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FIRST TRIMESTER MICROBIOLOGY OF THE CERVIX AND THE OUTCOME OF PREGNANCIES AT HIGH RISK FOR PREMATURITY

MIKROBIOLOGIJA VRATA MATERNICE PRVOGA TROMJESEČJA I ISHOD TRUDNOĆA S RIZIKOM ZA NEDONOŠENOST

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Original paper

Key words: first trimester cervical colonisation, Chlamydia trachomatis, Ureaplasma urealyticum, perinatal outcome

Summary. ***Objective.*** To examine and compare the course and outcome of pregnancies with microbiologically positive versus microbiologically negative cervical smears in the first trimester of pregnancy and particularly to determine the impact of chlamydial and ureaplasma colonization on perinatal outcome. ***Methods.*** In a group of 155 pregnancies at high risk for spontaneous abortion or preterm delivery, cared for at the Department of Gynecology and Obstetrics, University of Zagreb School of Medicine, cervical swabs collected during the first trimester were microbiologically analysed. Aerobes, anaerobes, and mycoplasmas were searched for by cultivation of agents, while Chlamydia trachomatis was analysed by ligase chain reaction. Antibiotic treatment was introduced immediately after receiving the results of analysis. Pregnant women were divided in two groups, among whom the Group I consisted of 55 women with a positive microbiological result of cervical smear, and Group II consisted of 100 women with microbiologically negative results. Additionally, as no one case of other mycoplasmas but Ureaplasma urealyticum was found, the infections due to Chlamydia trachomatis and Ureaplasma urealyticum were analysed separately. Student's t-test, Fisher exact test and chi-square test were used for statistical analysis, considering p value of <0.05 as statistically significant. ***Results.*** No difference in proportion of term deliveries and gestational age at the delivery was observed between the groups. In the Group I an increase in preterm rupture of membranes (two times) and intra-amniotic infection (p<0.006) was observed, and perinatal asphyxia and connatal infection in newborns was detected more often (18.7% Vs 2.3%, and 16.6% Vs 6.9%, respectively; p<0.001 for asphyxia). Three out of 50 liveborns in the Group I (6.0%) and 2 out of 88 liveborns in the Group II (2.3%) died early neonatally (p=n.s.). The most frequently isolated agents were Chlamydia trachomatis, isolated in 18, and Ureaplasma urealyticum in 17 pregnancies. The course of pregnancies with Chlamydia trachomatis, when compared to those with negative smear, was more frequently complicated with preterm contractions (6 out of 18 or 33,3%), mean gestational age at the delivery was 37.2 weeks, only 31% of infants were healthy (p=0.027). Neonatal death rate was 5.5%. Ureaplasma urealyticum colonization, when compared to pregnancies with sterile smear, was connected to significantly higher frequency of intra--amniotic infection (7 out of 17 or 41%), premature rupture of membranes before term was three times more frequent (3 out of 17 or 17,6%), gestational age at the delivery was shorter (35.1 weeks), only 25% of newborns were regarded as being healthy (p=0.029). No one child died early neonatally. ***Conclusion.*** Cervical colonization with aerobes, anaerobes and both Ureaplasma urealyticum and Chlamydia trachomatis, identified during the first trimester of pregnancy, complicated the pregnancy and had impact on frequent neonatal complications, irrespective of immediate cure.

Izvorni članak

Ključne riječi: infekcija u prvom tromjesječju, Klamidija trahomatis, Ureaplazma urealitikum, perinatalni ishod

Sažetak. ***Cilj.*** Ispitati i usporediti tijek i ishod trudnoća u trudnica s bakteriološki pozitivnim u odnosu na trudnice s bakteriološki negativnim cervikalnim obriskom tijekom prvog tromjesječja trudnoće, posebice učinak kolonizacije Klamidijom trahomatis i Ureaplazmom urealitikum na perinatalni ishod. ***Metode.*** Tijekom prvog tromjesječja u 155 ispitanica s visokim rizikom spontanoga pobačaja ili prijevremenog poroda, liječenih u Klinici za ženske bolesti i porode Medicinskog fakulteta Sveučilišta u Zagrebu, uzeti su cervikalni obrisci. Aerobi, anaerobi i mikoplazme dokazane su kultivacijom, a Klamidija trahomatis ligaza lančanom reakcijom. Ciljano antibiotsko liječenje provedeno je odmah nakon dokaza uzročnika. Trudnice su podijeljene u dvije skupine. U I. skupini bilo je 55 trudnica s pozitivnim cervikalnim obriskom, a u II. skupini

100 trudnica s negativnim obriscima. Infekcije Klamidijom trahomatis i Ureaplazmom urealitikum analizirane su odvojeno. Za statističku analizu korišten je Studentov t-test, Fisherov i χ^2 test uzimajući p<0,05 kao statistički značajno. ***Rezultati.*** Između skupina nije bilo razlike u raspodjeli ročnih poroda i trajanju trudnoće. U I. skupini primijećen je porast učestalosti prijevremena prsnuća vodenjaka (dva puta) i intraamnijske infekcije (p<0,006), a češća je perinatalna asfiksija i konatalna infekcija (18,7% prema 2,3% i 16,6% prema 6,9%); p<0,001. Rano neonatalno umrle djece u I. skupini je 3 od 50 živorođenih (6,0%), a u II. skupini 2 od 88 (2,3%) živorođenih, (p=n.s.). Najčešće izolirani uzročnik je Klamidija trachomatis u 18 i ureaplazma urealitikum u 17 trudnica. Trudnice s izoliranom Klamidijom trahomatis u odnosu na trudnice s negativnim cervikalnim obriskom imaju veću učestalost prijevremenih kontrakcija (6 od 18 ili 33,3%). Srednja gestacijska dob u terminu poroda bila je 37,2 tjedna, samo 31% djece je zdravo. Neonatalno umire 5,5% djece. Uspoređujući trudnoće s izoliranom Ureaplazmom urealitikum s trudnicama negativna obriska, utvrđena je povećana učestalost intraamnijalnih infekcija (7 od 17 ili 41%) i tri puta češće prerano prsnuće vodenjaka (3 od 17 ili 17,6%). Dob trudnoće pri porodu bila je kraća (35,1 tjedan), samo 25% djece je zdravo (p=0,029), ali nije bilo neonatalno umrlih. ***Zaključak.*** Pozitivni cervikalni obrisci tijekom prvog tromjesječja trudnoće povezani su s većim brojem komplikacija u trudnoći i povećavaju učestalost neonatalnih komplikacija bez obzira na provedeno liječenje.

Introduction

Chlamydia trachomatis is the most common and potentially preventable bacterial cause of sexually transmitted disease in women of reproductive age.[1,2] It can be cultured from the cervices of 2% to 24% of gravidas, depending on the demographic profile of the population.[3] Chlamydial infection in most pregnant women is subclinic.[4] The effects of asymptomatic chlamydial infection or colonization on pregnancy outcome are controversial. There is some evidence that untreated chlamydial infection in pregnancy may contribute to adverse complications such as premature rupture of membranes (PROM), preterm labor and birth, low birth weight, and stillbirth;[5–7] on the other hand, some authors have found that only women with recent chlamydial infection, characterised by a positive chlamydial culture and antichlamydial IgM antibodies, were more likely to have preterm labor, PROM or offspring with low birth weight and complications of prematurity,[8–12] so the impact of chlamydial colonization in high risk pregnancy is questionable. Genital mycoplasmas, especially Ureaplasma urealyticum, are more frequent genital agents.[13,14] It is less known about their impact on pregnancy course and adverse perinatal outcome too.[15] Although, many older studies negate correlation between Ureaplasma urealyticum colonization in the vagina and cervix with abortion or preterm delivery, it is the most commonly isolated microorganism from preterm birth placentas,[16] from amniotic fluids of pregnant women with PROM or pregnant women with preterm labor with intact membranes[17–19] and subacute intramniotic infection (SIAI).[20]

There is no doubt that target antibiotic treatment is possible,[21,22] but questions are when is it necessary and is it always necessary.[9] We tried to study the significance of microbiological analysis during the first trimester of the risk pregnancies on their outcome, so that special attention was paid to the colonization with Chlamydia trachomatis and Ureaplasma urealyticum too.

Pregnancies and methods

One hundred and fifty five (155) asymptomatic high-risk pregnant women with known results of their first trimester cervical microbiological cultures are included in the study. All were women with a history of late spontaneous abortion or spontaneous preterm delivery in at least two of their previous pregnancies.

Pregnant women were cared for during the period from 1991 to 1997 at the Department of Gynaecology and Obstetrics, Division of perinatal medicine, Zagreb University School of Medicine, tertiary level perinatal centre for Croatian population. Cervical swabs were collected during the first trimester of pregnancy, processed immediately and microbiologically analysed by cultivation on the presence of aerobes and anaerobes and genital mycoplasmas. Chlamydia trachomatis was searched for by ligase chain reaction.

The targeted antibiotic treatment was started immediately after positive results of microbiological specimen cultivation. The medication was administered perorally in all cases. Chlamydia trachomatis was treated by either erythromycin (»Eritromicin« Belupo, 2 grams daily for 10 days) or azithromycin (»Sumamed« Pliva, 500 mg daily for 3 days); Ureaplasma urealyticum was treated by erythromycin (2 grams daily for 10 days); other infections were treated according to the antibiogram by amoxicilin (»Amoxil«, Pliva, 2 grams daily for 10 days), cephalexin (»Ceporex« Pliva, 2 grams daily for 10 days), metronidazole (»Efloran« Krka, 1500 mg daily for 10 days). The male partner was treated too, although sexual intercourse was forbidden. The control cervical swabs were not collected regularly, so that after treatment results could not be classified according to the course and perinatal outcome.

Pregnant women were divided into two groups. The first group consisted of those having positive microbiological results of cervical swabs (Group I), while the second group had microbiologically negative cervical specimen (Group II). There were no significant differences between the groups regarding the age, other extragenital and genital diseases. As Ureaplasma urealyticum (the only mycoplasma isolated) and Chlamydia trachomatis were the most commonly isolated agents, the course and perinatal outcome was separately compared between the pregnant women with negative cultures and the pregnant women with treated Chlamydia trachomatis and Ureaplasma urealyticum colonisation.

Gestational age at the delivery, as well as spontaneous abortion or stillbirth, preterm labour and PROM, SIAI, perinatal loss rate, perinatal and neonatal death rate and

the status of the newborns after the delivery was analysed. SIAI was diagnosed by clinical and laboratory criteria.[17,18] SIAI was diagnosed if either overt clinical syndrome with uterine tenderness, foul smell of vaginal bloody discharge and fever occurred, or when elevated white blood cell count accompanied by elevated levels of immature leukocyte forms or elevated C-reactive protein persisted in at least two occasions two days apart, without other obvious extragenital course.[19] All infants were cared for by experienced neonatologists. Connatal infection in the newborn was diagnosed by clinical criteria, and only occasionally blood cultures were done prior to the start of antibiotic therapy, if there was no need for maternal antibiotic therapy prior to or during the delivery. Gestational age was based on the known date of the last period, conception or by the first trimester ultrasonography. Prematurity was defined as gestational age of less than 37 completed weeks of pregnancy, and spontaneous abortion when pregnancy ended with stillborn prior to 28 completed weeks. Respiratory distress syndrome (RDS) was diagnosed by attending neonatologist and confirmed by chest x-ray. When 5 minute Apgar score was under 7, perinatal asphyxia was diagnosed.[23] In children with convulsions, those who showed increased spasticity or hypotonia during the early neonatal period until discharge, the diagnosis of early signs of possible brain damage (newborn encephalopathy) was made, irrespective of the results of neonatal brain ultrasound examination, as stated in our previous reports.[24,25] Small for gestational age newborns were defined as birth weight $<10^{th}$ percentile for gestational age, parity and sex on the basis for standards for Croatian singletons.[26] Children without signs of perinatal asphyxia or else in no need for artificial oxygenation, medicamentous therapy, blood transfusion etc, were considered as having an uneventful early neonatal period and being healthy.[23] Perinatal loss was defined as the sum of fetal and early neonatal deaths irrespective of gestational age. Early neonatal death rate was defined as neonatal death rate after the completition of 22 weeks of pregnancy.

Data were presented as mean (+/– standard deviation) or as proportion, Student's t-test for independent variables, and Fisher exact test and chi-square test, for categorical variables, were used for statistical analysis. Values of $p<0,05$ were considered to be statistically significant.

Results

In 55 pregnant women (Group I) the bacteriological agent was identified, while in 100 pregnant women the swab was microbiologically sterile (Group II). Chlamydia trachomatis was recovered from 18, Ureaplasma urealyticum from 17 patients, so these were the most frequently isolated agents. No other mycoplasmas were encountered. Together, Chlamydia nad Ureaplasma made 64% of all isolated agents. Grampositive aerobes were isolated in 13 cases, gram-negative aerobes in 11, anaerobes in 7. Chlamydia was more frequently detected as sole than Ureaplasma (13 pregnancies from 18 or 76%). In two cases it was recovered together with Ureaplasma and in three cases together with either Klebsiella pneumoniae or Enterococcus. Ureaplasma was isolated together with other pathogens in 6 cases (Chlamydia, Candida, beta-hemolytic Streptococcus, E. coli, Enterococcus, and anaerobes).

The course of further pregnancy was without irregularities in 38.2% of Group I pregnancies and in 43% of Group II pregnancies. There was no difference in the frequency of intrauterine growth restriction, premature labour or preeclampsia among the groups. The PROM

Table 1. Course and outcome of pregnancies at risk for preterm delivery depending on the first trimester cervical smear
Tablica 1. Tijek i ishod trudnoće s rizikom prijevremenog rađanja ovisno o obrisku vrata maternice tijekom prvog tromjesečja

	Group I Skupina I (N=55)	Group II Skupina II (N=100)	p
Gestational age (weeks) Tjedni trudnoće	35.9±5.9	36.2±6.4	n. s.
Normal course Uredan tijek	21 (38.2%)	43 (43.0%)	n. s.
Term deliveries Ročni porod	37 (67.2%)	61 (61.0%)	n. s.
Spontaneous abortion Spontani pobačaj	4 (7.3%)	11 (11.0%)	n. s.
IUGR	9 (16.4%)	18 (18.0%)	n. s.
PROM	7 (12.7%)	6 (6.0%)	n. s.
Preterm labor Prijevremeni porod	14 (25.5%)	20 (20.0%)	n. s.
SIAI	14 (25.5%)	8 (8.0%)	0.006
Perinatal loss Perinatalni gubitak	6 (10.9%)	14 (14.0%)	n. s.
Sectio cesarea Carski rez	25 (46.7%)	29 (29.0%)	n. s.

Group I – microbiologically positive first trimester cervical smear
trudnice s mikrobiološki pozitivnim obriskom;
Group II – microbiologically negative first trimester cervical smear
trudnice s mikrobiološki negativnim obriskom;
IUGR – intrauterine growth restriction/intrauterini ograničeni rast;
PROM – preterm rupture of membranes/prijevremeno prsnuće vodenjaka;
SIAI – syndrome of intra-amniotic infection
sindrom intraamnijske infekcije

Table 2. Neonatal complications depending on maternal first trimester cervical smear
Tablica 2. Komplikacije u novorođenčadi ovisno o obrisku vrata maternice u prvom tromjesečju

	Group I Skupina I (n=50)	Group II Skupina II (n=88)	p
Connatal infection Konatalna infekcija	8 (16.0%)	6 (6.8%)	n. s.
Perinatal asphyxia Perinatalna asfiksija	9 (18.0%)	2 (2.3%)	0.001
Encephalopathy Encefalopatija	1 (2.0%)	1 (1.1%)	n. s.
Healthy newborn Zdravo dijete	32 (64.0%)	72 (81.8%)	n. s.
Early neonatal death Rano neonatalno umrli	3 (6.0%)	2 (2.3%)	n. s.

Group I – microbiologically positive first trimester cervical smear
trudnice s mikrobiološki pozitivnim obriskom;
Group II – microbiologically negative first trimester cervical smear
trudnice s mikrobiološki negativnim obriskom

was more frequent in Group I. Eleven out of 100 gestations in the Group II and 4 out of 55 in Group I ended as spontaneous abortions (p=n.s.). When observed for very early preterm deliveries, those between 24–32 weeks and 32–36 weeks, Group I and II had similar occurrence for either 24–32 week group (7.2% and 6% respectively) and 32–36 week group (12.7% and 13.0%). Significant difference was found in the proportion of SIAI (25.5% in Group I versus 8% in Group II, p=0.006), *(Table 1).* According to the further data *(Table 2),* connatal infection was two times higher in Group I, and perinatal asphyxia significantly more frequent in the same group (p<0.001), while healthy newborns were more present in the Group II. The proportion of caesarean deliveries was also higher in the group Group I *(Table 1).*

Mean gestational age in Ureaplasma urealyticum colonization was 35 and in chlamydial colonisation it was 37 weeks. Both chlamydial and ureaplasmatic colonization were frequently associated with preterm labor, but PROM was more frequent after Ureaplasma urealyticum colonization, as well as the occurrence of SIAI (p=0.002). In pregnant women with Ureaplasma urealyticum colonization there were 2 stillborns out of 17 babies. There was no one early neonatal death. There were no stillborns in women with Chlamydia trachomatis colonization, one out of 18 babies died early neonatally *(Table 4).* However, early neonatal development was disturbed in almost two thirds of surviving newborns of mothers with cervices colonized by either Chlamydia trachomatis or Ureaplasma urealyticum, (p<0.001) compared to newborns of mothers without cervical colonization *(Table 3).*

Table 3. Outcome of pregnancies at risk for preterm delivery with first trimester Chlamydia and Ureaplasma urealyticum colonization compared to pregnancies with negative smear

Tablica 3. Ishod trudnoće u trudnica s rizikom prijevremenog rađanja i klamidijom trahomatis, odnosno ureazplasmom urealitikum s trudnicama s negativnim obriskom

	Group II Skupina II (N=100)	Ureaplasma (N=17)	Chlamydia (N=18)	p
Gestational age (weeks) Dob trudnoće (tjedni)	36.2±6.4	35.1±5.9	37.2±3.6	n. s.
PROM	6 (6.0%)	3 (17.6%)	1 (5.5%)	n. s.
SIAI*	8 (8.0%)	7 (41.0%)	2 (11.0%)	0.002
Preterm labor Prerani porod	20 (20.0%)	5 (29.4%)	6 (33.3%)	n. s.
Cerclage Serklaža	45 (45.0%)	3 (17.6%)	6 (33.3%)	n. s.
Term delivery Ročni porod	61 (61.0%)	7 (41.0%)	7 (38.8%)	n. s.
Normal pregnancy Uredna trudnoća	43 (43.0%)	4 (23.5%)	4 (22.0%)	n. s.
Stillborns Mrtvorođeni	12 (12.0%)	2 (11.7%)	0	n. s.
Early neonatal death Rano neonatalno umrli	2 (2.3%)	0	1 (5.5%)	n. s.
Healthy newborns** Zdrava djeca	72 (83.7%)	3/12 (25.0%)	5/15 (31.0%)	<0.001

Group II – microbiologically negative first trimester cervical smear trudnice s mikrobiološki negativnim obriskom;
PROM – preterm rupture of membranes / prerano prsnuće vodenjaka;
SIAI – syndrome of intra-amniotic infection sindrom intraamnijske infekcije;
* p<0.001 (Group II Vs Ureaplasma); p=0.08 (Ureaplasma Vs Chlamydia);
** p=0.029 (Group II Vs Ureaplasma); p=0.027 (Group II Vs Chlamydia)

Table 4. Fetal and neonatal deaths depending on first trimester cervical smear

Tablica 4. Fetalna i neonatalna smrt ovisno o obrisku vrata maternice tijekom prvog tromjesečja

Case Trudnoća	Cerv. smear Obrisak	Outcome Ishod	Weeks Tjedni	Birth weight Težina	PHD
1.	Chlamydia	Neonatal death Neonatalna smrt	29	1400	Asphyxia
2.	Ureaplasma	Stillborn Mrtvorođeni	30	1130	Asphyxia
3.	Ureaplasma	Stillborn Mrtvorođeni	19	220	Immaturus
4.	E. coli	Stillborn Mrtvorođeni	17	170	Immaturus, infect
5.	Anaerobes	Stillborn Mrtvorođeni	12	?	?
6.	Anaerobes	Stillborn Mrtvorođeni	22	200	Immaturus
7.	Sterile	Stillborn Mrtvorođeni	38	4000	Infection
8.	Sterile	Stillborn Mrtvorođeni	27	930	Asphyxia
9.	Sterile	Stillborn Mrtvorođeni	9	?	?
10.	Sterile	Stillborn Mrtvorođeni	10	?	?
11.	Sterile	Stillborn Mrtvorođeni	14	?	?
12.	Sterile	Stillborn Mrtvorođeni	28	1680	Asphyxia
13.	Sterile	Stillborn Mrtvorođeni	24	620	Asphyxia
14.	Sterile	Stillborn Mrtvorođeni	24	300	Immaturity
15.	Sterile	Stillborn Mrtvorođeni	20	220	Immaturity
16.	Sterile	Stillborn Mrtvorođeni	21	370	Immaturity
17.	Sterile	Stillborn Mrtvorođeni	25	400	Immaturity
18.	Sterile	Stillborn Mrtvorođeni	22	220	Immaturity
19.	Sterile	Neonatal death Neonatalna smrt	26	980	RDS
20.	Sterile	Neonatal death Neonatalna smrt	29	1040	RDS

PHD – pathoanatomic diagnosis / patoanatomske dijagnoze;
RDS – respiratory distress syndrome / sindrom respiracijskog distresa

Discussion

In the paper presented we tried to find out the impact of cervical colonization with potential pathogens during the first trimester on the outcome of pregnancies at high risk for preterm delivery. We were well aware of the fact that preterm delivery is not a single entity but a cluster of conditions with different etiologies and our aim was not to try to find out a possible triggering event or etiol-

ogy. We just wanted to reveal whether bacteriological screening early in gestation in pregnancies at high risk could aid improving the outcome of gestation. As expected,[27,28] and proved in the paper, previous preterm birth carries significant risk for each further pregnancy. However, bacterial colonization could complicate such gestations even more. Numerous data from the literature[29] and our own results[30] clearly show how the colonization of the uterine cervix can disrupt the course of gestation. When untreated, endocervical colonization surely favour the development of chorioamnionitis, PROM, preterm delivery, delivery of the newborns with low birth weight (<2500 g), perinatal asphyxia, and connatal infections.[30–32] We have shown that among women at high risk there was no difference in the duration of pregnancy, newborn weight or term gestations, irrespective of microbiological finding and treatment. However, in women with microbiologically proven cervical colonization the frequency of SIAI was significantly higher, the proportion of the connatally infected was twice as high, the frequency of perinatal asphyxia and caesarean deliveries was increased. The ascendant development of the infection might start before the beginning of medical treatment and become harmful irrespective of it.[34] Additionally, even though the bacteria had been successfully destroyed, the adverse effect might appear by the ill effect of cytokines or other numerous small molecules present at the colonisation/inflammation site before and during the therapy on the process of implantation and placentation[33] or the early development of the brain of the fetus.[33,34] All that could lead to what appears to be perinatal asphyxia or newborns maladaptation, and today we might only speculate about possible long term consequences.[6–8,24,25,30,33]

Chlamydia trachomatis was, similarly to other reports,[4,13,35] the most commonly isolated agent. The pregnancy course as well as the perinatal outcome in pregnant women with chlamydial treatment within the first trimester does to some extent differs from the pregnancy outcome in pregnant women with negative cervical smears. The results of our study are in accordance with the thesis that the targeted antibiotic treatment of chlamydial infection in early pregnancy might diminish the probability of some, but not all complications.[14] The targeted treatment by erythromycin or azythromycin has proved to diminish the danger of PROM, but not the danger of preterm contractions,[16] and in spite to the hope that it also diminishes the probability of vertical transfer of infection to the newborn,[36] our results are not so encouraging; about 60% of newborns had certain complications during the early neonatal period, although only one died because of asphyxia. From our department the paper was presented with the results of 462 pregnant patients with previous spontaneous abortions and/or preterm deliveries with special regard to chlamydial colonization, and irrespective of other aerobic or anaerobic colonization. The incidence of chlamydial colonization was 26.8%. In the treated patients the rate of pregnancy wastage was significantly decreased when compared to untreated patients.[13]

In spite of early detection and targeted treatment Ureaplasma urealyticum colonization is suspected to carry increased risk for the development of intra-amniotic infection and PROM and rise the danger of frequent disturbance in the early neonatal course, especially in very premature newborns. Although there have been the reverse reports as well, the Ureaplasma urealyticum is the most commonly isolated microorganism from the amniotic fluid of women with premature contractions and PROM.[21,22,37] It shows that it is unusually important etiological factor in development of premature birth. The research that included the microbiological analysis, determination of interleukins 6- or 1-beta, tumour necrosis factor and leukocytes in amniotic fluid, and the pathohistological changes in placenta, together with the determination of interleukin 6 in the umbilical cord blood, has shown that the infection of Ureaplasma urealyticum provokes strong immunologic reaction in mother's amnion and decidua.[38] The study of Horowitz and colleagues has shown that the colonization of cervix by Ureaplasma urealyticum, if followed by the increased synthesis of antibodies, is a significant prognostic indicator for various pregnancy complications.[39] Even the successfully conducted treatment and the proven negativization of smear did not diminish the frequency of premature birth. Additionally, the efficacy of Ureaplasma urealyticum treatment in the early pregnancy is still sometimes questionable.[16,39] We must admit that the high frequency of disorders in our study and some previous studies[39] could be all the same the consequence of failure in treatment, in at least a part of the cases.

Considering the danger that they present, the comprehensive approach in dealing with infections in pregnancy is highly important, especially in pregnant women with the risk of giving premature birth.[35] Our data have clearly shown that, although the risk of prematurity was high in all analysed women, only the children of those colonized were prone to severe neonatal complications, as first to asphyxia (significantly more frequent), encephalopathy (two times more frequent) and connatal infection (two times more frequent). The doctrine of such an approach must be based primary on the prevention of colonization, adequate detection policy and the adequate treatment of potential pathogens. The worst outcome occurs in unscreened (and untreated) women, as we have previously shown.[13,30] Positive result in risk pregnancies by itself diminishes the changes for successful pregnancy, so each positive pregnant woman has to be treated. The identification of a pathogen is important, since it is obvious that not all the pathogens affect the pregnancy in the same way.[41] Although it is estimated that about 75% of colonizations are successfully treated, control smears might be recommended.[42,43]

The question still is, however, should the serological test[44] be conducted in order to differentiate the pregnant women with high risk of complications from the ones with chronic colonization and no potential risk, and also should all the women be screened at all. Some researchers recommend the selection of Chlamydia trachomatis during the first examination in pregnancy for all preg-

nant women and again during the third trimester for those older than 25, those with found agent, the pregnant women who incline to promiscuity and who had a new partner in the last three months, etc.[45] A few other, on the other hand, dispute the justification of routine identification of chlamydial colonization, considering that the additional control prospective studies of endocervical cultures are needed for such an attitude.[46] The majority speak in favour of additional research and constant reevaluation of results.[45,46] Our data can help in making the proper decision in at least pregnancies considered to be at high risk for prematurity. It showed that the microbiological analysis in early pregnancy is legitimate, the treatment needs to be undertaken, control of the treatment might be important although we never know if additional treatment is of any benefit.

Colonization by Ureaplasma urealyticum in early pregnancy proved, however, dangerous even besides the targeted treatment. Even after its bacteriological eradication, Ureaplasma urealyticum imperils significantly the outcome of pregnancy.[16,40,41] Prevention of Ureaplasma infection, preconceptional bacteriological, and even serological analysis and preconceptional treatment will probably show the best way to avoid complications.

Further research should thus be focused on evaluation of the necessity of preconceptional bacteriological and serological analyses and adequate treatment with the primary aim of preventing harmful consequences of both chlamydial and ureaplasma colonization/infection in pregnancy.

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