ORIGINAL ARTICLE

CONTENTS

The association of inflammatory changes of the uterus and chorioamniotic membranes with different types of labor activity anomalies

Kateryna L. Shatylovych, Leonid B. Markin
DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE

ABSTRACT

Aim: To clarify the association between different types of uterine contractility dysfunction and the inflammation of the uterus and chorioamniotic membranes.
Materials and Methods: The association between the inflammation of the uterine layers, chorioamniotic membranes, umbilical cord, and different types of labor activity abnormalities was examined in 382 patients with singleton pregnancies at 28-42 weeks' gestation who underwent Caesarean section (CS) for abnormal uterine contractions and other complications. Statistical analyses included the Mann-Whitney U, Chi-squared test, and logistic regression.
Results: In the control group, slight infiltration with polymorphonuclear leukocytes (PMNs) and macrophages of the myometrium and decidua of the lower uterine segment at term pregnancy was found in 59.7% and 73.6% of cases. The main clinical risk factors for placental and decidual membrane inflammation in patients with excessive uterine activity (EUA) were prematurity, multiparity, group B streptococcus (GBS) colonization, and duration of ruptured fetal membranes before the CS. Moderate or marked myometrial inflammation of both uterine segments in the EUA group was diagnosed only in patients with cervical dilation of >6 cm and duration of labor of >8h. In women with hypotonic uterine activity (HUA), decidual and myometrial inflammation was significantly associated with nulliparity and intrapartum factors, such as protracted active first stage of labor, advanced cervical dilation, and number of vaginal examinations. In all cases, inflammation of the myometrium was accompanied by deciduitis.
Conclusions: Mild inflammation of the decidual membrane and myometrium of the lower segment at term pregnancy is a common physiological phenomenon contributing to labor initiation. Uterine hyperfunction comes as the response of the unaffected myometrium to the release of high concentrations of pro-inflammatory cytokines produced by the inflamed decidual and chorioamniotic membranes into the bloodstream. Marked myometrial inflammation that occurs in prolonged labor is an additional factor aggravating the hypotonic uterine activity.

KEY WORDS: hypotonic uterine activity, excessive uterine activity, uterus, inflammation, chorioamniotic membranes

Wiad Lek. 2024;77(8):1582-1592. doi: 10.36740/WLek202408108 DOI

INTRODUCTION

Abnormal labor patterns are relatively prevalent obstetric complications that justify medical intervention during labor. Approximately 20% of labors are thought to be affected by these conditions [1-4]. Hypotonic uterine activity (HUA) is one of the most common reasons for labor arrest in primiparous women that increases the risk of operative vaginal delivery, CS, and postpartum hemorrhage [3-7]. Excessive uterine activity (EUA) or uterine tachysystole produce a significant negative impact on the mothers (uterine and birth canal trauma, amniotic fluid embolism, postpartum hemorrhage) and neonates (hypoxia, intracranial hemorrhage, trauma) due to excessive myometrial stimulation [2, 7-11].

Over the last decade, it has been established that intraamniotic inflammatory response represented by chorioamnionitis (CAM) and funisitis is characterized by an increased amniotic fluid white blood cell count [12-15] and increased concentrations of inflammatory mediators which play a crucial role in human parturition [16-20]. In more recent publications, Gonzales J.M. et al. (2011), Hamilton S. et al. (2012), Hamilton S. et al. (2013), Keelan J. et al. (2018), Shynlova O. et al. (2020) [21-25] have demonstrated intense inflammatory myometrial infiltration of monocytes, neutrophils and macrophages before labor and have shown that inflammatory cytokines, bacterial lipopolysaccharide and monocytes themselves can increase myometrial cell contractions and cause a hypertonic uterine dysfunction. On the contrary, other authors [26–33] have reported that intrauterine inflammation and/or hyperthermia associated with CAM reduces uterine contractility.

Despite a better understanding of the etiology and management of labor abnormalities [1–3, 7-10, 34], our knowledge about the effect of intrauterine inflammation on the course of labor is limited. Whether preexistent

inflammation produces abnormal labor or labor aberrations contribute to the development of inflammatory complications intrapartum is an issue that appears never to have been raised. There is no unequivocal data on whether inflammatory lesions of the myometrium are associated with different types of uterine activity pathology. Since there is currently no published data on the availability of a correlation between different types of dysfunctional labor and the inflammatory changes of the uterus and chorioamniotic membranes, the measurement of such potential complications is important for the development of possible preventive measures.

AIM

The aim of our study was to examine the association between different types of uterine contractility dysfunction and the inflammation of the uterus and chorioamniotic membranes.

MATERIALS AND METHODS

The study comprised 382 women with singleton pregnancy at 28-42 weeks' gestation who underwent CS due to abnormal uterine contractions and other complications.

Maternal information included maternal age, parity, gestational age (based on the last menstrual period and/or ultrasound examination findings), GBS colonization, clinical CAM status, duration of labor (defined as the presence of true labor pain and partograph data until the CS), duration of ruptured fetal membranes period prior to operation, level of cervical dilation at the surgery, number of vaginal examinations, oxytocin usage, antibiotic, antipyretic and tocolytic treatment.

The first observation group enrolled 168 women with HUA who were operated on due to the absence of labor progress. The second observation group consisted of 70 women with EUA who were made to deliver abdominally because of intrapartum cardiotocography (CTG) abnormalities, placental abruption, and combined indications. The control group included 144 women (65 women in the first stage of labor with regular uterine contractions and 79 women without labor) who underwent CS due to different indications.

Oxytocin was used for augmentation of labor in all patients in HUA group when the action line on partograph (four hours to the right of the alert line) was crossed [35–38] and for induction of labor in GBS-infected women with premature rupture of membranes in EUA and control group patients [39–40]. Prophylactic antibiotics were always administered after cord clamping and biopsy removal. Intrapartum antibiotics were administered to patients with GBS colonization, in the setting of prolonged membrane rupture (>18 hours) in women with an unknown GBS status as well as to patients with symptoms of clinical CAM [39–40]. Women with hyperthermia received antipyretic therapy [29–30, 32]. In cases of acute fetal distress combined with tachysystole, acute tocolysis with selective beta$_2$ (ß$_2$)-adrenergic agonists was used [10].

CARDIOTOCOGRAPHY

The CTGs on admission and during labor were carefully analyzed to define fetal heart rate and uterine activity abnormalities. The following criteria of fetal distress were applied: diminished short-term heart rate variability (variability < 5 beats per minute (bpm) persisting for >20 minutes); sustained tachycardia (basal heart rate > 160 bpm for > 20 minutes); sustained bradycardia (basal heart rate < 100 bpm >20 minutes); repetitive late or variable decelerations; sinusoidal pattern (visually apparent, smooth, sine wave-like, undulating pattern in fetal heart rate baseline with a cycle frequency of 3-5 per minute persisting for >20 minutes) [41].

External monitoring of uterine contractions using a tocodynamometer evaluates increased myometrial tension measured through the abdominal wall. 5 contractions with an intensity of >200 Montevideo units (MU) were considered to be adequate uterine activity (peak intensity of each contraction calculated in millimeters of mercury (mm Hg) minus basal uterine tone, summed over a 10-min period) but <300 MU with basal tone < 25 mmHg and > 50 mmHg contraction peak/active pressure in a 10-minute period for 2 hours [41]. Excessive uterine activity (EUA) was defined as increased intensity of contractions (MU >300), uterine tachysystole (the CTG showed more than 5 contractions in a 10-minute period, averaged over a 30-minute window), uterine hypertonus (a single contraction lasting for more than 2 min or contractions of normal duration occurring with a relaxation time of less than 60 seconds or resting pressure >25 mmHg) [2, 41]. Hypotonic uterine activity (HUA) was diagnosed when more than one of the following criteria was met: decreased intensity of contractions (MU <200), the frequency of contractions is <2 within 10 minutes, the peak/active pressure during contraction is < 25 mmHg at the cervical dilation of 4 to 8 cm and <40 mmHg at the cervical dilation of >9 cm, the duration of contraction is <20 to 30 seconds at the cervical dilation of >4 cm [41]. A protracted active first stage (once 4-cm cervical dilation is achieved) was defined as no cervical dilation after 6 hours of inadequate contractions, with ruptured membranes, despite oxytocin administration [1, 38].

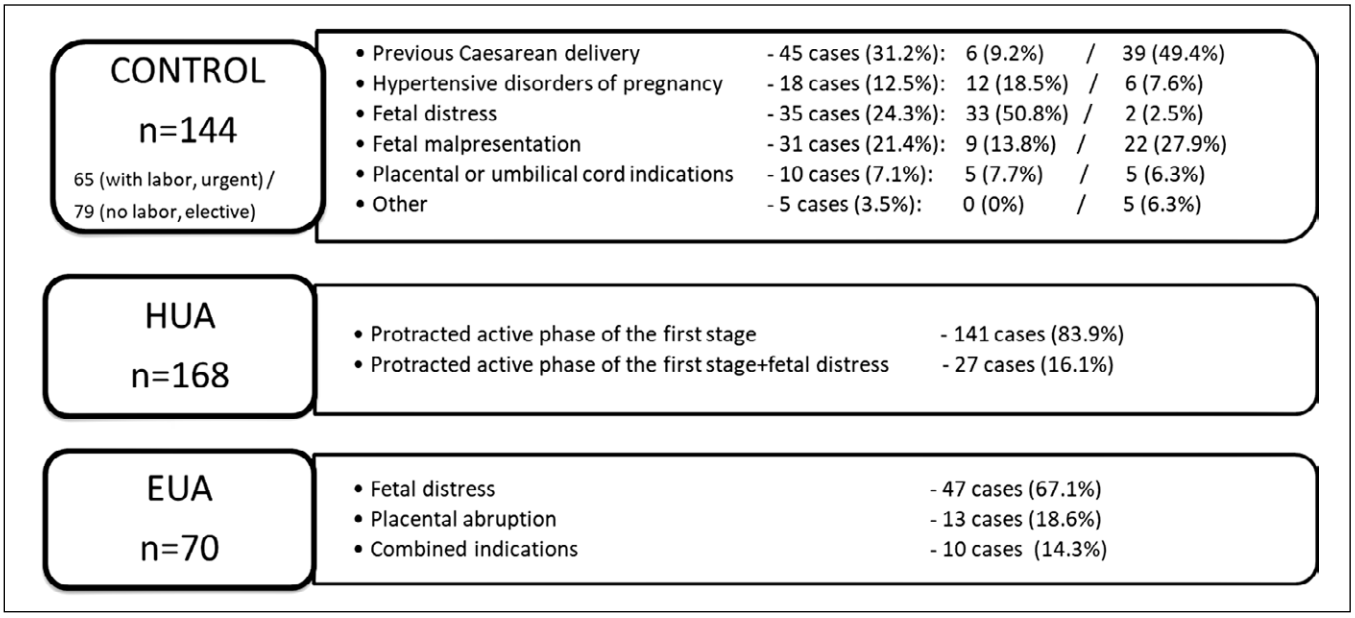

Fig. 1. Indications for Caesarean section.

HISTOLOGICAL EXAMINATION

Full-thickness biopsy specimens of endometrium (decidua) and myometrium from the upper margin of the lower uterine segment incision and upper uterine segment obtained through the dissection of a strip of myometrium from the inner surface of the posterior uterine wall during the CS were received immediately after delivery of the child and taken for histopathologic assessment. In 5 women in the HUA group, myometrial biopsies were taken from the anterior wall of the lower segment and upper uterine body, immediately following the hysterectomy.

The following sites of the placentas were sampled: chorion-amnion, the chorionic plate, and the umbilical cord. Three to nine sections of the placenta were examined, and at least one full-thickness section was taken from the center of the placenta; others were taken randomly from the placental disc [42].

Each of the samples was placed in 10% neutral buffered formalin for fixation and embedded in paraffin. Sections of tissue blocks were stained with hematoxylin and eosin. Samples were fixed for 24 hours at 4°C.

The presence of inflammatory reaction in the myometrium and endometrium (decidual tissue) was analyzed and correlated with the clinical parameters of the case. Evaluation of specimens was modified from the scale described by Keski-Nisula L.T. et al., 2003 [43]. Normal samples were graded 0, and those that contained clearly identifiable polymorphonuclear leukocytes (PMNs) and monocytes/macrophages were graded as positive for acute inflammation using a scale of 1 to 4: 1, or mild: 1 focus of at least 5 PMNs and 3 macrophages; 2, or moderate: >1 focus of grade 1 inflammation or at least 1 focus of 5-20 PMNs and 3-10 macrophages; 3, or marked: multiple and/or confluent foci of grade 2; 4, or very marked: diffuse and dense acute inflammation.

Inflammatory lesions of the placenta and umbilical cord were diagnosed according to established criteria [44-46]. Placental inflammation was defined as the infiltration of neutrophils into the chorion and amnion. Histologic chorioamnionitis (hCAM) was defined as the presence of acute inflammatory changes on examination of a membrane roll and chorionic plate of the placenta: stage 1 (hCAM1) – acute subchorionitis or chorionitis; stage 2 (hCAM2) – acute chorioamnionitis: PMNs extend into fibrous chorion and/or amnion; stage 3 (hCAM3) – necrotizing chorioamnionitis: karyorrhexis of PMNs, amniocyte necrosis, and/or amnion basement membrane hypereosinophilia. Funisitis was diagnosed in the presence of neutrophil infiltration into the umbilical vessel walls or Wharton's jelly, according to criteria of Amsterdam Placenta Workshoup Group [47]: stage 1 – chorionic vasculitis or umbilical phlebitis; stage 2 – involvement of the umbilical vein and one or more umbilical arteries; stage 3 – necrotizing funisitis.

The present study was approved by the institutional review board (Bioethics Commission) of Danylo Halytsky Lviv National Medical University (No. 156). All procedures in this study were performed in accordance with the ethical standards of the institutional and national research committee.

STATISTICAL ANALYSIS

Mann-Whitney U test and one-way analysis of variance were used to compare the continuous

Table 1. Clinical characteristics of the patients in the HUA, EUA, and control groups

Variable	Groups of patients			p-value
	HUA n=168	EUA n=70	Control n=144	
Maternal age, years (mean±SD)	27.6±5.7	32.1±4.8	30.3±4.2	NS
Gestational age at delivery, weeks (mean±SD)	40.2±1.4	33.3±4.6	38.4±4.1	<0.01[a]
Multiparous, n (%)	65 (38.7)	53 (75.7)	82 (56.9)	<0.05[b]
Primiparous, n (%)	103 (61.3)	17 (24.3)	62 (43.1)	<0.05[b]
Birth weight at delivery, g (mean±SD)	3680±458	1920±814	3440±465	<0.01[a]
GBS-colonization, n (%)	16 (9.5)	10 (14.3)	9 (6.3)	NS
Clinical CAM:	14 (8.3)	13 (18.6)		<0.05[b]
antenatally, n (%)	2 (1.2)	9 (12.9)	0	<0.01[b]
intrapartum, n (%)	12 (7.1)	4 (5.7)		<0.05[b]

Values are given as mean±standard deviation (SD) unless specified otherwise
[a] – p-value: one-way analysis of variance
[b] – p-value: chi-squared test
NS – p-value: not significant (p>0.05).

Table 2. Obstetric characteristics of the patients in the HUA, EUA, and control groups

Variable	Groups of patients			p-value
	HUA n=168	EUA n=70	Control n=65	
Mean interval from onset of labor to the surgery, h (mean±SD)	18.4±6.9	5.6±4.2	8.8±3.3	<0.05[a]
Premature rupture of fetal membranes, n (%)	81 (48.2)	57 (81.4)	14 (21.5)	< 0.05[b]
Duration of ruptured fetal membranes before the surgery, h (mean±SD)	16.2±8.0	51.7±41.7	6.2±1.4	<0.01[a]
Mean cervical dilation at the surgery, cm (mean±SD)	8.1±1.7	4.4±1.8	5.6±2.5	<0.05[a]
Number of vaginal examinations with membrane rupture before the surgery >4, n (%)	81 (48.2)	0	4 (6.2)	<0.01[b]
Uterine activity in the 0.5 h prior to delivery, MU (mean±SD)	94±37	422±66	168±53	<0.05[a]
Use of oxytocin, n (%)	168 (100)	6 (8.6)	3 (4.6)	<0.01[b]
Intrapartum antibiotics, n (%)	53 (31.6)	43 (61.4)	3 (4.6)	<0.01[b]
Use of antipyretics, n (%)	10 (5.9)	9 (12.9)	0	<0.05[b]
Acute tocolysis, n (%)	0	22 (31.4)	0	NS

Results are expressed as mean ±standard deviation (SD) unless specified otherwise
MU - Montevideo units
[a] - p-value: one-way analysis of variance
[b] - p-value: chi-squared test
NS – p-value: not significant (p>0.05).

variables. Chi-squared test was used to compare the categorical variables. Comparative analysis of the development of HUA, EUA, and availability of inflammation in the tissue samples, as well as identification of univariate associations between the labor abnormalities and preoperative clinical factors were carried out through logistic regression analysis performance. For each variable, one category as the control was chosen, and odds ratios (ORs) or adjusted odds ratios (aORs) and 95% confidence intervals (CI) for the other categories were calculated. Probability values p<0.05 were considered to be statistically significant. Statistica 10 software (StatSoft, USA) was used for the statistical analyses.

RESULTS

Figure 1 shows the main indications for cesarean section of the study participants.

Table 1 and Table 2 show the clinical and obstetric characteristics of the study patients in observed groups.

The mean maternal age was not different among the groups (p>0.05), although the HUA group tended to have more patients aged 18–25 years. The mean gestational age at delivery in patients in the HUA and control groups differed significantly from patients in the EUA group (40.2, 38.4 and 33.3 weeks, respectively (p<0.01). The rate of primiparous in the HUA group (61.3%) was far above that of the EUA (24.3%) and control groups (43.1%) (p<0.05).

Table 3. The grade of inflammatory infiltration of decidua and myometrium in the HUA, EUA, and control groups patients

Grade	Groups of patients			p-value[a]
	HUA, n=168	EUA, n=70	Control, n=144	
Decidual samples, n (%)				
0	0	0	14 (9.7)	NS
1	49 (29.2)	17 (24.3)	106 (73.6)	< 0.01
2	54 (32.1)	23 (32.9)	16 (11.1)	< 0.05
3	55 (32.7)	18 (25.7)	8 (5.6)	< 0.05
4	10 (6.0)	7 (10)	0	< 0.05
Grade ≥2	119 (70.8)	48 (68.6)	24 (16.7)	< 0.01
Myometrial samples (lower segment), n (%)				
0	0	0	48 (33.4)	NS
1	58 (34.5)	38 (54.3)	86 (59.7)	NS
2	82 (48.8)	14 (20)	10 (6.9)	< 0.01
3	23 (13.7)	3 (4.3)	0	< 0.01
4	5 (3)	0	0	NS
Grade ≥2	110 (65.5)	17 (24.3)	10 (6.9)	< 0.01
Myometrial samples (upper segment), n (%)				
0	13 (7.7)	18 (25.7)	122 (84.7)	< 0.01
1	55 (32.7)	25 (35.7)	15 (10.4)	< 0.05
2	74 (44.1)	12 (17.1)	7 (4.9)	< 0.01
3	11 (6.5)	0	0	NS
4	5 (3)	0	0	NS
Grade ≥2	90 (53.6)	12 (17.1)	7 (4.9)	< 0.01

[a] - p-value: chi-squared test

NS – p-value: not significant (p >0.05).

Due to the prevalence of preterm labor, the mean weight of newborns was much higher in the HUA and control groups than in the EUA group patients (3,680 g and 3,440 g vs 1,920 g, p<0.01).

Clinically evident CAM was diagnosed more frequently in the EUA group patients compared to those in the HUA group (18.6% vs 8.3%, p <0.05). However, in the HUA group, 12 out of 14 women developed clinical CAM intrapartum due to prolonged labor. The EUA group was dominated by the patients with clinical CAM (9/13), which developed antenatally against the background of a prolonged period (> 72 h) from rupture of the fetal membranes prior to delivery.

In the process of comparing the course of labor (Table 2), the following statistically significant differences among the study patients were found between the groups. Women in the EUA group had a higher incidence of premature rupture of membranes than women in the HUA and control groups (81.4% (EUA group) vs 48.2% (HUA group), and 21.5% (control group), p<0.05); a shorter mean interval from onset of labor to the CS (5.6±4.2 h vs 18.4±6.9 h, and 8.8±3.3 h, p< 0.05); a longer period of rupture of fetal membranes (51.7±41.7 h vs 16.2±8.0 h, and 6.2±1.4 h, p<0.01); a lower level of cervical dilation (4.4±1.8 cm vs 8.1±1.7 cm, and 5.6±2.5 cm, p<0.05) and stronger uterine activity (422±66 MU vs 94±37 MU, and 168±53 MU, p<0.05). More than 4 vaginal examinations after membrane rupture during the management of labor were performed in 81 (48.2%) women in the HUA group and in 4 (6.2%) women in the control group (p<0.01).

Intrapartum antibiotics in the HUA, EUA, and control groups were administered to 99 parturients (in all GBS-colonized women after rupture of membranes or beginning of labor (n=16; n=8; n=3); in patients with an unknown GBS status and the duration of ruptured fetal membranes >18h (n=25; n=26; n=0); in patients with symptoms of clinical CAM in labor (n=12; n=4; n=0). In all cases with CAM and fever (n=10 in the HUA group and n=9 in the EUA group) antipyretics were prescribed. 22 patients in the EUA group underwent acute tocolysis before surgery due to fetal distress.

The data of histological analysis of the uterine walls layers and fetal and placental membranes in studied groups are presented in Table 3 and Table 4.

Absence of decidual inflammation (0 grade) was found only in 14 patients in the control group (9.7%)

Table 4. The stage of hCAM and funisitis in the HUA, EUA, and control group patients

Stage	Groups of patients			p-value[a]
	HUA, n=168	EUA, n=70	Control, n=144	
hCAM stage, n (%)				
Not present	93 (55.4)	9 (12.9)	121 (84)	< 0.01
1	37 (22)	7 (10)	17 (11.8)	< 0.05
2	9 (5.4)	20 (28.6)	3 (2.1)	< 0.05
3	11 (6.5)	19 (27.1)	3 (2.1)	< 0.05
hCAM	57 (33.9)	46 (65.7)	23 (16)	< 0.05
Stage ≥2	20 (11.9)	39 (55.7)	6 (4.2)	< 0.01
Funisitis stage, n (%)				
Not present	140 (83.3)	46 (65.7)	139 (96.5)	< 0.05
1	16 (9.5)	6 (8.6)	3 (2.1)	NS
2	9 (5.4)	11 (15.7)	1 (0.7)	< 0.05
3	3 (1.8)	7 (10)	1 (0.7)	< 0.05
Funisitis	28 (16.7)	24 (34.3)	5 (3.5)	< 0.05
Stage ≥2	12 (7.2)	18 (25.7)	2 (1.4)	< 0.05

[a] - p-value: chi-squared test
NS – p-value: not significant.

who were delivered by elective CS at less than 36 weeks' gestation. Decidual PMN and macrophage infiltration of mild grade was detected in the HUA, EUA, and control groups in 29.2%, 24.3%, 73.6% cases, respectively (p<0.05). Moderate to marked decidual inflammation was diagnosed more frequently in the samples from the HUA and EUA groups than from the control group parturients (70.8% and 68.6% vs 16.7%, p<0.05).

In contrast to the decidual tissue, the 1st grade of inflammatory changes in the myometrium of the lower uterine segment was diagnosed more frequently, although no significant difference was noted between the observation groups (Table 3). Moderate to marked myometrial inflammation of both uterine segments was identified in 53.6%, 17.1%, and in 4.9% patients of the HUA, EUA, and control group, respectively (p<0.05). In all cases, inflammation of the myometrium was accompanied by inflammatory changes in the decidual tissue. Very marked myometrial inflammation of both uterine segments was detected in the tissue samples of 5 women in the HUA group who underwent hysterectomy due to hypotonic bleeding during the CS.

In contrast to clinical CAM, acute hCAM was diagnosed significantly more frequently and was observed in 33.9% of patients in the HUA group, in 65.7% of patients in the EUA group and in 16% of patients in the control group. It was noted that the incidence of histologically confirmed acute CAM of stage 2+ was only 11.9% among the HUA group cases but as high as 55.7% among the EUA group cases, p<0.01. The combination of hCAM and funisitis of stage 2+ was reported in the HUA, EUA, and control groups in 12 (7.2%), 18 (25.7%), and 2 (1.4%) cases, respectively (p< 0.05). There were no cases of isolated funisitis in all observation groups.

The presence of an inflammatory reaction in the myometrium, endometrium (decidual tissue), placental, and fetal membranes was analyzed and correlated with clinical parameters of the cases in the HUA and EUA groups (Table 5).

Analysis of data (Table 5) showed rather contradictory results in the observation groups, due to the pathophysiologic opposite of the main clinical complication by which the patients were selected into groups - excessive or hypotonic uterine activity in labor.

Multiple logistic regression analysis indicated that the frequency of deciduitis was associated with the gestational age (>37 weeks in the HUA group, but <37 weeks in the EUA group), parity (nulliparity in the HUA group, but multiparity in the EUA group), GBS colonization (in the EUA group), duration of active first stage before operation (>12 h in the HUA group and >8 h in the EUA group), duration of ruptured fetal membranes before the surgery (>24 h in both groups), cervical dilation (>6 cm in both groups), and a high number of vaginal examinations in labor (in the HUA group).

The odds of myometritis in both observation groups increased with the duration of labor, advanced cervical dilation, quantity of vaginal examinations, and nulliparity (in the HUA group).

hCAM and funisitis were significantly associated in both groups with GBS colonization, parity (nulliparity in the HUA group, multiparity in the EUA group), gestational age (>37 weeks in the HUA group, but <37 weeks in the EUA group), and prolonged (>24 h) duration of ruptured fetal membranes.

Table 5. Unadjusted odds ratios and 95% confidence intervals for grade 2+ deciduitis and myometritis, stage 2+ inflammation of the placental and fetal membranes associated with various clinical preoperative factors among parturients with HUA and EUA

Factors	Decuduitis		Myometritis (lower segment)		Myometritis (both segments)		hCAM		Funisitis	
	HUA	EUA	HUA	EUA	HUA	EUA	HUA	EUA	HUA	EUA
	Odds ratio (95% CI) p-value		Odds ratio (95% CI) p-value		Odds ratio (95% CI) p-value		Odds ratio (95% CI) p-value		Odds ratio (95% CI) p-value	
Gestational age (weeks) <37	0.4 (0.1-1.3) p < 0.05	6.9 (2.2-21.9) p < 0.001	0.9 (0.04-0.7) p < 0.05	0.8 (0.5-9.3) p < 0.05	0.7 (0.03-11.8) NS	0.3 (0.02-7.1) p < 0.05	0.1 (0.02-10.6) NS	1.7 (0.3-10.6) p < 0.01	0.1 (0.05-13.7) NS	1.9 (0.3-22.8) p < 0.001
37-41	2.1 (0.9-5.2) p < 0.001	0.9 (0.3-2.5) p < 0.05	0.8 (0.6-4.6) p < 0.05	0.3 (0.08-4.9) p < 0.05	0.6 (0.1-6.1) p < 0.01	0.8 (0.7-7.7) p < 0.05	0.9 (0.2-21.2) p < 0.05	0.5 (0.2-14.5) p < 0.05	0.2 (0.04-33.4) p < 0.05	0.5 (0.04-22.1) NS
>41	1.6 (0.2-3.4) p < 0.01	-	0.6 (0.1-2.2) p < 0.05	-	0.7 (0.1-3.3) p < 0.05	-	1.2 (0.6-9.2) p < 0.05	-	0.7 (0.2-9.7) p < 0.01	-
Nulliparous	1.8 (0.5-6.2) p < 0.05	0.7 (0.3-2.8) p < 0.05	1.6 (0.5-4.8) p < 0.05	0.1 (0.2-1.6) p < 0.05	1.4 (0.2-14.2) p < 0.05	0.2 (0.07-2.1) p < 0.05	1.1 (0.3-7.3) p < 0.05	0.3 (0.05-1.7) p < 0.05	0.7 (0.2-9.2) p < 0.05	2.9 (0.2-55.8) p < 0.05
Multyparous	0.6 (0.3-1.9) p < 0.05	1.4 (0.9-16.7) p < 0.05	0.3 (1.5-7.5) p < 0.05	0.9 (0.1-8.5) p < 0.05	0.1 (0.2-7.2) p < 0.05	0.1 (0.05-1.4) p < 0.05	0.7 (0.1-4.0) p < 0.05	4.4 (3.1-14.8) p < 0.05	0.1 (0.01-6.9) p < 0.05	4.8 (0.9-24.0) p < 0.01
GBS colonization	0.7 (0.1-1.2) p < 0.05	3.5 (0.6-26.6) p < 0.001	0.7 (0.08-8.1) p < 0.05	0.1 (0.05-18.0) NS	0.6 (0.05-16.9) NS	0.8 (0.04-14.9) NS	1.3 (0.2-4.8) p < 0.01	2.7 (0.5-14.9) p < 0.05	1.2 (0.01-9.7) p < 0.05	3.5 (0.5-23.3) p < 0.01
Duration of ruptured fetal membranes before the CS >24 h	1.9 (1.0-4.4) p < 0.001	2.6 (1.0-4.4) p < 0.001	0.7 (0.2-1.3) p < 0.05	0.3 (0.08-2.7) p < 0.05	0.9 (0.2-5.5) p < 0.01	0.5 (0.05-10.4) p < 0.01	0.6 (0.2-7.9) p < 0.05	1.3 (0.2-7.8) p < 0.001	1.1 (0.02-21.2) p < 0.05	1.2 (0.8-54.5) p < 0.01
Duration of active first stage before the CS 8-12h	0.7 (0.1-3.2) p < 0.01	1.6 (0.4-12.9) p < 0.05	0.8 (0.2-2.7) p < 0.05	1.9 (1.1-18.4) p < 0.05	0.8 (0.2-3.8) p < 0.01	1.5 (0.8-21.1) p < 0.05	0.6 (0.3-9.6) p < 0.01	0.7 (0.2-5.5) p < 0.01	0.5 (0.04-31.8) NS	0.6 (0.2-28.4) NS
>12h*	2.7 (0.9-8.3) p < 0.001	-	3.5 (1.2-10.4) p < 0.001	-	4.8 (1.5-15.7) p < 0.001	-	1.2 (0.4-3.8) p < 0.01	-	0.8 (0.02-50.6) NS	-
Advanced cervical dilation at CS (>6 cm)	3.8 (1.7-8.6) p < 0.001	1.8 (0.3-10.5) p < 0.01	1.3 (0.4-3.8) p < 0.001	4.3 (1.8-9.9) p < 0.001	1.7 (0.8-6.3) p < 0.01	3.9 (1.5-10.6) p < 0.01	1.6 (0.1-5.1) p < 0.05	0.7 (0.09-34.9) NS	0.3 (0.05-13.7) NS	0.4 (0.06-22.1) NS
Number of vaginal examinations >4	7.8 (2.8-21.9) p < 0.001	-	5.4 (7.1-23.8) p < 0.001	-	1.7 (0.3-10.2) p < 0.001	-	1.1 (0.1-9.8) p < 0.01	-	0.2 (0.04-31.4) p < 0.05	-

CI - confidence interval
NS – p-value: not significant
*Oxytocin usage.

After adjustment was made for clinically relevant variables, multiple logistic regression analysis indicated that a significant relationship remained between HUA and decidual and myometrial inflammation, between EUA and deciduitis, hCAM, and funisitis (Table 6).

DISCUSSION

The correlation between two different types of labor anomalies and availability of inflammation in the uterus, placental, and fetal membrane samples was examined. The results obtained in the control group confirmed the results of the previous researchers, according to whom macrophages and neutrophils infiltrate the uterine lower segment myometrium and decidua parietalis before and at the beginning of the physiological term labor [18, 21, 22, 25, 43]. Activated macrophages and neutrophils themselves are a powerful source of pro-inflammatory cytokines, prostaglandins, proteases, and reactive oxygen species [16-18, 23-24], which are capable of initiating and amplifying inflammatory responses of the decidua, adjacent myometrium, cervix, placental and fetal membranes, and finally triggering labor. Inflammatory mediators have many diverse functions in different parts of the uterus. Within the lower segment, they take part in connective tissue remodeling

Table 6. Unadjusted odds ratios, adjusted odds ratios and 95% confidence intervals for grade 2+ deciduitis and myometritis, stage 2+ inflammation of the placental and fetal membranes in the presence of HUA and EUA

Grade/Stage 2+	HUA			EUA		
	OR (95% CI)	aOR (95% CI) *	p-value	OR (95% CI)	aOR (95% CI) *	p-value
Deciduitis	3.1 (1.0-11.1)	1.4 (0.6-3.6)	p < 0.01	5.9 (3.1-11.3)	2.6 (1.4-4.8)	p < 0.01
Myometritis (lower segment)	5.4 (2.4-8.0)	2.1 (1.2-6.2)	p < 0.01	4.3 (1.8-9.9)	0.5 (0.4-1.3)	p < 0.01
Myometritis (both segments)	9.5 (8.6-21.3)	3.9 (1.3-14.7)	p < 0.01	4.1 (1.5-10.8)	0.7 (0.3-2.4)	p < 0.05
hCAM	1.8 (0.9-28.4)	0.8 (0.3-4.9)	p < 0.05	11.0 (2.9-32.8)	4.5 (3.4-12.1)	p < 0.01
Funisitis	1.5 (1.2-24.8)	0.3 (0.6-2.7)	p < 0.05	4.7 (1.9-12.6)	2.9 (1.3-10.6)	p < 0.01

OR - odds ratio
aOR - adjusted odds ratio
CI - confidence interval
*Adjusted for gestational age, parity, GBS colonization, duration of ruptured fetal membranes, duration of active first stage, cervical dilation, number of vaginal examinations before operation.

and thereby facilitate cervical dilation and passage of the fetus. In the upper segment, leukocyte products, including eicosanoids, interleukins, and tumor necrosis factor α may stimulate uterine contractions directly or indirectly by facilitating the production of prostaglandins [18, 22]. Thus, mild inflammatory changes in the decidual membrane and slight leukocyte infiltration of the lower segment of the uterus constitute a necessary prerequisite for the physiological onset of labor.

A significant difference in parity, gestational age, and birth weight at delivery among the HUA and EUA observation groups was found. Multiparity, early gestational age, and low birth weight of newborns were strongly associated with EUA. In contrast to the EUA group, primiparous patients at term pregnancies dominated in the HUA group.

When comparing the histological findings, the localisation of inflammatory changes between the groups also differed: myometritis prevailed in the HUA group, while hCAM and funisitis were predominant in the EUA group. Both groups had a high incidence rate of decidual inflammation. It should be noted that severe deciduitis was also diagnosed in the control group (16.7%), but only in those patients who underwent surgery after several hours of regular labor against the background of premature rupture of the amniotic membranes.

The main clinical risk factors for placental and decidual membrane inflammation in the EUA group were prematurity, multiparity, GBS colonization, and duration of ruptured fetal membranes before the CS (Table 5), which is indicative of the occurrence of inflammatory changes antenatally. Despite high incidence of deciduitis (68.6%) and hCAM (55.7%) in this group, moderate to marked myometrial inflammation of both uterine segments was diagnosed in only 17.1% of patients, mostly in women with cervical dilation of >6 cm and duration of labor of >8h. In all cases, myometrial changes occurred along with severe deciduitis.

We attribute such a low incidence of myometrial lesions in the EUA group to the rapid progression of labor (mean time from the beginning of contractions to the CS was 5.6±4.2 h), and insufficient time for significant leukocyte penetration into the deeper myometrial layers of the lower and upper uterine segments. High magnitude of aORs for deciduitis, hCAM and funisitis (2.6, 4.5, 2.9, respectively, p<0.01 (Table 6) in patients in the EUA group indicate involvement of not only the decidual but also the chorioamniotic membranes in the synthesis of proinflammatory cytokines. If physiological levels of inflammatory agents contribute to normal uterine contraction, it is reasonable to assume that their significantly elevated rates will cause stronger contractions and lead to hypertensive uterine dysfunction. In our opinion, the key factor in this process is that the myometrium remains intact by inflammation.

The inflammatory nature of tachysystole was also confirmed by some of our clinical and therapeutic observations. We noted the ineffectiveness of acute tocolysis in 13 of 22 patients (59.1%) who received tocolytic drugs alone, and a decrease of the uterine activity in the remaining 9 of 22 women (40.9%) who were prescribed tocolytics in combination with antipyretics against the background of clinical CAM symptoms (hyperthermia). Thus, uterine hyperfunction, which is insensitive to tocolytic agents, comes as a response of the unaffected myometrium to the release of huge concentrations of pro-inflammatory cytokines into the bloodstream. In such situations, the use of anti-inflammatory drugs rather than tocolytic agents may be more effective in the treatment of uterine tachysystole.

It is well-known that hCAM and funisitis demonstrate an inflammatory response of the placenta, fetal mem-

branes, and amniotic fluid to microbial invasion of the amniotic cavity [12-14, 19], and deciduitis indicates an ascending pathway of infection [15, 22-23]. However, in the HUA group our data showed the association of decreased uterine contractility with grade 2+ deciduitis (aOR: 1.4, 95% CI: 0.6-3.6), but no association with stage 2+ hCAM (aOR: 0.8, 95% CI: 0.3-4.9) and stage 2+ funisitis (aOR: 0.3, 95% CI: 0.6-2.7) (Table 6). The limitation of our study was the inability to obtain histological specimens before or at least at the beginning of labor in the observation groups. Therefore, we are unable to deny or state with certainty that inflammation of parietal decidua was present or absent before the labor. Such clinical risk factors for the development of severe deciduitis as protracted active first stage, advanced cervical dilation, and a large number of vaginal examinations (Table 5) revealed during statistical analysis in the HUA group indicate the progression of inflammatory pathology of the decidual membrane intrapartum. The latter suggests that progressive severe deciduitis may be an additional risk factor for the development of hypotonic uterine activity.

In contrast to the EUA group, moderate to severe myometritis was a common finding in patients of the HUA group (53.6% of cases). In multiple stepwise logistic regression analysis, myometrial inflammation was largely associated with nulliparity, protracted active first stage with oxytocin augmentation, advanced cervical dilation, and the number of vaginal examinations (Table 5). The results of our study partially coincide with the earlier works by L.T. Keski-Nisula and coauthors (2003) [43], and J.M. Gonzalez and coauthors (2011) [21] who noted inflammatory cell infiltration of the myometrium with an increase in the duration of labor and cervical dilation.

Severe myometrial inflammation in all cases was detected in conjunction with severe deciduitis (84/84), much less frequently with severe hCAM (15/84) and funisitis (7/84). Long-term weak contractions, only temporarily enhanced by oxytocin, allow decidual inflammation to spread deeper into the myometrium of both the lower and upper segments of the uterus. According to our histological data, it can be concluded that development of myometritis in patients with HUA is the result of ascending deciduitis that gradually progresses to grade 2+ during prolonged labor. Slow penetration of leukocytes into the myometrium leads to remodeling of the extracellular matrix, dysregulation of oxytocin receptor synthesis, and a decrease in the uterine response to both intrinsic and extrinsic oxytocin [26, 33, 37]. The consequence of long-lasting labor augmentation with oxytocin is insensitivity to this agent, complete uterine inertia, and postpartum hemorrhage [26, 27]. The latter occurred in 5 parturients with total leukocyte infiltration of the myometrium who underwent hysterectomy due to atonic uterine bleeding. In such situations, the possibility of prescribing other groups of uterotonics should be considered when choosing drugs for the prevention or treatment of postpartum bleeding.

CONCLUSIONS

Mild inflammation of the decidual membrane and the myometrium of the lower uterine segment at term pregnancy is a physiological phenomenon that contributes to the initiation of labor. Inflammation of the chorioamniotic and decidual membranes against the background of intact myometrium plays a fundamental role in the occurrence of hypertensive uterine dysfunction, particularly in preterm birth. Inflammatory changes in the myometrium of the lower and especially upper uterine segment arising during prolonged term labor are an additional factor contributing to the onset or aggravation of the hypotonic uterine activity. Strategies aimed at preventing the influx of inflammatory cells into the uterine cavity can be crucial for the prevention of preterm labor, as well as for the coordination of uterine activity at term labor.

REFERENCES

1. Gill P, Henning JM, Carlson K et al. Abnormal Labor. Treasure Island (FL): StatPearls Publishing. 2023.
2. Hobson SR, Abdelmalek MZ, Farine D. Update on uterine tachysystole. J Perinat Med. 2018;0(0):1-9. doi:10.1515/jpm-2018-0175. DOI
3. LeFevre NM, Krumm E, Cobb WJ. Labor dystocia in nulliparous women. Am Fam Physician. 2021;103(2):90-96.
4. Blankenship SA, Raghuraman N, Delhi A et al. Association of abnormal first stage of labor duration and maternal and neonatal morbidity. Am J Obstet Gynecol. 2020;223(3):445.e1-445.e15. doi:10.1016/j.ajog.2020.06.053. DOI
5. Ragusa A, Gizzo S, Noventa M et al. Prevention of primary caesarean delivery: comprehensive management of dystocia in nulliparous patients at term. Arch Gynecol Obstet. 2016;294(4):753–761. doi:10.1007/s00404-016-4046-5. DOI
6. Ende HB, Lozada MJ, Chestnut DH et al. Risk factors for atonic postpartum hemorrhage: a systematic review and meta-analysis. Obstet Gynecol. 2021;137(2):305-323. doi:10.1097/AOG.0000000000004228. DOI
7. Heuser CC, Knight S, Esplin MS et al. Tachysystole in term labor: incidence, risk factors, outcomes, and effect on fetal heart tracings. Am J Obstet Gynecol. 2013;209(1):32.e1–6. doi:10.1016/j.ajog.2013.04.004. DOI

8. Smith S, Zacharias J, Lucas V et al. Clinical associations with uterine tachysystole". J Matern Fetal Neonatal Med. 2014;27:709-13. doi:10.3109/14767058.2013.836484. DOI
9. Sims ME. Legal briefs: tachysystole, uterine rupture, and a bad outcome. Neoreviews. 2019;20(2):e110-e112. doi:10.1542/neo.20-2-e110. DOI
10. Leathersich SJ, Vogel JP, Tran TS et al. Acute tocolysis for uterine tachysystole or suspected fetal distress. Cochrane Database Syst Rev. 2018;7(7):CD009770. doi: 10.1002/14651858.CD009770.pub2. DOI
11. Reynolds AJ, Geary MP, Hayes BC. Intrapartum uterine activity and neonatal outcomes: a systematic review. BMC Pregnancy Childbirth. 2020;20(1):532. doi:10.1186/s12884-020-03219-w. DOI
12. Kim CJ, Romero R, Chaemsaithong P et al. Acute chorioamnionitis and funisitis: definition, pathologic features, and clinical significance. Am J Obstet Gynecol. 2015;213:S29–52. doi:10.1016/j.ajog.2015.08.040. DOI
13. Tita ATN, Andrews WW. Diagnosis and management of clinical chorioamnionitis. Clinics in Perinatology. 2010;37(2):339–354. doi:10.1016/j.clp.2010.02.003. DOI
14. Romero R, Chaemsaithong P, Korzeniewski SJ et al. Clinical chorioamnionitis at term III: how well do clinical criteria perform in the identification of proven intra-amniotic infection? J Perinat Med. 2015. doi:10.1515/jpm-2015-0044. DOI
15. Markin LB, Tatarchuk TF, Shatylovych KL. Pathogenetic therapeutic and preventive measures in women of risk group of isthmicocervical incompetence. Reprod Endocrin. 2017;4(36):44-47. doi:10.18370/2309-4117.2017.36.44-47. DOI
16. Slutsky R, Romero R, Xu Y et al. Exhausted and senescent T cells at the maternal-fetal interface in preterm and term labor. J Immunol Res. 2019;23:1–16. doi:10.1155/2019/3128010. DOI
17. Than NG, Hahn S, Rossi SW et al. Editorial: fetal-maternal immune interactions in pregnancy. Front Immunol. 2019;10:2729. doi:10.3389/fimmu.2019.02729. DOI
18. Gomez-Lopez N, StLouis D, Lehr MA et al. Immune cells in term and preterm labor. Cell Molecul Immunol. 2014;11(6):571-581. doi:10.1038/cmi.2014.46. DOI
19. Romero R, Chaemsaithong P, Korzeniewski SJ et al. Clinical chorioamnionitis at term II: the intra-amniotic inflammatory response. J Perinat Med. 2015;44(1):5-22. doi:10.1515/jpm-2015-0045. DOI
20. Sklyarova VO, Filipyuk AL, Shatylovych KL et al. Platelet-rich plasma in the management of chronic endometritis treatment in women with reproductive health disorders. Eur J Med Health Sci. 2020;2(6):1-3. doi:10.24018/ejmed.2020.2.6.560. DOI
21. Gonzalez JM, Franzke C-W, Yang F et al. Complement activation triggers metalloproteinases release inducing cervical remodeling and preterm birth in mice. Amer J Pathol. 2011;179(2):838–849. doi:10.1016/j.ajpath.2011.04.024. DOI
22. Hamilton S, Oomomian Y, Stephen G et al. Macrophages infiltrate the human and rat decidua during term and preterm labor: evidence that decidual inflammation precedes labor. Biol Reprod. 2012;86(2):39. doi:10.1095/biolreprod.111.095505. DOI
23. Hamilton SA, Tower CL, Jones RL. Identification of chemokines associated with the recruitment of decidual leukocytes in human labour: potential novel targets for preterm labour. PLoS ONE. 2013;8(2):e56946. doi:10.1371/journal.pone.0056946. DOI
24. Keelan JA. Intrauterine inflammatory activation, functional progesterone withdrawal, and the timing of term and preterm birth. J Reprod Immunol. 2018;125:89-99. doi:10.1016/j.jri.2017.12.004. DOI
25. Shynlova O, Nadeem L, Zhang J et al. Myometrial activation: Novel concepts underlying labor. Placenta. 2020;92:28-36. doi:10.1016/j.placenta.2020.02.005. DOI
26. Zackler A, Flood P, Dajao R et al. Suspected chorioamnionitis and myometrial contractility: mechanisms for increased risk of cesarean delivery and postpartum hemorrhage. Reprod Sci. 2019;26(2):178-183. doi:10.1177/1933719118778819. DOI
27. Wetta LA, Szychowski JM, Seals S et al. Risk factors for uterine atony/postpartum hemorrhage requiring treatment after vaginal delivery. Am J Obstet Gynecol. 2013;209(1):51.e1-e6. doi:10.1016/j.ajog.2013.03.011. DOI
28. Wiley RL, Racusin D, Chen HY et al. Chorioamnionitis and adverse outcomes in low-risk pregnancies: a population based study. Am J Obstet Gynecol. 2020;222:S244-S245. doi:10.1080/14767058.2021.1887126. DOI
29. Conde-Agudelo A, Romero R, Jung EJ et al. Management of clinical chorioamnionitis: an evidence-based approach. Am J Obstet Gynecol. 2020;223(6):848-869. doi:10.1016/j.ajog.2020.09.044. DOI
30. Wisner K. Intrapartum management of chorioamnionitis. MCN Am J Matern Child Nurs. 2018;43(1):52. doi:10.1097/NMC.0000000000000396. DOI
31. Burgess APH, Katz JE, Moretti M et al. Risk factors for intrapartum fever in term gestations and associated maternal and neonatal sequelae. Gynecol Obstet Invest. 2017;82(5):508-16. doi:10.1159/000453611. DOI
32. Wang C, Sirluck Schroeder I, Sosa Cazales A et al. Management of fever in labor after institution of a standardized order set at a maternity quaternary care center. Am J Obstet Gynecol. 2019;221(6):687. doi:10.1016/j.ajog.2019.10.041. DOI
33. Dior UP, Kogan L, Eventov-Friedman S et al. Very high intrapartum fever in term pregnancies and adverse obstetric and neonatal outcomes. Neonatology. 2016;109(1):62-8. doi:10.1159/000440938. DOI
34. Kissler K, Hurt KJ. The pathophysiology of labor dystocia: theme with variations. Reprod Sci. 2023;30(3):729-742. doi:10.1007/s43032-022-01018-6. DOI

35. Friedman EA, Cohen WR. The active phase of labor. Am J Obstet Gynecol. 2023;228(5S):S1037-S1049. doi:10.1016/j.ajog.2021.12.269. DOI
36. WHO recommendations for augmentation of labor. Executive summary. Geneva: World Health Organization. 2014. https://www.ncbi.nlm.nih.gov/books/NBK258881/. [Accessed 14 April 2023]
37. Brüggemann C, Carlhäll S, Grundström H et al. Labor dystocia and oxytocin augmentation before or after six centimeters cervical dilatation, in nulliparous women with spontaneous labor, in relation to mode of birth. BMC Pregnancy Childbirth. 2022;22(1):408. doi:10.1186/s12884-022-04710-2. DOI
38. Dike NO, Ibine R. Hypotonic Labor. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2023.
39. Prevention of Group B Streptococcal Early-Onset Disease in Newborns: ACOG Committee Opinion, Number 797. Obstet Gynecol. 2020;135(2):e51-e72. doi: 10.1097/AOG.0000000000003668. DOI
40. Committee Opinion No. 797: Prevention of Group B Streptococcal Early-Onset Disease in Newborns: Correction. Obstet Gynecol. 2020;135(4):978-979. doi: 10.1097/AOG.0000000000003824. DOI
41. Ayres-de-Campos D, Arulkumaran S. FIGO intrapartum fetal monitoring expert consensus panel. FIGO consensus guidelines on intrapartum fetal monitoring: Introduction. Int J Gynaecol Obstet. 2015;131(1):3-4. doi:10.1016/j.ijgo.2015.06.017. DOI
42. Altemani A, Gonzatti A, Metze K. How many paraffin blocks are necessary to detect villitis? Placenta. 2003;24(1):116-117. doi:10.1053/plac.2002.0875. DOI
43. Keski-Nisula LT, Aalto M-L, Kirkinen PP. Myometrial inflammation in human delivery and its association with labor and infection. Am J Clin Pathol. 2003;120:217-224. doi:10.1309/KC6KDTX98LFYB3J7. DOI
44. Nath CA, Ananth CV, Smulian JC et al. Histologic evidence of inflammation and risk of placental abruption. Am J Obstet Gynecol. 2007;197:319e1–319e6. doi:10.1016/j.ajog.2007.06.012. DOI
45. Keski-Nisula L, Aalto ML, Katila ML et al. Intrauterine inflammation at term: a histopathologic study. Hum Pathol. 2000;31:841–846. doi:10.1053/hupa.2000.8449. DOI
46. Redline RW. Placental pathology: a systematic approach with clinical correlations. Placenta. 2008;29:S86–91. doi:10.1016/j.placenta.2007.09.003. DOI
47. Khong TY, Mooney EE, Ariel I. Sampling and definitions of placental lesions Amsterdam placental workshop group consensus statement. Arch Pathol Lab Med. 2016;140:698–713. doi:10.5858/ arpa.2015-0225-CC. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Kateryna L. Shatylovych
Danylo Halytsky Lviv National Medical University
64 Pekarska st., 79010 Lviv, Ukraine
e-mail: shatik2@ukr.net

ORCID AND CONTRIBUTIONSHIP

Kateryna L. Shatylovych: 0000-0002-8465-0355 A B C D
Leonid B. Markin: 0000-0003-0237-7808 E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 13.10.2023
ACCEPTED: 17.07.2024