Bulletin of the *Transilvania* University of Braşov
Series VI: Medical Sciences • Vol. 10 (59) No. 2 - 2017

GENITOURINARY INFECTIONS AND THEIR IMPLICATIONS IN PRETERM BIRTH

O.G. DIMIENESCU[1] M.A. MOGA[1*] N. BÎGIU[1]
C. ANASTASIU[1] A. BĂRĂCAN[1] S. MOGA[1]

Abstract: *Preterm delivery is the leading cause of perinatal morbidity and mortality. The purpose of this study was to assess the incidence of preterm birth in women hospitalized in the "Clinical Obstetrics and Gynecology Hospital Dr. I. A. Sbârcea" Brasov during the years 2014-2016 and diagnosed with genitourinary infections. We observed an average incidence of preterm delivery of 15.33% and an incidence of preterm birth in pregnant women with positive cervical cultures and positive urine cultures between 19.73% (2014) and 14.95% (2016). 54.24% of cases came from rural areas compared to women from urban areas (45.75%), while lifestyle, diet, excessive effort, lack of education and hygiene of the intimate area had negative influences on the normal evolution of pregnancy and increased the incidence of birth before term in rural areas. Therefore, preterm birth is the largest global cause of neonatal mortality and morbidity and it should be seen as an important public concern.*

Key words: *preterm birth, preterm rupture of membranes, infection, pregnancy, neonatal mortality.*

1. Introduction

Preterm birth (PTB) is defined as the birth occurring in less than 37 complete gestational weeks, being considered a determinant factor of neonatal mortality and morbidity with long-term negative health consequences [4]. WHO recommends in The International Statistical Classification of Diseases and Related Health Problems that the inferior limit is set to 22 weeks of amenorrhea and 500 g for weight. Within the legislation of the European countries this value varies: 24 weeks in Norway, Hungary, France, Italy; 22 weeks in Germany, England; 28 weeks in Denmark and Sweden [4]. In Romania the inferior limit of the interval established for PTB is at 24 weeks if the conception product presents signs of life (spontaneous breathing, cardiac activity, umbilical cord pulse, or voluntary contraction of a muscle) [25], [32]. It is estimated that more than 1 million newborns in the world die each year because of PTB [21]. Neonatal complications such as respiratory distress syndrome, intraventricular hemorrhage, periventricular leucomalacia, sepsis and long-term complications are closely related to the gestational age at birth [26], [33].

[1] Faculty of Medicine, Transilvania University of Braşov.
* Correspondent author: mogas@unitbv.ro

PTB is the main cause of perinatal mortality and morbidity and complicates 5-12% of pregnancies worldwide. The premature newborn has a high risk of short-term morbidity, because of: respiratory distress syndrome, intraventricular hemorrhage, sepsis, ulcero-necrotic enterocolitis, retinopathy of prematurity and long-term morbidity because of: spastic paraparesis, neuromotor deficiency, respiratory sequelae, retinopathy and intellectual deficit [26], [33].

The etiopathogenic factors involved in triggering PTB are schematized in the table below.

Etiopathogenic factors involved in PTB Table 1

MATERNAL FACTORS	MATERNAL ANTECEDENTS	UTERINE FACTORS	FETAL AND ANEXAL CAUSES
• Infection, Inflammation • Age < 17 or >40 • Obesity • Smoking • Drug abuse • Increased stress • Low socio- economic status • Diabetes	• History of PTB • Personal history of abortion in the 2nd trimester • Coagulation abnormalities	• Short cervix • Congenital uterine abnormalities • Uterine supradistention • Uterine or cervical trauma	• Fetal malformations • Placenta praevia • PPROM (premature rupture of membranes) • Abruptio placentae • Choriamnionitis

Microbial colonization and inflammation of the genital tract are considered major risk factors associated with PTB. Preterm labor and/or preterm rupture of membranes in pregnant women with genital infections result from the action of pro-inflammatory cytokines because of fetal and/or maternal response to the microbial invasion and may trigger birth by activating the monocyte-macrophage system in the peripheral blood and decidua [2], [8], [15].

2. Objectives

The objective of this study was to determine the incidence of premature spontaneous deliveries in pregnant women with infections of the genitourinary tract, hospitalized in the Clinical Obstetrics and Gynecology Hospital "Dr. A.I. Sbârcea" Brasov.

The paper also emphasizes the importance of hygiene during the pregnancy in order to avoid the repercussions of genital and urinary infections that can affect both the mother and the fetus.

3. Material and Methods

The retrospective study was conducted in the Clinical Obstetrics and Gynecology Hospital "Dr. I.A. Sbârcea" Braşov for a 3-year period of time, during 2014 and 2016. There were registered 12291 births out of which 1812 (14.74%) were premature births. The study was based on the analysis of the patient's medical records: observation sheets and birth registration records.

The information was retrieved and then entered into an Excel database created specifically for this purpose. Statistical and graphical data processing was performed using the Microsoft Office.

4. Results

The study was conducted over a 3-year period of time, from 2014 to 2016. The

number of births slightly decreased from 4216 in 2014 to 4035 births in 2016. The number of prematurity cases also declined from 638 in 2014 down to 548 in 2016 (Figure 1).

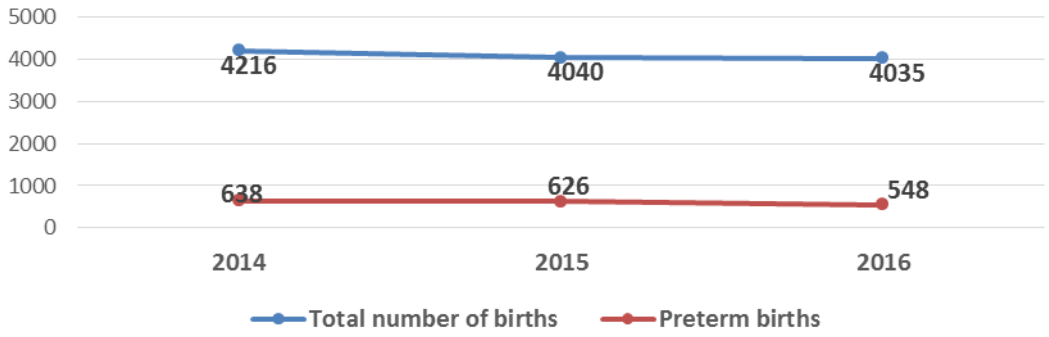

Fig. 1. *Distribution of total number of births and premature births between 2014-2016*

Out of the total number of premature births in the studied period, the highest incidence of genitourinary infections was in 2014 with 89 (13.94%) premature births associated with genital infections and 37 (5.79%) premature births associated with urinary tract infections. In 2015 the values obtained were similar to those of the previous year: 85 cases with genital infections (13.57%) and 34 cases with urinary tract infections (5.43%). The incidence continued to decrease in 2016: 55 cases (10.03%) with genital infections and 27 cases (4.92%) with urinary infections. The incidence of premature births in women with genital and urinary infections is schematically shown in Figure 2.

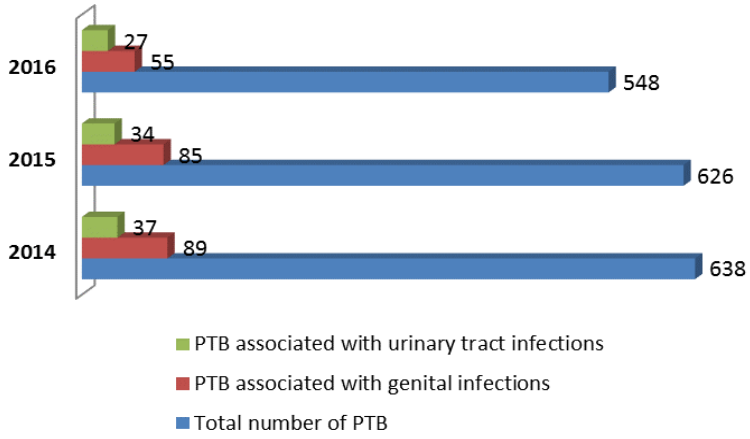

Fig. 2. *The incidence of premature births in women with genital and urinary infections*

The total number of premature births in women with genitourinary infections were 19.73% in 2014, reaching 14.95% in 2016. This number represents more than one third of all premature births. Of the total number of 1.812 premature births registered in the studied period of time, there were 474 cases (26.15%) (Table 2).

Table 2

Distribution of premature births in women with genital and urinary tract infections

Total PTB		**% PTB associated with genital infections**	**% PTB associated with urinary tract infections**	**% PTB associated with genito-urinary infections**
2014	638	13.94%	5.79%	19.73%
2015	626	13.57%	5.43%	19.01%
2016	548	10.03%	4.92%	14.95%
Total	1812	12.53%	5.40%	17.92%

Regarding the residence area, out of a total of 1.812 women who gave birth prematurely, 983 came from rural areas and 829 of them came from urban areas.

Vaginal infection was an important cause of premature rupture of membranes, representing the main risk factor for PTB. In our study the vaginal infection was certified by positive cervical cultures in 12.53% of cases of pregnant women who presented with preterm premature rupture of membranes (PPROM) for more than 24 hours.

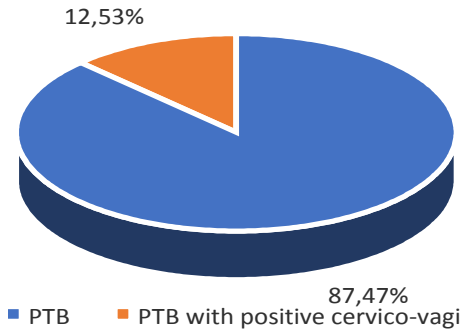

Fig. 3. *The incidence of PTB in pregnant with cervico-vaginal infections*

The laboratory tests revealed a wide range of cervico-vaginal bacteria in 227 women: *Group B Streptococcus, Chlamydia trachomatis, Trichomonas vaginalis, Mycoplasma hominis, Ureaplasma spp, Gardnerella vaginalis, Enterococcus, Escherichia coli, Klebsiella, Prevotella* (Table 3).

Table 3

The incidence of cervico-vaginal bacteria in pregnant with membranes rupture > 24 hours

Bacteria	**Percentage**
Group B Streptoccocus	21.14 %
Chlamydia Trachomatis	14.97%
Trichomonas vaginalis	12.77%
Mycoplasma hominis	12.77%
Ureaplasma	11.45%
Gardnerella vaginalis	3.96%
E. coli	8.37%
Enterococcus	6.6%
Klebsiella	5.28%
Prevotella	2.64%

Following our study we found that maternal age was also a risk factor for PTB. The most exposed age group consisted of women between 30 and 39 years old which also corresponded with the most fertile period and it represents 35.69% of the totality of PTB. It is followed by the 20-29 age group with a percentage of 30.15% while the age extremes represent 20.92% for those under 19 and 13.23% for women aged 40-49 (Figure 4).

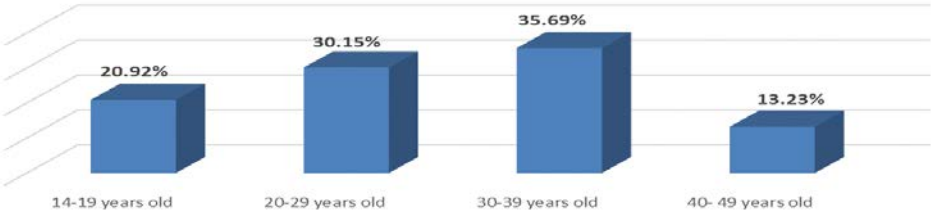

Fig.4. *Distribution of PTB in women with genito-urinary infections by age*

In our study the gestational age for premature births varied from 24 to 37 weeks. The incidence of PTB increased after week 34 of gestation, the maximum being at 36 weeks - 25.84% cases, followed by 17.23% of PTB at 35 weeks and 13.23% cases at 34 weeks , as it can be observed in the figure below.

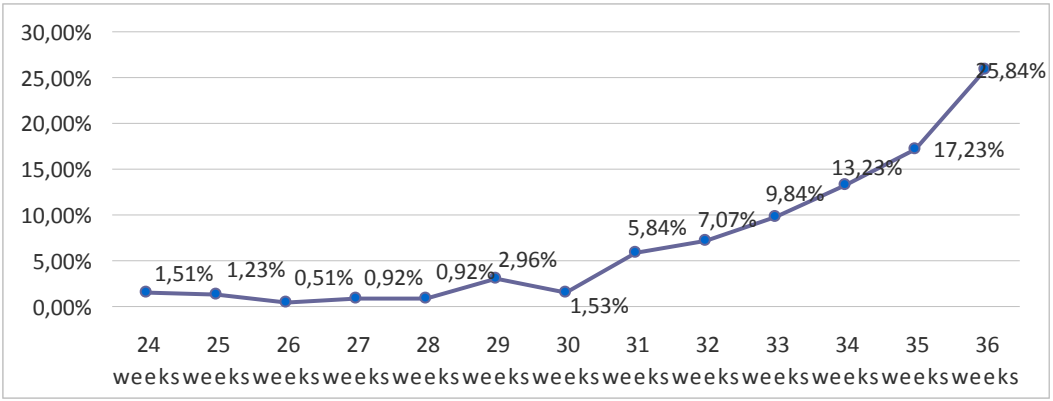

Fig. 5. *Distribution of preterm births based on gestational age*

In the period of our study, from the total number of premature births that occurred in women with genitourinary infection, the newborn were males in 51.69% cases. In terms of weight it was observed that an increased incidence of newborns with weight between 2.000 and 2.499 g (65.56%) which makes this category fall into the first degree of prematurity. We identified an incidence of 20.25% of newborns with weight between 1.500-1.999 g that corresponds to the second degree of prematurity, 8.55% of newborns were included in the range 1.001-1.499 g – third degree of prematurity, while 5.62% of newborns had under 1.000 g, representing the fourth degree of prematurity.

Most of the babies born prematurely have obtained an Apgar score of 9

(50.21%); 24% of them received Apgar 8, 11.07% received Apgar 7 and only 7.07% received Apgar 10. A total of 25 newborns (7.68%) received Apgar score below 6 (of which 1 premature with Apgar 1). Premature scores below 5 required reanimation and intensive care depending on their clinical situation.

Regarding the path chosen for the way of delivery, of the 325 cases of births from mothers with genitourinary infections, 43.38% gave birth vaginally and the rest of 56.62% by C-section. The most common indications for cesarean surgery were: fetal dystocic presentations, acute fetal distress, oligoamnios, placenta praevia, abruptio placentae, eclampsia and preeclampsia, thrombophilia, twin pregnancy.

5. Discussions

As a result of this retrospective analysis we observed that the natality has decreased slightly from 2014 to 2016 and the prematurity rate also. Approximately one-third of premature births had as risk factor genital or urinary infections that produced PPROM over time. The average incidence of premature births was 15.33%; the incidence of PB in pregnant women with positive cultures of the cervix and urine varied between 19.73% in 2014 and 14.95% in 2016.

The highest incidence of PTB (51.69%) occurred in the women with male fetuses. Although the difference is small, one cannot fail to consider a possible predisposition for male babies. *Challis et al*. conducted in 2013 a study based on the incidence of PB and on the link between PTB and the gender of the fetus. The result was that the incidence of PB is higher in pregnant women carrying a male fetus [7]. The explanation is that trophoblastic or chorionic cells in male babies pregnancies produce more TNFα and decreased concentration of IL-10 and granulocyte colony stimulating factor than trophoblastic cells from female fetuses, more prostaglandin synthase (PTGS-2) and less prostaglandin dehydrogenase (PGDH). These results suggested that in the presence of a male fetus the trophoblast has a higher potential to generate a pro-inflammatory environment which is a determinant factor of PB [8]. Hou et al. [20] conducted a study that included 109,722 women who gave birth to more than 28 weeks of gestation in 39 Chinese hospitals. The rate of premature delivery in women with male fetuses was 7.3% whereas in case of preterm female fetuses the labor triggered earlier in 6.5% of cases.

Regarding the environment of the pregnant women included in our study, 54.24% came from rural areas compared to 45.75% from urban areas. Hillemeier et al. [19] observed in a study from 2007 on a non-homogeneous cohort with women living in rural and urban areas and claimed that the risk of PB and low birth weight is lower in some rural areas compared to urban areas, but the difference is not significant.

As we mentioned, vaginal infection is an important cause of PPROM and this is the main risk factor for PTB and other complications such as maternal chorioamnionitis and fetal distress. In our study, vaginal infection was certified through positive cultures in 12.52% of pregnant women who had PPROM for more than 24 hours. A research of *Brown et al* included 17,678 women of whom 6.3% had positive cervical and vaginal cultures [5]. The study of Ronald F. Lamont also sustains the theory of negative influence of genital infections on pregnancy. Of 29,626 women included in the study, 22.07% had bacterial vaginosis associated with other infectious pathogens such as *Gardnerella vaginalis* and *Mycoplasma hominis* [24].

Bánhidy et al. at observed on a cohort of 38,151 parturient that 5.7% of them had a

urinary infection, condition that contributed as a trigger factor for premature labor [3]. A striking example of the high rates of asymptomatic urinary bacteriuria seen in some developing countries was conducted in Nigeria, on a group of 500 pregnant women, where the authors found asymptomatic bacteriuria in 86.6% of the cases. The microscopic examination also revealed that 72.4% of the women with positive asymptomatic bacteriuria had also a form of pyuria (*S. aureus* was isolated from the urine 15% of cases), but the most common bacteria encountered was *E. coli*. Positive samples taken from women with asymptomatic bacteriuria isolated *S. aureus* in 15.8% of all women [1].

The mechanism through which the microorganisms can cause premature labor is by ascending from the cervical / vaginal area to the intrauterine cavity and replicating in the placenta, decidua and membranes. We identified a study based on inoculation of *group B Streptococci* in the amniotic membranes of pregnant Rhesus monkeys. Subsequent samples of monkey amniotic fluid showed high levels of cytokines, such as interleukin-1 (IL-1β), interleukin-6 (IL-6) and prostaglandins (PGE2 and PGE2α). It is believed that IL-1 promotes the synthesis of IL-6 and IL-8, which triggers the production of prostaglandins E2 and F2α. These prostaglandins are known to stimulate uterine contractions [18].

It has been demonstrated that a long cervix with adherent mucus may serve as an anatomic and biochemical defense mechanism of the host against ascending intrauterine infection [10]. A short cervix may predispose to ascending intrauterine infections by shortening the distance between the lower genital tract microorganisms and the chorioamniotic membranes [29]. Cervical mucus contains antimicrobial properties attributed to antimicrobial peptides such as defensins, lactoferrin, calprotectin and bacterial permeability factor [11]. *Giunta et al.* pointed out a positive correlation between oral administration of lactoferrin and the decrease of IL-6 level in cervicovaginal fluid in women with high risk of PB, by normalization of the vaginal flora (disappearance of vaginal infection) [14].

Significant evidence derived from animal experiments indicates that the administration of microorganisms or microbial products to pregnant animals may induce premature labor and birth. Several authors demonstrated that the injection of *Shigella* and *Salmonella* endotoxin in mice and rabbits was able to induce abortion. *Takeda et al* have confirmed this observation through administration of endotoxin *Escherichia coli* in pregnant mice and rabbits [34]. Moreover, immunization of animals with an anti-endotoxin antibody improves the biological effect of endotoxin. Animal experiments of ascending intrauterine infection were developed by placing bacteria through a hysteroscope in the uterine cavity of the rabbits [27]. Using this model, Dombroski et al. and Romero et al. were able to induce premature labor and delivery [9], [28]. Gravett et al. have also developed a prematurely induced labor pattern of infection in *Rhesus* monkeys by inoculating the bacteria directly into the amniotic cavity or decidua [17].

Abnormal colonization of the lower genital tract with micro-organisms is a risk factor for premature delivery. These conditions include asymptomatic bacteriuria, bacterial vaginosis and *Neisseria gonorrhoeae* infection [30]. The results of four cohort studies that examined the relationship between asymptomatic bacteriuria and premature birth indicated that patients with this condition had a higher rate of PB than patients with negative cultures [6]. Because asymptomatic bacteriuria and bacterial

vaginosis are present before premature labor, the sequence of events sustains a causal role for these conditions in premature delivery. The precise mechanisms by which these abnormal conditions lead to premature labor have not been established [21].

Regarding the management of women with high risk of preterm delivery, it is necessary to be hospitalized, absolute rest in bed is required and serial ultrasound should assess fetal viability, gestational age, number and morphology of fetus, fetal respiratory movements, amniotic fluid volume and the location of the placenta. Cultures from the cervix and urine are required in order to indicate if genitourinary infections are present or not, complete blood count, the level of C reactive protein and in case of suspicion of PPROM, the presence of amniotic fluid should be confirmed. Fetal pulmonary maturation is also an important factor that needs to be investigated [4], [13].

The reports of Fonseca et al. and Rouse et al. raises important issues regarding the efficacy and safety of progestative treatment to prevent premature birth [12], [31]. Rouse et al. observed an increase in the birth number that occurred before 28 week and an insignificant increase in the number of newborns weighing less than 1,500 g after exposure to 17-alpha-hydroxyprogesterone caproate (17P). Other studies in which 17P were used in less than 20 weeks of gestation also observed insignificant increases in spontaneous abortion. The authors suggest an important role of regular controls as a method of screening and prophylactic treatment for PTB with progesterone [12], [31].

Regarding the antibiotic therapy in women with genitourinary infections and high PTB risk, *Kenyon et al.* conducted a study in 2013 that assessed the immediate and long-term effects of antibiotics in women with PROM before 37 weeks. The result of the use of antibiotic therapy was associated with a statistically significant decrease in chorioamnionitis, neonatal infections and the use of surfactant and oxygen therapy in neonates [23].

Referring to the way of birth in prematurely triggered labor, our study revealed that of the 325 cases of premature births in patients with genitourinary infection, there were 141 vaginal births and 184 cesarean deliveries. C-section was the choice in case of premature extraction of fetuses who already have significant chronic distress [22]. Low gestational age and chronic fetal distress exclude the possibility of vaginal delivery. It is known the negative effect of uterine contractions on utero-placental hemodynamics. For the breech presentation, fetal prognosis is reserved, with an increased risk of immediate neonatal mortality and morbidity (hypoxia, acidosis, cerebrovascular bleeding, trauma) and long-term neurological sequelae. *Goldenberg et al*. suggests prophylactic C-section, finding that fetuses born prematurely by vaginal way in breech presentation were 16 times more likely not to survive compared to those born in the cephalic presentation [16].

6. Conclusions

Based on our study, we found that natality is steadily decreasing as does the number of premature births, but one cannot state whether this happened because of the interdependence between natality and premature birth or a better evidence of patients and adequate bacterial vaginosis screening contributed to this.

We also found that premature births from women who had positive cultures of the cervix and vagina accounted for about one-third of all premature births and the number of small ages pregnant women is steadily increasing, which may be an

explanation for the large number of cases with genital and urinary infections, lack of awareness of the pregnancy and self-care needed during this period.

Through this paper, we want to emphasize the importance of hygiene during pregnancy to avoid the repercussions of genital and urinary infections during the pregnancy that can seriously harm the mother, but especially the fetus.

References

1. Akerele, J., Abhulimen, P. et al.: *Prevalence of asymptomatic bacteriuria among pregnant women in Benin City, Nigeria*. In: J Obstet Gynaecol (2001); Vol 21 (2), p. 41–4.
2. Bastek, JA., Gómez, LM. Et al.: *The role of inflammation and infection in preterm birth*. In: Clinics in Perinatology (2011); Vol. 38(3), p. 385-406.
3. Bánhidy, F., Acs, N., et al.: *Rate of preterm births in pregnant women with common lower genital tract infection: a population-based study based on the clinical practice.* In: J Matern Fetal Neonatal Med (2009); Vol. 22(5), p.410-8.
4. Beck, S., Wojdyla, D., et al.: *The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity*. In: Bull World Health Organ (2010); Vol. 88 (1), p. 31-8.
5. Brown, H.K., Speechley, K.N., et al.: *Biological determinants of spontaneous late preterm and early term birth: a retrospective cohort study*. In: BJOG (2015); Vol. 122(4), p. 491-499.
6. Carey, J.C., Blackwelder, W.C., et al.: *Antepartum cultures for Ureaplasma urealyticum are not useful in predicting pregnancy outcome. The vaginal infections and prematurity study group.* In: Am J Obstet Gynecol (1991); Vol. 164 (3), p. 728-33.
7. Challis, J., Newnham, J., et al.: *Fetal sex and preterm birth*. In: Placenta (2013) Vol. 34 (2), p. 95-9.
8. Cappelletti, M., Della Bella, S., et al.: *Inflammation and preterm birth.* In: Journal of Leukocyte Biology (2016); Vol. 99 (1), p. 67-78.
9. Dombroski, R.A., Woodard, D.S., et al.: *A rabbit model for bacteria-induced preterm pregnancy loss.* In: Am J Obstet Gynecol (1990); Vol. 163 (6), p.1938–1943.
10. Eggert-Kruse, W., Botz, I., et al.: *Antimicrobial activity of human cervical mucus*. In: Hum Reprod (2000); Vol. 15 (4), p.778-84.
11. Espinoza, J., Chaiworapongsa, T., et al.: *Antimicrobial peptides in amniotic fluid: defensins, calprotectin and bacterial/permeability-increasing protein in patients with microbial invasion of the amniotic cavity, intra-amniotic inflammation, preterm labor and premature rupture of membranes.* In: J Matern Fetal Neonatal Med (2003); Vol. 13 (1), p. 2-21.
12. Fonseca, E.B., Celik, E., et al.: *Progesterone and the risk of preterm birth among women with a short cervix*. In: N Engl J Med (2007); Vol. 357(5), p. 462-9.
13. Gibbs, R.S., Romero, R., et al.: *A review of premature birth and subclinical infection.* In: Am J Obstet Gynecol (1992); Vol. 166(5), p.1515-28.
14. Giunta, G., Giuffrida L., et al.: *Influence of lactoferrin in preventing preterm delivery: a pilot study*. In: Mol Med Rep (2012); Vol 5 (1), p. 162-6.
15. Goldenberg, R.L., Hauth, J.C., et al.: *Intrauterine Infection and Preterm Delivery*. In: N Engl J Med (2000); Vol. 342(20), p. 1500-1507.

16. Goldenberg, R.L., Nelson, K.G.: *The premature breech.* In: Am J Obstet Gynecol (1977); Vol. 127(3), p. 240–244.
17. Gravett, M.G., Hummel, D., et al.: *Preterm labor associated with subclinical amniotic fluid infection and with bacterial vaginosis*. In: Obstet Gynecol (1986); Vol. 67 (2), p. 229-37.
18. Gravett, M.G., Witkin, S.S., et al.: *An experimental model for intraamniotic infection and preterm labor in rhesus monkeys.* In: Am J Obstet Gynecol (1994); Vol. 171 (6), p. 1660–7.
19. Hillemeier, M.M., Weisman, C.S., et al.: *Individual and community predictors of preterm birth and low birthweight along the rural-urban continuum in central Pennsylvania*. In: J Rural Health (2007); Vol. 23 (1), p. 42-8.
20. Hou, L., Wang, X., et al.: *Cross sectional study in China: fetal gender has adverse perinatal outcomes in mainland China*. BMC Pregnancy Childbirth (2014); Vol. 14 (1), p.14-372.
21. Howson, C.P., Kinney, M.V., et al.: *Born Toon Soon: Preterm birth matters*. In: Reprod Health (2013); Vol. 10 (Suppl 1), p. 51.
22. Ionescu, CA., Pleș, L., et al.: *Present tendencies of elective caesarean delivery in Romania: Geographic, social and economic factors*. In: The Journal of the Pakistan Medical Association (2017); Vol. 67(8), p. 1248-53.
23. Kenyon, S., Boulvain, M., et al.: *Antibiotics for preterm rupture of membranes*. In: Cochrane Database Syst Rev (2013); Vol. 12, CD001058.
24. Lamont, R.F.: *Advances in the Prevention of Infection-Related Preterm Birth Front*. In: Front Immunol (2015); Vol. 16, p. 6.
25. Moga, M.A.: *Nasterea prematura*. In: Obstetrică – Ginecologie pentru asistență medicală. Editura Universității Transilvania Brașov (2010), p.151.
26. Moore, T., Hennessy, E.M., et al.: *Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the epicure studies*. In: BMJ (2012); Vol. 345, p. 7961.
27. Rioux-Darrieulat, F., Parant, M., et al.: *Prevention of endotoxin-induced abortion by treatment of mice with antisera.* In: J Infect Dis (1978); Vol. 137 (1), p.7-13.
28. Romero R., Munoz H., et al.: *Antibiotic therapy reduces the rate of infection-induced preterm delivery and perinatal mortality.* In: Am J Obstet Gynecol (1994); Vol. 170, p. 390.
29. Romero, R., Gomez, R., et al.: *Cervical mucus inhibits microbial growth: a host defense mechanism to prevent ascending infection in pregnant and non-pregnant women.* In: Am J Obstet Gynecol (1993); Vol. 168, p. 312.
30. Romero, R., Oyarzun E., et al.: *Meta-analysis of the relationship between asymptomatic bacteriuria and preterm delivery/low birth weight.* In: Obstet Ginecol (1989); Vol. 73(4), p. 576–582.
31. Rouse D.J., Caritis, S.N., et al.: *A trial of 17 alphahydroxyprogesterone caproate to prevent prematurity in twins.* In: N Engl J Med (2007) Vol. 357 (5), p. 454-61.
32. Steer, P.: *The epidemiology of preterm labour*. In: BJOG: An International Journal of Obstetrics & Gynaecology. (2005); Vol. 112 (s1), p.1-3.
33. Stoll, B.J., Hansen, N.I., et al.: *Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network.* In: Pediatrics (2010); Vol. 126 (3), p.443-56.
34. Takeda, Y., Tsuchiya, I.: *Studies on the pathological changes caused by the injection of the Shwartzman filtrate and the endotoxin into pregnant rabbits.* In: Jpn J Exp Med (1953); Vol. 21, p.9–16.