Intrauterine Infections and Preterm Birth: Literature Review

Yessi Rahmawati[1], Titin Andri Wihastuti[2], Tita Hariyanti[3], Bambang Raharjo[3]

[1]*Doctoral Program in Medical Sciences, Faculty of Medicine, Universitas Brawijaya, Malang/ Waluyo Jati Hospital, Probolinggo, East Java Indonesia*
[2]*Department of Nursing, Faculty of Health Sciences, Universitas Brawijaya, Malang, Indonesia*
[3]*Department of Public Health, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia*
Corresponding Author: Yessi Rahmawati, Email: rahmawati.yessi76@gmail.com

KEYWORDS
preterm labor, intrauterine infection.

ABSTRACT
Objective: Premature birth is involved in the worldwide health sector problem and an important part challenge. This incidence rate continues to increase and currently, premature births occur in developing countries at 12.5% of all births. Infections within the uterus are associated with at least 40% of births occurring prematurely. Genitourinary tract infections can affect around 41% of women in their reproductive years worldwide may be affected, with 60-80% of these pregnancy-related infections being symptom-free. This article attempts to review the link relating intrauterine infections to premature birth. Data source: This study was taken from six electronic bibliographic databases, namely PubMed, Science Direct. ProQuest, Scopus, EBSCO and DOAJ employing the terms "intrauterine infection", or "premature delivery". Data from all journal articles, summarized according to the categories of the framework of concepts. The following summarization involves the compilation, analysis, and understanding of study data. Results: 10- 12% of intrauterine infections were found in pregnant women, and 20% of premature births were caused by intrauterine infections. The risk factors for this infection are known to be nullipara, lifestyle, and generally women of reproductive age who frequently change partners. There are several types of intrauterine infections, including Bacterial vaginosis, Chlamydia, Asymptomatic bacteriuria, Trihcomonas, and Syphilis. Conclusion: preterm birth has several risk factors, one of which is intrauterine infection that occurs during pregnancy. A quick and accurate diagnosis will help the process of treating intrauterine events in pregnant women to prevent preterm birth.

1. Introduction

Labor that begins before 37 weeks of gestation is classified as preterm labor. Based on gestational age, premature birth is classified into various subcategories, namely: a.) extremely premature, where the gestational age is less than 28 weeks at the time of delivery; b.) very premature, gestational age is in the range of 28 to 32 weeks; c.) moderate prematurity, delivery occurs when the gestational age is in the range of 32 to 37 weeks (1). Premature birth is a major cause of morbidity and mortality worldwide (2).

Premature birth is a global health problem and a major challenge. This incidence rate continues to increase and currently, premature births occur in developing countries at 12.5% of all births, linked to a considerable increase in rates of mortality and morbidity (3). Throughout the world, around 15 million babies are born prematurely every year and around 12 million (81.1%) of babies born prematurely occur in Asia and Sub-Saharan Africa 5-18% of pregnancies face complications due to premature birth, which significantly impacts maternal and fetal health, leading to increased morbidity and mortality (4). The incidence regarding preterm and preterm infant mortality in Indonesia is still relatively high. Indonesia is ranked in the top 10 out of 184 countries with a high preterm incidence rate, namely 15.5 preterm births per 1,000 live births. Indonesia is the fifth country with the highest number of preterm babies in the world, namely 675,700 babies (5). The frequency of preterm births is highest in Indonesia compared to other ASEAN countries, the Philippines comes next at 14.9 per 1,000 live births, followed by Myanmar at 12.4 per 1,000 live births. Preterm birth contributes to the highest infant mortality in Indonesia.

The gestational age is called term when it is ranging from 37 to 41 weeks, calculated from the first day of the last menstrual cycle assuming a 28-day cycle, childbirth that takes place before reaching 37 weeks of gestational age is referred to as premature labor which can cause one million deaths every year (6). Preterm birth is one of the primary contributors to neonatal morbidity and mortality globally caused by preterm labor, such a syndrome that encompasses a wide range of etiologies (6).

Babies can be born prematurely due to spontaneous preterm labor or due to medical indications to prepare for an early labor induction or surgical birth. In the year 2020, an estimated 13.4 million infants were born too early, exceeding the ratio of 1 in 10. Nearly 900,000 children passed away in 2019 due to complications associated

with being born prematurely. Prematurity is the primary cause of mortality in children younger than 5 years old across the globe. The disparity in the rates of survival across the globe is striking. Half of the babies born at or under 32 weeks (two months early) in low-income countries die. (1).

Most preterm births are spontaneous and idiopathic, with causes largely unknown (4). There are numerous underlying reasons that can result in premature birth, including: emotional strain, contamination, placental abruption, low-lying placenta, drug user, previous background of preterm delivery or termination of pregnancy, insufficient pregnancy-related medical care, cigarette consumption, maternal age under 18 or over 40 years, inadequate nutrition, underweight body mass index fetal abnormalities, restricted fetal growth, oligohydramnios, polyhydramnios, vaginal bleeding, premature rupture of membranes (PPROM), and environmental effects (7).

Approximately 40% of preterm births can be attributed to infections occurring in the uterus. At times, it is hard to identify whether the infection is the origin or the outcome of the circumstances that resulted in premature birth. However, it is evident that there is mounting findings that demonstrate the connection between infection and the inflammation it causes, regardless of being in the pregnancy tissue or elsewhere, is the main cause of the majority of premature births (8).

Genital tract infections (GTI) continue to pose a considerable health issue. According to estimates, 370 million individuals had chlamydia, gonorrhea, and trichomoniasis in 2016, and an additional 708 million were afflicted with genital herpes and condyloma acuminatum. Research indicates that there is an association between GTIs and premature birth among pregnant women. The mechanism of preterm labor associated with GTI needs to be further understood to prevent neonatal mortality and morbidity which can be a risk factor for impaired growth and development of neonates. (9).

Up to 41% of women of reproductive age worldwide may experience genitourinary tract infections, and around 60-80% of these infections during pregnancy often show no symptoms. Significant associations have been found between maternal genitourinary tract infections and a variety of adverse outcomes for both mothers and infants, including miscarriage, stillbirth, premature birth, fetal growth restriction, neonatal and postpartum sepsis, neonatal encephalopathy, and mortality in both mothers and newborns (10). This article attempts to review the correlation of intrauterine infections in relation to premature birth.

2. Research Methods

Search Strategy

The research was taken based on six electronic bibliographic databases, namely PubMed, Science Direct. ProQuest, Scopus, EBSCO and DOAJ employing the terms "intrauterine infection", otherwise "premature delivery". The researchers additionally looked for additional publications accessible through the Google Scholar search platform and performed manual reference checks of the identified review articles. Relevant articles will be identified by screening the titles and abstracts of each publication. Full-text and published access (not preprints) is a consideration when selecting articles for review.

Study Selection

After obtaining journal articles according to keywords, the author carried out extraction. Filtering and extraction of articles to retrieve information covering four domains: 1) author; 2) study identification (article title; author; year of publication); 3) region or nation of the population under investigation.

4) methodological elements (study structure; aims of the study; research inquiries or hypotheses; sample attributes; sampling procedures; and statistical analysis techniques) 5) major discoveries; and 7) concluding statement. The data from each journal article were condensed according to the categories of the framework of concepts. The following summarization involves summing up, analyzing, and interpreting the data derived from the research.

3. Result

Epidemiology

Intrauterine infection is considered one of the main maternal diseases during pregnancy. The incidence rate varies between 10%-20%. Based on histological examination, this occurs in 20% of preterm births compared with 60% of preterm births. Pregnant women experience anatomical and hormonal changes that increase their vulnerability to Urinary Tract Infections (UTIs). Representing a critical health issue, urinary tract infections are reported in 20% of pregnant women and are the most common reason for hospitalization in obstetric

departments. Bacteriuria with symptoms and without symptoms occurred in 17.9% and 13% of pregnant women (11).

The primary reasons for this infection include bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis. In identified cases, bacterial vaginosis is responsible for 40%-50%, with vulvovaginal candidiasis accounting for 20%-25% and trichomoniasis for 15%-20% (12). Asymptomatic bacteriuria is a primary contributor to UTI during the period of pregnancy, accounting for around 70% of cases. Asymptomatic bacteriuria influences 2–10% of pregnant women on a global scale. (13).

Risk Factor

Several research has identified factors that increase the risk of chorioamnionitis, such as extended duration of membrane rupture, extended labor, having no prior pregnancies, ethnicity of African-Americans, internal observation during childbirth, recurrent vaginal evaluations, meconium-stained amniotic fluid, cigarette consumption, substance abuse, including alcohol, disorders of the immune system, anesthesia administered epidurally, colonization by group B Streptococcus, bacterial vaginosis, sexually transmitted genital infections, and vaginal colonization by urea plasma (14). Young women who have multiple sexual partners may be more likely to be involved in activities with high risk, for example cigarette consumption while pregnant, which likewise increases the possibility of harmful obstetric effects complications (15).

Various types of intrauterine infections

Several types of intrauterine infections can move to the uterus, including Bacterial vaginosis, Chlamydia, Asymptomatic bacteriuria, Trichomonas, and Syphilis.

Bacterial vaginosis

An imbalance of normal vaginal bacteria is known as bacterial vaginosis. Chorioamnionitis is the main cause of premature birth, and previous reports have suggested that chorioamnionitis occurs in the background of bacterial vaginosis. If BV causes vaginitis or cervicitis and then develops into inflammation of the entire fetal membrane, this can then cause premature rupture of membranes and labor (16).

Bacterial vaginosis (BV) is a condition affecting the vagina that frequently affects women in their reproductive years. Three of the four Amsel criteria are common vaginal conditions that occur during bacterial vaginosis.: 1) watery discharge that is grayish or white in color; 2) fluid release of a foul-smelling "fishy" liquid after incorporating 10% potassium hydroxide; 3) elevated vaginal pH levels (greater than 4.5), and 4) determination of vaginal epithelial cells that are thoroughly covered in bacteria. BV is generally diagnosed by evaluating the morphotype of vaginal bacteria based on Gram staining applying the Nugent score, where a score of 7 or higher signifies bacterial vaginosis (17).

Bacterial vaginosis occurs in 25-25% of women of reproductive age and causes an increase in vaginal pH from normal values, 3.8-4.2 to 7 (18). Rates of bacterial vaginosis are higher among women in Southern and East Africa, with 68% in Mozambique, 51% in Lesotho, 44% in Kenya, and 37% in Gambia in contrast to women in West Africa, where the rate is 7% in Burkina Faso [21]. In Norway (24%), Turkey (23%), and Poland (19%), there are notable rates of bacterial vaginosis among women. Rates of bacterial vaginosis among women in Southeast Asia, Australia, New Zealand, and Indonesia are generally over 30% (17).

Chlamydia

Globally, around 131 million cases of sexually transmitted infections occur due to chlamydia each year (19). Several causes of sexually transmitted infections in women, such as pelvic inflammatory disease, tubal infertility, ectopic pregnancy, and abdominal pain, are referred to as Chlamydia trachomatis. Chlamydia Infections that happen while pregnant can also affect pregnancy outcomes causing early breaking of the amniotic sac, early birth, low birth weight, death occurring around the time of birth, causing conjunctival condition in newborns as well as respiratory infections (20).

Asymptomatic Bacteriuria

Asymptomatic bacteriuria (ASB) is a condition in which urine culture shows significant bacterial growth greater than or equal to one hundred five colony-forming units for every milliliter of urine taken from a clean midstream urine but the patient does not show symptoms such as genitourinary tract infection. Pregnant women are twice as likely to get this disease as non-pregnant women of the same age range. Asymptomatic bacteriuria can be both symptomatic and asymptomatic urinary tract infections (13). Asymptomatic bacteriuria during pregnancy

if left untreated, can lead to acute pyelonephritis, premature labor, low birth weight (21).

Trichomonas Vaginalis

The most common non-viral sexually transmitted infection in the world is trichomoniasis. Women and men aged around 15 to 49years experience approximately 156 million cases of trichomoniasis globally each year. Considering the impact of trichomoniasis on women of childbearing age, effect on this infection on being pregnant is especially associated resulting in unfavorable birth outcomes (22). Women who give birth prematurely with trichomoniasis have a 1.27 times greater chance in facing preterm delivery (PTD) compared with female counterparts who are not infected. Females diagnosed with trichomoniasis have a 1.87 times greater chance in facing premature rupture of membranes (incorporating PPROM) in contrast to women who are uninfected (23).

Although trichomoniasis commonly distinguished by vaginal discharge, dysuria, irritation, vulvar irritation, along with abdominal pain, up to 50% of infected women do not show any symptoms (19). T. vaginalis occurs majority frequently among women of reproductive age. There is an estimate that up to 25 million pregnant women worldwide carry this bacterium. Typically, the protozoan T.vaginalis causes infections without symptoms, However, symptomatic urethritis, vaginitis, or vulvitis may also occur occasionally. Studies have linked T. vaginalis to preterm rupture of membranes, premature birth, and low birth weight. One study it was discovered that T. vaginalis in pregnant women was significantly associated accompanied by an increased potential for premature birth (24).

Mechanism of infection becomes preterm

The female reproductive organs are the part of the body most susceptible to infection. This is because the distance between the anus and urethra is quite close, causing germs such as fungi, bacteria, parasites and viruses to easily develop in the vaginal area. The vagina is one of the organs most sensitive to microorganisms. The vaginal defense system against pathogenic microorganisms is very dependent on the normal flora that lives there, including lactobacilli, streptococcus, staphylococci, enterocouc, Gardnerella, mycoplasma, urea plasma, ureplasma, Enterobacteriaceae and various types of anaerobic bacteria. other. Within the vagina, there exist various kinds of bacteria, around 95% Lactobacillus, 5% pathogens. In conditions of a balanced vaginal ecosystem, pathogenic bacteria will not interfere. If this balance is disturbed, for example the acidity level decreases, then natural defenses will also decrease and we are susceptible to infection.

There are many factors that cause an imbalance in the vaginal ecosystem due to many factors, one of which is pregnancy. In a pregnant state, the vagina has a normal pH $\leq$ 4.5. This needs to be maintained because the acidic pH of Lactobacillus will thrive and this is an important mechanism in inhibiting pathogenic microorganisms in the vagina. Changes in pH acidity in the vagina will trigger pathogenic bacteria such as Gardnerella vaginalis, Mycoplasma hominis and Bacteroides sp. This change in vaginal flora can cause bacterial vaginosis.

BV is an abnormal condition of female ecological change which features a shift regarding the balance of vaginal microbiota where the dominance of Lactobacillus is replaced by anaerobic bacteria, including Gardnerella vaginalis, mobiluncus, prevotella, Bacteroides, and Mycoplasma sp. This bacterial infection is caused by an imbalance of bacteria in a woman's vagina, which leads to factors disrupting the pH (acid-base) balance in the vagina. Usually, BV is characterized by complaints of smelly vaginal discharge, but around 50% of BV cases do not show any symptoms. Vaginal discharge itself is usually caused by infection and several factors, namely due to fungi, bacteria, parasites and viruses (Yudin and Money,2008).

Various studies that have been carried out have found the fact that the impact of BV during pregnancy can cause serious complications, especially during pregnancy, including preterm birth and LBW babies, chorionic and amniotic infections, and amniotic fluid infections. BV can also increase the risk of pelvic inflammatory disease and infection with HIV or other sexually transmitted infections, during pregnancy, women with bacterial vaginosis are more prone to having infants who are born prematurely or weigh less than 5.5 pounds.

Research conducted previously stated that there was a relationship between Mycoplasma genitalium, Gardnerella vaginalis, Ureaplasama urealitycum, Streptococcus agalactiae and Chlamydia trachomatis with the incidence of premature labor and LBW babies (Sharoon et al., 2016). In other research it was also found that Nesseria gonorrhea was also detected in preterm birth and abortion (Kataoka et al.,2006).

There are various ways in which intrauterine infection can affect the fetus. The transplacental route is the most probable pathway for intrauterine infection during pregnancy. Organisms obtained through the transplacental route enter the fetal bloodstream and are subsequently filtered by the liver and spleen of the fetus. As a result,

the identification of the organism within the liver or spleen of the fetus during an autopsy, can serve as proof of infection obtained in the perinatal period. Hematogenously infected live-born infants may show signs of septicemia, infection of the meninges, adrenal glands, liver, or spleen. Fetal aspiration of contaminated amniotic fluid may also lead to infection following migration of the organism via the fetal membranes or after infection of the surrounding decidual tissue and placental villi. The risk of infection-related complications rises for both the mother and fetus as time passes after membrane rupture (25).

Impact on the Fetus

Vertical transmission of infection can affect the fetus in different ways. As a result, a normal baby may be born, or there could be outcomes such as miscarriage, stillbirth, premature birth, low birth weight, developmental abnormalities, congenital conditions, and/or persistent infections in newborns

Miscarriage and Stillbirth

Infections in the mother caused by numerous pathogens capable of crossing the placenta, including rubella, syphilis, toxoplasmosis, cytomegalovirus, and herpes simplex virus, can result in miscarriage or stillbirth. However, it should be emphasized that infection of the fetus is not the cause of recurrent miscarriage (25). Intrauterine infection causes stillbirth in the percentage range of 5% -22%. In developed countries, infections account for 19% of stillbirths before 28 weeks' gestation (26).

Restricted Fetal Growth

Symmetrical fetal growth restriction and associated sonographic indicators, including brain and/or liver echogenicity and calcification, as well as hydrops, suggest the presence of fetal infections such as cytomegalovirus, toxoplasmosis, rubella, and varicella. A specialized PCR test on amniotic fluid is conducted if the mother shows signs of infection based on serology and avidity testing. It has been confirmed that rubella infection in pregnant women can cause babies to be born small. The mechanism by which this occurs seems like directly associated with the virus inhibits cell multiplication by disrupting mitotic activity. The virus also leads to obliterative angiopathy of small blood vessels and capillaries, resulting in progressive damage to the placental blood vessels with persistent infection. (25).

In addition, BV-associated GV acts as a standalone risk factor for LBW babies and accounts for 56% of pregnancies affected by IUGR. Several possible mechanisms that could restrict intrauterine fetal growth include placental malfunction, placental vascular blood clot, and tissue necrosis. Intrauterine infections also impact fetal lung development (27)

Diagnosis

There are several ways to carry out examinations to determine the diagnosis of vaginal bacteria. Gram staining is regarded as the standard diagnostic method. Bacterial vaginosis has typically been diagnosed based on the Amsel Criteria. The criteria involve a slender and homogeneous liquid; constructive smell test; the identification of clue cells under the microscope; and a vaginal pH exceeding 4.5. Three out of the four criteria needed for diagnosis, exhibiting sensitivity between 70% and 97% and specificity ranging from 90% to 94%, were evaluated against Gram stain. Recent lab tests using DNA probes for Gardnerella vaginalis or vaginal fluid sialidase detection show 92% to 100% sensitivity and 92% to 98% specificity compared to Gram stain. Vaginal culture and the Papanicolaou (Pap) test are less effective for diagnosing bacterial vaginosis due to its polymicrobial nature. (12).

Examination of pH and vaginal wet flora is recommended as a form of initial screening before a planned pregnancy or at the beginning of pregnancy. This diagnostic measure can be used to treat genital infections with a high level of confidence and in a shorter time. This examination applies especially to women with a history of premature birth (28).

On the other hand, BV examination is able to be diagnosed through Gram staining of vaginal fluid (Nugent Score). The Nugent scoring method is considered the benchmark for laboratory-based diagnosis of BV. Using this method, Gram stains of vaginal fluid are analyzed to evaluate the prevalence of Gram-positive Lactobacillus morphotypes in comparison to Gram-negative organisms and Gram-variable Actinobacteria, including Gardnerella, Autopodium, and Mobiluncus. This method produces a score indicating the microbiota status: a score of 0–3 signifies a "normal" lactobacilli-dominated microbiota, 7–10 indicates bacterial vaginosis (BV), and a score of 4–6 is classified as a significantly incompletely characterized "intermediate microbiota." Collectively, samples that yield A Nugent score exceeding 3, which includes both intermediate and BV, is

termed "abnormal" vaginal flora or microbiota (29).

Examinations also need to be carried out on fetuses that may have been infected by the mother. Awareness of the impact of infection on the fetus is increasing and this has led to the need to update diagnostic measures for intrauterine diseases. Fetal sonography and serological tests to detect specific infectious agents are traditionally employed to obtain a prenatal diagnosis of fetal infection manifestations. Conventionally, the primary method for diagnosing infections in the fetus involves identifying microorganisms through culture, immunological methods, and specialized molecular biology techniques. Infection manifestations in the fetus can be direct, such as fetal malformations or fetal death confirmed through heritage or histopathological techniques, or indirect, including restricted growth within the uterus and hardening of fetal organs (25).

Treatment

Whenever intraamniotic infection is confirmed, it is recommended to administer antibiotics, which should also be considered in isolated cases of maternal fever. However, antibiotics are not recommended if intraamniotic infection is not identified (30). Antibiotics should be administered immediately and maintained throughout labor, to reduce neonatal and maternal morbidity (Grade B). Treatment should rely on a combination of betalactamines and aminoglycosides (Grade B). After vaginal delivery, a dose of antibiotics is required (31). First-line therapy includes seven days of oral metronidazole (Flagyl), intravaginal metronidazole (Metrogel), or intravaginal clindamycin (12).

Antipyretics should be administered alongside antibiotics. The proper improvement of childbirth should be monitored, given the link between intraamniotic infections and the occurrence of malfunctioning childbirth. If there are no contraindications, increasing prolonged childbirth among women experiencing intraamniotic issues infections is circumspect. Obstetric indications are the majority of situations that indicate immediate delivery, while intraamniotic infection is rare and does not serve as an indication for immediate delivery. If it occurs, this indication is used for delivery as a cesarean section (30).

4. Conclusion

The increase in preterm birth rates is a challenge throughout the world. Intrauterine infection is one of the factors causing preterm birth in pregnant women. Improper handling of infections will have a negative impact on the fetus and mother, even causing anatomical disorders in the baby from birth or even death. Investigating the epidemiology of intrauterine infections in the form of prevalence, risk factors, and treatment during pregnancy is fundamental for health care providers to ensure appropriate intervention is provided.

Reference

[1] World Health Organization (WHO). Preterm birth [Internet]. 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/preterm-birth

[2] Gomez-Lopez N, Galaz J, Miller D, Farias-Jofre M, Liu Z, Arenas-Hernandez M, et al. The immunobiology of preterm labor and birth: intra-amniotic inflammation or breakdown of maternal–fetal homeostasis. Reproduction. 2022;164(2): R11–45.

[3] García-Blanco A, Diago V, Serrano De La Cruz V, Hervás D, Cháfer-Pericás C, Vento M. Can stress biomarkers predict preterm birth in women with threatened preterm labor? Psychoneuroendocrinology [Internet]. 2017; 83:19–24. Available from: http://dx.doi.org/10.1016/j.psyneuen.2017.05.021

[4] Green ES, Arck PC. Pathogenesis of preterm birth: bidirectional inflammation in mother and fetus. Semin Immunopathol. 2020;42(4):413–29.

[5] UNICEF. Maternal and newborn health: Indonesia. UNICEF for every child. 2015.

[6] Daskalakis G, Arabin B, Antsaklis A, Cabero Roura L. Preterm Labor: Up to Date. Biomed Res Int. 2019; 2019:1–2.

[7] Suman V, Luther EE. Preterm Labor [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK536939/

[8] Agrawal V, Hirsch E. Intrauterine infection and preterm labor. Semin Fetal Neonatal Med [Internet]. 2012;17(1):12–9. Available from: http://dx.doi.org/10.1016/j.siny.2011.09.001

[9] Satria YAA, Susilawati TN. Genital Tract Infection during Pregnancy and its Association with Preterm Delivery Preterm delivery is an important health literature search in Pubmed, ScienceDirect, and the underlying mechanisms of GTI causing Condyloma acuminatum Human papillomavirus. Indones J Trop Infect Dis. 2021;9(1):45–56.

[10] Lee ACC, Quaiyum MA, Mullany LC, Mitra DK, Labrique A, Ahmed P, et al. Screening and treatment of maternal genitourinary tract infections in early pregnancy to prevent preterm birth in rural Sylhet, Bangladesh: A cluster

randomized trial. BMC Pregnancy Childbirth. 2015;15(1):1–14.

[11] Hamdan HZ, Ziad AHM, Ali SK, Adam I. Epidemiology of urinary tract infections and antibiotics sensitivity among pregnant women at Khartoum North Hospital. Ann Clin Microbiol Antimicrob. 2011;10(2):2–5.

[12] Paladine HL, Desai UA. Vaginitis : Diagnosis and Treatment. 2018;321–9.

[13] Edae M, Teklemariam Z, Weldegebreal F, Abate D. Asymptomatic Bacteriuria among Pregnant Women Attending Antenatal Care at Hiwot Fana Specialized University Hospital, Harar, Eastern Ethiopia: Magnitude, Associated Factors, and Antimicrobial Susceptibility Pattern. Int J Microbiol. 2020; 2020:3–10.

[14] Tita ATN, Andrews WW. Diagnosis and management of clinical chorioamnionitis. Clin Perinatol. 2010;37(2):339–54.

[15] Reekie J, Roberts C, Preen D, Hocking JS, Donovan B, Ward J, et al. Chlamydia trachomatis and the risk of spontaneous preterm birth, babies who are born small for gestational age, and stillbirth: a population-based cohort study. Lancet Infect Dis. 2018;18(4):452–60.

[16] Shimaoka M, Yo Y, Doh K, Kotani Y, Suzuki A, Tsuji I, et al. Association between preterm delivery and bacterial vaginosis with or without treatment. Sci Rep [Internet]. 2019;9(1):1–8. Available from: http://dx.doi.org/10.1038/s41598-018-36964-2

[17] Bautista CT, Wurapa E, Sateren WB, Morris S, Hollingsworth B, Sanchez JL. Bacterial vaginosis: A synthesis of the literature on etiology, prevalence, risk factors, and relationship with chlamydia and gonorrhea infections. Mil Med Res [Internet]. 2016;3(1):1–10. Available from: http://dx.doi.org/10.1186/s40779-016-0074-5

[18] Giakoumelou S, Wheelhouse N, Cuschieri K, Entrican G, Howie SEM, Horne AW. The role of infection in miscarriage. Hum Reprod Update. 2016;22(1):116–33.

[19] Navarro A, Tiongco RE, Bundalian R. Knowledge, attitude, practices, and health beliefs of pregnant women about urinary tract infection and its associated risk factors: A local filipino community experience. Kesmas Natl Public Heal J. 2019;14(2):82–7.

[20] Rours GIJG, Duijts L, Moll HA, Arends LR, De Groot R, Jaddoe VW, et al. Chlamydia trachomatis infection during pregnancy associated with preterm delivery: A population- based prospective cohort study. Eur J Epidemiol. 2011;26(6):493–502.

[21] Jain V, Das V, Agarwal A, Pandey A. Asymptomatic bacteriuria & obstetric outcome following treatment in early versus late pregnancy in North Indian women. Indian J Med Res. 2013;137(4):753–8.

[22] Van Gerwen OT, Craig-Kuhn MC, Jones AT, Schroeder JA, Deaver J, Buekens P, et al. Trichomoniasis and adverse birth outcomes: a systematic review and meta-analysis. BJOG An Int J Obstet Gynaecol. 2021;128(12):1907–15.

[23] Silver BJ, Guy RJ, Kaldor JM, Jamil MS, Rumbold AR. Trichomonas vaginalis as a cause of perinatal morbidity: A systematic review and Meta-analysis. Sex Transm Dis. 2014;41(6):369–76.

[24] Daskalakis G, Psarris A, Koutras A, Fasoulakis Z, Prokopakis I, Varthaliti A, et al. Maternal Infection and Preterm Birth: From Molecular Basis to Clinical Implications. Children. 2023;10(5):1–17.

[25] Dadwal V, Bhatt RK. Intrauterine Fetal Infections: Do-Able Approaches. J Fetal Med [Internet]. 2020;07(01):5–8. Available from: https://doi.org/10.1007/s40556-020-00252-9

[26] Dunkerton SE, Brewster J. Infections in pregnancy. Obstet Gynaecol Reprod Med. 2021;31(11):303–9.

[27] Cheah FC, Lai CH, Tan GC, Swaminathan A, Wong KK, Wong YP, et al. Intrauterine Gardnerella vaginalis Infection Results in Fetal Growth Restriction and Alveolar Septal Hypertrophy in a Rabbit Model. Front Pediatr. 2021;8(January):1–10.

[28] Mendling W, Martius J, Hoyme UB. S1-guideline on bacterial vaginosis in gynecology and obstetrics. Geburtshilfe Frauenheilkd. 2014;74(1):51–4.

[29] Amegashie CP, Gilbert NM, Peipert JF, Allsworth JE, Lewis WG, Lewis AL. Relationship between nugent score and vaginal epithelial exfoliation. PLoS One. 2017;12(5):1–11.

[30] Heine RP, Puopolo KM, Beigi R, Silverman NS, El-Sayed YY. Intrapartum Management of Intraamniotic Infection. Obstet Gynecol. 2017;130(2):E95–101.

[31] G B, C C, C C. nfection intra-utérine : diagnostic et traitement. RPC rupture prématurée des membranes avant terme CNGOF [Diagnosis and management of intra-uterine infection: CNGOF Preterm Premature Rupture of Membranes Guidelines]. Gynecol Obs Fertil Senol [Internet]. 2018; Dec;46(12):1054–67. Available from: 10.1016/j.gofs.2018.10.022