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Management of Abnormal Vaginal Flora as a Risk Factor for Preterm Birth

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1. Introduction

Prevention of preterm birth remains a major challenge in obstetrics. While over the years a lot of attention has been given to the structural deficiencies, like uterine abnormalities, or 'weak' or 'insufficient' cervix, during the last decades the importance of ascending infection as a possible cause of preterm birth, preterm rupture of the membranes and intrauterine infection has become increasingly evident (Martius & Eschenbach, 1990). The earlier the preterm labor starts, the higher the likelihood an underlying chorio-amnionitis will be found. While for term deliveries the risk of chorio-amnionitis is around 1%,it is more than 45% in preterm deliveries (Scherman et al., 1997). The damage intrauterine infection causes to the fetus is not limited to the complications and sequels of being born preterm, but also is due to brain damage, like intra- or peri-ventricular hemorrhages and cerebral palsy, caused by the inflammatory reaction due to infection (Romero et al., 2007). Furthermore, such gestational ascending infections may cause maternal complications like sepsis, septic arthritis, maternal respiratory distress (Garland et al., 2002).

Bacterial vaginosis (BV) in pregnancy has an acknowledged increased risk of preterm delivery, but treatment with metronidazole is not beneficial, and if anything, harmful for the pregnancy. Use of broader spectrum antibiotics like clindamycin, or combination antibiotherapy, have shown better results, but still not all studies are in agreement with this. Therefore, critical reappraisal of the prevailing data are crucial, and new studies may need to incorporate new findings and insights. For one, the diagnostic accuracy needs to be refined, as it became increasingly clear that aerobic pathogens and the inflammation caused by aerobic vaginitis (AV), may play a more important role than previously thought. In recent studies meticulously discriminating these differences between BV, AV and mixed AV-BV flora by phase contrast microscopy, it became evident that not only BV may be primarily associated to intrauterine growth restriction and preterm birth, but also the aerobic component may lead to inflammatory reactions in placenta, amniotic fluid and fetus, preterm rupture of the membranes and preterm birth. In this review, emphasis is placed on the most crucial differential diagnostic characteristics, and the treatment adjustments these findings require. Part of this review has been published in the British Journal of Gynecology (Donders et al, 2011).

2. Definition of AV

Diagnosis of AV is based on wet mount microscopy. Normal and abnormal lactobacillary flora are divided into 3 to 4 flora types, also depicted as lactobacillary grades (LBG's). LBG 1 corresponds to a 'healthy' microflora, and has predominant lactobacillary morphotypes of variable size. Lactobacillary grade III is a condition wherein the lactobacillary morphotypes are completely replaced by other bacterial morphotypes. Lactobacillary grade II is an intermediate group, with partial replacement of the lactobacilli by other bacteria. Due to their specific link to pathology, we refined the three grades, and divided grade 2 (LBGII) in a less severe (LBGIIa) and a more severe (LBGIIb) variety (Donders, 1999). As LBG 3, and to a lesser extent LBG IIb are more likely to be linked with pathological conditions, they are entitled 'abnormal vaginal flora'. LBG's are the basis for a composite score to which the following four variables were added: 1) proportional number of leukocytes, 2) presence of toxic leukocytes, 3) presence of parabasal epithelial cells and 4) type of background flora (Donders, 2002). This condition is a screening tool that should not be confused with bacterial vaginosis. Bacterial vaginosis is a condition with abnormal vaginal flora, but abnormal vaginal flora is not always bacterial vaginosis. Some studies demonstrate that the absence of lactobacilli is a more powerful predictor of preterm birth than the presence of bacterial vaginosis (Donders et al., 2008a; Hay et al., 1994). In order to diagnose such abnormal lactobacillary grades, the use of wet mount is preferred above the use of Gram stains due to superior accuracy (Donders et al., 2000c; Donders et al 1996) and better correlation with lactate in the vaginal content (Donders et al., 1998), a functional test for lactobacillary defence function.

Therefore, in this classification, the immune reaction of the host is also taken into account for the diagnosis. Parabasal cells are considered a sign of severe epithelial inflammation usually not seen in uncomplicated BV. They are encountered only in moderate or severe forms of aerobic vaginitis (AV), such as in desquamative inflammatory vaginitis (Newbern et al., 2002; Sobel, 1994). Background flora was allocated score 0 if the background flora was unremarkable or showed debris and bare nuclei from lysed epithelial cells (cytolysis), score 1 if the lactobacillary morphotypes were very coarse or resembled small bacilli (rather than lactobacilli), and 2 if there were prominent cocci, or chained cocci visible. Leukocytes were scored according to their proportional number when compared with epitheliocytes. More than 10 leukocytes per epithelial cell is assigned 2 points, while less than 10 per epithelial cell, but more than 10 per high power field corresponds to 1 point. Adding these points together comprises a composite score, the 'AV'-score. A composite score of 1 to 4 represents normal flora. A score of 5 to 6 to moderate AV, and a score above 6 (to max. 10) to severe AV. In practice, a score of 8 to 10 matches the definition of 'desquamative inflammatory vaginitis'.

The use of this AV criterion enables us to divide the flora in a more detailed and comprehensive way, avoiding undefined and unclear categories. Bacterial flora is lactobacillary type predominant (normal), or it is abnormal. If abnormal the flora can be disturbed by anaerobic overgrowth (BV) or by aerobic micro-organisms, such as E coli, group B streptococci, enterococci etc (AV), or can be a mixture of both (mixed AV-BV). Therefore one has to be continuously aware that concomitant infections may occur, and also concurrent infections with *Candida sp*., *Trichomonas vaginalis*, mycoplasmata or cervicitis (*Chlamydia trachomatis*, *Neisseria gonorrhoeae* and other) (Donders et al., 1993b).

One of the disadvantages of the Nugent score system that is used on Gram stained specimens to diagnose BV (Nugent et al., 1991), is that one does not realize more than one condition may co-occur. In studying wet mounts and applying the BV and AV criteria at the same time, pure BV can be clearly distinguished from pure AV, but at the same time combined forms can be discovered where wherein anaerobic BV flora and AV flora coincide. This mixed AV-BV flora may well be a transient condition between BV and AV, but most likely a prolonged co-infection of both may also occur.

3. Abnormal vaginal flora subtypes in pregnancy

For a few genital infections with severe impact on the outcome of the pregnancy, such as syphilis and gonorrhoea, a 'screen and treat' policy is almost always cost-effective (Donders et al., 1993a; Elliot et al., 1990), while for other infectious conditions, like vaginal overgrowth with mycoplasmata, the jury is still out there to define its precise role in the pathogenesis of infection related preterm birth and fetal injury (Lee et al., 2009; Harada et al., 2008; Carey et al., 1991; Gravett & Eschenbach, 1986).

From the early 90ies it became evident that not only typical pathogens like *C. trachomatis*, *T. vaginalis* and *N. gonorrhoeae* could harm the pregnancy, but also merely aberrations from the normal lactobacilli dominant vaginal flora could endanger the fetus. Although all in the same line, these aberrations were all studied form a different perspective. Most studies used Nugent's or Spiegel's score on Gram stains to detect an association between bacterial vaginosis (BV) and intermediate flora with adverse pregnancy outcome (Hay et al., 1994; Elliot et al., 1990; Lee et al., 2009; Thorp et al., 2008; Cauci et al., 2002c; Hauth et al., 2003; Kekki et al., 2001; Kiss et al., Klebanoff et al., 2005; McDonald et al., 1997; Oakeshott et al., 2004; Verstraelen et al., 2007), but similar findings could be obtained with clinical Amsel criteria to diagnose BV (Honest et al., 2004; Rouse et al., 2009), abnormal lactobacillary grades on both Pap smears, gram stains, and wet mount preparations (Hay et al., 1994; Donders et al., 1993b; Mass et al., 1999; Donders et al., 2009) and with other abnormalities of the bacterial flora than full BV (Donders et al., 2002; Donders et al., E pub ahead of print 2010; Donders et al., 2009).

As is generally acknowledged, Nugent score above 7 on Gram stained specimens corresponds well with BV, and is nowadays accepted as golden standard for the diagnosis of BV in most clinical trials. Compared to this method, wet mount is said to be less sensitive. However, some constraints have to be taken into consideration. First of all, on a continuous scale of 1 to 10, there is no consensus on what the intermediate group with a score of 4 to 6 stands for. If Nugent were an ideal scoring system for bacterial vaginosis, with score 1 to 3 being normal and 7 or above being full blown BV, score 4 to 6 should be transitional, partial or intermediate BV, but in reality it is not. Ideally this intermediate flora state represents a turning point from a normal state into BV, or on the opposite, from BV to normal. However, most of these women with so-called intermediate BV according to Nugent will neither have BV, nor will they become normal. In fact, as they are not having normal flora, nor BV, they rather resemble a sort of 'garbage bin', but this does not mean that they do not represent important pathology. Most intriguing, in almost all studies addressing the importance of BV and the intermediate group as a separate category, it was clear that the intermediate group was linked to a different, and usually more serious scope of complications (e.g. mid trimester pregnancy loss) than the 'classic', full-blown BV (Hay et al., 1994; McDonald et al., 1994).

4. Pathogenesis, immunology and genetics

As AV only rather recently became recognized as an entity that differs in several aspects from BV, lot of its ethiology and pathogenesis remains unraveled. It is not known why the vagina harbours 2 to 3 predominant lactobacillary species (e.g. L. gasseri, L. cripatus, L. iners or L.) in normal women (Verstraelen et al., 2009) while in others anaerobes or aerobic commensals overgrow the vagina. It may well be that AV and BV are both ends of the same spectrum of bacterial abnormalities in the vagina, explaining the frequent occurrence of both conditions combined, also in pregnancy (Zodzika et al, 2011). Although it is not clear how the one condition can evolve into the other, it is certainly evident that both conditions express a completely different immunology pattern. Pro-inflammatory cytokines IL1b, IL6 and IL 8 are clearly linked to LBG's in pregnant women, cytokines going up with decreasing numbers of lactobacilli (Donders et al., 2003; Donders et al., 2000a). As was also shown by Cauci et al, BV does express an elevated pro-inflammatory cytokine IL1 b as well, but not the promoter cytokines of the prostaglandin cascade, IL-6 and IL-8 (Cauci et al., 2003), whereas in AV not only IL1b but also dramatic concentrations of IL6 and IL 8 are formed in the vagina (Donders, 2002). As the pro-inflammatory cytokine producers, especially IL-8, in BV women have a different pathogenesis than the (more common) non-producers, and are linked to several risk factors in pregnancy (Cauci et al., 2008; Cauci et al. 2002a, 2002b), likewise the enormous production of prostaglandin provoking cytokines IL 6 and IL 8 in AV patients make them likely candidates for causing preterm labor and delivery (Donders, 2002; Donders, 2007). The links between the presence of vaginal infections, increased levels of IL 6 and IL 8 in both vagina and amniotic fluid and chorio-amnionitis, PPROM and preterm birth are confirmed in several studies (Massaro et al., 2009; Hitti et al., 2001; Rizzo et al., 1996).

5. Prevalence

Prevalence of BV in pregnancy is very variable according to the geographical and socio-demographic area of sampling and ranges from as low as 9% (Larsson et al., 2007) to as high as 48% (Tann et al., 2006). Longitudinal studies show invariably a decrease of BV during pregnancy and a lower likelihood to acquire I with the weeks the gestation progresses (Waters et al., 2008). The prevalence of abnormal aerobic flora or aerobic vaginitis is much more difficult to determine. Besides the prevalence studies on GBS colonization, which ranges between 7 and 25% between 35 and 37 weeks, until recently only sporadic papers have been published on the frequency of AV. Due to the high concentrations of circulating estrogens, severe AV, typically with increased numbers of parabasal cells, is infrequent in pregnancy. However, the prevalence of less extensive types , mild to moderate AV, may range from 8 to 10% according to sporadic studies done during pregnancy (Donders et al., 2009; Zodzika et al., 2011; Rezeberga et al., 2008). Also, it has to be acknowledged that many BV patients have AV to a certain extent as well, - only, the score obtained by Nugent's method will never tell you. Therefore we plea to look for both AV and BV in pregnancy as both conditions are present, need different management approaches and are both linked to adverse pregnancy outcome.

6. Diagnostic techniques and screening

Some authors used aspecific substitute markers instead of Nugent Score for BV detection for exploring risk factors in the vaginal flora during pregnancy. Being one of the crucial criteria

of the Amsel diagnosis of BV, pH is often used as such a surrogate point of care test for BV (Madhivanan et al., 2009). However, in a study where pH was used as a screening tool in pregnancy, only 40% of women with increased vaginal pH had BV (Zodzika et al., 2011). When screening random women in Uganda, we discovered BV in only 27% of women with pH above 4.4 and 39% of women with pH above 4.7 had BV, while another 11% and 25% had coccoid AV respectively (unpublished results). The study demonstrated that AV and mixed AV-BV flora is also a frequent cause of abnormal pH in pregnancy. Hoyme et al. installed a screening in a German state by self measurements of the vaginal pH followed by treatment and found a dramatic reduction of preterm births (<37 gestational weeks at delivery) and early preterm births (<32 weeks) (Hoyme & Saling, 2004). As no specific search for BV was done, the proportion of women treated for other conditions than BV in this study in unkown.

On several occasions, our group could demonstrate that the finding of decreased lactobacilllary morphotypes in the beginning of pregnancy is a marker which is strongly linked to preterm birth, even more convincingly so than full BV on its own (Donders et al., 2008a; Donders et al., 1993b; Donders et al., 2009; Madhivanan et al., 2009; Donders et al., 2008b). As is the case with increased pH, also deficient lactobacillary grades are part of the clinical diagnosis of BV, without implying that all abnormal cases necessarily have BV.

7. Outcome

7.1 Miscarriage

Although BV is linked to the increased incidence of spontaneous first and second trimester miscarriage (Hay et al., 1994; Donders et al., 2000b; Larsson et al., 2006; Oakeshott et al., 2002) and reduced baby-take-home-rates in pregnancies obtained through assisted fertility procedures like in vitro fertilization, these data are less clear for AV. In in vitro fertilization procedures, a relation was found between BV and implantation failures (Ralph et al., 1999), but this relation was not confirmed in another observation (Liversedge et al., 1999). Furthermore, amongst these patients a clear relation of BV with tubal infertility was present, (Liversedge et al., 1999; Wilson et al., 2002) indicating indirectly BV is a risk factor for ascending infection and tubal damage. Interestingly, in one study, not BV, but decreased lactobacilli (AVF) was found to be the risk factor of implantation failure at IVF (Eckert et al., 2003). In animals, experiments have shown that *E. coli* derived lipopolysaccharides (LPS) cause implantation failure associated with increased anti-inflammatory cytokines (Deb et al., 2004a, 2004b). No data are available yet about the chances to conceive and keep the pregnancy in women with clinical AV or AV flora, but in sporadic cases pathogenic *E. coli* serotypes were involved in recurrent abortion cases (Blum-Oehler et al., 1997).

7.2 Midtrimester chorioamnionitis

The problem of amniotic fluid infection is that most of the time regular culture techniques are insufficiently sensitive to detect bacterial infection. Therefore, if PCR is used, frequent infection with E coli could be detected amongst these cases even when cultures were negative (Daoud et al., 2008). Also GBS and gram negative rods (Sherman et al., 1997) are frequent causes of intrauterine infections and histologic chorioamnionitis, often leading to midtrimester abortion, and even recurrences in two thirds of the women who have experienced it before.

7.3 Preterm birth

In one study H Mc Donald et al. found an association between midtrimester vaginal colonization with *U urealyticum* and bacterial vaginosis (culture of *G vaginalis*) and preterm birth, but not with enteropathogens such as E coli and enterococci (McDonald et al., 1992), but in another study the same authors found such enteropathogens and *S. aureus* to be predictive for preterm birth before 37 and 34 weeks (McDonald et al., 1991). Others have consistently linked colonization of *U urealyticum* of *M hominis* with preterm labor, short cervix, intrauterine infection and preterm birth (Donders et al., E pub ahead of print 2010; Donati et al., 2010; Holst et al., 2006; Hassan et al., 2006). In studies addressing the different subtypes of abnormal vaginal flora, aerobic vaginitis, mixed flora, and partial bacterial vaginosis show a significant relation with preterm birth alongside bacterial vaginosis (Donders et al., E pub ahead of print 2010; Donders et al., 2009; Donati et al., 2010), the latter being more related to growth restriction. After analyzing their studies, Carey and Klebanoff came to the conclusion that rather than just anaerobic BV, overgrowth with *S. aureus* and *E. coli* were the only vaginal bacterial flora linked to preterm birth (Carey et al., 2005). By looking at the microscopic flora patterns as possible risk factors early in pregnancy, we and others came to exactly the same conclusions, namely that aerobic abnormal flora early in pregnancy constitutes a significant risk of preterm labor, chorioamnionitis and funisitis of the newborn (Donders et al., 2008a; Donders et al., 2009; Rezeberga et al., 2008). Our hypothesis is that this link of preterm birth risk with the presence of vaginal flora disturbances associated with overgrowth of aerobic commensal bacteria may be the main reason why treatment with the broader spectrum antibitiotic clindamycin is a better approach to reduce preterm birth and preterm rupture of the membranes than metronidazole, which eliminates only the anaerobes (Donders et al., 2009; Larsson et al., 2006; Lamont et al., 2003).

7.4 Intrauterine infection

This would also explain why the pro-inflammatory cytokines that are most closely linked to intrauterine infection and preterm labor, IL 6 and IL 8 are not produced in uncomplicated full BV, but are found in dramatic concentrations in AV (Donders, 2002) and explain the closer association with these cytokines with lactobacillary grades than with anaerobic BV (Donders et al., 2003). In a comprehensive review Roberto Romero and coworkers summarized their voluminous work showing the importance of intrauterine inflammation induced by ascending infection and causing periventricular leucomalacia and cerebral palsy (Romero et al., 2004). Furthermore he and others emphasized the role of genetic variations in polymorphisms creating different responses amongst women to intrauterine infectious challenges (Holst & Garnier, 2008). While it was known since a long time that anaerobic BV associated bacteria can frequently recovered from the uterine cavity in amniocentesis specimens of women with preterm labor (Martius & Eschenbach, 1990; Hitti et al., 2001; Rizzo et al., 1996; Newton et al., 1997; Krohn et al., 1995; Hillier et al., 1995; Newton, 1993; Gibbs, 1993), most cases of neonatal sepsis are not caused by these BV associated bacteria, but by aerobic bacteria, mainly group B streptococcus, *E. coli* and *S. aureus.* Only recently, for the first time, Rezeberga et al could demonstrate that AV at the first prenatal visit before 12 weeks, detected both clinically as on cultures, was related to an increased risk of chorioamnionitis and funisitis (Rezeberga et al., 2008). Neonatal sepsis, most with *S. aureus* , was also a frequent finding in growth restricted fetuses (Vedmedovska et al., 2010a).

7.5 Intrauterine growth restriction

While women with AV and inflammatory reaction are more likely to develop intrauterine infection, chorioamnionitis, funisitis (Rezeberga et al., 2008) and preterm delivery, the merely non-inflammatory bacterial vaginosis may rather cause growth restriction and preterm delivery of small for date fetuses (Rezeberga et al., 2008). Also in the work of Vedmedovska et al., it was found that genital infections, primarily bacterial vaginosis, was linked to fetal growth restriction (Vedmedovska et al., 2010b).

8. Treatment

8.1 Antibiotics

It is not yet clear which should be the best approach to treat for AV in non-pregnant women, let alone during pregnancy. The inflammatory component of most patients with AV makes one think that antibiotics may not be the best, or not the only approach. But IF is chosen to give antibiotics in pregnancy to reduce preterm birth and intrauterine infection, it became clear after a placebo controlled studies that metronidazole is not the answer as it does not decrease the preterm birth rate in women with bacterial vaginosis (McDonald et al., 1997; McDonald et al., 2007; Carey et al., 2000; Odendaal et al., 2002). Even worse, Klebanoff's (Klebanoff et al., 2001) and Odendael's study (Odendaal et al., 2002) on the treatment of trichomoniasis and BV, respectively, rather demonstrated an increased risk of preterm birth after treatment with metronidazole, leading several authors to the compelling conclusion that metronidazole should not be used in pregnancy with the purpose to reduce the risk of preterm birth (Donders et al., 2009; Odendaal et al., 2002; Carey et al., 2003; Morency & Bujold, 2007). Investigators using broader spectrum antibiotics, also covering gram positive cocci and E coli, on the other hand, were successful in the reduction of preterm birth in several placebo controlled studies (Larsson et al., 2006; Lamont et al., 2003; Ugwumadu et al., 2003), although not all (Kekki et al., 2001; Kurkinen-Raty et al., 2000; Rosenstein et al., 2000). As most studies used a single treatment course of 5 to 7 days, and test of cure was not always done, one can ask whether a more intensive and repetitive treatment regimen would not be indicated, but studies are lacking.

Use of other antibiotics, aiming at *U urealyticum* and *C trachomatis*, like amoxicillin and erythromycin, have not been successful in the reduction of preterm birth or other infection-related complications in pregnancy (Andrews et al., 2003; Goldenberg et al., 2006; McGregor et al., 1990). Tempera et al tested local kanamycin for paitents with AV and performed a detailed analysis of the culture results, proving this may be a successful approach (Tempera et al., 2004). However, even though this antibiotic is not absorbed, tests in pregnancy with this and other similar products have not yet been done yet. Some local, non absorbable with antibiotics, like rifaximin, may have a special promise, due to favorable anti- inflammatory action reducing pro-inflammatory cytokine production as a surplus (Brown et al., 2010). As this has lead to high cure rates in inflammatory bowel diseases such as Crohn's disease, diverticulitis and colitis ulcerosa (Guslandi, 2010; Shafran & Burgunder, 2010; Latella & Scarpignato, 2009), and given the non-absorbable nature, studies exploring the potential of this antibiotic in the treatment of vaginal flora disturbances could be interesting, also in pregnancy.

Finally, also the level of preterm threat may play a crucial role in the efficiency of the BV treatment. Women with BV who have contractions and other symptoms of preterm labor extend their gestation longer when treated for BV than when untreated, whereas asymptomatic women show no difference between treatment versus placebo (Stevens et al, 2004; Briery et al, 2011).

8.2 Antiseptics

Only sporadic and older studies addressed the topic of using antiseptic medication with chlorhexidin, povidine iodine or chloramine as a preventive measure to prevent perinatal and maternal infectious complications in pregnancy, usually without any success (Watanabe et al., 1998; Rouse et al., 1997; Broe et al., 1992). Hence the therapy has been largely abandoned during pregnancy. A recent study shows a beneficial effect of dequalinium chloride vaginal tablets on BV that is comparable to treatment with intravaginal clindamycin, but the effect of this new disinfectant on AV is not known, and studies in pregnancy were not yet performed (Weisenbacher et al., 2011).

8.3 Probiotics

Acidifying or probiotic therapy has also sporadically been tested for women with AVF or BV in pregnancy, but not specifically for AV. In 1990, Holst et al reported a clear benefit of using acidifying cream for BV in a small group of women during pregnancy (Holst & Brandberg, 1990), but this paper was never followed by larger series. A Cochrane review of all randomized trial using probiotics indicated a clear reduction of vaginal infection after the use of oral or vaginal lactobacillus acidophilus containing milk products or yogurt, but data on the outcome of pregnancy were lacking (Othman et al., 2007).

9. References

Andrews WW, Sibai BM, Thom EA, Dudley D, Ernest JM, McNellis D et al. Randomized clinical trial of metronidazole plus erythromycin to prevent spontaneous preterm delivery in fetal fibronectin-positive women. Obstet Gynecol 2003; 101(5 Pt 1):847-855.

Blum-Oehler G, Heesemann J, Kranzfelder D, Scheutz F, Hacker J. Characterization of Escherichia coli serotype O12:K1:H7 isolates from an immunocompetent carrier with a history of spontaneous abortion and septicemia. Eur J Clin Microbiol Infect Dis 1997; 16(2):153-155.

Briery CM, Chauhan SP, Magann EF, Martin RW, Bofill JA, Cushmanh JL, Morrison JC. Treatment of bacterial vaginosis does not reduce preterm birth among high-risk asymptomatic women. J of MSMA 2011; 52:72-75.

Broe D, Van DJ, Cowley D, Vacca A, Voreteliac V, Maquire D et al. Detection of premature rupture of membranes by measuring diamine oxidase in vaginal fluid: false-negative results caused by obstetric antiseptic creams. Clin Chem 1992; 38(5):784.

Brown EL, Xue Q, Jiang ZD, Xu Y, Dupont HL. Pretreatment of epithelial cells with rifaximin alters bacterial attachment and internalization profiles. Antimicrob Agents Chemother 2010; 54(1):388-396.

Carey JC, Blackwelder WC, Nugent RP, Matteson MA, Rao AV, Eschenbach DA et al. Antepartum cultures for Ureaplasma urealyticum are not useful in predicting pregnancy outcome. The Vaginal Infections and Prematurity Study Group. Am J Obstet Gynecol 1991; 164(3):728-733.

Carey JC, Klebanoff MA, Hauth JC, Hillier SL, Thom EA, Ernest JM et al. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. N Engl J Med 2000; 342(8):534-540.

Carey JC, Klebanoff MA. What have we learned about vaginal infections and preterm birth? Semin Perinatol 2003; 27(3):212-216.

Carey JC, Klebanoff MA. Is a change in the vaginal flora associated with an increased risk of preterm birth? Am J Obstet Gynecol 2005; 192(4):1341-1346.

Cauci S, Driussi S, Guaschino S, Isola M, Quadrifoglio F. Correlation of local interleukin-1beta levels with specific IgA response against Gardnerella vaginalis cytolysin in women with bacterial vaginosis. Am J Reprod Immunol 2002; 47(5):257-264.

Cauci S, Guaschino S, Driussi S, De SD, Lanzafame P, Quadrifoglio F. Correlation of local interleukin-8 with immunoglobulin A against Gardnerella vaginalis hemolysin and with prolidase and sialidase levels in women with bacterial vaginosis. J Infect Dis 2002; 185(11):1614-1620.

Cauci S, Hitti J, Noonan C, Agnew K, Quadrifoglio F, Hillier SL et al. Vaginal hydrolytic enzymes, immunoglobulin A against Gardnerella vaginalis toxin, and risk of early preterm birth among women in preterm labor with bacterial vaginosis or intermediate flora. Am J Obstet Gynecol 2002; 187(4):877-881.

Cauci S, Guaschino S, De AD, Driussi S, De SD, Penacchioni P et al. Interrelationships of interleukin-8 with interleukin-1beta and neutrophils in vaginal fluid of healthy and bacterial vaginosis positive women. Mol Hum Reprod 2003; 9(1):53-58.

Cauci S, Culhane JF, Di SM, McCollum K. Among pregnant women with bacterial vaginosis, the hydrolytic enzymes sialidase and prolidase are positively associated with interleukin-1beta. Am J Obstet Gynecol 2008; 198(1):132-137.

Daoud GA, Suzuki Y, Yamamoto T, Suzuki T, Suzumori N, Tanemura M. Establishment of a polymerase chain reaction method for detection of Escherichia coli in amniotic fluid in patients with chorioamnionitis. Fetal Diagn Ther 2008; 24(2):132-139.

Deb K, Chaturvedi MM, Jaiswal YK. Comprehending the role of LPS in Gram-negative bacterial vaginosis: ogling into the causes of unfulfilled child-wish. Arch Gynecol Obstet 2004; 270(3):133-146.

Deb K, Chatturvedi MM, Jaiswal YK. Gram-negative bacterial endotoxin- induced infertility: a birds eye view. Gynecol Obstet Invest 2004; 57(4):224-232.

Donati L, Di VA, Nucci M, Quagliozzi L, Spagnuolo T, Labianca A et al. Vaginal microbial flora and outcome of pregnancy. Arch Gynecol Obstet 2010; 281(4):589-600.

Donders GG, Desmyter J, De Wet DH, Van Assche FA. The association of gonorrhoea and syphilis with premature birth and low birthweight. Genitourin Med 1993; 69(2):98-101.

Donders G, De Wet HG, Hooft P, Desmyter J. Lactobacilli in Papanicolaou smears, genital infections, and pregnancy. Am J Perinatol 1993; 10(5):358-361.

Donders GG, Vereecken A, Salembier G, Van BB, Spitz B. Assessment of Vaginal Lactobacillary Flora in Wet Mount and Fresh or Delayed Gram's Stain. Infect Dis Obstet Gynecol 1996; 4(1):2-6.

Donders GG, Desmyter J, Vereecken A. Vaginitis. N Engl J Med 1998; 338(21):1548.

Donders GG. Microscopy of the bacterial flora on fresh vaginal smears. Infect Dis Obstet Gynecol 1999; 7(3):126-127.

Donders GG, Bosmans E, Dekeersmaecker A, Vereecken A, Van BB, Spitz B. Pathogenesis of abnormal vaginal bacterial flora. Am J Obstet Gynecol 2000; 182(4):872-878.

Donders GG, Van BB, Caudron J, Londers L, Vereecken A, Spitz B. Relationship of bacterial vaginosis and mycoplasmas to the risk of spontaneous abortion. Am J Obstet Gynecol 2000; 183(2):431-437.

Donders GG, Vereecken A, Dekeersmaecker A, Van BB, Spitz B. Wet mount microscopy reflects functional vaginal lactobacillary flora better than Gram stain. J Clin Pathol 2000; 53(4):308-313.

Donders GG. Definition of a type of abnormal vaginal flora that is distinct from bacterial vaginosis: aerobic vaginitis. Br J Obstet Gynecol. 2002; 109: 1-10.

Donders GG, Vereecken A, Bosmans E, Dekeersmaecker A, Salembier G, Spitz B. Definition of a type of abnormal vaginal flora that is distinct from bacterial vaginosis: aerobic vaginitis. BJOG 2002; 109(1):34-43.

Donders GG, Vereecken A, Bosmans E, Spitz B. Vaginal cytokines in normal pregnancy. Am J Obstet Gynecol 2003; 189(5):1433-1438.

Donders GG. Definition and classification of abnormal vaginal flora. Best Pract Res Clin Obstet Gynaecol 2007; 21(3):355-373.

Donders GGG, Odds A, Vereecken A, Van Bulck B, Caudron J, Londers L, Salembier G and Spitz B. Abnormal vaginal flora in the first trimester, but not full blown bacterial vaginosis is associated with preterm birth. Prenat Neonat Med 2008;(3):588-593.

Donders GGG, Spitz B, Vereecken A, Van Bulck B, Cornelis A, Dekeersmaeker A, Klerckx P, Londers L and Caudron J. The Ecology of the Vaginal Flora at First Prenatal Visit is Associated with Preterm Delivery and Low Birth Weight. The Open Inf Dis J 2008; 2:45-51.

Donders GG, Van Calsteren K, Bellen G, Reybrouck R, Van den Bosch T, Riphagen I et al. Predictive value for preterm birth of abnormal vaginal flora, bacterial vaginosis and aerobic vaginitis during the first trimester of pregnancy. BJOG 2009; 116(10):1315-24.

Donders GG, Van Calsteren C, Bellen G, Reybrouck R, Van den Bosch T, Riphagen I et al. Association between abnormal vaginal flora and cervical length as risk factors for preterm birth. Ultrasound Obstet Gynecol, E pub ahead of print 26 Jan 2010.

Donders GG, Bellen G, Rezeberga D. Aerobic vaginitis in pregnancy. BJOG, 2011;118:1163-70.

Eckert LO, Moore DE, Patton DL, Agnew KJ, Eschenbach DA. Relationship of vaginal bacteria and inflammation with conception and early pregnancy loss following in-vitro fertilization. Infect Dis Obstet Gynecol 2003; 11(1):11-17.

Elliott B, Brunham RC, Laga M, Piot P, Ndinya-Achola JO, Maitha G et al. Maternal gonococcal infection as a preventable risk factor for low birth weight. J Infect Dis 1990; 161(3):531-536.

Garland SM, Ni CF, Satzke C, Robins-Browne R. Mechanisms, organisms and markers of infection in pregnancy. J Reprod Immunol 2002; 57(1-2):169-183.

Gravett MG, Eschenbach DA. Possible role of Ureaplasma urealyticum in preterm premature rupture of the fetal membranes. Pediatr Infect Dis 1986; 5(6 Suppl):S253-S257.

Gibbs RS. Chorioamnionitis and bacterial vaginosis. Am J Obstet Gynecol 1993; 169(2 Pt 2):460-462.

Goldenberg RL, Mwatha A, Read JS, Adeniyi-Jones S, Sinkala M, Msmanga G et al. The HPTN 024 Study: the efficacy of antibiotics to prevent chorioamnionitis and preterm birth. Am J Obstet Gynecol 2006; 194(3):650-661.

Guslandi M. Rifaximin for Inflammatory Bowel Disease. Dig Dis Sci 2010.

Hassan S, Romero R, Hendler I, Gomez R, Khalek N, Espinoza J et al. A sonographic short cervix as the only clinical manifestation of intra-amniotic infection. J Perinat Med 2006; 34(1):13-19.

Harada K, Tanaka H, Komori S, Tsuji Y, Nagata K, Tsutsui H et al. Vaginal infection with Ureaplasma urealyticum accounts for preterm delivery via induction of inflammatory responses. Microbiol Immunol 2008; 52(6):297-304.

Hauth JC, Macpherson C, Carey JC, Klebanoff MA, Hillier SL, Ernest JM et al. Early pregnancy threshold vaginal pH and Gram stain scores predictive of subsequent preterm birth in asymptomatic women. Am J Obstet Gynecol 2003; 188(3):831-835.

Hay PE, Lamont RF, Taylor-Robinson D, Morgan DJ, Ison C, Pearson J. Abnormal bacterial colonisation of the genital tract and subsequent preterm delivery and late miscarriage. BMJ 1994; 308(6924):295-298.

Hillier SL, Krohn MA, Cassen E, Easterling TR, Rabe LK, Eschenbach DA. The role of bacterial vaginosis and vaginal bacteria in amniotic fluid infection in women in preterm labor with intact fetal membranes. Clin Infect Dis 1995; 20 Suppl 2:S276-S278.

Hitti J, Hillier SL, Agnew KJ, Krohn MA, Reisner DP, Eschenbach DA. Vaginal indicators of amniotic fluid infection in preterm labor. Obstet Gynecol 2001; 97(2):211-219.

Holst E, Brandberg A. Treatment of bacterial vaginosis in pregnancy with a lactate gel. Scand J Infect Dis 1990; 22(5):625-626.

Holst RM, Jacobsson B, Hagberg H, Wennerholm UB. Cervical length in women in preterm labor with intact membranes: relationship to intra-amniotic inflammation/microbial invasion, cervical inflammation and preterm delivery. Ultrasound Obstet Gynecol 2006; 28(6):768-774.

Holst D, Garnier Y. Preterm birth and inflammation-The role of genetic polymorphisms. Eur J Obstet Gynecol Reprod Biol 2008; 141(1):3-9.

Honest H, Bachmann LM, Knox EM, Gupta JK, Kleijnen J, Khan KS. The accuracy of various tests for bacterial vaginosis in predicting preterm birth: a systematic review. BJOG 2004; 111(5):409-422.

Hoyme UB, Saling E. Efficient prematurity prevention is possible by pH-self measurement and immediate therapy of threatening ascending infection. Eur J Obstet Gynecol Reprod Biol 2004; 115(2):148-153.

Kekki M, Kurki T, Pelkonen J, Kurkinen-Raty M, Cacciatore B, Paavonen J. Vaginal clindamycin in preventing preterm birth and peripartal infections in asymptomatic women with bacterial vaginosis: a randomized, controlled trial. Obstet Gynecol 2001; 97(5 Pt 1):643-648.

Kiss H, Petricevic L, Husslein P. Prospective randomised controlled trial of an infection screening programme to reduce the rate of preterm delivery. BMJ 2004; 329(7462):371.

Klebanoff MA, Carey JC, Hauth JC, Hillier SL, Nugent RP, Thom EA et al. Failure of metronidazole to prevent preterm delivery among pregnant women with asymptomatic Trichomonas vaginalis infection. N Engl J Med 2001; 345(7):487-493.

Klebanoff MA, Hillier SL, Nugent RP, Macpherson CA, Hauth JC, Carey JC et al. Is bacterial vaginosis a stronger risk factor for preterm birth when it is diagnosed earlier in gestation? Am J Obstet Gynecol 2005; 192(2):470-477.

Krohn MA, Hillier SL, Nugent RP, Cotch MF, Carey JC, Gibbs RS et al. The genital flora of women with intraamniotic infection. Vaginal Infection and Prematurity Study Group. J Infect Dis 1995; 171(6):1475-1480.

Lamont RF, Duncan SL, Mandal D, Bassett P. Intravaginal clindamycin to reduce preterm birth in women with abnormal genital tract flora. Obstet Gynecol 2003; 101(3):516-522.

Larsson PG, Fahraeus L, Carlsson B, Jakobsson T, Forsum U. Late miscarriage and preterm birth after treatment with clindamycin: a randomised consent design study according to Zelen. BJOG 2006; 113(6):629-637.

Larsson PG, Fahraeus L, Carlsson B, Jakobsson T, Forsum U. Predisposing factors for bacterial vaginosis, treatment efficacy and pregnancy outcome among term deliveries; results from a preterm delivery study. BMC Womens Health 2007; 7:20.

Latella G, Scarpignato C. Rifaximin in the management of colonic diverticular disease. Expert Rev Gastroenterol Hepatol 2009; 3(6):585-598.

Lee SE, Romero R, Kim EC, Yoon BH. A high Nugent score but not a positive culture for genital mycoplasmas is a risk factor for spontaneous preterm birth. J Matern Fetal Neonatal Med 2009; 22(3):212-217.

Liversedge NH, Turner A, Horner PJ, Keay SD, Jenkins JM, Hull MG. The influence of bacterial vaginosis on in-vitro fertilization and embryo implantation during assisted reproduction treatment. Hum Reprod 1999; 14(9):2411-2415.

Kurkinen-Raty M, Vuopala S, Koskela M, Kekki M, Kurki T, Paavonen J et al. A randomised controlled trial of vaginal clindamycin for early pregnancy bacterial vaginosis. BJOG 2000; 107(11):1427-1432.

Madhivanan P, Krupp K, Hardin J, Karat C, Klausner JD, Reingold AL. Simple and inexpensive point-of-care tests improve diagnosis of vaginal infections in resource constrained settings. Trop Med Int Health 2009; 14(6):703-708.

Martius J, Eschenbach DA. The role of bacterial vaginosis as a cause of amniotic fluid infection, chorioamnionitis and prematurity--a review. Arch Gynecol Obstet 1990; 247(1):1-13.

Mass SB, Brennan JP, Silverman N, van Hoeven KH. Association between a shift in vaginal flora on Papanicolaou smear and acute chorioamnionitis and preterm delivery. Diagn Cytopathol 1999; 21(1):7-9.

Massaro G, Scaravilli G, Simeone S, Capuano S, Pastore E, Forte A et al. Interleukin-6 and Mycoplasma hominis as markers of preterm birth and related brain damage: our experience. J Matern Fetal Neonatal Med 2009; 22(11):1063-1067.

McDonald HM, O'Loughlin JA, Jolley P, Vigneswaran R, McDonald PJ. Vaginal infection and preterm labour. Br J Obstet Gynaecol 1991; 98(5):427-435.

McDonald HM, O'Loughlin JA, Jolley P, Vigneswaran R, McDonald PJ. Prenatal microbiological risk factors associated with preterm birth. Br J Obstet Gynaecol 1992; 99(3):190-196.

McDonald HM, O'Loughlin JA, Jolley PT, Vigneswaran R, McDonald PJ. Changes in vaginal flora during pregnancy and association with preterm birth. J Infect Dis 1994; 170(3):724-728.

McDonald HM, O'Loughlin JA, Vigneswaran R, Jolley PT, Harvey JA, Bof A et al. Impact of metronidazole therapy on preterm birth in women with bacterial vaginosis flora (Gardnerella vaginalis): a randomised, placebo controlled trial. Br J Obstet Gynaecol 1997; 104(12):1391-1397.

McDonald HM, Brocklehurst P, Gordon A. Antibiotics for treating bacterial vaginosis in pregnancy. Cochrane Database Syst Rev 2007;(1):CD000262.

McGregor JA, French JI, Richter R, Vuchetich M, Bachus V, Seo K et al. Cervicovaginal microflora and pregnancy outcome: results of a double-blind, placebo-controlled trial of erythromycin treatment. Am J Obstet Gynecol 1990; 163(5 Pt 1):1580-1591.

Morency AM, Bujold E. The effect of second-trimester antibiotic therapy on the rate of preterm birth. J Obstet Gynaecol Can 2007; 29(1):35-44.

Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. J Clin Microbiol 1991; 29(2):297-301.

Newbern EC, Foxman B, Leaman D, Sobel JD. Desquamative inflammatory vaginitis: an exploratory case-control study. Ann Epidemiol 2002; 12(5):346-352.

Newton ER. Chorioamnionitis and intraamniotic infection. Clin Obstet Gynecol 1993; 36(4):795-808.

Newton ER, Piper J, Peairs W. Bacterial vaginosis and intraamniotic infection. Am J Obstet Gynecol 1997; 176(3):672-677.

Oakeshott P, Hay P, Hay S, Steinke F, Rink E, Kerry S. Association between bacterial vaginosis or chlamydial infection and miscarriage before 16 weeks' gestation: prospective community based cohort study. BMJ 2002; 325(7376):1334.

Oakeshott P, Kerry S, Hay S, Hay P. Bacterial vaginosis and preterm birth: a prospective community-based cohort study. Br J Gen Pract 2004; 54(499):119-122.

Odendaal HJ, Popov I, Schoeman J, Smith M, Grove D. Preterm labour--is bacterial vaginosis involved? S Afr Med J 2002; 92(3):231-234.

Othman M, Neilson JP, Alfirevic Z. Probiotics for preventing preterm labour. Cochrane Database Syst Rev 2007;(1):CD005941.

Ralph SG, Rutherford AJ, Wilson JD. Influence of bacterial vaginosis on conception and miscarriage in the first trimester: cohort study. BMJ 1999; 319(7204):220-223.

Rezeberga D, Lazdane G, Kroica J, Sokolova L, Donders GG. Placental histological inflammation and reproductive tract infections in a low risk pregnant population in Latvia. Acta Obstet Gynecol Scand 2008; 87(3):360-365.

Rizzo G, Capponi A, Rinaldo D, Tedeschi D, Arduini D, Romanini C. Interleukin-6 concentrations in cervical secretions identify microbial invasion of the amniotic cavity in patients with preterm labor and intact membranes. Am J Obstet Gynecol 1996; 175(4 Pt 1):812-817.

Romero R, Chaiworapongsa T, Kuivaniemi H, Tromp G. Bacterial vaginosis, the inflammatory response and the risk of preterm birth: a role for genetic epidemiology in the prevention of preterm birth. Am J Obstet Gynecol 2004; 190(6):1509-1519.

Romero R, Gotsch F, Pineles B, Kusanovic JP. Inflammation in pregnancy: its roles in reproductive physiology, obstetrical complications, and fetal injury. Nutr Rev 2007; 65(12 Pt 2):S194-S202.

Rosenstein IJ, Morgan DJ, Lamont RF, Sheehan M, Dore CJ, Hay PE et al. Effect of intravaginal clindamycin cream on pregnancy outcome and on abnormal vaginal microbial flora of pregnant women. Infect Dis Obstet Gynecol 2000; 8(3-4):158-165.

Rouse DJ, Hauth JC, Andrews WW, Mills BB, Maher JE. Chlorhexidine vaginal irrigation for the prevention of peripartal infection: a placebo-controlled randomized clinical trial. Am J Obstet Gynecol 1997; 176(3):617-622.

Rouse AG, Gil KM, Davis K. Diagnosis of bacterial vaginosis in the pregnant patient in an acute care setting. Arch Gynecol Obstet 2009; 279(4):545-549.

Shafran I, Burgunder P. Adjunctive antibiotic therapy with rifaximin may help reduce Crohn's disease activity. Dig Dis Sci 2010; 55(4):1079-1084.

Sherman DJ, Tovbin J, Lazarovich T, Avrech O, Reif R, Hoffmann S et al. Chorioamnionitis caused by gram-negative bacteria as an etiologic factor in preterm birth. Eur J Clin Microbiol Infect Dis 1997; 16(6):417-423.

Sobel JD. Desquamative inflammatory vaginitis: a new subgroup of purulent vaginitis responsive to topical 2% clindamycin therapy. Am J Obstet Gynecol 1994; 171(5):1215-1220.

Stevens AO, Chauhan SP, Magann EF, Martin RW, Bofill JA, Cushman J, Morrison JC. Fetal fibronectin and bacterial vaginosis are associated with preterm birth in women symptomatic for preterm labor. Am J Obstet Gynecol 2004;190(6):1582-9.

Tann CJ, Mpairwe H, Morison L, Nassimu K, Hughes P, Omara M et al. Lack of effectiveness of syndromic management in targeting vaginal infections in pregnancy in Entebbe, Uganda. Sex Transm Infect 2006; 82(4):285-289.

Tempera G, Bonfiglio G, Cammarata E, Corsello S, Cianci A. Microbiological/clinical characteristics and validation of topical therapy with kanamycin in aerobic vaginitis: a pilot study. Int J Antimicrob Agents 2004; 24(1):85-88.

Thorp JM, Jr., Dole N, Herring AH, McDonald TL, Eucker B, Savitz DA et al. Alteration in vaginal microflora, douching prior to pregnancy, and preterm birth. Paediatr Perinat Epidemiol 2008; 22(6):530-537.

Ugwumadu A, Manyonda I, Reid F, Hay P. Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomised controlled trial. Lancet 2003; 361(9362):983-988.

Vedmedovska N, Rezeberga D, Teibe U, Polukarova S, Donders G. Fetal growth restriction in Latvia. Int J Gynecol obstet 2010; 111 (2): 185-186.

Vedmedovska N, Rezeberga D, Teibe U, Zodzika J, Donders G. Preventable maternal risk factors and association of genital infection with Fetal Growth Restriction. Gynecol Obstet Invest 2010; 70 (4): 291-298.

Verstraelen H, Verhelst R, Roelens K, Claeys G, Weyers S, De BE et al. Modified classification of Gram-stained vaginal smears to predict spontaneous preterm birth: a prospective cohort study. Am J Obstet Gynecol 2007; 196(6):528-6.

Verstraelen H, Verhelst R, Claeys G, De BE, Temmerman M, Vaneechoutte M. Longitudinal analysis of the vaginal microflora in pregnancy suggests that L. crispatus promotes the stability of the normal vaginal microflora and that L. gasseri and/or L. iners are more conducive to the occurrence of abnormal vaginal microflora. BMC Microbiol 2009; 9:116.

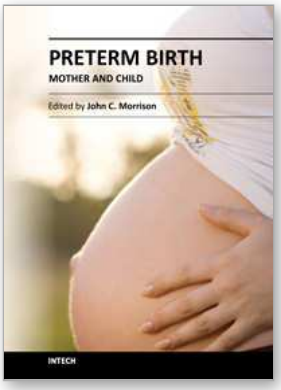
Watanabe T, Minakami H, Matsubara S, Honma Y, Uchida A, Sato I. Effect of daily vaginal disinfection on duration of gestation after premature rupture of the membranes and on infant outcome. J Obstet Gynaecol Res 1998; 24(4):285-290.

Waters TP, Denney JM, Mathew L, Goldenberg RL, Culhane JF. Longitudinal trajectory of bacterial vaginosis during pregnancy. Am J Obstet Gynecol 2008; 199(4):431-435.

Weissenbacher ER, Dvorak V, Donders G, Spacek J et al. A Comparison of Dequalinium Chloride Vaginal Tablets (Fluomizin) and Clindaycin Vaginal Cream in Local Treatment of Bacterial Vaginosis. Gynecol Obstet Invest, 2011, in press

Wilson JD, Ralph SG, Rutherford AJ. Rates of bacterial vaginosis in women undergoing in vitro fertilisation for different types of infertility. BJOG 2002; Dec 23, e-pub ahead of press. 109(6):714-717.

Zodzika J, Jermakova I, Rezeberga D, Vasina O, Vedmedovska N, Donders G, Teibe U. Factors related to elevated vaginal pH in the first trimester of pregnancy. Acta Obstet Gynecol Scand 2011; 90: 41-46.



Preterm Birth - Mother and Child
Edited by Dr. John Morrison

ISBN 978-953-307-828-1
Hard cover, 368 pages
Publisher InTech
Published online 27, January, 2012
Published in print edition January, 2012

While there are many studies and books regarding preterm birth, both the obstetric and in the neonatal/pediatric literature, what is missing is the integration of data from obstetrics through neonatal course and into pediatrics as the neonate transverses childhood. A continued dialogue between specialties is essential in the battle against preterm birth in an attempt to relieve the effects or after-effects of preterm birth. For all of our medical advances to date, preterm birth is still all too common, and its ramifications are significant for hospitals, families and society in general.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Gilbert G.G. Donders and Gert Bellen (2012). Management of Abnormal Vaginal Flora as a Risk Factor for Preterm Birth, Preterm Birth - Mother and Child, Dr. John Morrison (Ed.), ISBN: 978-953-307-828-1, InTech, Available from: http://www.intechopen.com/books/preterm-birth-mother-and-child/management-of-abnormal-vaginal-flora-as-a-risk-factor-for-preterm-birth

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