UJMR, Volume 2 Number 1 June, 2017 *ISSN: 2616 - 0668*
https://doi.org/10.47430/ujmr.1721.014
Received: 9th Dec, 2016 **Accepted:** 27th Jan, 2017

The Role of Infections in Preterm Labour and It's Control: A Review

Ummasalma Aliyu Saulawa, Fatima Muktar and Kamaluddeen Kabir
Department of Microbiology, Faculty of Natural and Applied Sciences, Umaru Musa Yar'adua University Katsina.

Abstract
Preterm labour (PTL) is described as the premature contraction of the uterus before 37 weeks of the gestation cycle, which could results in preterm premature rupture of the membranes (PPROM) and in most cases may lead to preterm birth. Preterm labour that results in preterm birth is a leading precursor of neonatal morbidity and mortality. Infection in the uterus occurs by the aptness of pathogenic microbes to ascend from the female genital area to the uterus. *Lactobacilli* species constitute about 95% of the female genital normal flora. But the invasion and colonisation of the genital area by gram-negative anaerobes has endangered the female genital area and exposed it to infection. Pathogens such as *Neisseria gonorrhoeae*, *Candida albican*, adenovirus and many more are indicated to play a role in preterm labour.The symptoms and clinical diagnosis of infections in the female genital area include itching and inflammation of the vaginal area, heavy, copious yellow-grey, fishy smell discharge etc. Routine clinical investigations from the first trimester of gestation cycle and the administration of probiotics, antibiotics as well as proper toiletry hygiene have contributed to reducing the prevalence of preterm labour.
Keywords: Preterm labour, Preterm birth, Bacterial vaginosis, Preterm premature rupture membrane.

INTRODUCTION

Preterm labour is described as an obstetrics dilemma that occurs as a result of myometrial contractions leading to the opening of the cervix (Agrawal and Hirsch, 2012) before 37 weeks of the pregnancy cycle (Lori*et al.*, 2002). The normal human gestation period occurs within 40-42 weeks (Espel *et al.*, 2014). Not all Preterm labour ends into a preterm birth, but approximately 50% of preterm labour ends in the premature rupture of the amniotic sac membrane resulting into a premature birth (Funai, 2015). A premature labour that leads to a premature birth is one of the leading causes of neonatal mortality and morbidity rate (Liu, *et al.*, 2016), such as delay in child development, *intraventricular* haemorrhage as well as chronic lung infection especially in developed countries (Agrawel and Hirsch, 2012; ACOG, 1995). Microbial infection during pregnancy makes these health problemsmore detrimental, and evidently played a part in 40% of the neonatal sepsis (Bolton, *et al.*, 2012). Statistically, the mortality rate of preterm babies is 40 times higher compared to that of term babies (Reid and Blocking, 2003). A study carried out by Martin,*et al.*, (2010) showed that at least 12% of babies in the United States are delivered before 37 weeks of pregnancy. The cost of preterm neonatal care in the US hospitals was estimated at $4billion per year (Reid and Blocking, 2003). Furthermore, the cost of health care for women with the risk of preterm labour has exceeded $360million (Reid and Blocking, 2003). In Canada alone, the incidence of preterm birth was 7%, with an estimated health care cost of $1500 per day (Reid and Blocking, 2003). The world health organisation (WHO) gave an estimated frequency data on the worldwide incidence of preterm birth, which showed African and Asian countries capturing the highest prevalence rates of preterm birth cases (Table 1)(Beck, *et al.*, 2010). Although, there was no accurate and complete population and medical records in developing countries which is driven mostly by traditional and custom believes, national differences in birth registration processes as well as variation in religious believes (Beck, *et al.*, 2010). The method used by WHO systematic review on preterm birth incidence has been described by Beck,*et al.*, (2010).

Table 1. Preterm birth rates, number of preterm births by United Nations geographical region and percentage of births covered by the estimates in a systematic review of the worldwide incidence of preterm birth.

Preterm birth			Preterm birth rates		
Region[a]	No in 1000s	95% CI[b]	%	95% CI[b]	Percentage estimates of coverage
World Total	12870	12,228-13,511	9.6	9.1-10.1	85.8
Africa	4047	3783-4311	11.9	11.1-12.6	72.7
Asia	6907	6328-7486	9.1	8.3-9.8	90.9
Europe	466	434-498	6.2	5.8-6.7	94.8
LA and the Caribbean	933	858-1009	8.1	7.5-8.8	79.3
North America[d]	480	479-482	10.6	10.5-10.6	100

(Beck, *et al.*, 2010)

CI, confidence interval; PI, prediction interval.

[a] Countries categorized according to United Nations classification.

[b] Whereas PIs were calculated for country estimates based on the model, CIs were derived for the regional aggregate estimates that utilized data from studies as well as modelled estimates.

[c] Refers to the proportion of live births for which data were available and model-based estimates were not generated.

[d] Excluding Mexico, which is included under Latin America.

Therefore, the aims of this review is to illustrates the role of microbial infections in causing preterm labour dilemma and the effective measures to be taken in order to prevent it occurrence.

Microbial infections in preterm labour

Infections during pregnancy have contributed to preterm labour and birth obstacles (Goldenberg, *et al.*, 2000). Bacterial infection is a leading cause of preterm labour (Agrawal and Hirsch, 2012). The presence of bacterial vaginosis during the second trimester of pregnancy triggered the risk of having premature rupture of the membranes and preterm birth (Purwan, *et al.*, 2001). Though it is hard to rule out whether infection is the precursor of preterm labour in individual cases (Agrawal and Hirsch, 2012), nevertheless, it's been affirmed that about 40% of preterm labour cases are caused by infection (Leittieri, *et al.*, 1993). Therefore, microbial infections are fundamental geneses of preterm labour (Agrawal and Hirsch, 2012). In most cases, preterm birth arises not as a result of individual or single cause, but rather it is a multi-factorial issue(Novy, *et al.*, 1995). Significant findings have revealed that microbial infection co-associates with maternal and foetal factors to promote preterm labour(Kirchner, *et al.*, 2000). The possibility of a preterm birth is high in women with short and funnelled cervix and who are also affected by bacterial infection (Andrews, *et al.*, 1997), the interaction between infection and the high volume of amniotic fluid in the uterus also known as polyhydramnios, illegal intoxication, uterine membrane bleeding, have all contributed to preterm labour issues(McGregor and French, 1999). Foetal factors that can trigger PT include multi-foetal pregnancy as well as foetal endocrine signalling (McGregor and French, 1999).

An in vivo analysis carried out by the inoculation of group B *Streptococci* bacteria, into the innermost layer of Rhesus Monkeys' placenta, followed by the subsequent examination of their amniotic fluid indicated a rise in prostaglandins and cytokines levels (Lorie, *et al.*, 2002). The synthesis of cytokines (interleukin-6 and 8) by interleukin-1β stimulated the production of prostaglandins, consequently increasing the rate of uterine contraction (Lorie, *et al.*, 2002). Basically, the membranes of term patients during labour is devoid of interleukin-1β, therefore, the synthesis of interleukins in the membrane can be a ladder through which infections can influence preterm labour (Lorie, *et al.*, 2002). Intrauterine pro-inflammatory cytokines response in addition to the disproportion that occurred between interferon gamma (INF-ϒ), interleukin-2 (IL-2), tumour necrosis factor (TNF-α) significantly contributes to pre-eclampsia mayhem (Bolton, *et al.*, 2012).

Primarily, pregnant women are more susceptible to bacterial vaginosis and urinary tract infections (UTI) (McGregor, *et al.*, 1999), which can be as a result of hormonal and mechanical modification encountered by the body system during pregnancy (McGregor, *et al.*, 1999). This changes encountered by the body can lead to increase exposure of the pregnant women's cervix to urinary stasis as well as vesicoureteral reflux (McGregor, *et al.*, 1999).

It was estimated that about a hundred of thousand pregnant women are suffering from an infection in the United States annually (Kirchner, *et al.*, 2000). Naturally, the amniotic fluid is hygienic; as such bacteria in the amniotic fluid can only be detected in a small percentage of pregnant-term women who are not in labour (Agrawal and Hirsch, 2012). The perception is that; opportunistic pathogens detected in both the placenta and amniotic fluid originates from the vagina (Kirchner, *et al.*, 2000)An in vivo model of pyelonephritis (UTI-kidney) demonstrated an induced preterm birth in addition to low birth weights off-springs (Bolton, *et al.*, 2012).

Mechanism of microbial infection in preterm labour

Microorganisms can cause preterm labour by ascending from the cervical region into the uterus, followed by subsequent colonisation and replication in the placenta and membranes regions (Lorie, *et al.*, 2002). The potentiality of bacteria to invade the choriodecidual space and the release of both endotoxins and exotoxins stimulates the secretion of cytokines (INF-ϒ, TNF-α and IL-17) which leads to an inflammatory reaction (Bolton, *et al.*, 2012). The secretion of cytokines, endotoxin and exotoxin mediate and stimulates the production of prostaglandins; which increases the rate of myometrial contractions and metalloproteinase (Nelson, *et al.*, 2009). Metalloproteinase' attack on the chorioamnionitis membranes then triggers the premature rupture of the membranes and weakening of the cervix collagen (Nelson, *et al.*, 2009). In addition to this, evidence has also showed that increase in the production of cytokine followed by endometrial inflammation increased the incidence of premature rupture of membranes and preterm birth in bacterial vaginosis's patients(Nelson, *et al.*, 2009). Another physiological activity that occurred in the presence of myometrium infection is the expression of tumour necrosis factor α (TNF-α), which triggered the production of oxytocin receptor, prostaglandin receptors, and other contraction-associated proteins(Liu, *et al.*, 2016). The stimulation of these factors results in the onset of labour (Liu, *et al.*, 2016).

Furthermore, bacteria such as *Gardnerella vaginalis* and anaerobic bacteria are capable of producing phospholipase A2 in large quantity compared to other bacteria (Bejar, *et al.*, 1981). Phospholipase A2 promotes the synthesis of prostaglandins; which is capable of liberating the arachidonic acid molecule of the embryonic membrane, which in turn increase the rate of contraction resulting to preterm labour and/or PPROM (Bejar, *et al.*, 1981). A schematic diagram summarizing the possible mechanisms that are involved in preterm labour is shown below in Fig 1. (Bejar,*et al.*, 1981; Bolton,*et al.*, 2012; Liu, *et al.*,2016; Lorie, *et al.*, 2002 and Nelson,*et al.*, 2009).

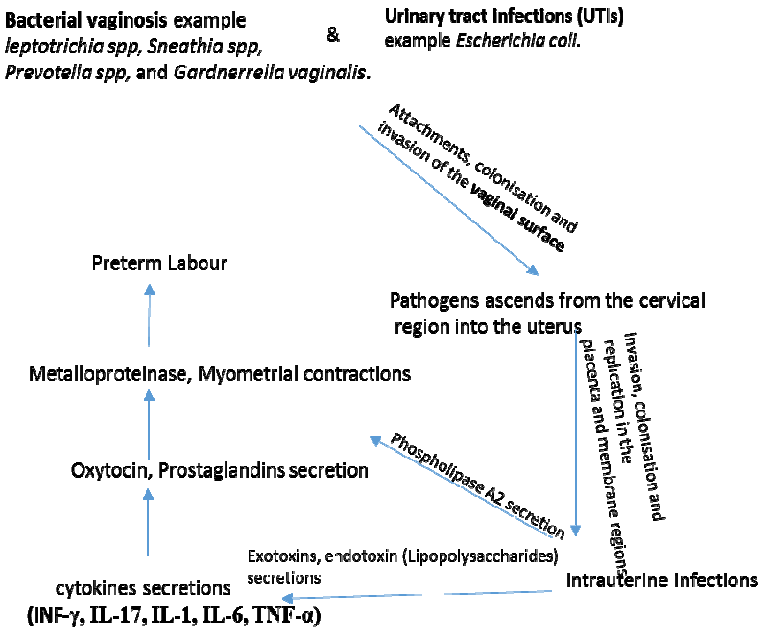

Fig 1.
Summary of the possible mechanisms through which pathogenic microbes can induce Preterm Labour. INF- Interferons, IL- Interleukins, TNF- tumour necrosis factor

(

Prevalence of microbes isolated in preterm labour.

Lactobacilli are gram-positive anaerobic-facultative bacteria that reside as normal flora in the female genital area (Othman, *et al.*, 2007). However, the invasion, alteration and excessive growth of gram-negative anaerobic bacteria in the female genital area, as well as imbalance of the normal flora, is termed bacterial vaginosis, which is a leading cause of vaginal infection (Shambeker, 2012). Clinical investigations have shown the prevalence of bacterial vaginosis as a two-fold increase in women with preterm labour (Hillier, *et al.*, 1995). The prevalence of bacterial vaginosis in urban pregnant women is high and in most cases the infection is chronic (Kurki, *et al.*, 1992). Bacteria such as *Leptotrichiaspp,* and *Megasphaera*-like *spp* are more prevalent in pregnant women with bacterial vaginosis compared to *Lactobacillusspp*(Nelson, *et al.*, 2009) In a clinical analysis, the pervasiveness of *Gardneralla vaginalis* was indicated to be high among women with spontaneous preterm birth (SPTMB) (Nelson, *et al.*, 2009), but the prevalence of *Chlamydia trachomatis*, *Trichomonas vaginalis* and *Escherichia coli* was low (Shambeker, 2012). Furthermore, SPTMB is more common in pregnant women that are suffering from bacterial vaginosis(Klebanoff, *et al.*, 2005). Statistically, the frequency of infection as a result of bacterial vaginosis among pregnant women can be up to 60% although the prevalence of bacterial vaginosis infection varies between different geographical areas, age and other clinical criteria (Nelson, *et al.*, 2009). Notably, other bacterial vaginosis-associated microbes such as *Prevotella* and *Mobiluncus* are strongly associated with preterm labour and birth. *Mycoplasma horminis* was also diagnosed in women with idiopathic preterm birth (Holst, *et al.*, 1994).

Sexually transmitted diseases are also playing a vital role in preterm labour. *Neisseria gonorrhoeae* a bacteria as well as *Trichomonas vaginalis* a protozoan are clinically detected in preterm labour cases (Romero, *et al.*, 1991; ACOG, 1994). Cervicitis; an inflammation of the neck of the womb caused by *N. gonorrhoea* mediated by other co-factors such as the use of illicit drugs, multiple sexual mates, and other sexual transmitted disease is capable of inducing preterm labour and birth (Romero, *et al.*, 1991; ACOG, 1994). *Chlamydia trachomatis* was prevalent in most asymptomatic vaginosis, although infected pregnant women sometimes produce a vaginal discharge that is mucopurulent in nature (ACOG, 1994). The frequency of *Chlamydia trachomatis* infection in pregnant women ranges between 5-26% (ACOG, 1995).

The rate of fungal infection leading to preterm labour is very low. Clinical analysis of the micro-biota of the amniotic sac indicates a low establishment of *Candida albican* in pregnant women (Goldenberg, *et al.*, 2000). Subsequently, not much proof was shown on the role played by a viral infection in relation to the incidence of preterm labour, but it was demonstrated that the capability of a virus to invade trophoblast cells leads to cell apoptosis and the inflammatory activities that follow through can cause preterm labour and/or birth (Kai, *et al.*, 2011). Studies have confirmed the presence of a viral DNA in the amniotic fluid of some women with asymptomatic low-risk pregnancy(Agrawal and Hirsch, 2012). In most obstetric cases of viral infection related to preterm labour, incidences are that the DNA of adenovirus, enterovirus and cytomegalovirus are more prevalent in the amniotic sac(Agrawal and Hirsch, 2012). Pregnant women diagnosed with hepatitis B virus are more prone to preterm labour and birth (Reddick, *et al.*, 2011). An in vivo experiment using a mice model has demonstrated that the injection of polyinosine: cytidylic acid into the mice uterus induced a preterm birth (Koga, *et al.*, 2009).

Symptoms associated with urogenital microbial infection.

Increase in the rate of vaginal discharge/smell.
Cloudy or red discolouration of the urine appearance.
The uncontrollable urge to urinate as well as intense sensation during urination.
Sensational pain in the pelvic region.
Itching in the vaginal area.
Inflammation of the cervix
Discharge can be either copious yellow-grey or malodorous homogeneous (ACOG, 1994).

Clinical diagnosis

Detection of mobile flagellated bacteria with many leukocytes in the case of gonorrhoeae.
The addition of potassium hydroxide on discharge yields a fishy smell (*T. vaginalis*).
The microscopy of *T. vaginalis* shows epithelial cells with cohesive organisms.
Alkaline vaginal pH (*N.gonorrhoeae*).
Increase in vaginal pH level to 4.5 (*T. vaginalis*)(McGregor, *et al.*, 1999).

Prevention and Control

A remarkable number of preterm labour and birth cases can be prevented through routine clinical investigations, screening and treatment of bacterial infection in pregnant women from the first trimester of their gestation period to the last trimester (McGregor, *et al.*, 1999)..

The clinical investigations should include urine culture investigation, vaginal swab among many others(Kirchner, *et al.,* 2000)It was recommended that pregnant women should be screened for gonococcal infection, especially in women with the history of gonococcal infection and other sexual transmitted diseases(Kirchner, *et al.*, 2000). In addition, pregnant women with a history of preterm labour who are subsequently under the threat of having another preterm labour or preterm premature rupture of the membranes should also be screened for infections, in order to tackle neonatal morbidity and subsequent mortality (Kirchner,*et al.*, 2000).

The use of antibacterial drugs that are effective against bacterial infection can extremely reduce the risk of preterm labour and birth (Kirchner, *et al.,* 2000). A clinical investigation and trial were conducted on women with a history of a short gestational period and low body weight of less than 50kg; oral dosage of 500mg metronidazole and 300mg enteric-coated erythromycin was administered to the study group (McGregor, *et al.*, 1999). The outcome indicated that a considerable number of preterm births were reduced between the two groups (McGregor, *et al.*, 1999). Furthermore, a subsequent analysis carried out using same therapeutic drugs and concentrations showed 70% reduction in preterm birth in women with asymptomatic cases (McGregor, *et al.*, 1999).

The treatment of gonococcal cavities infection can be effective by an intramuscular dose of 125mg ceftriaxone. Medically, it is recommended to treat gonococcal patients with antibiotic for a chlamydial infection, due to the frequent co-infection by Chlamydia trachomatis. Therefore, oral dosages of 600mg azithromycin, 400mg cefixime or 500mg erythromycin are recommended (McGregor, *et al.*, 1999; ACOG, 1994). But in the case of chlamydial infection alone, an oral dosage of 500mg erythromycin and 1g azithromycin or 500mg amoxicillin are highly effective (McGregor, *et al.*, 1999; ACOG, 1994). An oral dosage of 2g metronidazole or 500mg of metronidazole is an effective treatment for *Trichomonas vaginalis* infection. Intravaginal drug inoculation of clotrimazole is also recommended in the first trimester of the gestation period. In order to prevent the reoccurrence of gonococcal and chlamydial infections, sexual partners are also considered during treatment (McGregor, *et al.*, 1999). Although, there is some health problems associated with the administration of some of these clinical drugs like erythromycin on pregnant women, however, there are not adverse in effect and most of these drugs are not known to cause harm to the unborn baby such as azithromycin.

Interestingly, probiotics are health-beneficial microbes. These organisms can inhibit the growth of pathogenic microbes, restore and regulate the immune response by obstructing pathogenic activities that lead to preterm labour and birth (Othman, *et al.*, 2007). *Lactobacillus* species are probiotics, the presence of *Lactobacillus* species like *L. jensenii* in the genital area prevent the colonisation and invasion of pathogenic microbes and their aptness to cause urinary tract infection as well as bacterial vaginosis (Othman, *et al.*, 2007). Several mechanisms are used by probiotics in its capability to inhibit the growth of pathogenic microbes residing the vagina (Othman, *et al.*, 2007). The prevalence of bacterial vaginosis in women with *Lactobacilli spp* capable of producing hydrogen-peroxide (H_2O_2) is very low as compared with those women that lack the organism in substantiated numbers (Othman, *et al.*, 2007). The production of hydrogen-peroxide, secretion of proteinaceous toxins known as bacteriocins in the vagina inhibits the growth of pathogenic microbes colonising the area (Othman, *et al.*, 2007). *Lactobacilli* secrete lactic and can also regulate immunity response (Othman, *et al.*, 2007). In addition, oral and / or intravaginal administration of lactobacilli is effective against vaginal infection (Othman, *et al.*, 2007). The recommended dosage for both administrations of lactobacilli is 10^9 - 10^{11} air-dried or freeze-dried concentration (Othman, *et al.*, 2007). The treatment is safe and also very effective in the control and treatment of urogenital infections (Othman, *et al.*, 2007).

Earlier in this review, it was indicated that endotoxin (Lipopolysaccharides) mediates the production of prostaglandins which plays a role in myometrial contractions. A recent in vivo study has demonstrated that the endogenous gaseous signalling of hydrogen sulfide in the form of NaHS has significantly contributed in restraining myometrial endotoxin-induced inflammation as well as obstruction of endotoxin-induced preterm labour (Liu, *et al.*, 2016).

The study further suggested that the clinical use of H_2S donors like NaHS and GYY4137 if further analysed can significantly contribute in attenuating inflammation and can also serve as a therapeutic agent in controlling endotoxin-induced preterm labour(Liu, *et al.*, 2016).

Conclusion

The numerous evidence reviewed in this article, has no doubt indicated the contribution of microbial infection in the genesis of preterm labour. The amniotic sac and uterus of pregnant women harbour divergent pathogenic opportunistic microbes ranging from bacteria, fungi, and a virus that gained access by rising from the vagina through urethral pathways. These microbes are involved in not only preterm labour but also play a vital role in preterm premature rupture of the membranes and also in preterm birth. Proper toilet hygiene is recommended especially in pregnant women. Oral sex should be avoided during pregnancy and in the partners who are planning to conceive in order to prevent gonococcal infection. It is also recommended that women should go for clinical investigations during the period of pregnancy as some preterm labour infection are asymptomatic.

REFERENCES

ACOG technical bulletin. (1994). Gonorrhoea and Chlamydial Infections. Number 190. *International Journal of Gynecoogyl Obstetric* 45: 169-74.

ACOG Technical Bulletin. (1995). Preterm Labour. Number 206. *International Journal Gynecology Obstet* 50: 303-13

Agrawal, V. and Hirsch, E. (2012). Infection and preterm labour. *Seminars in Fetal and Neonatal Medicine* 17: 12-19.

Andrews, A.A. (1999). The preterm prediction study: Association of mid-trimester genital *Chlamydia* infection and subsequent spontaneous preterm birth. *American Journal of Obstetric Gynecology* 176: S52.

Beck, S., Wojdyla, D., Say, L., Betran, A.P., Merialdi, M., Requejo, J.H., Rubens, C., Menon, R. and Van Look, P.F.A.(2010). The Worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bulletin of the World HealthOrganisation* 88: 31-38

Bejar, R., Curbelo, V., Davis, C. et al., (1981). Premature Labour II. Bacterial sources of phospholipase. Obstetric Gynecology 57,479.

Bolton, M., Horvath, D.J. Jr., Li, B., Cortado, H., Newson, D., White, P., Partida-Sanchez, S. and Justice, S. S. (2012). Intrauterine Growth Restriction Is a Direct Consequence of Localized Maternal Uropathogenic Escherichia coli Cystitis. PLoS ONE 7(3): e33897.doi:10.137/journal.

Espel,E.V., Glynn, L.M., Sandman, C.A., and Davis, E.P. (2014). Longer Gestation among Children Born Full Term Influences Cognitive and Motor Development. PLoS ONE 9(11): e113758. Doi:10.11371/journal.

Funai, E.D. (2015). Patient Information: Preterm Labour (Beyond the Basics). https://www.update.com/contents/preterm-labour-beyond-the-basics.UpToDate, Inc .Release: 25.1 - C25.74

Goldenberg, R.L., Hauth, J.C. and Andrews, W.W.(2000). Intrauterine infection and preterm delivery. *National English Journal of Med* 342: 1500-1507.

Hillier, S.L., Nugent, R.P., Eschenbach, D.A., Krohn, M.A., Gibbs, R.S., Martin, D.H., Cotch, M.F., Edelman, R., Pastorek, J.G., Rao, A.V., McNellis, D., Regan, J.A., Carey, J.C., and Klebanoff, M.A. (1995). Association between bacterial vaginosis and preterm delivery of a low-birthweight infant. The vaginal infections and prematurity study group. *National English Journal of Medicine* 333: 1737-1742.

Holst, E., Goffeng, A.R., and Andersch, B.(1994). Bacterial vaginosis and vaginal microorganism in idiopathic premature Labour and association with pregnancy outcome. *Journal of Clinical Microbiology* 33: 176-186.

Kirchner, J.T. (2000). The Role of Bacterial Vaginosis in Preterm Labour. *American Family Physician* 62: 652-655.

Klebanoff, M.A., Hillier, S.L., Nugent, R.P. and Longer, O. (2005). Is bacterial vaginosis a stronger risk factor for preterm birth when it is diagnosed earlier in gestation? *American Journal of Obstetric Gynecology* 192: 470-7.

Kurki, T., Sivonen, A., Renkonen, O.V, *et al*., (1992). Bacterial vaginosis in early pregnancy and pregnancy outcome. *Obstetric Gynecology* 80: 173-177.

Koga, K., Cardenas, I., Aldo, P., Abrahams, V.M., Peng, B., Fill, S., Romero, R., Mor, G. (2009). Activation of TLR3 in the trophoblast is associated with preterm delivery. *American Jounarl of Reproductive Immunology* 61: 196-212.

Koi, H., Zhang, J. and Parry, S.(2001). The mechanism of placental viral infection. *Annual New York Academic Science* 943: 148-56.

Lettieri, L., Vintzileos, A.M., Rodis, J.F., Albini, S.M. and Salafia, C.M.(1993). Does 'Idiopathic' preterm labour resulting in preterm birth exist? *American Journal Obstetric Gynecology* 168: 1480-1485.

Liu, W., Xu, C., You, X., Olson., D.M., Chemtob, S., Gao, L. and Ni, X. (2016). Hydrogen Sulfide Delays LPS-Induced Preterm Birth in Mice via Anti-Inflammatory Pathways. PLoS ONE 11(4):e0152838.doi:10.1371/journal.pone.0152838

Lorie, F.C., Zapata, M.I., Toy, E.C. and Baker, B.(2002). Genitourinary infection and their Association with Preterm Labour. *American Family Physician* 65(2): 241-249.

Martin, J.A., Hamilton, B.E., Sutton, P.D., Ventura, S.J., Mathews, T.J., Kirmeyer, S. and Osterman, M.J.K.(2010). Births: final data for 2007. National vital statistics reports: from the Centers for Disease Control and Prevention, National Center for Health Statistics, *National Vital Statistics System* 58:1-85.

McGregor, J.A. and French, J.I. (1999). Preterm Birth: The Role of Infection and Inflammation. *Medscape Women's Health* 2,1.

Nelson, D.B., Hanlon, A., Hassan, S., Britto, J., Geifman-Holtzman, O., Haggerty, C. and Fredricks, D.N.(2009). Preterm labour and bacterial vaginosis-associated bacteria among urban women. *Journal of Perinetal Medicine* 37: 130-134

Novy, M.J., McGregor, J.A. and Iams, J.D. (1995). New prospective on the prevention of extreme prematurity. *Clinical Obstetric Gynecology* 8: 790-808.

Othman, M., Neilson, J.P. and Alfirevic, Z. (2007) Probiotic for preventing preterm labour.[Review] *Cochrane Database Syst Rev*; CD005941;PMID, 17253567.

Purwan, M., Bhayat, B., Agrawal, V. and Kulkami, H. Purwar. (2001) Bacterial vaginosis in early pregnancy and adverse pregnancy outcome. *Journal Obstetric Gynecology Research* 27(4): 175-181.

Reddick, K.L., Jhaveri, R., Gandhi, M., James, A.H. and Swamy, G.K.(2011) Pregnancy outcomes associated with viral hepatitis. *Journal of Viral Hepatitis* 18(7):e394-8.

Reid, G. and Blocking, A. (2003) The potential for probiotics to prevent bacterial vaginosis and preterm labour. *Am J Obstet Gynecol* 189(4): 1202 - 1208.

Romero. R., Avila, C., Brekus, C.A and Morotti, R.(1991) The role of systematic and intrauterine infection in preterm parturition. *Annual New York Academic Science* 622: 355-75.

Shembeker, C. (2012) Prediction, Recognition, and Management of Preterm Labour. Critical issues in Obstetrics and Gynecology. ECAB Clinical Update: *Obstetric Gynecology*. ISBN 978-81-312-3061-9.