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Reviews

The role of bacterial vaginosis as a cause of amniotic fluid infection, chorioamnionitis and prematurity – a review

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Introduction

One of the most urgent objectives of perinatology remains the reduction of the number of babies born prematurely. The significance of this problem is illustrated by the fact that only 7% of all liveborn are premature but they account for 80% of the perinatal mortality [1]. Despite the widespread use of potent tocolytic agents there has not been a significant reduction in the rate of prematurity [1]. As long as symptoms rather than the causes of prematurity are treated, the prematurity rate can be expected to remain fairly constant. It is essential to discover more about the pathogenesis of premature labor. To date, causes of prematurity can be found in less than half of all cases [2]. The key to reducing prematurity will be to delineate the causes of so-called idiopathic prematurity where the mechanism is not evident. Results of research conducted in recent years indicates that at least a portion of idiopathic prematurity is related to ascending genital infections [3].

The following review summarizes data that link one infection, bacterial vaginosis, to prematurity. Bacterial vaginosis appears to predispose to the development of an ascending genital tract infection of the chorioamnion and amniotic fluid that eventually leads to preterm labor and/or premature rupture of membranes.

Bacterial vaginosis

Bacterial vaginosis is one of the most frequent vaginal infections of sexually active women [4–6]. Bacterial vaginosis has been found in 15% to 20% of pregnant women [7–10]. Complaints of an increased amount of a watery discharge and a fishy odor occur in symptomatic women. However, about half

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of patients with this infection have no or only very mild symptoms. Therefore, an accurate prevalence of bacterial vaginosis can be found only by including both asymptomatic and symptomatic patients.

The microbiology of bacterial vaginosis has consistently demonstrated an increased prevalence of *Gardnerella vaginalis*, selected anaerobic bacteria (most notably, *Bacteroides* and *Mobiluncus*), *Mycoplasma hominis* and a decreased prevalence of facultative lactobacilli [10–11]. Perhaps more importantly, a 1000-fold increase in the concentration of anaerobic microorganisms and a 100-fold increase in the concentration of *G. vaginalis* [11] has been found in patients with bacterial vaginosis using quantitative microbiology. H_2O_2-producing facultative *Lactobacillus sp.* are found significantly less often whereas anaerobic non-H_2O_2-producing *Lactobacillus sp.* are found more often in women with bacterial vaginosis compared to control women without bacterial vaginosis [12]. The production of H_2O_2 by lactobacilli may be a mechanism by which growth inhibition of other bacteria occurs, particularly of catalase negative bacteria.

The diagnosis of bacterial vaginosis can be made clinically or by using direct Gram stain of vaginal fluid [13–15]. The standard clinical diagnosis of bacterial vaginosis has become well established and it includes the presence of at least three of the following four characteristics of the vaginal discharge: a thin homogeneous appearance, a pH higher than 4.5, the release of a fishy amine odor upon alkalinization of the discharge with 10% potassium hydroxide and clue cells on wet mount [13, 15]. Clue cells are vaginal epithelial cells so covered with bacteria that the cell border is obscured.

The Gram stain method described by Spiegel et al. [14] uses the identification of certain bacterial morphotypes in the Gram stain to make the diagnosis of bacterial vaginosis with a high sensitivity and specificity [15]. Other laboratory methods including quantitative vaginal cultures, gasliquid chromatography (GLC), and proline aminopeptidase can be used to diagnose bacterial vaginosis, but none of these tests offers the availability, ease, and accurracy of the Gram stain.

Bacterial vaginosis and prematurity

A relationship between bacterial vaginosis and premature labor and/or premature rupture of membranes has been reported in several studies where bacterial vaginosis was present significantly more often among patients who delivered before 37 weeks gestation than among control patients who delivered at term [7, 8, 10, 16]. A cohort of patients with bacterial vaginosis were also found to deliver prematurely more frequently than those without bacterial vaginosis [9] (Table 1).

Eschenbach et al. [7] diagnosed bacterial vaginosis in 28 (49%) of 57 women who delivered at a gestational age of 37 weeks or less and in 27 (24%) of 114 control women who delivered at term ($P = 0.001$). In this study, bacterial vaginosis was detected by abnormal levels of organic acids in the vaginal fluid determined by GLC [11]. The influence of demographic and obstetrical factors and of other genital infections were not studied in this preliminary report.

Table 1. Relationship between bacterial vaginosis and prematurity

Study (Ref.)	Bacterial vaginosis/ total examined (%)		Univariate	Multivariate
	Women delivering prematurely	Women not delivering prematurely	Odds ratio (95% CI)[d]	Odds ratio (95% CI)[d]
Eschenbach [7]	28/57 (49)	27/114 (24)	3.1 (1.6– 6.0)	–
Gravett [9]	24/77 (31)	78/457 (17)	2.2 (1.3– 3.8)	2.0 (1.1–3.5)[a]
Gravett [8][b]	19/44 (43)	6/44 (14)	3.8 (1.2–11.6)	–
Martius [10]	21/61 (34)	21/115 (18)	2.3 (1.2– 4.7)	2.3 (1.1–5.0)[c]

[a] Multivariate analysis was used to control for demographic and obstetrical factors and *C. trachomatis*. [b] Compared women in preterm labor with matched controls not in labor. Matched to control for gestational age, demographic and obstetrical factors. *C. trachomatis*, Group B Streptococcus, *G. vaginalis*, Herpes simplex virus, genital mycoplasmas were also studied. [c] Multivariate analysis used to control for demographic and obstetrical factors and *C. trachomatis, Lactobacillus sp.*, black-pigmented *Bacteroides sp., Mobiluncus sp.*, and *U. urealyticum*. [d] 95% Confidence interval

Gravett et al. [9] prospectively investigated the relationship between pregnancy outcome and four genital infections (bacterial vaginosis, *Chlamydia trachomatis, Neisseria gonorrhoeae* and group B streptococci) among 534 pregnant women. Bacterial vaginosis was diagnosed in 102 (19%) of the 534 patients using GLC criteria. The mean birthweight of neonates born of mothers with bacterial vaginosis was 2960 g compared to 3184 g in the group without bacterial vaginosis ($P < 0.01$). In this study, 14 obstetrical, demographic factors and infections were examined for their possible influence on the relationship between prematurity and genital infections including bacterial vaginosis. Bacterial vaginosis was detected in 24 (31%) of 77 patients delivering before 37 weeks gestation and in 78 (17%) of 457 women who delivered at term ($P < 0.01$). Bacterial vaginosis remained significantly correlated to premature delivery <37 weeks in a multivariate analysis in which nonmicrobiologic factors and *C. trachomatis* were controlled (Odds Ratio = 2.0, 95% Confidence Interval 1.1 to 3.5). Additionally premature rupture of membranes before 37 weeks gestation was significantly associated with bacterial vaginosis. *C. trachomatis* was also associated with bacterial vaginosis in this study although an exhaustive list of other organisms were not examined.

Gravett et al. [8] also compared the genital flora of 44 pregnant patients who had signs of premature labor without rupture of membranes or clinical signs of infection with 44 matched control patients who had no premature labor. The patients were matched for gestational age, maternal age, race, parity, social status, and marital status. Bacterial vaginosis identified by GLC was found in 19 (43%) of 44 women with premature labor and in 6 (14%) of 44 matched control women without premature labor ($P = 0.02$). Other microorganisms (*N. gonorrhoeae* group B streptococcus, *G. vaginalis, C. trachomatis,* Herpes simplex virus and the genital mycoplasmas) did not significantly differ between the two

groups in this small sample of patients although *C. trachomatis* was isolated more frequently from women with compared to those without premature labor.

Fischbach et al. [16] in a prospective study of 147 pregnant women found a significant correlation between the recovery of *G. vaginalis* and premature rupture of the membranes (Relative Risk 2.0, $P < 0.05$) and prematurity less than 37 weeks (Relative Risk 2.1, $P < 0.05$).

The relationship between genital infections in pregnancy and pregnancy outcome was also investigated by Martius et al. [10] in a case control study that included 212 patients. The 97 patients in the case group were further divided into two separate groups of 61 women who delivered before 37 weeks gestation and 36 women who had signs of premature labor but eventually delivered at a gestational age of 37 weeks or greater. All 115 control women delivered at a gestational age of 37 weeks or greater and none of the control women had signs of premature labor. Bacterial vaginosis was diagnosed using Gram stain criteria [14]. The data were controlled for a series of demographic, behavioral and pregnancy characteristics associated with either prematurity or bacterial vaginosis in this population. Cases and controls differed significantly only in the following parameters: women with premature labor were younger, had more prior premature births, and, during the current pregnancy, had a higher rate of premature rupture of membranes and a higher rate of fever (both intrapartum and postpartum) than the controls. Bacterial vaginosis was diagnosed in 21 (34%) of the 61 women who delivered before 37 weeks gestation compared to 21 (18%) of the 115 women who delivered at term ($P < 0.05$). In this study, the presence of group B streptococci, *G. vaginalis,* black-pigmented *Bacteroides sp., Mobiluncus sp., M. hominis, Ureaplasma urealyticum, Trichomonas vaginalis* and *Candida sp.,* was examined by multivariate analysis to determine which microorganisms were independently related to bacterial vaginosis as diagnosed by Gram stain. Black-pigmented *Bacteroides sp., Mobiluncus sp., G. vaginalis* and *M. hominis* were found to be significantly and independently related to bacterial vaginosis. Multivariate analysis was also used to study maternal flora associated with delivery <37 weeks independent of demographic and other flora differences. Bacterial vaginosis was associated with a delivery <37 weeks in the multivariate analysis (Odds Ratio 2.3, 95% Confidence Interval 1.1 to 5.0, $P = 0.03$). *C. trachomatis* was independently related to a premature delivery, while lactobacilli were negatively related to prematurity (Odds Ratio 0.2, $P = 0.002$).

The combined results of these studies indicate a consistent association between prematurity and bacterial vaginosis, defined either by GLC or Gram stain criteria. The association between bacterial vaginosis and prematurity has remained when adjustment was made using multivariate analysis for demographic or obstetrical variables that are associated with either bacterial vaginosis or prematurity. The relationship between bacterial vaginosis and prematurity has also been independent of selected other genital flora. However, many vaginal-cervical microorganisms have been related to premature delivery in various prior studies [3], and in none of the studies of bacterial vaginosis were enough subjects enrolled to exclude the possibility of a significant relationship between many of the other microorganisms (except *C. trachomatis*) and prematurity.

Thus, more study is required of the importance of bacterial vaginosis relative to other infections. In fact, data will soon be available from a large collaborative United States study of over ten thousand women in which the relationship between multiple genital microorganisms and prematurity has been examined.

In the meantime, data relating microorganisms to prematurity would be more convincing if the microorganisms recovered from otherwise sterile upper genital tract sites such as amniotic fluid or placenta were related to prematurity. Recent information indicate that microorganisms, especially microorganisms associated with bacterial vaginosis, can be isolated more frequently from the amniotic fluid or chorioamnion of women who deliver prematurely than those who deliver at term.

Microorganisms in the amniotic fluid of pregnant women with premature labor and intact membranes

In five studies, abdominal amniocentesis had been performed in women who were in premature labor with intact membranes [8, 17–20] (Table 2). Abdominal amniocentesis avoids contamination of the specimens with normal flora that often occurs with transvaginal sampling using a needle or an intrauterine pressure catheter. The majority of women enrolled into these studies had no clinical signs of infection at the time of amniocentesis. A positive amniotic fluid culture was present in a total of 35 (16%) of 214 women in premature labor who underwent amniocentesis. Of those with a positive culture, 13 (37%) had anaerobic bacteria recovered from their amniotic fluid. Microorganisms commonly associated with bacterial vaginosis *(Bacteroides sp., M. hominis* and *G. vaginalis)* were isolated from 11 (31%) of the 35 women with a positive culture.

In all five studies, women with a positive amniotic fluid culture delivered within 24 h of the amniocentesis despite the common use of tocolytic agents (Table 3). Women with sterile amniotic fluid had a mean pregnancy prolongation of between 25 and 51 days. The presence of microorganisms in the amniotic fluid of women in premature labor was highly correlated with delivery in each

Table 2. Amniotic fluid infection among women in premature labor with intact fetal membranes

Study (Ref.)	Number patients studied	Positive amniotic fluid culture (%)	Anaerobe recovery (%)	Organisms associated with bacterial vaginosis[a] (%)
Hameed [20]	37	3 (8)	–	–
Leigh [19]	59	7 (12)	4 (57)	4 (57)
Wahbeh [18]	33	4 (12)	4 (100)	2 (50)
Gravett [8]	54	13 (24)	3 (23)	5 (38)
Bobitt [17]	31	8 (26)	2 (33)	–
Total	214	35 (16)	13 (37)	11 (31)

[a] Bacterial vaginosis associated organisms include *Bacteroides sp., M. hominis* and *G. vaginalis*

Table 3. Mean interval in days between amniocentesis and delivery among women with premature labor and intact membranes stratified for organisms or no organisms in amniotic fluid

Study (Ref.)	Interval between amniocentesis and delivery (days)	
	Any bacterial micro-organism	No bacterial micro-organism
Bobitt [17]	< 1	25
Gravett [8]	< 1	34
Leigh [19]	1	35
Wahbeh [18]	1	42
Hameed [20]	< 1	51

study. Either the amniotic fluid infection initiates premature labor, or the presence of microorganisms in amniotic fluid further increases the likelihood of delivery among women already in premature labor or both. The finding that 31% of the microorganisms isolated from the amniotic fluid were related to bacterial vaginosis suggests that bacterial vaginosis may play a substantial role in an ascending infection among women with premature labor and intact membranes. Since most women with infection of the chorioamnion do not have amniotic fluid infection, it is apparent that only a small proportion of pregnant women with upper genital tract infection can be identified by positive amniotic fluid cultures.

Other indirect data from GLC analysis of amniotic fluid [21] and from C-reactive protein (CRP) determination of sera [22] also suggests the presence of infection in the amniotic fluid, fetal membranes or decidua among women in premature labor with seemingly sterile amniotic fluid. Iams et al. [21] performed amniocentesis among five women in premature labor with intact membranes and no clinical signs of infection. GLC was used to identify short chain organic acid byproducts of bacterial metabolism in the amniotic fluid. The amniotic fluid was cultured for aerobic and anaerobic bacteria, *C. trachomatis* and genital mycoplasmas. All amniotic fluids from the five patients with preterm labor had a GLC pattern consistent with that previously observed in amniotic fluids containing bacterial growth [23], although cultures of these five amniotic fluids were negative. The authors postulated that extraamniotic bacterial growth in the fetal membranes or the decidua could cause premature labor and explain the presence of short chain organic acids in the amniotic fluid.

Potkul et al. [22] investigated the association between preterm birth and possible subclinical infection identified by CRP. The authors performed CRP assays on patients in premature labor between 24 and 36 weeks gestation who had intact membranes and no clinical signs of infection. The CRP was positive in 16 (40%) of the 40 patients. As will be evident in the next section, histologic chorioamnionitis is highly associated with the presence of microorganisms in the chorioamnion. Histologic chorioamnionitis was present in 62% of the patients with a positive CRP and 18% of patients with a negative CRP ($P < 0.01$). Tocolysis was significantly more successful in reducing the premature labor of

patients with a negative CRP than a positive CRP. The mean number of days to delivery was 35 days in the CRP negative group and 14 days in the CRP positive group ($P < 0.01$). Duff et al. [24], were not able to isolate microorganisms from the amniotic fluid of women in premature labor who continued to contract despite tocolytic therapy. This is not unexpected because, paradoxically, the women in premature labor with amniotic fluid infection may have delivered before the amniocentesis was performed leading to the negative finding in this report.

The combined culture evidence from amniotic fluid studies indicates that approximately 15% of women in premature labor have microorganisms isolated from the amniotic fluid. With the insensitivity of amniotic fluid cultures, an additional number of women probably have microorganisms present in the fluid. As will be shown by evidence in the next section, a larger number of patients have fetal membrane or decidual infection without amniotic fluid infection. Women with microorganisms in the amniotic fluid usually deliver within a day of the amniocentesis while women with sterile amniotic fluid usually deliver over a month later. These data suggest either that the presence of microorganisms in the amniotic fluid causes premature labor as a result of an ascending cervical, decidual, and membrane infection or, alternatively, that premature labor provides a mechanism for the ascent of microorganisms into amniotic fluid. Regardless of whether the amniotic fluid infection is primary or secondary, the presence of microorganisms in the amniotic fluid has been highly associated with premature delivery.

Bacterial vaginosis, chorioamnionitis and the recovery of microorganisms in the placenta

It is well established that histologic chorioamnionitis is highly related to preterm birth [25–27]. Further, the highest prevalence of chorioamnionitis occurs in the most premature pregnancies [26–28]. If a causal relationship exists between ascending infection and prematurity, the isolation of microorganisms would be expected more commonly from the placenta and membranes of pregnancies that deliver premature compared to those who deliver at term. One would also expect to find a close relationship between the isolation of microorganisms from the placenta and histologic chorioamnionitis.

Many possible explanations have been postulated as to the cause of histologic chorioamnionitis. However, it is now clear that the majority of histologic chorioamnionitis is caused by microorganisms. Using advanced microbiological techniques, a significant correlation has now been established in several studies between the recovery of microorganisms from the placenta and chorioamniotic membranes and histologic chorioamnionitis [27–29] (Table 4). In most studies the amnion was separated from the chorion and a culture was obtained of this space, although some investigators have cultured the maternal floor of the placenta after sterilizing the surface with cautery. A reduced recovery rate of fastidious microorganisms may be expected with refrigeration or a prolonged interval between delivery and culture. Placenta refrigeration and the time between delivery and culture has varied considerably between studies and both

Table 4. The relationship between histologic chorioamnionitis and positive placental culture

Study (Ref.)	Positive placental culture (%)		Odds ratio	(*P*-value)
	Chorioamnionitis	No chorioamnionitis		
Pankuch [27]	18/25 (72)	6/39 (15)	14	(0.001)
Hillier [28]	21/29 (72)	14/65 (22)	7.2	(0.001)
Quinn [29]	10/14 (71)	8/29 (28)	6.5	(0.01)

factors may explain some of the disparite microbiologic results found in the different studies particularly among patients with histologic chorioamnionitis and negative cultures.

A very consistent 70% positive chorioamnion culture rate has been present among placentas with histologic chorioamnionitis in all three studies listed in Table 4. Significantly lower chorioamnion positive culture rates (15–28%) was present in placentae without histologic chorioamnionitis. The combined weight and the consistency of these studies provide clear evidence that microorganisms cause histologic chorioamnionitis.

Pankuch et al. [27] found that 50% of the microorganisms isolated from the placenta were strictly anaerobic. In other reports, genital mycoplasma were isolated from the placenta. Quinn et al. [29] found *U. urealyticum* related to chorioamnionitis and premature delivery. Kundsin et al. [30] cultured 801 placentae for *U. urealyticum, M. hominis, C. trachomatis,* bacteria and cytomegalovirus. *U. urealyticum* recovery from the placenta was strongly related to birthweight under 2500 g and to a gestational age <36 weeks. There was also a highly significant correlation between the isolation of *U. urealyticum* from the placenta and histologic chorioamnionitis. Placentae were refrigerated in this study but details of the interval between delivery and placental culture was not provided [30]. Embree et al. [31] cultured a total of 554 placentae for the presence of *U. urealyticum* and *M. hominis* and found a significant relationship between the recovery of *U. urealyticum* and *M. hominis* from the placenta and histologic chorioamnionitis. The isolation of *U. urealyticum* was also significantly associated with prematurity and low birthweight. Bacteria were not cultured. Although in some studies, the possible influence of demographic factors and obstetrical events on the results were mentioned, the influence of these potentially confounding factors on the results had not been sufficiently studied in most of these earlier reports.

Hillier et al. [28] used a case-control design to study the relationship between chorioamnionitis, recovery of microorganisms between the fetal membranes, prematurity and bacterial vaginosis. The cases consisted of 56 pregnant women with premature labor before 37 weeks gestation and the controls consisted of 56 pregnant women who delivered at more than 37 weeks gestation without prior signs of premature labor. The cases were further divided into 38 women who delivered before 37 weeks and 18 women who had signs of premature labor but delivered at more than 37 weeks. Microorganisms were recovered between the divided amnion and chorion in 23 (61%) of 38 placentae of women who

Table 5. Microorganisms recovered from the divided chorion and amnion of the placenta among women in preterm labor (cases) and women who delivered at term (controls)

Organisms	Number (%) culture positive for each organism		
	Cases in preterm labor[a]		Term controls
	< 37 Weeks gestation (n = 38)	≥ 37 Weeks gestation (n = 18)	≥ 37 Weeks gestation (n = 56)
U. urealyticum	18 (47%)	3 (17%)	11 (20%)
M. hominis	3 (8%)	2 (11%)	2 (4%)
G. vaginalis	10 (26%)	1 (6%)	3 (5%)
Mobiluncus sp.	4 (11%)	2 (11%)	–
Bacteroides sp.	3 (8%)	–	1 (2%)
Peptostreptococcus sp.	3 (18%)	–	1 (2%)
Streptococci	4 (11%)	1 (6%)	1 (2%)
Lactobacilli	1 (3%)	–	–
Any organism other than *M. hominis* or *U. urealyticum*	17 (45%)	5 (28%)	4 (7%)
Any organism isolated	23 (61%)	4 (28%)	12 (21%)

[a] Women in preterm labor are further stratified as to whether delivery occured at < 37 weeks or at ≥ 37 weeks. Includes women who had at least one episode of preterm labor but who delivered at term. Reproduced with permission of N Engl J Med (1988) 319:972–978

delivered before 37 weeks and from 12 (21%) of 56 placentae of control women ($P < 0.001$, Table 5). *U. urealyticum* was the most common organism isolated from the chorioamnion and *U. urealyticum* isolation from this space was related to prematurity. *U. urealyticum* was isolated from 47% of the premature delivered and from 20% of term delivered placentae ($P < 0.001$). Bacteria (any microorganism other than *M. hominis* or *U. urealyticum*) were isolated from 45% of those who delivered prematurely and only 7% of controls who delivered at term ($P < 0.001$). The majority of bacteria isolated from the membranes were those associated with bacterial vaginosis. Logistic regression analysis was used to control for factors that could otherwise explain the microbiology findings including demographic variables, duration of labor, duration of ruptur of membranes, premature rupture of membranes, and fever in labor. Both positive chorioamnion culture (Odds Ratio 3.8, $P < 0.01$) and chorioamnionitis (Odds Ratio 5.0, $P < 0.001$) were significantly related to prematurity in the multivariate analysis. Bacterial vaginosis diagnosed by Gram stain was also related to a positive placenta culture (Odds Ratio 3.2, $P < 0.006$) and to chorioamnionitis (Odds Ratio 2.6, $P = 0.05$) in the multivariate analysis. A positive chorioamnion culture was highly related to histologic chorioamnionitis in this study (Table 4).

Data from studies of the placentae demonstrate a strong consistent relationship between the isolation of microorganisms from the placenta and histologic chorioamnionitis, with occasional exception [32]. Histologic chorioamnionitis has a well established relationship with premature delivery and recent evidence

confirms a strong relationship between the isolation of microorganisms from the placenta and premature delivery. In some studies, potentially confounding variables such as duration of labor, duration of membrane rupture, premature membrane rupture, and maternal fever have been controlled to add further weight and confidence of a cause and effect relationship between these associations. Microorganisms associated with bacterial vaginosis are commonly isolated from the placenta. Further, bacterial vaginosis has been related both to infection of the chorioamnion and to chorioamnionitis in a multivariate analysis which provided added strength to these associations.

Summary

Antepartum bacterial vaginosis in pregnancy has been related to premature delivery, the recovery of microorganisms from amniotic fluid of women in premature labor with intact membranes, to histologic chorioamnionitis and to the recovery of microorganisms from the placenta or membranes. Microorganisms associated with bacterial vaginosis are commonly recovered from the amniotic fluid and chorioamnion of patients who deliver prematurely. In addition, bacterial vaginosis is associated with maternal infectious morbidity during labor and in the postpartum period [5, 7, 9, 33, 34].

Very little is known of the pathophysiologic mechanisms by which bacterial vaginosis may cause preterm labor and/or premature rupture of the membranes. However, it is of interest to speculate on possible mechanisms. The high concentration of potentially pathogenic microorganisms in the vagina and cervix of pregnant women with bacterial vaginosis may increase the possibility of an ascending infection via the cervix, decidua, fetal membranes, maternal placenta and amniotic fluid. Some of the bacteria associated with bacterial vaginosis such as *Bacteroides sp.* are particularly virulent.

Certain bacteria produce enzymes that potentially could affect the fetal membranes or maternal deciduae. *Bacteroides sp.* and group B streptococcus produce proteases [35]. Protease enzymes reduce the chorioamniotic membrane strength in vitro [36]. It is even possible that a high concentration of bacteria in the lower genital tract could produce enough proteases to weaken the fetal membrane strength causing premature rupture of the membranes. Bacterial lipases could also produce tissue injury. Schwarz et al. [37] demonstrated that lysosomes within fetal membrane cells contain phospholipase A_2 in high concentrations. Phospholipase A_2 is a precursor of prostaglandin synthesis and the destruction of lysosomes within deciduae or chorioamnion cells may induce prostaglandin synthesis resulting in uterine contractions. Bejar et al. [38] found a high rate of phospholipase A_2 production by *Bacteroides sp.*, anaerobic streptococci, *Fusobacterium sp.*, and *G. vaginalis*. Benett et al. [39] demonstrated that bacterial products of group B streptococci, viridans streptococci, *Escherichia coli* and *Bacteroides fragilis* but not of *Lactobacillus sp.* increase the synthesis of prostaglandins in the membranes. Thus, selected bacteria, including some closely related to bacterial vaginosis may play a role in the initiation of uterine contractions by stimulating prostaglandin synthesis.

In an alternative mechanism, either the release of prostaglandin in the membrane or uterine contraction could cause microbreaks of the membrane that allow bacterial colonization of the membrane. Membrane colonization would be particularly likely if a high concentration of virulent bacteria were present in the vagina such as occurs with bacterial vaginosis. Membrane infection produces chorioamnionitis and if unchecked in turn causes positive amniotic fluid cultures.

Additionally, the inflammatory response itself may initiate uterine contractions or enhance the myometrial stimulation of an already contracting uterus. Local inflammation in response to infection in the chorioamnion or deciduae may also cause the destruction of lysosomes and cell disruption within the fetal membranes. The combined effect of the inflammatory response on the uterine muscle and fetal membranes may further explain the associations found between infection and events leading to premature birth.

At this point controlled studies are in order to demonstrate whether or not treatment of bacterial vaginosis and other genital infections during pregnancy will reduce the prematurity rate. Tetracycline given to abacteriuric women led to reduced prematurity [40]. Studies by McGregor et al. [41] and McCormack et al. [42] showed a promising effect of erythromycin treatment given to patients with *U. urealyticum* in the reduction of prematurity. However, in a recent collaborative study, erythromycin administered to over 1000 patients with *U. urealyticum* (but not *C. trachomatis* or group B streptococci) had no effect on the rate of prematurity or birthweight [43]. Thus, one needs to be cautious before concluding that effective therapy of bacterial vaginosis would necessarily reduce prematurity without well designed controlled studies. None of the antibiotics have been specifically given to treat bacterial vaginosis nor were any of the antibiotics expected to be particularly effective against bacterial vaginosis in these studies. Treatment of bacterial vaginosis with effective antibiotics versus placebo is necessary to further clarify the role of bacterial vaginosis in prematurity, premature rupture of membranes, and postpartum endometritis.

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