

Genital infection with *Ureaplasma urealyticum* and its effect on pregnancy

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Abstract. Chorioamnionitis or intra-amniotic infection is an infection that affects the intrauterine content during pregnancy. Numerous studies have reported vaginal colonization with various types of infectious agents as a risk factor for chorioamnionitis. Although this complication occurs due to the ascending polymicrobial bacterial infection at the time of membrane breakage, it may also occur in pregnant women with intact membranes, mainly due to *Ureaplasma urealyticum* (*U. urealyticum*) and *Mycoplasma hominis* (*M. hominis*). The main aim of the present study was to identify a region-specific panel of infectious agents that can be used more accurately determine premature birth, as well as the premature rupture of membranes (PROM). Thus, a 10-year retrospective study was conducted. A total of 1,301 pregnant women with PROM and premature birth or spontaneous abortion were included in the study. It was observed that the main infectious agent varied in the five groups analyzed in total. The infectious agent distribution also varied depending on environmental parameters. *Ureaplasma* was found to be the most frequently detected germ amongst the infectious agents of the vaginal cultures from pregnant women enrolled in the present study, regardless of gestational age. On the whole, the findings of the present study suggest that additional studies are required, in order to confirm that diagnosis and treatment according to laboratory

results of vaginal infections with *U. urealyticum*/*M. hominis* during the first trimester of pregnancy could prevent premature birth, abortion or chorioamnionitis.

Introduction

It has been proven that vaginal infections may negatively affect pregnancy, leading to complications such as spontaneous abortion, premature rupture of membranes (PROM), preterm delivery, intrauterine growth restriction, intrauterine death, neonatal infections and postpartum infections (1-7). Genital tract infections in pregnancy account for ~15% of first trimester miscarriages and 66% of late miscarriages (8,9). In addition, the implication of infection in the etiology of recurrent loss remains unclear, with an incidence of 0.5-5% (8,10).

The microorganisms most frequently involved in women genital tract infections are group B *Streptococcus*, *Escherichia coli* (*E. Coli*), *Enterococcus faecalis*, *Enterobacter spp.*, *Candida spp.*, *Ureaplasma urealyticum* (*U. urealyticum*), *Mycoplasma hominis* (*M. hominis*), *Chlamydia trachomatis* and bacterial vaginosis (BV; a disruption in the normal vaginal flora with less or absent Lactobacilli and consequent infection with Gram-negative bacteria) (1,4). A previously published revealed the importance of normal vaginal microflora and the negative impact of bacterial vaginosis on pregnancy outcomes (5). Emerging evidence has indicated that the presence of *Candida* and BV in pregnancy may increase the risk of abortion and preterm birth (PTB). Vaginosis in pregnancy can lead to a series of severe complications, such as spontaneous abortion, preterm delivery, chorioamnionitis, low birth weight and endometritis (1,11-13).

U. urealyticum infection has been identified in the urogenital tract of both healthy and symptomatic women (14), having been isolated from asymptomatic healthy women and also from amniotic fluid (15), and associated with chorioamnionitis in only a few cases (16). According to the pathogenesis, the evasion of the local immune response has been suggested. Endometrial immunity is activated by bacterial infections and an intense immune response follows, affecting the beginning of a pregnancy (2,8). Further evidence recently emerged in favor of the association between *U. urealyticum*, alone or

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Abbreviations: PROM, premature rupture of membranes; *E. coli*, *Escherichia coli*; *U. urealyticum*, *Ureaplasma urealyticum*; *M. hominis*, *Mycoplasma hominis*; BV, bacterial vaginosis; PTB, preterm birth

Key words: chorioamnionitis, infection, pregnancy, *Ureaplasma* species, premature rupture of membranes, preterm birth

in combination with *M. hominis* and obstetrical pregnancy complications, including premature rupture of membranes, preterm delivery and abortion (17). However, there is controversy concerning the specific role of *Mycoplasma* species in adverse pregnancy outcomes (8,18).

Previous studies have revealed that the prevalence of *Mycoplasma* in the genital tract of women in a population is affected by a number of aspects, including age, race, socio-economic status, use of contraceptives, menstruation, menopausal changes and pregnancy (19-21). Immunological and hormonal changes attributed to pregnancy may also affect vaginal colonization. Animal research has demonstrated the influence of estrogen and progesterone on vaginal colonization by different types of *Mycoplasma* and *Ureaplasma* (18). To determine the real prevalence of *U. urealyticum* in the genital tract of pregnant women compared with non-pregnant women, all the aforementioned factors need to be taken into consideration. For this reason, reliable data are not yet available, although these species of infectious agents are identified more often in pregnant than in non-pregnant women. The prevalence of *U. urealyticum* infection in the general community is also affected by the same factors, not being precisely established (19,21).

PTB is defined as delivery before the 37th week of gestation according to the last menstrual period of a woman and the data provided by ultrasound (22,23). PTB can be classified according to gestational age as follows: i) Ranging from 24-28 weeks of gestation as extremely preterm; ii) from 29-32 weeks of gestation as very preterm; and iii) from 32-36 weeks of gestation as moderately or late-preterm (24,25). PTB is the major cause of neonatal morbidity and mortality (24). It has an annual global incidence of ~15 million cases. PTB is classified as spontaneous preterm labor, PROM and medically induced PTB, determined by fetomaternal complications (23). The etiology of PTB is multifactorial; however, infection and/or inflammation remain the only etiologies that have a solid evidenced-based background (22,23).

Half of all PTBs occurring prior to 30 weeks of pregnancy are clearly attributed to chorioamnionitis. *Ureaplasma* and *Mycoplasma* species remain the most commonly isolated infectious agents associated with chorioamnionitis, regardless of gestational age (26,27). The risk of developing chorioamnionitis is increased in pregnant women with a temperature >38°C and/or one or more of the following clinical signs: Maternal leukocytosis (>15,000 cells/mm³), maternal and/or fetal tachycardia and purulent leukorrhea (28,29). The aim of the present study was to identify a region-specific panel of infectious agents that may be used to more frequently determine abortion, PTB and PROM.

Patients and methods

Patient data collection. The present retrospective observational study was conducted at the Iasi 'Cuza Voda' University Hospital of Obstetrics and Gynecology (Iasi, Romania), in a tertiary obstetrics referral center in Northeastern Romania. A total of 1,301 women with ruptured membranes and with pregnancies >17 weeks of gestation were enrolled in the study, between January, 2010 to December, 2019. The corresponding demographic data included age, residency, obstetric pregnancy

and current symptoms when the patient was admitted to the center. All women provided a written informed consent for study participation prior to sample collection. Ethical approval was obtained from the Ethics Committee of 'Cuza Voda' Obstetrics and Gynecology Clinical Hospital (Approval no. 10426/2021).

Eligibility criteria included a singleton intrauterine pregnancy, a gestational age ranging between 17 weeks, 0 days and 40 weeks, 0 days at the time of enrolment, a maternal age >23 years and admission for delivery at the 'Cuza Voda' Iasi University Hospital. Gestational age was determined by last menstrual period declared by the patient, in association with the ultrasound data. The exclusion criteria included the following: The existence of any genetic disorders, birth defects and antibiotic treatment within 1 month prior to the study. Women with any mental disabilities were not included in the study.

Patient sample collection. Vaginal fluid samples were obtained from the enrolled participants prior to antibiotic treatment at the time of admission to the obstetrics referral center. Samples were collected without the use of antiseptics and cultures were performed. Patients were categorized into 5 groups according to gestational age as follows: i) group 1, ranging between 17-23 weeks of gestation; ii) group 2, 24-28 weeks of gestation; iii) group 3, 29-32 weeks of gestation; iv) group 4, 33-36 weeks of gestation; and v) group 5, ≥37 weeks of gestation. Blood samples from all patients were collected in search for infection response (leukocytosis). All patients were also monitored for fever.

The primary outcome was preterm delivery prior to 37 weeks of gestation, whereas the secondary outcomes were delivery after 37 weeks of gestation and chorioamnionitis. Pregnant women were classified depending on their age and the gestational age of the pregnancy at the time of admission. The most frequently involved infectious agent associated with preterm delivery, chorioamnionitis and the implication of *M. hominis/U. Urealyticum* were also investigated in the pathological evaluation. Since infection plays a crucial role in the initiation of PTB, it was investigated whether an infectious agent mostly associated with PTB and/or chorioamnionitis could be detected, depending on confounding variables (age, residency and gestational age).

Detection of pathogens. For *Ureaplasma* and *Mycoplasma* detection, bioMérieux kits (REF42505) were used, with cultures performed on a selective medium (bioMérieux Mycoplasma IST 2 containing 25 strips of 22 tests, 25 R1 vials and 25 lyophilised R2 vials) that inhibits commensal flora by the addition of antibiotics and antifungal agents (bioMérieux-Lincomicina, Eritromicina), using urea substrate (bioMérieux) for *Ureaplasma* and arginine substrate (bioMérieux) or *Mycoplasma*. For the detection of the other bacteria involved in genital infections in pregnant women, selective and differential culture mediums (Macconkey Agar, Oxoid; Clumbia Agar and sheep blood, Oxoid; Sabouraud glucose selective agar with gentamicin and chloramphenicol, Oxoid) were used, and for bacterial identification we utilized a MicroScan WalkAway analyzer manufactured by Beckman Coulter, Inc. For fungal detection, an ELITech CANDIFAST® kit was used.

Statistical analysis. SPSS version 18 (PASW Statistics for Windows, SPSS, Inc.) was used for the statistical analysis. Categorical variables are presented as absolute and relative frequencies and for comparisons, the Chi-squared test was used. A P-value ≤ 0.05 was considered to indicate a statistically significant difference.

Results

Several particularities depending on the environment were observed. All patients were classified according to gestational age as follows: i) Group 1: between 17-23 weeks of gestation; ii) group 2: between 24-28 weeks of gestation; iii) group 3: between 29-32 weeks of gestation; iv) group 4: between 33-36 weeks of gestation; and v) group 5: ≥ 37 weeks of gestation. Among the patients included in the study: i) 70.3% of the patients in group 1 originated from rural areas and 29.7% from urban areas; ii) 54.3% of patients in group 2 originated from rural areas and 45.7% from urban areas; iii) 41.5% of patients in group 3 were from rural areas and 58.5% from urban areas; iv) 45% of patients in group 4 were from rural areas and 55% from urban areas; and iv) 46.5% of patients in group 5 originated from rural areas and 53.5% from urban areas (Table I). The Chi-squared test was applied to verify whether the proportions of patients from the rural and urban areas were equal. A statistically significant value of < 0.001 was obtained, with the majority of the cases being from rural areas. However, the proportions were relatively close (total patients from urban area 46.7% and rural area 53.3%).

It was also noted that the bacteria detected in the vaginal cultures of the patients included in the present study varied between the five groups. *U. urealyticum* was detected in: i) 57.3% of the vaginal cultures of patients between 17 and 23 weeks of gestation; ii) in 49.7% of patients between 24-28 weeks of gestation; iii) in 40.7% of patients between 29-32 weeks of gestation; iv) in 40.2% of patients between 33-36 weeks of gestation; v) in 45.1% in patients ≥ 37 weeks of gestation. *E. coli* was also encountered in the patient cultures as follows: 27.2% in group 1, 26.8% in group 2, 30.9% in group 3; and at a similar percentage of 33.3% in groups 4 and 5. *Streptococcus* had a lower implication in the occurrence of vaginitis: i) 5.9% in group 1; ii) 13.5% in group 2; iii) 19.3% in group 3; iv) 18% in group 4; and v) 11.8% in group 5. Additionally, *Candida* infection was involved in vaginitis, of which higher percentages were observed: i) 38.7% in group 1; ii) 33.2% in group 2; iii) 23.3% in group 3; iv) 31.2% in group 4; and v) 25% in group 5. The alteration of the vaginal flora due to the appearance of vaginosis was observed in similar percentages in the first four groups: 8.4% in group 1, 8.6% in group 2, 8.4% in group 3, 7.9% in group 4 and at a lower percentage (6.3%) in group 5. *Enterobacter* infection was detected as follows: 3.1% in group 1, 3% in group 2, 2.2% in group 3, 3.7% in group 4, and 2.8% in group 5. *Enterococcus* infection was as follows: 1.5% in group 1, 5.1% in group 2, 8% in group 3, 6.9% in group 4, and 3.5% in group 5, with statistically significant differences when analyzing the data using the Chi-squared test (0.004) (Table I).

In the present study, the percentages of pregnant women with fever and/or leukocytosis were as follows: 42.4% with leukocytosis and 43.3% fever in group 1, 39.7% with leukocytosis and the same percentage with fever in group 2, 35.6% with

leukocytosis and 36.7% with fever in group 3, 34.9% with leukocytosis and 35.4% with fever group 4 and finally 43.1% with leukocytosis and 44.4% with fever in group 5. Several particularities were also observed, concerning the distribution of chorioamnionitis in these five groups, in relation to environmental parameters. The current data revealed higher percentages of this pathology in the first two groups in cases from rural areas (70.1 and 52.7%) compared with higher percentages of chorioamnionitis in cases from urban areas in pregnancies with a gestational age > 29 weeks (58.2, 66.7 and 53.2% in groups 3, 4 and 5, respectively), but the differences were not statistically significant. (Table II).

U. urealyticum was detected in the vaginal cultures of pregnant women enrolled in the present study as follows: of the patients with chorioamnionitis, in group 1, 54.7% had *U. urealyticum* infection; in group 2, 45.9% had *U. urealyticum* infection; in group 3, 40.8% had *U. urealyticum* infection; in group 4, 34.9% had *U. urealyticum* infection; and in group 5, 41.9% had *U. urealyticum* infection. However, the presence of *U. urealyticum* in the vaginal cultures of patients without signs of chorioamnionitis was also detected. The bacteria most frequently detected in patient vaginal cultures regardless of the gestational age, was *U. urealyticum*.

Other bacteria more frequently involved in chorioamnionitis were as follows: *Streptococcus*, with an incidence of 9.5% in group 1, 15.8% in group 2, 13.3% in group 3, 15.2% in group 4 and 12.9% in group 5; *E. coli* with an incidence of 27.0% in group 1, 26.0% in group 2, 33.7% in group 3, 30.3% in group 4 and 32.3% in group 5; *Candida spp.* in 40.9% cases from group 1, 29.5% cases from group 2, 24.5% from cases in group 3, in 27.3% cases from group 4 and in 11.3% from group 5. Furthermore, vaginosis was detected in 7.3% of cases from group 1, in 11.6% of cases from group 2, in 11.2% of cases from group 3, in 9.1% of cases from group 4 and in 9.7% of cases from group 5 (Table III).

No marked association was noted between BV and *U. urealyticum* in the present study; however, a notable association between *Candida spp.* and *U. urealyticum* was detected in 28.5% of the cases in group 1, in 25.9% of then cases in group 2, in 16% of the cases in group 3, in 19.0% of the cases in group 4 and in 15.3% of the cases from group 5 (Table IV).

Discussion

PTB remains the leading cause of perinatal morbidity and mortality, affecting $\sim 10\%$ of pregnancies worldwide. The percentage varies, depending on a multitude of factors, such as ethnicity, race and socioeconomic conditions (19). The infectious agents associated with ruptured membranes and abortion or premature delivery are *C. trachomatis*, *N. gonorrhoeae* and *M. hominis/U. urealyticum*. The detection of *M. hominis* and *U. urealyticum* in vaginal cultures is associated with chorioamnionitis, premature birth and spontaneous abortion (30).

Previously published data by Capoccia *et al* (31) indicated that *U. urealyticum* infection in pregnancy was detected in almost half of the preterm cases. The detection of *U. urealyticum* in the amniotic fluid of pregnant women increases the risk of clinical or histological chorioamnionitis and PTB (22,32,33). The accuracy in the establishment of the

Table I. Distribution of patients according to gestational age, area and infectious agents.

Parameter	Gestational age (weeks)					Significance (P-value)
	17-23 (n=323), count (%)	24-28 (n=370), count (%)	29-32 (n=275), count (%)	33-36 (n=189), count (%)	≥37 (n=144), count (%)	
Area of residency						
Rural	227 (70.3)	201 (54.3)	114 (41.5)	85 (45.0)	67 (46.5)	<0.001
Urban	96 (29.7)	169 (45.7)	161 (58.5)	104 (55.0)	77 (53.5)	
<i>Ureaplasma urealyticum</i> infection	185 (57.3)	184 (49.7)	112 (40.7)	76 (40.2)	65 (45.1%)	<0.001
<i>Streptococcus</i> infection	19 (5.9)	50 (13.5)	53 (19.3)	34 (18.0)	17 (11.8)	<0.001
<i>Escherichia coli</i> infection	88 (27.2)	99 (26.8)	85 (30.9)	63 (33.3)	48 (33.3)	0.314
<i>Enterobacter</i> infection	10 (3.1)	11 (3.0)	6 (2.2)	7 (3.7)	4 (2.8)	0.912
<i>Enterococcus</i> infection	5 (1.5)	19 (5.1)	22 (8.0)	13 (6.9)	5 (3.5)	0.004
Bacterial vaginosis	27 (8.4)	32 (8.6)	23 (8.4)	15 (7.9)	9 (6.3)	0.930
<i>Candida</i> infection	125 (38.7)	123 (33.2)	64 (23.3)	59 (31.2)	36 (25.0)	0.001

Table II. Distribution of patients with chorioamnionitis according to residence area and gestational age.

Parameter	Gestational age (weeks)					Significance (P-value)
	17-23 (n=323), count (%)	24-28 (n=370), count (%)	29-32 (n=275), count (%)	33-36 (n=189), count (%)	≥37 (n=144), count (%)	
Leukocytosis (>15,000 cells/mm ³)	137 (42.4)	147 (39.7)	98 (35.6)	66 (34.9)	62 (43.1)	0.262
Fever	140 (43.3)	147 (39.7)	101 (36.7)	67 (35.4)	64 (44.4)	0.235
Chorioamnitis						
Total	137 (42.4)	146 (39.5)	98 (35.6)	66 (34.9)	62 (43.1)	0.265
Rural residency	96 (70.1)	77 (52.7)	41 (41.8)	22 (33.3)	29 (46.8)	<0.01
Urban residency	41 (29.9)	69 (47.3)	57 (58.2)	44 (66.7)	33 (53.2)	

diagnosis of chorioamnionitis with *U. urealyticum* in pregnancy is strongly suggested. There are increasingly available data that underline the implications of this infectious agent in PTB (22).

In the present study, infection with *U. urealyticum* was the most frequent one in pregnancy, regardless of whether having been associated with chorioamnionitis or not. This conclusion is also supported by the study by Cassel *et al* (34), according to which *U. urealyticum* was the most frequently detected microorganism in the amniotic fluid of pregnant women. This infection was associated with preterm delivery, involving higher perinatal mortality and morbidity rates. *Candida* was the most frequently associated vaginitis in the present study. Additionally, co-infection was associated with an increased risk of PTB and chorioamnionitis. The data obtained herein are in disagreement with those in the study by Cassel *et al* that detected the presence of BV, in association with *U. urealyticum* vaginitis, as being the most frequently associated pathology with PTB and chorioamnionitis (34).

The main cause of PTB is female upper genital tract infection (24,35). Almost 30% of women experience an

upper genital tract infection during pregnancy. Data from the literature suggest that 25-40% of all PTBs have something in common, infection with *U. urealyticum* (24,32,33). In previous studies on PTB from the literature, the rate of *U. urealyticum* infection has been reported to be ~42%. The implications of *U. urealyticum* infection in this pathology are very complex, as upper genital female tract infections that occur <32 weeks of gestation are frequently polymicrobial (24,25,36). The decreased virulence of this infectious agent accounts for the absence of clinical symptoms in a variety of cases. This may explain the chronicity that can be observed in some of the cases, with *U. urealyticum* infection being able to persist for several weeks in the upper female genital tract before preterm labor or rupture membranes occur (37).

Additionally, differences between the most frequently involved infectious agents in chorioamnionitis depending on the environment and the gestational age were detected in the present study. This difference may be attributed to changes in immune response of women and the presence of a specific vaginal bacteria, as opposed to the presence or absence of bacterial species (38,39). As Bhat *et al* (39) demonstrated in

Table III. The most frequent infectious agents involved in chorioamnionitis according to gestational age.

Parameter	Gestational age (weeks)				
	17-23 (n=137), count (%)	24-28 (n=146), count (%)	29-32 (n=98), count (%)	33-36 (n=66), count (%)	≥37 (n=62), count (%)
<i>Ureaplasma urealyticum</i> infection	75 (54.7)	67 (45.9)	40 (40.8)	28 (42.4)	26 (41.9)
<i>Streptococcus</i> infection	13 (9.5)	23 (15.8)	13 (13.3)	10 (15.2)	8 (12.9)
<i>Escherichia coli</i> infection	37 (27.0)	38 (26.0)	33 (33.7)	20 (30.3)	20 (32.3)
<i>Enterobacter</i> infection	9 (6.6)	4 (2.7)	3 (3.1)	2 (3.0)	1 (1.6)
<i>Enterococcus</i> infection	1 (0.7)	7 (4.8)	7 (7.1)	5 (7.6)	2 (3.2)
Bacterial vaginosis	10 (7.3)	17 (11.6)	11 (11.2)	6 (9.1)	6 (9.7)
<i>Candida</i> infection	56 (40.9)	43 (29.5)	24 (24.5)	18 (27.3)	7 (11.3)

Table IV. Dependence of *Ureaplasma urealyticum* infection and *candida*/bacterial vaginosis association levels on gestational age.

Parameter	Gestational age (weeks)				
	17-23 (n=185), count (%)	24-28 (n=184), count (%)	29-32 (n=112), count (%)	3-36 (n=76), 3 count (%)	≥37 (n=65), count (%)
<i>Ureaplasma urealyticum</i> and bacterial vaginosis	3 (0.9)	-	-	-	-
<i>Ureaplasma urealyticum</i> and <i>Candida</i>	92 (28.5)	96 (25.9)	44 (16.0)	36 (19.0)	22 (15.3)

their study, the immune system appears to respond differently to a certain bacteria presence, depending on the environment. In the present study, *U. urealyticum* infection was detected in the majority of the patients under 28 weeks of gestation (groups 1 and 2) originating from rural areas. By contrast, it was revealed that women from urban areas have vaginal cultures positive to other infectious agents.

Studies have demonstrated that pro and anti-inflammatory responses to bacteria are simultaneously present in the amniotic fluid. The immune response varies due to the environment, gestational age and the pathogens detected. This aspect underlines the need to evaluate patients in a more individualized basis, in order to completely elucidate and comprehend the effects of bacterial pathogens on the immune response and pregnancy (38,39). Vogel *et al* (40) described a combined effect of vaginal *U. urealyticum* along with the presence of abnormal vaginal flora, that facilitates the ascending of the infection with this particular agent, possibly increasing the risk of preterm delivery. Moreover, another possible explanation is that the microbial disturbances that occur in cases with abnormal vaginal flora enhance the growth of *U. urealyticum* causing a very high *Ureaplasma* load. Vaginal infection with *Candida*, also suggests disruptions in the normal constellation of germs in the vaginal flora (37,40).

There is a discrepancy in the results from previously published studies concerning the incidence of different types of vaginal bacterial infections in pregnancy. This may be attributed to the different diagnostic criteria used in the

detection of BV and bacteria, as well as differences in the risk profile of pregnant women (parity, use of antibiotic treatment and gestational age at enrollment). The complex mechanism resulting in the association between a certain type of a vaginal flora and *U. urealyticum* colonization in determining preterm labor is likely to be multifactorial. The virulence aspects and the magnitude of the immune response have been reported to be the key for pregnancy outcomes (38,39). Information about the efficiency of antibiotic treatment in intra-amniotic *U. urealyticum* infection is scarce. Insufficient data and the lack of management guidelines force clinicians to adopt empiric antibiotic treatment, culminating in treatment failure in a number of cases (22,41). Pregnant women are not routinely screened for *U. urealyticum* infection because this is not covered by insurance in Romania. Hence, this infection is not usually detected and treated.

In conclusion, this marked association between the *U. urealyticum* intra-amniotic infection and PTB is strongly supported by the existing data and has also been revealed in many previously published studies. The findings of the present study may prove useful in updating clinical practice guidelines, based on local and regional epidemiologic particularities, with the aim of preventing management errors and also underlying the need for supplementary first trimester screening for *U. urealyticum*. Further future studies focusing on novel antibiotic regimens protocols for the intra-amniotic infection with *U. urealyticum* are necessary in order to provide insight into treatment and management strategies for bacterial infections and for the

improvement of long-term perinatal outcomes. Thus, further research is required in order to obtain a better understanding of the association between socioeconomic factors, BV, *U. urealyticum* infection and the immune system response, which finally lead to adverse outcomes, including premature birth and severe neonatal complications of prematurity.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

DRM, AU, IEB and CMS were involved in the conception of the study and data interpretation, and also wrote the manuscript. AA, DR, CEM, ID and VLB contributed to data collection and performed the statistical and descriptive analysis. DRM, AU and ID revised the manuscript for important intellectual content and confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Ethical approval was obtained from the Ethics Committee of the 'Cuza Voda' Obstetrics and Gynecology Clinical Hospital, Iasi and written consent was obtained from all participants (Approval no. 10426/2021).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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