in pregnant women with threatened PD. Timely detection of local inflammation in patients at high risk of PD can help to expedite adequate measures aimed to prolong pregnancy.

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