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Effect of *Ureaplasma/Mycoplasma* genital tract infection on preterm labor

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ABSTRACT

Objectives: Genitourinary tract infections in pregnant women are one of the causes of abnormal pregnancy development including miscarriages, premature labor or premature rupture of membranes (PPROM). Atypical bacteria responsible for reproductive tract infections include *Mycoplasma genitalium*, *Mycoplasma hominis*, *Ureaplasma urealyticum* and *Ureaplasma parvum*. Identification of pathogens and appropriately selected therapy can improve obstetric outcomes in patients with symptoms of threatened miscarriage or threatened preterm labor. The purpose of our study is to analyze the impact of reproductive tract infections with *ureaplasma* and *mycoplasma* bacteria during pregnancy.

Material and methods: In the presented study, we retrospectively analyzed the cases of 201 pregnant patients hospitalized in the Obstetrics and Gynecology Department of Poznan Regional

Hospital in 2019-2022, who had a swab taken from external os area of the cervix for atypical bacteria - *Ureaplasma* and *Mycoplasma*. Only patients with symptoms of threatened miscarriage or threatened preterm labor were included in the study group. Microbiological tests were performed in the hospital laboratory with the Mycoplasma IST 3 test from Biomerieux.

Results: We found a higher incidence of preterm labor in patients with symptoms of threatened preterm labor and a genital tract infection with *Ureaplasma/Mycoplasma* bacteria, compared to patients not infected with *Mycoplasma/Ureaplasma* — 31.1% vs 20% (p = 0.098). This observation in the case of *Ureaplasma/Mycoplasma* monoinfection group applied to 6 patients. — 75% of the group. Pregnant patients who had co-infection with other types of bacteria (48 patients in total) gave birth before 37 weeks of pregnancy in 27.1% of cases. We obtained a significant difference (p = 0.007) when comparing groups with positive and negative cultures for *Ureaplasma/Mycoplasma* by the presence of monoinfection/coinfection and the week of pregnancy in which delivery occurred. We also noted the effect of atypical bacterial infection for PPROM — this complication preceded preterm delivery in 40% of ureaplasma-positive patients, compared to 20% of PPROM without infection. We found a similar rate of preterm labor and pregnancy loss in *Ureaplasma/Mycoplasma*-positive patients who received antibiotic therapy (35.7%) compared to a group of pregnant women who did not receive treatment (31.6%).

Conclusions: Infection of the genital tract with atypical bacteria *Ureaplasma* and *Mycoplasma* has a negative impact on the course of pregnancy. Identification of the type of microorganisms in cervical canal secretions of pregnant patients with symptoms of threatened miscarriage or preterm labor seems crucial. The impact of antibiotic therapy though, requires further analysis.

Keywords: *Ureaplasma*; *Mycoplasma*; preterm labor; birth tract infection; premature preterm rupture of membranes (PPROM); miscarriage

INTRODUCTION

One of the groups of pathogens responsible for genitourinary infections are atypical bacteria, such as *Mycoplasma genitalium, Mycoplasma hominis, Ureaplasma urealyticum* and *Ureaplasma parvum*. They can be found both in the normal bacterial flora of the vagina in sexually active women and may be the causative agent of chorioamnionitis, inflammation of the appendages, bacterial vaginosis or endometritis in the puerperium [1–3]. They often cause infections with an asymptomatic course, making diagnosis and treatment difficult.

Ureaplasma bacteria are present in the vaginal secretions of about 50% of pregnant women, but only a fraction of them become infected by the ascending route,

leading to intrauterine infection and preterm labor [4–6]. Each year, about 15 million babies worldwide are born prematurely, accounting for about 11% of all births. In Europe, the number of births before 37 weeks of pregnancy is gradually increasing [7]. Although *Ureaplasma* infection is an independent risk factor for adverse pregnancy outcome, the greatest risk is in patients with additional aggravating factors, such as bacterial vaginosis in pregnancy [8] or a previous history of preterm labor [9].

The exact mechanism of this phenomenon is not known. Abnormal vaginal bacterial flora can pave the way for ascending infection by *Ureaplasma* bacteria by weakening local immunity in the lower parts of the reproductive tract as well as affect the increase in the number of atypical bacteria [4]. At the same time, the urease produced by *Ureaplasma* breaks down urea to ammonia and *Mycoplasma* produces ammonia from arginine. These reactions lead to an increase in the pH of vaginal secretions and facilitate genital tract infections with other pathogens facilitating the development of, for example, bacterial vaginosis [10].

Ureaplasma are the most isolated pathogens in cervical secretions and of the amniotic cavity in patients who have had a preterm delivery or PPROM [11–13]. These pathogens found in upper respiratory tract secretions, blood serum or cerebrospinal fluid in premature babies, increase the risk of bronchopulmonary dysplasia, open ductus arteriosus, chronic lung disease, intraventricular brain hemorrhage leading to severe complications and increasing neonatal and child mortality [14, 15].

The gold standard in identification of *Ureaplasma* is the microbiological culture, which allows simultaneous determination of an antibiogram when the pathogen is found in the material under examination. A more modern and accurate method of pathogen identification uses polymerase chain reaction (PCR), which is particularly applicable for the determination of a specific bacterial species. The disadvantage of the method is the inability to perform an antibiogram. Treatment of asymptomatic vaginal infections in pregnancy remains a contentious issue. Given the prevalence of *Ureaplasma* infections in pregnant women, it seems that the intervention group should be more carefully selected [4]. At the same time, studies on the treatment of vaginal infections in pregnancy have shown that the inclusion of oral or vaginal antibiotic therapy prolongs the duration of pregnancy [16, 17]. The drugs of choice in pregnant women and children remain macrolides including erythromycin, azithromycin and clarithromycin [18–22].

Purpose

The purpose of our study is to analyze the impact of lower genital tract infections with *Ureaplasma* or *Mycoplasma* bacteria in pregnant patients with symptoms of threatened miscarriage or threatened preterm labor illustrated by pregnant women hospitalized at the Obstetrics and Gynaecology Department at Regional Hospital in Poznan in 2019–2022. We will retrospectively analyze the frequency of genital tract infections with atypical bacteria in the study group based on available medical records. We will check whether infection with *Ureaplasma/Mycoplasma* bacteria affects the subsequent course of pregnancy, including the incidence of preterm labor or premature preterm rupture of membranes (PPROM). We will compare the type of delivery, number of past pregnancies and type of pregnancy (single or multiple) in patients with positive and negative cultures for atypical bacteria. We will determine the prevalence of infections with aerobic, anaerobic bacteria or fungi in the lower genital tract in both groups of patients and their impact on the timing of delivery. We will also evaluate whether the lack of treatment for *Ureaplasma/Mycoplasma* in a swab taken from the external os area of the cervical canal significantly affects the subsequent course of pregnancy.

MATERIAL AND METHODS

In this study, we retrospectively analyzed the cases of 201 pregnant patients. hospitalized in the Obstetrics and Gynecology Department of Poznan Regional Hospital in 2019–2022, who were swabbed for atypical bacteria — *Ureaplasma* and *Mycoplasma* — from the external orifice of the cervical canal due to symptoms of threatened miscarriage or threatened preterm labor. These patients manifested the following clinical symptoms: lower abdominal pain, spotting or bleeding from the genital tract, uterine contraction activity, cervical shortening, dilation of the cervical canal or preterm premature rupture of the membranes.

Our department belongs to the second level of referral of perinatal care.

The analysis was based on medical records - results of bacteriological cultures and electronic records, including discharge cards available in the hospital integrated information system, as well as information obtained directly from patients whose deliveries took place outside our center. The group of patients included both primiparous and multiparous women, in single and twin pregnancies.

Microbiological tests were performed in the hospital laboratory using the Mycoplasma IST 3 test from Biomerieux. The antibiogram included the reaction to:

- azithromycin, clarithromycin, erythromycin, ciprofloxacin, ofloxacin, doxycycline;
- tetracycline, iosamycin, and pristinamycin in tests performed in 2019 and 2020;

— erythromycin, levofloxacin, moxifloxacin, telithromycin, and tetracycline in tests performed in 2021 and 2022.

Microbiologists interpreted the antibiogram according to The European Committee on Antimicrobial Susceptibility Testing (EUCAST) bacteria v 9.0, 10.0, 11.0 and 12.0 depending on when the test was performed (2019–2022).

Positive culture results were considered those in which bacteria were present at the level of $\geq 10^4$/mL.

Statistical significance p was calculated using Pearson's Chi-square test or Fisher's exact test, depending on whether the relevant assumptions were met. A $p \leq 0.05$ value was considered as the cutoff point.

RESULTS

During the analyzed years (2019–2022), bacterial cultures were performed from the area of the external os of the cervical canal for Ureaplasma and Mycoplasma in 236 pregnant women. The inclusion criterion for the study was the known type and time of delivery. The studies of 61 positive and 140 negative (Fig. 1, 2) patients were used for further analysis (Fig. 1, 2). The remaining 35 patients were excluded from the study, due to incomplete data on the course of the pregnancy. In 4 patients at the time of writing the paper the pregnancy was still ongoing.

Figure 1. The number of patients with positive and negative culture results from the cervical canal for *Ureaplasma/Mycoplasma* bacteria, considering the calendar year in which the test was performed

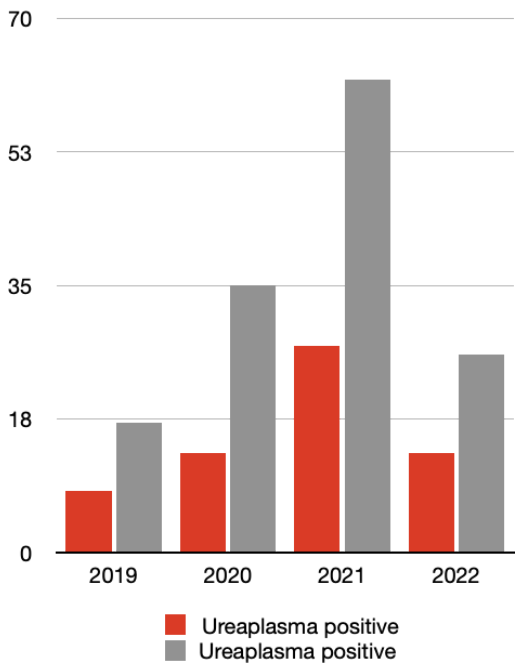
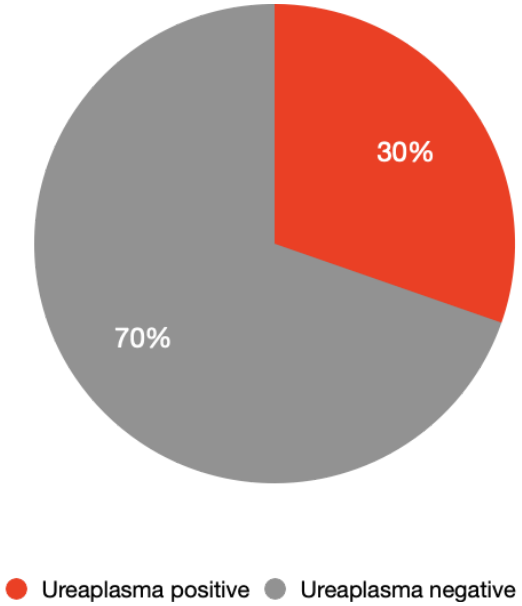


Figure 2. Total number [%] of positive and negative *Ureaplasma* patients in 2019–2022



The gestational age of positive patients ranged from 13-36 completed weeks of pregnancy. Patients with threatened miscarriage accounted for 9.8% and the remaining 90.2% of cases included pregnant women with features of threatened preterm labor. The gestational age of the patients in whom we obtained a negative result for *Ureaplasma/Mycoplasma* was in the range of 12–36 weeks. In this group, signs of threatened miscarriage affected 11.4% and threatened preterm labor affected 88.6% of women (Tab. 1).

Table 1. Comparison of characteristics in groups of patients with positive and negative cultures for *Ureaplasma/Mycoplasma*. Groups were compared using Pearson's Chi-square test or Fisher's exact test (F), depending on whether assumptions were met

Attribute	**Culture result for *Ureaplasma/Mycoplasma***		**p-value (statistical significance)**
	Positive	**Negative**	
Number of cultures performed in 2019–2022	61 (100.0)	140 (100.0)	–
Gestational age at which culture was performed			

	< 22	6 (9.8)	16 (11.4)	0,931
	> 21+6	55 (90.2)	124 (88.6)	
Type of antibiotics used				
	Azithromycin	36 (59.0)	–	
	Clarithromycin	2 (3.3)	–	
	Clindamycin	2 (3.3)	–	
	Azithromycin + clarithromycin	1 (1.6)	–	
	Azithromycin + clindamycin	1 (1.6)	–	–
	No information available	19 (31.1)	–	
Time of pregnancy completion				
	< 22	2 (3.3)	2 (1.4)	
	> 21 + 6 **i {PL?}** <37	19 (31.1)	28 (20.0)	0,098 (F)
	> 36 + 6	40 (65.6)	110 (78.6)	
Time of pregnancy completion				
Patients treated				
	< 37	15 (24.6)	–	
	> 36 + 6	27 (44.3)	–	
Patients who did not take treatment				–
	< 37	6 (9.8)	–	
	> 36 + 6	13 (21.3)	–	
Type of delivery				
	Vaginal delivery	35 (59.3)	77 (55.8)	
	Caesarean section	24 (40.7)	61 (44.2)	0.764
Cervical culture result for aerobic bacteria, anaerobic bacteria and fungi				
	Positive	49 (80.3)	118 (84.3)	
	Negative	8 (13.1)	21 (15.0)	0.063 (F)
	Not performed	4 (6.6)	1 (0.7)	
The result of the cervical culture for aerobic bacteria, anaerobic bacteria and fungi, and the week of pregnancy in which the delivery occurred*				
	Positive			
	< 37	13 (23.2)	26 (19.0)	
	> 36 + 6	35 (62.5)	91 (66.4)	
	Negative			**0.007**

	< 37	6 (10.7)	2 (1.5)	
	> 36 + 6	2 (3.6)	18 (13.1)	
Obstetric history (number of current pregnancy)				
	I	24 (39.3)	61 (43.6)	
	> I	37 (60.7)	79 (56.4)	0.687
Type of current pregnancy				
	Singelton pregnancy	55 (90.2)	133 (95.0)	
	Multiple pregnancy	6 (9.8)	7 (5.0)	0.220 (F)
Time of delivery				
	< 22	2 (3.3)	2 (1.4)	
	> 21 + 6 **i** < 37	19 (31.1)	28 (20.0)	0.139
	> 36 + 6	40 (65.6)	110 (78.6)	
Time of delivery				
	< 22 and > 21 + 6 and < 37	21 (34.4)	30 (21.4)	
	> 36 + 6	40 (65.6)	110 (78.6)	0.077
Cervical culture result for aerobic bacteria, anaerobic bacteria and fungi*				
	Positive	48 (85.7)	117 (85.4)	
	Negative	8 (14.3)	20 (14.6)	> 0.999
The week of pregnancy in which the delivery occurred*				
	< 37	19 (33.9)	28 (20.4)	
	> 36 + 6	37 (66.1)	109 (79.6)	0.072
Positive: Cervical culture results for aerobic bacteria, anaerobic bacteria and fungi, and the week of pregnancy in which the delivery occurred*				
	< 37	13 (27.1)	26 (22.2)	
	> 36 + 6	35 (72.9)	91 (77.8)	0.641
Negative: The result of the cervical culture for aerobic bacteria, anaerobic bacteria and fungi, and the week of pregnancy in which the delivery occurred*				
	< 37	6 (75.0)	2 (10.0)	

	> 36 + 6	2 (25.0)	18 (90.0)	**0.002**

*Excludes patients with miscarriage and patients without aerobic and anaerobic bacterial cultures

In the microbiological results obtained, *Ureaplasma* was responsible for the infection of the lower genital tract (96.7% of positive results), in two cases *Mycoplasm*a was cultured (3.3% of positive results).

Among the analyzed group, preterm labor between 22 and 36 + 6 weeks of gestation occurred in 19 patients, representing 31.1% of pregnant women with positive smear results for atypical bacteria and known course of pregnancy. 3.3% of *Ureaplasma* positive patients had a miscarriage, in both cases at 17 weeks of pregnancy. Timely deliveries, above 36 + 6 weeks' gestation, occurred in 40 patients, accounting for 65.6% of cases (Tab. 1).

Patients were treated within the department or included in outpatient treatment. The most used drug was azithromycin — 36 cases, clarithromycin in two patients or clindamycin in two patients. In two cases, two drugs were used in therapy — azithromycin with clarithromycin and azithromycin with clindamycin. In 19 patients, no information was found regarding the included treatment, which was mainly due to the lack of final culture results before discharge from the ward and failure to report for the test result within the indicated timeframe, transfer of the pregnant woman to a higher referral center, or the occurrence of miscarriage or preterm labor within a short period of time after the swab collection (Tab. 1).

We performed a similar analysis in patients with negative cultures from the area of the external os of the cervical canal for atypical bacteria. In the analyzed group, preterm labor occurred in 28 out of 140 patients with a known week and method of delivery, which is 20% of the group (Tab. 1).

Ureaplasma/Mycoplasma-positive patients. Our observations shows that regardless of the inclusion of treatment in patients with confirmed infection with atypical bacteria, the incidence of preterm labor or miscarriage in both groups is similar and it is, interestingly, 35.7% in the treated group and 31.6% in the group without antibiotic therapy (Tab. 1).

To broaden the diagnosis and try to determine the cause of symptoms of threatened miscarriage or preterm labor, we additionally performed cultures from the area of the external orifice of the cervical canal for aerobic bacteria, anaerobic bacteria and fungi. The positive results were obtained in 49 *Ureaplasma/Mycoplasma*-positive pregnant women, which accounted for 80.3%. results. In the group of *Ureaplasma/Mycoplasma*-negative patients, we found genital tract infection with other types of bacteria or fungi in 118 pregnant women which was 84.3%. In addition, we contrasted the above data with the weeks of gestation in which delivery occurred. In the group of *Ureaplasma/Mycoplasma*-positive patients, preterm

labor occurred in 13 out of 48 cases of established infection with other types of bacteria and fungi (27.1%) and in 6 of 8 cases with monoinfection (75%). In the *Ureaplasma/Mycoplasma*-negative group, preterm labor occurred in 26 out of 117 patients with infection with aerobic bacteria, anaerobic bacteria or fungi (22.2%) and 2 out of 20 patients without genital tract infection (10%). When comparing these three characteristics, we obtained statistical significance at the level of $p = 0.007$. For the group with negative cultures for aerobic bacteria, anaerobic bacteria and fungi (*Ureaplasma/Mycoplasma* negative and positive, split by week of delivery), we achieved significance at the level $p = 0.002$ (Tab. 1).

On analyzing the medical records, it was found that *Ureaplasma/Mycoplasma*-positive patients had the complication of PPROM with subsequent delivery before 37 weeks of gestation, accounting for 47.4% of preterm deliveries in the group under study. In all of them, the delivery occurred between 33–36 weeks of gestation. In 3 cases, the situation involved twin pregnancies. Accordingly, in the *Ureaplasma/Mycoplasma*-negative group, PPROM occurred in 12 cases, of which in 11 patients' delivery occurred before 37 weeks of pregnancy, which accounts for 39.3% of preterm deliveries in this group. The situation in 3 cases involved twin pregnancies. In one of the pregnant women with PPROM found at 24 weeks of gestation, delivery took place on time (38 weeks of gestation).

When interpreting the results of the study, *Ureaplasma/Mycoplasma*-positive patients were also divided according to their obstetric history — 24 pregnant women were primiparous (39.3%), for the remaining 37 women it was a second or subsequent pregnancy (60.7%). The youngest of the analyzed patients was 16-years-old at the time of the study, while the oldest was 43. Among *Ureaplasma/Mycoplasma*-negative patients, the majority were also, accounting for 56.4% of patients in this group, 43.6% were primiparous. The age range in this group of patients was 22–46 years. No significant statistical difference was obtained in the compared groups ($p = 0.687$) (Tab. 1).

The group with positive cultures for atypical bacteria included both patients with single pregnancies — 90.2% and twin pregnancies — 9.8%. One of the multiple pregnancies was a monochorionic diamniotic twins, while the other 5 were dichorionic diamniotic twins. All multiple pregnancies ended prematurely (between 33–36 weeks).

In the group of *Ureaplasma*-negative patients, among the 7 dichorionic diamniotic twins (5% of the study group), 4 ended between 34–36 weeks of gestation, 3 patients gave birth after 36 + 6 weeks of gestation. Patients with singleton pregnancies made up 95% of the *Ureaplasma*-negative group (Tab. 1).

DISCUSSION

In the group of 201 of analyzed patients, which were hospitalized at the Obstetrics and Gynecology Department of Poznan Regional Hospital in 2019–2022, for threatened

miscarriage or threatened preterm labor, there were 61 positive cultures from the area of the external outlet of the cervical canal for *Ureaplasma/Mycoplasma* and 140 negative results. Cases with a known course of pregnancy were included in the analysis. Patients with positive cultures accounted for about one-third of all pregnant women on the ward with a risk of preterm labor or pregnancy loss. In the literature, the percentage of at-risk of infection, pregnant women were as high as 57% [23]. A positive vaginal *Ureaplasma/Mycoplasma* culture is an independent predictive factor for preterm birth in patients with symptomatic threatened preterm labor and short cervix [23].

Ureaplasma accounted for 96.7% of positive culture results. The tests we use do not differentiate between *Ureaplasma* for *U. urealyticum* and *U. parvum*. Determination of the specific bacterial genus could provide additional relevant information, especially considering reports of a higher risk of pregnancy complications with *U. parvum* infection [24].

We mostly used azithromycin to treat genital tract infections with atypical bacteria. The decision on treatment was primarily made based on the antibiogram (2019 and 2020 cultures) and in view of the relative safety of macrolides in pregnant women [20]. Interestingly, we noted no significant difference in the incidence of miscarriage or preterm labor in *Ureaplasma*-positive patients receiving antibiotic therapy compared to pregnant women who did not receive treatment. A team investigating the effects of treatment for *Ureaplasma/Mycoplasma* infection in patients with high-risk factors for preterm birth came to similar conclusions [25]. This observation warrants further analysis. Data obtained in other previously described studies indicate a positive correlation of antibiotic therapy on prolongation of pregnancy duration and successful neonatal outcomes [26].

Approximately 30% of patients with positive cultures for atypical bacteria had a preterm delivery, of which nearly half of the pregnancies were complicated by PPROM. The percentage of preterm deliveries in the group of *Ureaplasma/Mycoplasma*-negative patients was lower, accounting for 20%, of which 40% were associated with PPROM.

There was a higher percentage of pregnant women with symptoms of threatened miscarriage or preterm labor who additionally had a genital tract infection with aerobic and anaerobic bacteria or fungi. In *Ureaplasma/Mycoplasma*-positive patients, co-infection with other types of microorganisms occurred in 80.3% of the studied population and in *Ureaplasma/Mycoplsma*-negative patients in 84.3%. The presence of aerobic and anaerobic bacteria in the genital tract may influence the facilitation of *Ureaplasma* or *Mycoplasma* expansion and the incidence of pregnancy complications [4, 8, 9]. In the group of patients that we have studied, the risk of preterm delivery was paradoxically higher in patients with known monoinfection of the genital tract with *Ureaplasma* bacteria compared to patients with additional infection with other types of pathogens (75% vs 27%). The least frequent delivery before 37 weeks occurred in the case of negative results of both types of cultures — 10%. We

obtained a statistically significant difference in the compared groups (p = 0.007). And for the group with negative cultures for aerobic bacteria, anaerobic bacteria and fungi the differences were also significant (p = 0.002).

There was no significant predominance of either type of delivery in patients with positive or negative cultures for *Ureaplasma/Mycoplasma*. In both groups of patients, differentiated based on the presence of atypical bacteria in the genital tract, the vaginal route of pregnancy completion prevailed. *Ureaplasma/Mycoplasma*-positive patients had a lower percentage of deliveries by cesarean section, 40.7%, than representatives of the other group, 44.2%.

Ureaplasma/Mycoplasma-positive patients were predominantly women with second or subsequent pregnancy (61%) and in 12% of cases these were multiple pregnancies. All patients in twin pregnancies with positive cultures gave birth prematurely.

CONCLUSIONS

Infection with *Mycoplasma/Ureaplasma* bacteria of the reproductive tract has a significant impact on the course of pregnancy. It increases the risk of pregnancy loss and preterm labor preceded by, among others, cervical shortening or PPROM. Identification of pathogens in cervical canal secretions is particularly important in patients with pregnancy risk symptoms. Although we were not able to obtain better obstetric outcomes in *Ureaplasma*-positive patients receiving treatment compared to pregnant women not receiving therapy, this observation requires further analysis on a larger number of cases.

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Available from the author.

Ethics statement

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Conflict of interest

All authors declare no conflict of interest.

Supplementary material

None.

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