ORIGINAL ARTICLE

CONTENTS

Association of the key immunological and hemodynamic determinants with cervix ripening in pregnant women

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ABSTRACT

Aim: To investigate a correlation between cervical ripening, the immunological features and the hemodynamic characteristics of the cervix during the preparation for vaginal labor.

Materials and Methods: We examined 75 pregnant women at different gestational age. General clinical and immunological studies were conducted in order to check serum concentration of cytokines IL-6, IL-1β, and TNF-α. Ultrasound and Doppler study were used to determine resistance index and systolic-diastolic ratio of blood flow in the common uterine artery as well as the descending and ascending parts and cervical stromal arteries.

Results: Pregnant women with high cervical ripening score had high concentrations of the major proinflammatory cytokines (IL-1β, IL-6, and TNF-α). Analysis of the of the cervical blood flow indicators of the studied groups showed significant differences in the indices of vascular resistance in the vessels that feed the cervix. Our data showed a significant correlation between the cervix ripening and both the serum levels of the studied cytokines and the level of peripheral vascular resistance indices in the common uterine arteries of the cervix, and the blood flow indices in the cervical stromal vessels.

Conclusions: Our study shows that the process of preparing the woman's body for labor is associated with immunological adjustment and increased hemodynamics of the cervix. We report that cervical ripening is associated with the immunological components and hemodynamic parameters of the cervix at late-stage pregnancy. Measuring cervix ripening and the accompanied changes in cytokine levels and hemodynamic parameters will form a more accurate assessment of birth preparedness and labor complications.

KEY WORDS: cytokines, cervical ripening, vaginal labor, cervical blood flow

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INTRODUCTION

To date one of the most important ways to reduce perinatal morbidity in Ukraine and in the world is the concept of safe motherhood and this is primarily due to improved methods of reliable prediction of labor and complications of labor for mother and fetus [1, 2]. Determining the birth preparedness is one of the most difficult and relevant issues in modern obstetrics. Additionally, the effective monitoring of the cervix during preparation to pre-induction of labor is also important. Timely assessment of the state of cervix ripening is critical in determining the prognosis of labor, especially when it comes to choosing the method of induction. Therefore, characterizing the mechanisms and factors contributing to spontaneous labor is key in establishing the steps for safe childbirth [3].

According to the literature, pre-induction of cervical ripening before spontaneous vaginal labor depends on the interaction of complex multilevel mechanisms that result in changes in morphological and biochemical state of the cervix. Of note many studies have focused on the immunological aspects of cervical ripening due to the observed local inflammatory reaction in the cervix during the process [4-6]. Before the onset of labor, the inflammatory process is accompanied by cervix infiltration with leukocytes, synthesis of a wide range of mediators as well as changes in the physical state of collagen and extracellular matrix [7].

Immunohistochemical analysis revealed that leukocytes infiltrating the cervix before vaginal labor are the main source of increasing synthesis of proinflammatory cytokines, which along with prostaglandins are involved in the inflammatory reaction associated with cervix remodeling before labor [8-10]. The physiological course of labor plays an important role in the balance of proinflammatory cytokines. Interleukins (IL) such as IL-1β, IL-6 and TNF-α, which have previously been shown to trigger abortion, are central mediators of local and systemic inflammatory reactions [11, 12]. Furthermore, these cytokines activate the neutrophil migration to the peripheral tissue and increase the production of matrix metalloproteinases that affect the conversion of collagen in the cervix.

It has previously been shown that local and systemic cytokine profiling at different stages of pregnancy can allow to identify risk groups for gestational complica-

tions such as preterm labor, intrauterine infection and others [13-15].

Cervix preparedness for labor depends on a number of parameters. Previous studies focused largely on prenatal biometric indicators of the cervix preparedness for labor including length, width, thickness of the cervix, diameter of the inner eye and location of the cervix in the pelvic cavity [16]. There is evidence in the literature that the ultrasound Doppler assessment of the cervix hemodynamic parameters can also be used to predict the course of labor. Interestingly, a number of recent studies have demonstrated the initial role of immunostimulation in the processes of neovascularization and blood supply during pregnancy [17, 18]. Despite a number of studies focusing on the regulation of initiation mechanism of women's spontaneous parturition, the ambiguity in the field persists and further research is needed to define and optimize the reliable markers and indicators that can effectively be used to assess the preparedness for labor for a mother and a fetus.

Taking into account that before labor cervix is undergoing both immunological and hemodynamic changes, we aimed to investigate whether there is a link between immunological signalling and cervical blood flow parameters before the induction of labor. Our results demonstrate that cervix ripening is associated with both the uterine blood flow parameters and the major pro-inflammatory cytokines indicating that blood flow and cytokine levels can be used together as a screening tool to assess the course of labor.

AIM

The aim of the study is to investigate if there is a link between the state of the cervix ripening, the immunological features and the hemodynamic characteristics of the cervix during the preparation for vaginal labor.

MATERIALS AND METHODS

75 pregnant women at a gestational age of 38-40 weeks were examined in the Kharkiv Regional Perinatal Clinical Hospital, Kharkiv, Ukraine. The study groups included primiparous women without severe extragenital and obstetric pathology. The study did not include women with repeated pregnancies and births, pregnant women admitted for planned cesarean section, or women with exacerbations of chronic extragenital diseases, fever, and severe preeclampsia. The study was conducted in compliance with the standards of the Declaration of Helsinki and approved by the independent ethics committee of the Kharkiv National Medical University protocol No. 32 of 01/03/2023). All patients gave their written in- formed consent to participate in the study.

The examined women were divided into two clinical groups on admission to the hospital, depending on the degree of cervical ripening. The degree of cervical ripening was assessed with the help of Bishop (1964) score. Group 1 consisted of 29 patients with high cervical ripening score (9-13 points), group 2 included 31 pregnant women with low cervical ripening score (6-8 points). The control group consisted of 15 primiparous women with a gestational age of 35-36 weeks before the start of physiological processes of cervical remodeling. These women had no signs of emergency preterm birth according to somatic status or medical records.

All pregnant women underwent complete clinical and laboratory examination, regulated by the Order of the Ministry of Health of Ukraine. Their fetuses were studied using ultrasound and cardiotocography.

Immunological studies were performed once upon admission to the hospital. The serum concentration of cytokines IL-6, IL-1β and TNF-α was determined by solid-phase enzyme-linked immunosorbent assay using commercial kits (CJSC "Vector Best").

Ultrasound and Doppler examination was performed using ultrasonic diagnostic device Aloka SSD – 3500 SV (Japan) with color Doppler mapping, applying transabdominal and transvaginal sensors. In transabdominal examination we studied the blood flow parameters in the common uterine artery in the descending and ascending parts. In transvaginal examination we determined the blood flow parameters in the arteries of the cervical stroma and in the isthmus. We measured the resistance index (IR), systolic-diastolic ratio (SDR).

Statistical processing of the obtained results was performed using the program "STATISTICA-6". The results are presented as medians and standard deviation. The Mann–Whitney U test was used to determine the significance of the differences between the studied groups. Spearman's correlation analysis was used to assess possible correlations between cervix ripening and inflammatory cytokines IL-1β, IL-6 and TNF-α) and uterine blood flow parameters (systolic diastolic ratio SDR and resistance index RI). A P value of $\leq$0.05 was considered statistically significant.

RESULTS

The main clinical characteristics of the studied groups are presented in (Table 1). The age of the examined pregnant women ranged from 18 to 33 years and on average it was 25.7. Patients were compared with each other by age, features of sexual and menstrual function ($p \leq 0.05$). In their medical records among gynecological pathology there were inflammatory diseases of the female genital organs in 49.4% of women (group 1)

Table 1. Clinical and demographic characteristics of the participants in the studied groups

	Group 1	Group 2	Control	P
	n=29	n=31	n=15	
Age, years	25.7 (18-33)	25.7 (18-33)	25.7 (18-33)	n/a
Cervical ripening score (Bishop score)	9-13	6-8	n/a	0,02
Inflammatory disease of female genitals, n (%)	14 (48.2%)	20 (64.5%)	7 (46.5%)	0,03
Cervical ectopia, n (%)	11 (37.5%)	16 (51.6%)	6 (40%)	0,04
Childhood infections, n (%)	4 (13.7%)	15 (48.3%)	2 (13.13%)	0,02
Neurocirculatory pathology, n (%)	1 (3.4%)	3 (9.6%)	1 (6.7%)	0,03
Thyroid pathology, n (%)	2 (6.8%)	5 (16.1%)	1 (6.7%)	0,02
Miscarriage in 1st semester, n (%)	2 (6.8%)	1 (3.2%)	1 (6.7%)	0,04

Listed characteristics were compared between group 1, group 2 and the control group. Values for the age and cervical ripening score are expressed as median and ranges. n – indicates a number of patients along with percentage (%) of the total number of patients in a given group. Mann–Whitney U tests was used. A P value of ≤0.05 was considered statistically significant. n/a: non applicable.

Table 2. Comparison of cytokine levels in the blood of the control and studied groups

	Group 1	Goup 2	Control group
	n=29	n=31	n=15
IL-6 pg/ml	79.8 ± 9.6*	22.6 ± 2.7	20.5 ± 2.3
IL-1β pg/ml	197.4 ± 23.7*	64.7 ± 7.5	62.9 ± 7.2
TNF-α pg/ml	2.8 ± 0.3*	0.9 ± 0.1	0.8 ± 0.09

Concentrations of IL-6, IL-1β and TNF-α were compared between group 1 and control group and group 2 and control group. Values are expressed as mean and standard deviation. Mann–Whitney U test was used. A P value of ≤0.05 (* – p ≤0.05) was considered statistically significant.

Table 3. Characterization of the uterine and cervical blood flow in the studied groups

	Group 1	Group 2	Control group
	n=29	n=31	n=15
Common uterine artery			
SDR	1.70 ± 0.03*	1.74 ± 0.02	1.82 ± 0.03
RI	0.38 ± 0.04*	0.47 ± 0.05	0.51 ± 0.04
Ascending uterine artery			
SDR	1.71 ± 0.02*	1.85 ± 0.05	1.88 ± 0.02
RI	0.38 ± 0.04*	0.47 ± 0.05	0.49 ± 0.05
Descending uterine artery			
SDR	1.61 ± 0.17*	1.82 ± 0.25	1.86 ± 0.27
RI	0.38 ± 0.04*	0.47 ± 0.03	0.49 ± 0.05
Stromal arteries of the cervix			
SDR	2.41 ± 0.3*	2.82 ± 0.31	2.86 ± 0.4
RI	0.48 ± 0.06*	0.67 ± 0.08	0.69 ± 0.07

Systolic diastolic ratio (SDR) and resistance index (RI) were compared between group 1 and control group and group 2 and control group. Values are expressed as mean and standard deviation. Mann–Whitney U test was used. A P value of ≤0.05 (* – p ≤0.05) was considered statistically significant.

and 64.6% of patients (group 2). Cervical ectopia was present in 38.5% of group 1 representatives and 51.6% of patients in group 2 ($p \leq 0.05$). Analysis of extragenital pathology showed that childhood infections and acute respiratory diseases were recorded in group 2 more often than in group 1 (48.5% in group 2 compared to 15.4% in group 1). Neurocirculatory disorders and thyroid pathology were significantly more common in group 2 (10.2%, and 16.8%) compared to group 1 (1.7%, and 3.3%) ($p \leq 0.05$). Regarding the complications of the current pregnancy, significant differences were found in the frequency of miscarriage in the 1st trimester, which was 3.6% in patients of group 1 and 21% of pregnant women in group 2 ($p \leq 0.05$).

Table 4. Correlation coefficient between cervical ripening score and inflammatory cytokines and uterine and cervix blood flow parameters (SDR and RI)

	Correlation coefficient	P
Cytokines		
IL-6	0,78	0,001
IL - 1β	0,7	0,001
TNF-α	0,65	0,002
SDR		
Common uterine artery	-0,478	0,012
Ascending uterine artery	-0,442	0,018
Descending uterine artery	-0,653	0,003
Stromal arteries of the cervix	-0,689	0,001
RI		
Common uterine artery RI	-0,675	0,004
Ascending uterine artery	-0,466	0,041
Descending uterine artery	-0,723	0,003
Stromal arteries of the cervix	-0,747	0,001

Spearman's correlation was used to calculate the correlation between cervical ripening and the given parameters. A P value of ≤0.05 was considered statistically significant

The analysis of the major cytokines production (IL-1β, IL-6, and TNF-α) as a possible indicator in preparing the body for labor, revealed high concentrations of studied proinflammatory cytokines (Table 2) in the serum of pregnant women of groups 1 and 2. In pregnant women of group 1, the concentration of IL-6 exceeded that in group 2 and in the control group (79.8 ± 9.6 pg / ml, 22.6 ± 2.7, and 20.5 ± 2.3 pg / ml g, respectively) ($p \leq 0.05$). The level of IL-1β in group 1 was twice as high as that in group 2, and in the control group (197.4 ± 23.7 pg / ml, 64.7±7.5, and 62.9 ± 7.2 pg / ml, respectively) ($p \leq 0.05$). The maximum concentration of TNF-α was observed during the onset of labor in pregnant women of group 1 compared to group 2 and control group (2.8 ± 0.3 pg / ml, 0.9 ± 0.01, and 0.8 ± 0.09 pg / ml, respectively) ($p \leq 0.05$) (Table 2). Patients in group 1 with high cervical ripening score had high level of major proinflammatory cytokines and displayed lack of cervix preparedness for labor. Taken together we conclude that these immune markers can serve as a prognostic factor to ensure a timely labor and to assess the effectiveness of pre-induction and induction of labor.

Over the course of the last few years, assessing the hemodynamic changes in uterine arteries using Doppler ultrasound has successfully been used to diagnose and predict pregnancy outcomes [19].

Next, we aimed to examine whether there might be a correlation between the inflammatory cytokines and the hemodynamic processes in the cervix. To address this, we measured the cervical blood flow in the studied groups. The main indicators of cervical blood flow that were taken using Doppler in the studied groups included systolic diastolic ratio (SDR) and resistance index (RI) in the vessels that feed the cervix: common uterine artery, ascending and descending parts of the uterine artery and cervical stromal arteries. We observed significantly lower rates of SDR and RI in women of group 1 compared with pregnant women of group 2 and a control group in the common uterine artery, ascending and descending parts and in the arteries of the cervical stroma (Table III). Lower SDR values were recorded in group 1 in common, ascending and descending uterine arteries as well as stromal arteries of the cervix in patients in group 1 (1.70 ± 0.03, 1.71 ± 0.02, 1.61 ± 0.17 and 2.41 ± 0.3 respectively) compared to group 2 and control groups. Similarly, resistance index in group 1 was significantly lower compared to group 2 and the control group with the values 0.38 ± 0.04 in common, ascending and descending uterine arteries and 0.48 ± 0.06 in stromal arteries of the cervix (Table 3).

Analysis of the cervix hemodynamics in the examined women showed a significant decrease in vascular resistance indices in pregnant women of group 1 in the common uterine artery, its ascending and descending parts, as well as in stromal arteries of the cervix (Table 3). This is consistent with the previous observations

that shows that during the ripening of the cervix before labor there is an increased blood supply to the cervix [20]. A significant decrease in the average blood flow in this group of pregnant women suggests that the cervix is undergoing the process of increasing the capacity of its vascular bed during blood deposition in cervical vessels, which is part of the physiological course of prenatal transformation.

Next, we investigated the correlation between the determined immunological and hemodynamic parameters. Significant correlations were found between cervix ripening and the levels of the studied pro-inflammatory cytokines IL-1β, IL-6 and TNF-α (Table 4, Spearman's r coefficient r= 0.78, 0.7, 0.65 respectively). Significant inverse correlations were observed between cervix ripening and SDR and RI parameters in the uterine arteries of the cervix and cervical stromal arteries summarized in Table 4. Statistically significant correlation indicates that there is an association between the parameters studied. The associative link between the cytokines studied, SDR and RI parameters and cervix ripening suggests that these parameters may be investigated further as predictors of women's labor.

DISCUSSION

In this study we evaluated whether cervical ripening indicators can be used in conjunction with immunological and hemodynamic paraments to accurately predict successful labor onset in female patients at 38-40 gestational weeks. Cervical ripening score (Bishop score) along with cervical length have long been used as a preferred method of defining cervical preparedness for labor. However, these methods might not be the best way to assess birth preparedness primarily due to variations in the observation along with the discomfort that these examinations bring to the pregnant women [21, 22]. In this report we aimed to expand the existent methods of assessing cervical readiness and investigate other parameters that may improve the accuracy of predication markers for labor outcomes.

Cardiovascular adaptations and immunological changes play a major role in pregnancy. The change in immunoreactivity on the eve of spontaneous labor is accompanied by a significant activation of the production of pro-inflammatory cytokines at the systemic level and local changes in cervical hemodynamics. Monitoring maternal hemodynamics has previously been explored as a tool to predict obstetric risk in early labor [23]. In line with previous studies, we used several parameters to assess maternal cardiovascular adjustments during preparedness for labor. Our results show an association between cervical ripening and hemodynamic changes implying that in early stages of labor, it is important to monitor hemodynamic indices.

Similarly, immunological adjustments are the key features of pregnancy. Systemic and local inflammatory activation is affecting preparedness for labor along with the labor and parturition. Serum cytokines and chemokines have previously been tested as reliable tools to predict a number of labor complication and pathologies such as preeclampsia and labor complications [24]. Cytokines have many different ways of regulating tissues and tissue environments. For example, IL-6 pro-inflammatory cytokine has angiogenic and mitogenic effects and plays an important role in reproductive function by regulating ovarian steroid hormone production, folliculogenesis and early implantation events. The angiogenic properties of pro-inflammatory cytokines and subsequent formation of the blood vessels can partly explain the link that we observe between the increased level of cytokines and the decrease in hemodynamic blood flow parameters that correlates with cervical ripening. This correlation may suggest an important immunoregulatory effect of cytokines during pregnancy on vascularization process and blood supply of the uterine vessels in late pregnancy. However further studies are needed to decipher the exact link between the pro-inflammatory cytokines and angiogenesis during late-stage pregnancy and labor onset.

Moving towards a better prediction of labor remains a high priority in women's health [25]. Accurate and reliable ways of monitoring late stages of labor preparedness will undoubtedly decrease labor complications and will allow for interventions to be administered timely. Our work advances our understanding of the markers that can be used as a screening tool to assess the onset of labor and paves way to discovering correlations between different parameters that can be assessed during pregnancy. Future work will involve finding additional markers that may correlate with cervical ripening and immunological and hemodynamic state of the cervix to establish an accurate template for predicting birth preparedness and labor complications.

CONCLUSIONS

The process of cervix remodeling before labor is characterized by an increase in the proinflammatory cytokines in blood serum due to increased immunological activity of peripheral neutrophils. We observe an increase in the pre-inflammatory cytokines in patients with high cervical ripening. Interestingly, high cervical ripening was associated with a decrease in the hemodynamic features of the cervix including decreased arterial blood flow in the descending uterine artery and stromal vessels. The

results presented here establish a correlation between the cervix ripening and the immunological and hemodynamic aspects of late pregnancy. Multifunctional immunoregulatory properties of proinflammatory cytokines during physiological pregnancy and labor may play an important role in ensuring hemodynamic adjustment of the cervix before labor. Thus, combining multiple parameters to identify pregnancy outcomes may help us tackle a clinical challenge posed by pregnancy risks and labor complications.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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