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UREAPLASMA IN PREGNANCY. IS THERE ANY RISK FOR PRETERM LABOR?

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Keywords:
Ureaplasma, preterm birth, pregnancy outcomes, inflammation, NAAT, fetal membranes.

Introduction. *Ureaplasma species, particularly Ureaplasma urealyticum and Ureaplasma parvum, inhabit the lower genital tract of sexually active women and have been linked to adverse reproductive outcomes. This review highlights their role in preterm delivery, along with detection challenges and pathogenic mechanisms.*

Material and methods. *This review compiles data from 25 studies, encompassing a total of approximately 15,700 patients. These studies include retrospective and prospective cohorts, cross-sectional designs, and case-control studies. Key parameters evaluated included impact of Ureaplasma species on pregnancy outcomes, such as preterm labor and chorioamnionitis.*

Results. *The studies reviewed (2000–2024) included 10 retrospective, 8 prospective, 4 cross-sectional, and 3 case-control designs. Ureaplasma parvum was found in 40.5% of healthy women and Ureaplasma urealyticum in 20.3%. Intra-amniotic infection increased preterm delivery risk (OR: 2.76–3.0), with preterm birth rates ranging from 26% to 58.6%. Ureaplasma induces pro-inflammatory cytokines, activates neutrophils and TLR-9, and increases prostaglandin and matrix metalloproteinase activity, weakening fetal membranes and triggering preterm labor.*

Conclusions. *Ureaplasma spp. significantly contribute to preterm delivery, primarily through inflammatory processes and membrane damage. Further research with prospective randomized studies is recommended.*

Cuvinte-cheie:
Ureaplasma, naștere prematură, rezultate ale sarcinii, inflamație, NAAT, membrane fetale.

UREAPLASMA ÎN SARCINĂ. FACTOR DE RISC PENTRU NAȘTEREA PREMATURĂ?

Introducere. *Speciile de Ureaplasma, în special Ureaplasma urealyticum și Ureaplasma parvum, colonizează tractul genital inferior al femeilor active sexual și, în timp, au fost asociate cu diverse complicatii reproductive. Aceast review analizează rolul speciilor de Ureaplasma în nașterea prematură, concomitent cu posibilele dificultăți de identificare și mecanismele patogenice.*

Material și metode. *Aceast review sintetizează date din 25 de studii, care au inclus 15.700 de paciente. Studiile analizate cuprind cohorte retrospective și prospective, studii transversale și studii de caz-control. Principalele aspecte evaluate sunt impactul speciilor Ureaplasma asupra rezultatelor sarcinii, în special în travaliul prematur și corioamniotită.*

Rezultate. *Materialele analizate (2000–2024) includ 10 studii retrospective, 8 prospective, 4 transversale și 3 studii de caz-control. Astfel, Ureaplasma parvum a fost identificată la 40,5% dintre femeile sănătoase, iar Ureaplasma urealyticum la 20,3%. Infecția intra-amniotică a crescut riscul de naștere prematură (OR: 2,76–3,0), cu rate ale nașterii premature între 26% și 58,6%. Ureaplasma determină producerea de citokine proinflamatorii, activează neutrofilele și receptorul TLR-9, crescând producția de prostaglandine și activitatea metaloproteinazelor matriceale, ceea ce duce la slăbirea membranelor fetale și declanșarea travaliului prematur.*

Concluzii. *Speciile de Ureaplasma contribuie semnificativ la provocarea nașterii premature, în principal prin mecanisme inflamatorii și deteriorarea membranelor fetale, de aceea, sunt necesare cercetări suplimentare prin studii prospective randomizate.*

INTRODUCTION

Numerous asymptomatic, healthy individuals have *Ureaplasma* species (*Ureaplasma* spp.) colonization in their genitourinary tract. Mycoplasmas are rarely the only organisms isolated from a genitourinary specimen, therefore determining whether they are co-isolates or pathogens that cause illness can occasionally be challenging. Publicly available research on these species pathogenicity frequently has significant design flaws. These species have historically been challenging and complex to detect. Recognition of *Ureaplasma urealyticum* (*U. urealyticum*) in unfavorable pregnancy outcomes is rising. Adverse outcomes in a pregnant woman include chorioamnionitis, preterm premature rupture of membranes, spontaneous preterm labor, spontaneous abortions and even stillbirth. These microorganisms may not be necessary for pathological conditions to arise from the vaginal flora on their own. Additional factors may also need to be present in order for certain events to happen.

MATERIAL AND METHODS

This review synthesizes data from studies published between 2000 and 2024. We were particularly interested in the type of study, study design, the number of patients involved, methods used to detect *Ureaplasma* spp., and key findings related to *Ureaplasma* spp. colonization and pregnancy outcomes.

We conducted a comprehensive search across multiple databases (e.g., PubMed, Scopus, and Web of Science) using a combination of Boolean operators and keywords to identify relevant studies. The search terms included variations of "*Ureaplasma*," "preterm birth," "pregnancy outcomes," and "infection." The following Boolean operators were used:

- "*Ureaplasma* and preterm birth"
- "*Ureaplasma* or *Mycoplasma* and pregnancy"
- "*Ureaplasma* and infection and preterm labor"

We did not apply any language restrictions to the search, but studies published in English and widely spoken languages were prioritized for inclusion. The search was last updated in May, 2024 to ensure that the most current research was included. We used the PRISMA flow diagram to visually represent the study selection process (fig. 1). This diagram is included in the supplementary materials for clarity.

Studies were included if they met the following criteria:

1. Investigated the presence and effects of *Ureaplasma* spp. in pregnant women.
2. Reported outcomes related to preterm birth.
3. Utilized reliable detection methods such as NAAT or culture-based techniques.

Data from the selected studies were extracted and categorized. We were particularly interested in:

- Study type (retrospective, prospective cohort, cross-sectional, case-control).
- Number of patients included in each study.
- Detection methods used and their accuracy.

Descriptive statistics were used to summarize the data from the selected studies. Odds ratios (OR) and percentages were calculated to quantify the association between *Ureaplasma* colonization and adverse pregnancy outcomes. The statistical significance of these associations was assessed to determine the reliability of the findings. To mitigate publication bias, we conducted a comprehensive search without language restrictions.

There was significant heterogeneity in the reporting methods used across the included studies. While most studies relied on PCR for detecting *Ureaplasma* species, other methods such as bacterial cultures or serological tests were also used. This variation in diagnostic standards may introduce bias and affect the comparability of study results.

We acknowledge that the differences in diagnostic techniques and the lack of uniformity in defining preterm birth and other pregnancy outcomes may contribute to heterogeneity and potential bias in the findings.

RESULTS

This review analyzed 25 studies published between 2000 and 2024 (fig.1), involving 15,700 patients. The studies included 10 retrospective, 8 prospective cohort, 4 cross-sectional, and 3 case-control designs (tab. 1).

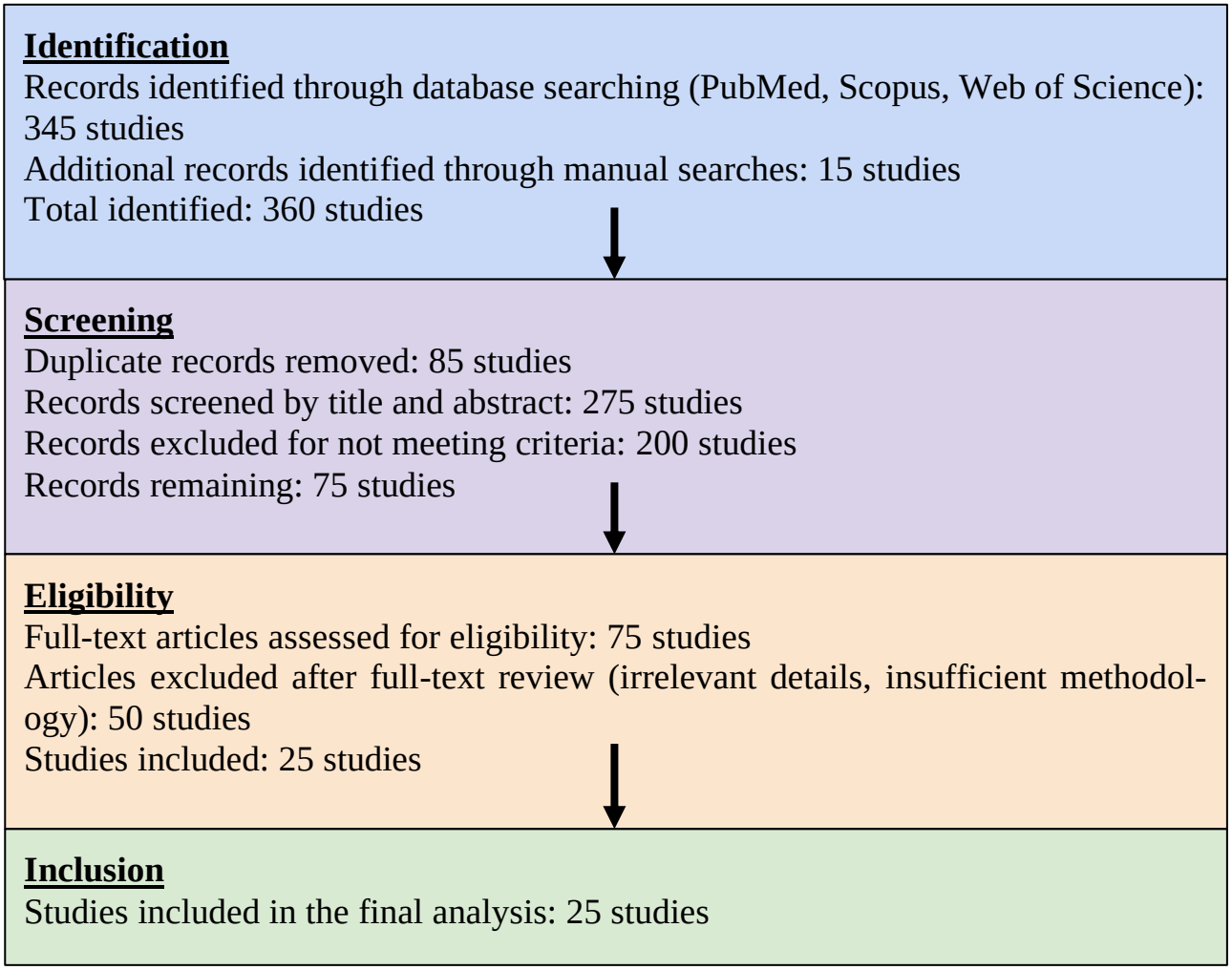

Figure 1. PRISMA diagram. Summary of study selection.

Ureaplasma parvum was detected in 40.5% of healthy women, while *Ureaplasma urealyticum* was found in 20.3%. Detection using NAAT was found to be superior to culture-based methods due to its speed and accuracy. The studies consistently showed that intra-amniotic infection with *Ureaplasma* increased the risk of preterm delivery, with odds ratios ranging from 2.76 to 3.0. Preterm birth rates among *Ureaplasma*-positive women varied from 26% to 58.6%. In a prospective cohort, 58.6% of women with second-trimester *Ureaplasma* infection experienced preterm labor, compared to 4.4% of uninfected women. Detection of *Ureaplasma parvum* in the vagina was identified as a significant risk factor for preterm birth with an odds ratio of 3.0. Vaginal colonization with *Ureaplasma parvum* in the first trimester increased the risk of spontaneous preterm birth with an odds ratio of 1.7. Intra-amniotic inflammation was present in 25% of cases with *Ureaplasma* DNA. The Gardnerella Lactobacillus *Ureaplasma* test demonstrated sensitivities of 37.9% for predicting preterm birth before 37 weeks and 44.4% for predicting preterm birth before 34 weeks. 68% of newborns born to carrier mothers were carriers as well. Infection rates among newborns were 100% for Ureaplasma parvum, and 28.5% for *Ureaplasma urealyticum*. *Ureaplasma* infections were found to induce pro-inflammatory cytokines, activate neutrophils and TLR-9, and increase prostaglandin and matrix metalloproteinase activity, leading to fetal membrane weakening and rupture.

DISCUSSIONS

Ureaplasma is one of the common species found in the lower genital tract of sexually active women. The first publications about colonization with Ureaplasma in women date back to 1954. The first publication discussing *Ureaplasma* was by Shepard MC in 1960, who reported the recovery of pleuropneumonia-like organisms from the

urogenital tract. This study laid the groundwork for understanding *Ureaplasma* as a significant pathogen in human health (1).

Ureaplasma is a very small, atypical bacterium, the detection of which was quite challenging in the past. With the development of new techniques, questions about the harmlessness of *Ureaplasma* infection are being raised. *Ureaplasma* spp. is a bacterium belonging to the class Mollicutes, which consists of 8 genera, including *Mycoplasma*. The two most commonly observed species are *U. urealyticum* and *U. parvum* (2).

Ureaplasmas are among the smallest microorganisms without a cell wall, which is why gram-staining is not reliable. The pleomorphic nature of *Ureaplasma* species results from their lack of structural integrity, allowing individual organisms to vary in size from 100 nm to 1 µm. Originally identified as tiny-form pleuropneumonia-like organisms, *Ureaplasma* spp. were also known as T-mycoplasmas. However, urease, an enzyme that hydrolyzes urea to provide 95% of its energy needs, distinguishes *Ureaplasma* from other *Mycoplasma* species. Ammonia is produced when urea is hydrolyzed, which increases the proton electrochemical potential and initiates the synthesis of ATP from scratch. One characteristic that sets *Ureaplasma* spp. apart in culture is the generation of ammonia. Numerous techniques have been reported for serotyping *Ureaplasma* spp., including the use of rabbit antisera in growth inhibition tests, immunoperoxidase tests, enzyme-linked immunosorbent assays, and colony indirect epi-immunofluorescence. Multiple cross-reactions between serovars and the absence of standardized reagents have contributed to the poor results obtained from these tests (3).

The *retrospective* study by Kusanovic JP et al., 2020, was designed to compare the identification and susceptibility of *Ureaplasma* spp. and *Mycoplasma hominis*. They compared NAAT) with the culture-based method, followed by antibiotic susceptibility testing. The results were then compared in terms of identification accuracy, time to result, and susceptibility profile. The study highlighted the importance of rapid and accurate identification of *Ureaplasma* spp. and *Mycoplasma hominis* in managing high-risk pregnancies. The faster turnaround time of NAAT makes it a valuable tool for timely clinical decision-making, especially in acute settings (4). The retrospective nature of the study and its focus on high-risk pregnancies may introduce selection bias, as well as potential information bias from the use of medical records for data collection.

Ureaplasma is one of the common species found in the lower genital tract of sexually active women. Rumyantseva T. et al., 2018, *in a cross-sectional study* including 2,594 female patients, found that *U. parvum* was detected in 40.5% of healthy women, while *U. urealyticum* was found in 20.3% of healthy women (5). As a cross-sectional study, the design limits causal inferences and may be subject to information bias, as it provides a snapshot of the population at one point in time and may not accurately reflect causal relationships or variations over time. This study shows that even asymptomatic pregnant women can be colonized with *Ureaplasma* spp., highlighting that colonization can occur without symptoms at the beginning of pregnancy.

In gynecology, *Ureaplasma* spp. has been widely linked to pelvic inflammatory disease, urinary tract infections, and bacterial vaginosis. The bacterial burden of *Ureaplasma* spp. in females with bacterial vaginosis can be significantly higher than in those without this condition. Mollicutes do not cause inflammatory vulvovaginitis. There has been speculation about *Ureaplasma* working in symbiosis with other BV pathogens. Although not in pure culture, *Ureaplasma* species have been directly isolated from affected fallopian tubes.

The *cross-sectional study* by Cox C. et al., 2016, aimed to determine the clinical significance of four mollicutes species: *Mycoplasma genitalium, Mycoplasma hominis, U. urealyticum*, and *U. parvum*, in the context of non-chlamydial, non-gonococcal urethritis. The study found a significantly higher prevalence of *U. parvum* in non-gonococcal urethritis patients (17.3%) (6). This study indicates that, among the four mollicutes species examined, *U. parvum* was the most frequently associated with complications. This finding could help guide screening options for pregnant women, particularly in high-risk populations. By focusing on *U. parvum*, healthcare providers may be able to implement more specific and timely interventions to improve pregnancy outcomes. This study may be subject to selection bias, as it is a cross-sectional study that examines a specific patient group without random sampling, limiting the generalizability of its findings.

In the *retrospective study* by Zeng J. et al., 2022, out of the 1,736 patients examined, 461 (26%) were found to be positive for *U. urealyticum* (7). This retrospective study may be prone to recall bias, as it relies on historical patient data and may not have accounted for all relevant variables, potentially affecting the accuracy of the reported prevalence rates.

Ureaplasma infections also occur when the woman is pregnant. Usually, the causative organism is detected after the onset of adverse outcomes or after the delivery has occurred (8).

The *prospective cohort* by Abele-Horn M. et al., 2000, examines the impact of *U. urealyticum* colonization on pregnancy outcomes. It included 172 women with *U. urealyticum* and 123 women without the infection. Results showed that higher colonization levels were significantly associated with decreased birth weight and gestational age, and increased rates of chorioamnionitis and preterm delivery. High-density colonization was identified as an independent risk factor for these adverse outcomes, while low colonization levels had no significant effect (9). This study may be subject to selection bias, as it compares women with *U. urealyticum* colonization to those without, potentially overlooking confounding factors that could influence pregnancy outcomes, such as other infections or underlying health conditions.

The study by Gerber S. et al., 2003, aimed to investigate the relationship between intra-amniotic *U. urealyticum* in asymptomatic second-trimester pregnant women and subsequent pregnancy outcomes, particularly PTB. The researchers obtained transabdominal amniotic fluid from 254 asymptomatic women at 15-17 weeks of gestation (wg) and tested it for *U. urealyticum* using polymerase chain reaction (PCR). They found that *U. urealyticum* was identified in 29 subjects (11.4%). Subsequent PTB occurred in 17 (58.6%) of the *U. urealyticum*-positive women compared to 10 (4.4%) of the *U. urealyticum*-negative women, a statistically significant difference ($P < .001$). PTB was documented in 7 (24.1%) of the *U. urealyticum*-positive women compared to only 1 (0.4%) of the *U. urealyticum*-negative women, which was also statistically significant ($P < .0001$). The study further revealed that *U. urealyticum*-positive women had a higher prevalence of PTB in a prior pregnancy (20.7%) compared to the negative women (2.7%; $P = .0008$) (10). This study may be subject to selection bias, as it only included asymptomatic women, potentially excluding those who showed symptoms of infection and might have different outcomes.

Kataoka S. et al., 2006 in a *prospective cohort* explored the relationship between *U. urealyticum* and PTB. It involved 1,040 women initially, with singleton pregnancies less than 11 wg. However, after excluding some participants for various reasons such as induced abortions and unavailability for follow-up, a total of 877 women were analyzed for the final results. *U. parvum* was detected in 52.0% of the women. *U. urealyticum* was detected in 8.7% of the women. Detection of *U. parvum* in the vagina was identified as a significant risk factor for late abortion or PTB. Women with *U. parvum* had an odds ratio (OR) of 3.0 for experiencing these outcomes, with a 95% confidence interval from 1.1 to 8.5, indicating a statistically significant increase in risk (11). The study's observational design and lack of control group may introduce selection bias and confounding factors that could influence the results regarding PTB rates.

The study by Harada K. et al., 2008, involved 145 participants, comparing 100 women with full-term deliveries and 45 women with preterm deliveries. It was a clinical investigation analyzing the presence of *U. urealyticum* in vaginal secretions. The study found that *Ureaplasma* infection was significantly higher in the preterm delivery group (51.1%) compared to the full-term group (30.0%). The presence of this bacterium was associated with an increased production of IL-8 and apoptotic cell death, suggesting a potential causative link to preterm delivery outcomes (12). This study may be affected by selection bias, as the inclusion of only women with full-term or preterm deliveries may not account for other factors influencing *Ureaplasma* infection.

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The *cross-sectional comparative study* by Jones HE et al., 2009, investigated the role of intrauterine infection in preterm delivery, analyzing bacterial DNA in the placenta and fetal membranes from 74 women. The groups included PPROM <32 weeks, PTL with intact membranes <32 weeks, indicated preterm delivery <32 weeks, and term deliveries. Bacterial prevalence was significantly higher in the preterm groups, especially PTL with intact membranes (89%) and PPROM (55%), compared to term deliveries (14). This study may suffer from selection bias, as the groups are based on different types of preterm deliveries (PPROM, PTL, and indicated preterm delivery), which could introduce variability in the factors contributing to PTB, potentially skewing the results on bacterial prevalence.

The observational cohort study by Agger WA et al., 2014, investigated the link between urogenital infections and PTB among 676 pregnant women from various urban and rural settings. Results showed an 8% overall PTB rate, with higher rates in large urban areas (12.1%) compared to midsize urban (8.8%), small city (9.4%), and rural areas (2.3%). *U. parvum* infections were particularly prevalent in large urban sites, correlating with increased PTBs. Significant risk factors included prior PTB (aOR 2.76) and urinary tract infection (aOR 2.62), while protective factors included good health (aOR 0.42) and group B streptococcal infection treatment (aOR 0.38) (15). This study may be subject to confounding bias, as various factors such as prior PTB, urinary tract infections, and urban versus rural settings could influence the results, making it difficult to isolate the specific impact of *U. parvum* on PTB.

The retrospective cohort study by Freitas AC et al. examined the relationship between vaginal microbiota composition and spontaneous PTB. Conducted as a retrospective cohort study, it included 46 pregnant women who delivered preterm and 170 who delivered at term. *Ureaplasma* species were found in 14 out of 46 (30%) women who had PTBs, with all testing positive for *U. parvum* and none for *U. urealyticum* (16). This study may have selection bias, as the sample of 46 women with PTBs might not be representative of the broader population, potentially skewing the findings regarding the relationship between *Ureaplasma* species and PTB.

The study by Payne MS. et al., 2016, found that detection of *U. parvum* was significantly higher in women who experienced spontaneous preterm birth (PTB) compared to those who delivered at term. Specifically, *U. parvum* was detected in 77% of preterm cases versus 36% at term. This association was even stronger when the *U. parvum* genotype SV6 was present, with detection in 54% of preterm cases compared to 15% at term. Additionally, smoking was found to increase the likelihood of detecting these organisms (17). This study may have confounding bias due to the influence of smoking on the likelihood of detecting *U. parvum*, which could have contributed to the observed association with PTB.

The prospective multicenter study by Rittenschober-Böhm J. et al., 2017, analyzed the impact of first-trimester vaginal colonization by *Ureaplasma* biovars on PTB outcomes in 4,330 pregnant women. The results showed that *U. parvum* was detected in 37% of the women. The rate of spontaneous PTB in this group was 10.4%, with an odds ratio (OR) of 1.7 (95% confidence interval [CI] 1.3, 2.2; $p < 0.001$), indicating a significantly increased risk. *U. urealyticum* was detected in 5.9% of the women, with a PTB rate of 8.9% and an OR of 1.4 (95% CI 0.9, 2.3; $p = 0.193$), which was not statistically significant. Compared to women with negative PCR results for *Ureaplasma*, who had a 6.4% rate of preterm birth, the study concluded that vaginal colonization with *U. parvum* is a statistically significant and independent risk factor for spontaneous PTB, with an adjusted OR of 1.6 (95% CI 1.2, 2.1; $p < 0.001$), regardless of other risk factors (18).

Another study by Judith Rittenschober-Böhm J. et al., 2019, showed that vaginal colonization with *U. parvum* serovar 3 significantly increases the risk of spontaneous PTB at very low (<32 weeks, $P < 0.005$) and extremely low (<28 weeks, $P < 0.005$) gestational ages. The presence of serovar 3 was most common, found in 43.3% of *U. parvum* positive samples, compared to 31.4% for serovar 6 and 25.2% for serovar 1. The study suggests a targeted approach for women with serovar 3 colonization, especially those with a history of PTB or bacterial vaginosis (19). This study may have selection bias, as it focused on women with a history of PTB or bacterial vaginosis, which could influence the generalizability of the findings to the broader pregnant population.

A *case-control study* by Oliveira CNT. et al., 2020, aimed to investigate the presence of *Ureaplasma*

spp. in placental tissue and its association with adverse pregnancy outcomes. PCR was utilized to identify Mollicutes in cervical mucus and placental tissue samples. *U. parvum* was found in 66.3% of placental tissue samples from women who had spontaneous abortions. A positive correlation was observed between the presence of *U. parvum* in placental tissue and abortion. The study included 98 women who miscarried and 20 women who had healthy pregnancies. This study suggests that *Ureaplasma* can reach the maternal-fetal surface and contribute to unwanted pregnancy outcomes (20). This case-control study may be subject to selection bias, as the comparison between women who miscarried and those with healthy pregnancies may not fully account for other confounding factors, such as maternal health conditions or environmental influences, which could also affect pregnancy outcomes.

The study led by Peretz A. et al., 2020, investigated the prevalence and transmission of *Ureaplasma* species among pregnant women, along with the potential implications for pregnancy outcomes and newborn health. The study included 214 pregnant women who were tested for vaginal pathogen carriage using standard culture and PCR assays, and pharyngeal swabs were collected from the newborns of carrier mothers. A total of 19 (8.8%) women were found to be carriers of *Ureaplasma* species, with 4.19% testing positive for *U. parvum* and 2.32% for *U. urealyticum*. Carriage was more common in younger women, with 10.5% of women aged 18-29 being carriers, compared to 7.5% of women aged 30-39. No women over the age of 40 were found to carry *Ureaplasma.* Among the women who carried *Ureaplasma*, 5 (26.3%) delivered preterm. Specifically, 3 out of 5 women carrying *U. urealyticum* and 1 out of 9 women carrying *U. parvum* delivered preterm (21). This study may be subject to selection bias, as the sample of 214 pregnant women may not be representative of the general population, particularly since carriage of *Ureaplasma* was more common in younger women. Additionally, the reliance on standard culture and PCR assays for pathogen detection may introduce detection bias, as the sensitivity of these methods can vary depending on microbial load, potentially leading to false negatives or overestimation of *Ureaplasma* prevalence.

Bartkeviciene D. et al., 2020, conducted a *retrospective study* to analyze the impact of *Ureaplasma* infections on pregnancy complications. The study included 50 pregnant women with signs of threatened preterm delivery. Samples from the endocervical canal and cervix surface were tested for several pathogens, including *Ureaplasma* species. The study found that 46% of the patients had premature rupture of membranes, and 76% experienced preterm delivery. *Ureaplasma* infections were significantly associated with premature rupture of membranes ($p < 0.004$), placental inflammation ($p < 0.025$), and newborn respiratory distress syndrome ($p < 0.019$) (22). The small sample size and potential selection bias from focusing on a single hospital setting may limit the generalizability of the findings.

The study by Kacerovsý M. et al., 2022, was a prospective cohort study involving 115 women, aged 22-35 weeks of gestation, complicated by PTB. The diagnosis of microbial invasion of the amniotic cavity was made using molecular biology techniques in addition to culture methods. The level of interleukin-6 in the amniotic fluid was used to measure intra-amniotic inflammation. Sterile inflammation was found in 14% of the women, while 25% had intra-amniotic infection. DNA from *Ureaplasma* spp. was found in the cervical fluid of 51% of the participants. Women with intra-amniotic infection had greater levels of *Ureaplasma* spp. and *Mycoplasma hominis* DNA (42%) compared to women with sterile intra-amniotic inflammation (7%) and those without intra-amniotic inflammation (7%; $p = 0.001$) (23). The study's retrospective design may introduce recall and selection bias, as it relies on past medical records and does not control for confounding variables in a non-randomized setting.

The *prospective cohort study* by Payne MS. et al., 2021, included 936 women who provided midvaginal swabs between the 12th and 23rd weeks of gestation, which were analyzed using quantitative PCR to detect 23 microbial DNA targets associated with PTB risk. The study found that the overall PTB rate was 12.6%, with a spontaneous PTB rate of 6.2% for those under 37 weeks and 2.9% for those under 34 weeks. The rate of preterm premature rupture of membranes (PPROM) was 4.2%. The final predictive model, called the Gardnerella Lactobacillus Ureaplasma test, demonstrated sensitivities of 37.9% for predicting PTB before 37 weeks and 44.4% for predicting PTB before 34 weeks (24). This study may

be subject to detection bias due to its reliance on quantitative PCR for detecting microbial DNA, which may not fully account for the variability in microbial load or composition. Additionally, the relatively low sensitivity of the predictive model (37.9% for PTB before 37 weeks and 44.4% for PTB before 34 weeks) could introduce measurement bias, as it might fail to accurately predict PTB, leading to potential misclassification of patients at risk. This could affect the generalizability and clinical applicability of the findings.

The study conducted by Matasariu DR. et al., 2020, included 1,301 pregnant women with ruptured membranes and pregnancies over 17 weeks, observed from January 2010 to December 2019. The prevalence of *U. urealyticum* infection was 57.3% in women between 17-23 weeks, 49.7% between 24-28 weeks, 40.7% between 29-32 weeks, 40.2% between 33-36 weeks, and 45.1% in those ≥37 weeks. The infection was significantly associated with adverse pregnancy outcomes, including PTB and chorioamnionitis (25). The study may be impacted by recall bias, as the retrospective design relies on patient histories and the potential for confounding factors due to the absence of randomization.

The research conducted by Przybylski M. et al., 2024, was a retrospective study involving 201 pregnant women who were hospitalized at the Obstetrics and Gynecology Department of Poznan Regional Hospital between 2019 and 2022. The study showed a higher occurrence of PTB among the infected group (31.1%) compared to the non-infected group (20%). PPROM occurred in 40% of *Ureaplasma*-positive patients preceding preterm delivery, compared to 20% in non-infected cases, indicating a significant effect of the infection on this specific complication. The effectiveness of antibiotic therapy did not show a clear benefit, as PTB and pregnancy loss rates were similar in treated (35.7%) and untreated patients (31.6%) (26). This study may be subject to bias due to its retrospective design, which could be influenced by incomplete patient records, selective reporting of PTB cases, or differences in treatment protocols between the infected and non-infected groups.

This *retrospective observational study* by Marti DT. et al., 2024, included 71 pregnant women who experienced PTBs and 94 women with genital infections who delivered at term. The odds ratio (OR) for PTB associated with this pathogen is reported as 2.76, with a p-value of 0.009, indicating a statistically significant association. This suggests that the presence of *U. urealyticum* in pregnant women substantially increases the risk of delivering preterm (27). The retrospective design and the comparison of two distinct groups (PTBs and term deliveries with genital infections) could introduce confounding variables, such as differences in maternal health, socioeconomic factors, or other infection-related conditions, potentially affecting the likelihood of PTB and introducing selection bias.

The study by Prodan-Barbulescu C. et al., 2024, conducted between 2019 and 2023, is a retrospective case-control study comparing vaginal microbiota from 89 women who delivered preterm and 106 women who delivered at term. The analysis centered on vaginal cultures taken during the third trimester, comparing various microbiological and immunological parameters between the two groups. *U. urealyticum* was significantly associated with increased PTB risk, with an odds ratio of 2.43 ($p = 0.001$). This study provides robust evidence that the presence of *U. urealyticum* in the vaginal microbiota is critically associated with the risk of PTB. It underscores the potential benefits of targeted microbial management as part of strategies to reduce PTB rates (28). This study may be subject to recall and selection bias, as it relies on retrospective data and the comparison of preterm and term birth groups, which could involve unaccounted-for differences in other factors affecting PTB risk, such as socioeconomic status or access to prenatal care.

The mechanism by which *Ureaplasma* species contribute to preterm birth (PTB) involves several complex processes:

1. Induction of Pro-inflammatory Cytokines and Chemokines**:**
   Ureaplasma infection induces the production of pro-inflammatory cytokines and chemokines in the amniotic fluid and fetal membranes. This inflammatory response can activate matrix metalloproteinases (MMPs), which degrade the extracellular matrix of the fetal membranes, weakening them and making them more susceptible to rupture (29).
2. Neutrophil Activation**:**

The infection also activates neutrophils, which release enzymes and reactive oxygen species that further damage the fetal membranes. Neutrophils can form neutrophil extracellular traps (NETs) that contribute to tissue damage and inflammation (30).

3. Prostaglandin Production:
Ureaplasma infection increases the production of prostaglandins, which are known to induce uterine contractions. Elevated levels of prostaglandins in the amniotic fluid can lead to the premature initiation of labor (31).
4. Cervical Epithelial Damage:
Ureaplasma can ascend from the lower genital tract to the upper genital tract, leading to cervical epithelial damage. This damage promotes further infection and inflammation, contributing to cervical remodeling and shortening (32).

In addition, *Ureaplasma* species contribute to PTB through the activation of Toll-Like Receptor 9 (TLR-9). TLR-9 is an innate immune receptor that recognizes unmethylated CpG motifs in bacterial and viral DNA, triggering an immune response. In the case of *Ureaplasma* infections, bacterial DNA activates TLR-9 on immune cells like macrophages and dendritic cells. This activation initiates a signaling cascade involving MyD88, which leads to the activation of NF-κB and the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β (33).

Once the infection ascends to the choriodecidual area and crosses the fetal membrane, *Ureaplasma* spp. move placentally into the amniotic cavity. In addition to their direct impact, they raise the levels of many cytokines and other inflammatory mediators (34).

The activation of TLR-9, a DNA sensor, by neutrophil extracellular traps and ERK signaling facilitates the fetal membrane response. During infection, neutrophils drawn to the membranes have the ability to spread inflammation and weaken the tissue. This can cause damage at the maternal-fetal interface, raising the risk of early fetal membrane rupture and PTB in women with an intrauterine infection (35).

An increase in IL-6 concentration has been linked to the presence of *U. parvum* and *U. urealyticum*, while an increase in IL-12p70 concentration is associated with *U. parvum* presence. Regarding gene expression, the presence of *U. parvum* led to the downregulation of genes associated with the immune response, while the spontaneous abortion group showed an elevation of genes linked to the activation of apoptosis. Taken together, these findings demonstrate that *U. parvum* colonizes the placentas of pregnant women at any gestational age and may be connected to spontaneous abortion (36).

Ureaplasma causes preterm premature rupture of membranes (PPROM) by infecting the amniotic fluid. This was demonstrated by measuring intra-amniotic inflammatory responses in pregnant women. White blood cell counts and amniotic fluid matrix metalloproteinase-8 concentrations were used to measure the degree of the intra-amniotic inflammatory response, while the amount of white blood cells and C-reactive protein in the mother's blood during amniocentesis reflected the maternal inflammatory response (37).

The study by Tong M. et al. (2021) investigated the role of activated neutrophils in propagating fetal membrane inflammation and weakening through ERK and TLR-9 signaling. The researchers found that neutrophils contribute to this process by releasing neutrophil extracellular traps (NETs) that activate TLR-9. The findings suggest that targeting neutrophil activation and these specific signaling pathways could potentially prevent inflammation-induced weakening of fetal membranes, reducing the risk of PPROM and related complications (38).

A study conducted by Tripathy S. et al. (2024) examined the effects of *U. parvum* infection on the chorioamnion membranes in a non-human primate model. The experimental group was inoculated with *U. parvum* (10^5 CFU/mL) at the choriodecidua, while the control group received sterile media. Significant increases in the expression of MMP-9 and PTGS2 were noted in the fetal membranes, indicative of an inflammatory response. More notably, there was a marked increase in the expression of inflammasome components like NLRP3, NLRC4, AIM2, NOD2, and the adaptor ASC (PYCARD), alongside pro-inflammatory cytokines such as IL-1β and IL-18 (39).

The study by Tantengco OAG et al. investigates the impact of *U. parvum* on exosome biogenesis and the proteomic profile of exosomes in ectocer-

vical epithelial cells. *U. parvum* was able to colonize ectocervical epithelial cells, demonstrating colocalization with CD9-positive intraluminal vesicles, which are indicative of exosome compartments. The proteomic analysis revealed that exosomes derived from infected cells had decreased protein abundance and exhibited distinct protein profiles compared to those from uninfected cells. Key proteins like clathrin, ALIX, CD9, and CD63, which are involved in exosome formation and release, were found to be decreased. Proteins such as TSG101, Rab5, Rab35, and UGCG, which play roles in vesicular trafficking and lipid biosynthesis, were increased in infected cells. This study enhances our understanding of how *U. parvum* interacts with host cells at a molecular level, particularly through modifications in exosome biogenesis and protein cargo. These findings underscore the importance of exosomal processes in the pathophysiology of *U. parvum* infections and their potential consequences for female reproductive health (40).

CONCLUSIONS

1. The compiled studies from 2000 to 2024 demonstrate a significant association between *Ureaplasma* spp. colonization and adverse pregnancy outcomes, particularly PTB.
2. Detection using NAAT was found to be superior to culture-based methods due to its speed and accuracy. The studies consistently showed that intra-amniotic infection with *Ureaplasma* spp. increased the risk of preterm delivery, with odds ratios ranging from 2.76 to 3.0.
3. *Ureaplasma* infections were found to induce pro-inflammatory cytokines, activate neutrophils and TLR-9, and increase prostaglandin and matrix metalloproteinase activity, leading to fetal membrane weakening and rupture.
4. Prospective randomized studies are recommended to validate these findings and develop targeted therapeutic strategies to mitigate the risks associated with *Ureaplasma* spp. infections. By improving detection and management protocols, healthcare providers can better support maternal and neonatal health, ultimately reducing the incidence of preterm births and related complications.

CONFLICT OF INTEREST

There is no conflict of interest regarding the material presented in the paper.

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