

## Association of Viridans Group Streptococci from Pregnant Women with Bacterial Vaginosis and Upper Genital Tract Infection

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The prevalence and role of viridans group streptococci in the female genital tract have not been well described. In this study of 482 pregnant women, 147 (30%) were culture positive for viridans group streptococci. Of 392 women with predominant *Lactobacillus* morphotypes by Gram stain (normal), 110 (28%) were colonized with viridans group streptococci, compared with 37 (41%) of 90 women with bacterial vaginosis (BV) ( $P = 0.02$ ). To determine whether any species were associated with BV, 177 consecutively isolated viridans group streptococci from the vagina were identified to the species level by using the Facklam scheme. The most frequently isolated species from the vagina was *Streptococcus intermedius* (13%), followed by *Streptococcus acidominimus* (6%), *Streptococcus constellatus* (5%), *Streptococcus sanguis* II (4%), *Streptococcus mitis* (2%), *Streptococcus salivarius* (2%), *Streptococcus morbillorum* (2%), *Streptococcus sanguis* I (1%), *Streptococcus mutans* (0.2%), and *Streptococcus uberis* (0.2%) with an average of 1.2 species per woman. The distribution of the species among women with BV compared with normal women was not significantly different, with the exception of two species which were associated with BV: *S. acidominimus* (18% versus 3%,  $P < 0.001$ ) and *S. morbillorum* (6% versus 0.7%,  $P = 0.005$ ). Amniotic fluid and placenta cultures yielded 54 isolates: *S. sanguis* II (13 isolates), *S. acidominimus* (9 isolates), *S. intermedius* (10 isolates), *S. constellatus* (3 isolates), *S. mitis* (4 isolates), *S. sanguis* I (4 isolates), *S. morbillorum* (5 isolates), *S. mutans* (2 isolates), *S. uberis* (1 isolate), mannitol-positive *S. intermedius* (1 isolate), and 2 isolates which were not classified. The distribution of species isolated from the upper genital tract was not a reflection of the distribution in the lower genital tract. Dextran-producing species of viridans group streptococci may have a greater pathogenic potential in the placenta than the non-dextran-producing species.

Viridans group streptococci are facultative gram-positive cocci and are characteristically alpha- or nonhemolytic on sheep blood agar. They can be isolated from the nasopharynx (14), the throat (14, 25), the surface of teeth (19), or the gingival crevice (19) and are detected as part of the flora of the gastrointestinal (25) and urogenital (8, 27) tracts. Viridans group streptococci are associated with endocarditis (8, 23) and infections of the central nervous (8, 23), respiratory (8), and musculoskeletal systems (23).

Published studies of the vaginal flora report a wide range of colonization rates for the viridans group streptococci (3, 4, 6, 11, 12, 17, 22, 35). Levison et al. reported that 52% of 25 women were colonized with alpha- or nonhemolytic streptococci (16), while Sautter and Brown reported that only 10% of 65 sequential specimens collected from 7 women yielded viridans group streptococci (29). More recently, vaginal screening of 270 women yielded viridans group streptococci from 14% of the women (6). The frequency of viridans group streptococci in the flora of women with bacterial vaginosis (BV) or normal (*Lactobacillus*-predominant) flora has not been reported in published vaginal flora studies (24, 31, 36).

Viridans group streptococci have been isolated from the amniotic fluid of women with clinical amnionitis with (20) and without (21, 37) ruptured placental membranes, from fetal membranes (1, 34), and from the subchorionic fibrin of the placenta (1). While viridans group streptococci can be recovered from sterile genital tract sites, their role as primary pathogens is unclear since they are usually present as part of mixed aerobic and anaerobic infections.

In these studies, the isolates have rarely been identified to

the species level and no attempt has been made to correlate the species of viridans group streptococci in the vagina with those isolated from upper genital tract infections. The objective of this study was to determine the frequency of viridans group streptococci in a large population of pregnant women with normal vaginal flora or with BV and to determine whether any species of viridans group streptococci was associated with BV. Viridans group streptococci isolated from upper genital tract sites were also identified to the species level, and their relative frequency was compared to the species present in the vagina.

### MATERIALS AND METHODS

**Patient population.** A total of 482 pregnant women seeking prenatal care at the University of Washington were enrolled, and cultures were obtained at 23 to 26 weeks gestation. In addition, cultures were obtained from 121 of these women at a later prenatal visit. Cultures were obtained from 134 of the women at delivery. Cultures of amniotic fluid and placenta were obtained from these women and from a second group which included women undergoing cesarean section who had at least 4 h of labor or rupture of the membrane.

**Specimen collection.** Before routine patient culturing, a smear for Gram stain evaluation was obtained from the vagina by rolling a swab on the posterior fornix. The Gram stains were evaluated and assigned to one of two designations according to the method of Spiegel et al. (32): (i) normal (predominance of *Lactobacillus* morphotypes) or (ii) BV (decreased *Lactobacillus* morphotypes with increased numbers of small gram-negative rods, small gram-positive rods, and gram-positive cocci).

Enrollment and prenatal cultures of the women were obtained by instilling 3.5 ml of a sterile balanced salt solution

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TABLE 1. Frequency of viridans group streptococci throughout the pregnancy

Visit type	Gram smear interpretation <sup>a</sup>			<i>P</i> <sup>b</sup>
	Total	Normal	BV	
Enrollment	147/482 (30)	110/392 (28)	37/90 (41)	0.02
Repeat	42/121 (35)	28/94 (30)	14/27 (52)	0.06
Delivery	59/134 (44)	48/112 (43)	11/22 (50)	0.70

<sup>a</sup> No. positive/total no. of women tested (percent positive). The chi-squares for trend for normal, BV, and total women tested were  $P = 0.005$ ,  $P = 0.33$ , and  $P = 0.003$ , respectively.

<sup>b</sup> *P* value for normal versus women with BV at each visit.

(18) into the vagina and were transported to the laboratory. Cultures from women in labor and at time of delivery were collected by rolling a sterile swab across the vaginal wall. The swab was placed into an anaerobic transport tube (Port-A-Cul; BBL Microbiology Systems, Cockeysville, Md.) and transported to the laboratory.

Amniotic fluid and decidual specimens were collected from women in the cesarean section group at the time of surgery. The amniotic fluid was transported to the laboratory in a syringe from which the air had been evacuated. The decidual samples for culture were obtained by direct swabbing of the exposed maternal bed surface after delivery of the placenta. The swab was placed in an anaerobic transport tube for transport to the laboratory. For placental membrane (chorioamnion) cultures, from both groups of women, the placenta and membranes were spread on a clean surface and the chorion and amnion were peeled apart. The exposed surface was cultured at least 4 cm from the site of rupture, using sterile cotton-tipped swabs, and was inoculated directly onto culture media (see below) for immediate incubation. Culture results from the chorioamnion and the decidua have been combined for analysis.

**Culture conditions.** Specimens were inoculated onto heart infusion agar (Difco Laboratories, Detroit, Mich.) supplemented with 5% sheep blood and onto brucella agar (GIBCO Diagnostics, Madison, Wis.) supplemented with 5% sheep blood, 1% hemin, and vitamin K (10 µg/ml). In addition, a chopped-meat carbohydrate broth was used for placenta and amniotic fluid cultures. The blood agar plate was incubated in an aerobic atmosphere containing 5% CO<sub>2</sub> at 37°C for a minimum of 48 h, and the brucella agar and broth were incubated in anaerobic conditions with 85% N<sub>2</sub>-10% H<sub>2</sub>-5% CO<sub>2</sub> at 37°C for a minimum of 96 h.

**Bacterial characterization.** All isolates of alpha- and non-hemolytic streptococci in this study were evaluated and identified by Gram stain reaction, colony morphology, and catalase production and were identified to the species level by the Facklam method (8). Acid formation from lactose, mannitol, raffinose, sorbitol, and inulin broths; hydrolysis of arginine, esculin, and hippurate (15); urease production (28); litmus milk; bile-esculin reaction; and growth in 6.5% NaCl were determined after incubation at 37°C for 5 days.

## RESULTS

Of the 482 women enrolled, 392 were characterized as normal and 90 were characterized as having BV. Of the women enrolled, 147 were colonized with viridans group streptococci (Table 1). A total of 177 isolates of viridans group streptococci were obtained, with a mean of 1.2 isolates per woman. Of 392 women having a normal flora, 110 (28%) yielded viridans group streptococci, compared with 37

(41%) of 90 women with bacterial vaginosis ( $P = 0.02$ ). From the time of enrollment to the time of delivery, the frequency of viridans group streptococci increased significantly (30% versus 44%,  $P = 0.003$ , chi-square for trend). While both groups of women had an increase in the frequency of viridans group streptococci, it was significant only in the normal group ( $P = 0.005$ , chi-square for trend). By the time of delivery, the frequency of viridans group streptococci was not significantly different for women with BV compared with women with normal flora (50% versus 43%,  $P = 0.7$ ). The fact that viridans group streptococci were isolated from half of women with BV and 28 to 43% of normal women during pregnancy implies that these microorganisms are part of the normal vaginal flora of pregnant women.

The frequency of each species among all women is shown in Table 2. *Streptococcus intermedius* was the most common isolate but was not significantly associated with BV ( $P = 0.20$ ). Both *Streptococcus acidominimus* and *Streptococcus morbillorum* were significantly more prevalent in women with BV ( $P < 0.001$  and  $P = 0.005$ , respectively). Dextran-producing species of viridans group streptococci, including *Streptococcus sanguis* II, *S. sanguis* I, and *Streptococcus mutans*, although common in the oral cavity, were relatively rare in the vagina (0.2 to 4.0%).

From the amniotic fluid and placenta, there were 54 isolates of viridans group streptococci (Table 3). These isolates were from the women in either the cohort group (the group from which the vaginal isolates were obtained) or the group of women undergoing cesarean section. *S. sanguis* II was the most common isolate, accounting for 24% of the total isolates, followed by *S. intermedius* (19%), *S. acidominimus* (17%), *S. morbillorum* (9%), *S. sanguis* I (7%), *Streptococcus mitis* (7%), *Streptococcus constellatus* (5%), *S. mutans* (4%), unclassified viridans group streptococci (4%), mannitol-positive *S. intermedius* (2%), and *Streptococcus uberis* (2%). The two unclassified isolates from a single placental culture could not be identified by using the Facklam key.

If all species of viridans group streptococci are equally likely to cause upper genital tract infections, one would expect the frequency of viridans group streptococcal species in the upper genital tract to be a reflection of the frequency of the species isolated from the lower genital tract. When the isolation rate of viridans group streptococci from sterile sites was compared with the vaginal rate of isolation, there were

TABLE 2. Frequency of each species of viridans group streptococci among pregnant women

Streptococcus species	Gram smear interpretation (no. positive [%])			<i>P</i> <sup>a</sup>
	Total (n = 482) <sup>b</sup>	Normal (n = 392)	BV (n = 90)	
<i>S. intermedius</i>	64 (13)	48 (12)	16 (18)	0.2
<i>S. acidominimus</i>	29 (6)	13 (3)	16 (18)	<0.001
<i>S. constellatus</i>	26 (5)	25 (6)	1 (1)	0.08
<i>S. sanguis</i> II	21 (4)	15 (4)	6 (7)	0.37
<i>S. mitis</i>	11 (2)	8 (2)	3 (3)	0.73
<i>S. salivarius</i>	10 (2)	7 (2)	3 (3)	0.60
<i>S. morbillorum</i>	8 (2)	3 (0.7)	5 (6)	0.005
<i>S. sanguis</i> I	6 (1)	3 (0.7)	3 (3)	0.15
<i>S. mutans</i>	1 (0.2)	0 (0)	1 (1)	
<i>S. uberis</i>	1 (0.2)	1 (0.3)	0 (0)	

<sup>a</sup> Statistical test for normal compared with women with BV.

<sup>b</sup> A total of 22 women (12 normal and 10 with BV) had more than one species of viridans group streptococci.

four species which had an apparent excess isolation rate from the sterile sites: *S. sanguis* II (24% versus 12%), *S. sanguis* I (7% versus 3%), *S. mutans* (4% versus 0.5%), and *S. morbillorum* (9% versus 5%). *S. sanguis* II was the only isolate which was recovered at a significantly higher frequency from sterile sites than from the vagina ( $P = 0.05$ ).

### DISCUSSION

In this study, the frequency of viridans group streptococci in pregnant women was 30%, with a range of 28% in women with normal flora to 41% in women with BV. The relative frequency of colonization increased during the pregnancy (Table 1). *S. intermedius* was the most frequently isolated species from the vagina, followed by *S. acidominimus*, *S. constellatus*, and the oral species of viridans group streptococci. Studies which have examined the distribution of viridans group streptococci from urogenital and other body sites have also shown *S. intermedius* to be a common isolate, accounting for 17 to 60% of all viridans group streptococci isolated from clinical specimens (8, 26, 27). In these studies, all genital sites were grouped together, and in two of the studies (8, 26), urinary isolates were included. In a study of vaginal cultures from 167 pregnant women, Haffar et al. found that *S. sanguis* II was the most frequently isolated species (53%), followed by *S. intermedius* (28%). They did not report isolation of *S. acidominimus*, *S. constellatus*, or *S. morbillorum* (12). Both *S. morbillorum* and *S. acidominimus* were associated with BV in our study. While the lack of *S. acidominimus* and *S. morbillorum* in the Haffar et al. study may be due to a lower prevalence of BV in their population, it is difficult to ascribe the lack of *S. constellatus* to population differences. The medium used by Haffar et al. for initial discovery contained 8  $\mu$ g of gentamicin per ml, a level known to inhibit many strains of viridans group streptococci (5).

The only significant difference in the distribution of the species of viridans group streptococci among women with normal vaginal flora compared with women with BV was the frequency of *S. acidominimus* (3% versus 18%,  $P < 0.001$ ) and *S. morbillorum* (0.7% versus 6%,  $P = 0.005$ ), which were isolated more often from women with BV. Little has been written about these two organisms because of their rare occurrence in clinical specimens. *S. morbillorum*, an anaerobic or aerotolerant streptococcus, has been isolated from intestinal contents (13) and a wide range of clinical specimens at a low rate of isolation (8). The habitat of *S. acidominimus* is reported to be the bovine vagina, the skin of calves, and raw milk (13). Of 1,227 viridans group streptococci isolated from clinical specimens, Facklam identified 5 *S. acidominimus*, 4 of these from urogenital sites, and 46 *S. morbillorum* isolates (8). In a study of 1,391 extrarespiratory isolates of viridans group streptococci at the New York Hospital (26), only 3 *S. acidominimus* and 9 *S. morbillorum* were identified. Comparing the rare frequency of isolation of *S. acidominimus* and *S. morbillorum* from clinical specimens with our observations of a high frequency of isolation in women with BV suggests that these species may be enhanced by the presence of an anaerobic microflora characteristic of BV.

The mannitol-positive variant of *S. intermedius* (9) was described in studies by Ruoff et al. as being the most frequently isolated species from urine (27). Ball and Parker reported that 13 (4%) of 346 *Streptococcus milleri* (*S. intermedius* and *S. constellatus*) isolates were mannitol positive. The majority of these isolates were from vaginal cultures (2).

TABLE 3. Relative frequency of viridans group streptococci isolated from the placenta and amniotic fluid compared with their frequency in the vagina

<i>Streptococcus</i> species	No. of isolates from site:		Frequency (%) of isolates from:	
	Placenta	Amniotic fluid	Sterile sites	Vagina
<i>S. intermedius</i>	8	2	10 (19)	64 (36)
<i>S. acidominimus</i>	6	3	9 (17)	29 (16)
<i>S. constellatus</i>	1	2	3 (5)	26 (15)
<i>S. sanguis</i> II	10	3	13 (24)	21 (12)
<i>S. mitis</i>	2	2	4 (7)	11 (6)
<i>S. salivarius</i>	0	0	0 (0)	10 (6)
<i>S. morbillorum</i>	2	3	5 (9)	8 (5)
<i>S. sanguis</i> I	3	1	4 (7)	6 (3)
<i>S. mutans</i>	2	0	2 (4)	1 (0.5)
Unclassified	2	0	2 (4)	0
Mannitol-positive variant of <i>S. intermedius</i>	1	0	1 (2)	0
<i>S. uberis</i>	1	0	1 (2)	1 (0.5)

Mannitol-positive isolates have also been recovered from two cases of neonatal sepsis (7). From our 177 consecutive viridans group streptococcus vaginal isolates from normal pregnant women, none of the 90 *S. intermedius* and *S. constellatus* (*S. milleri*) isolates were mannitol positive. Our failure to isolate this strain from the vagina is not surprising, since the mannitol-positive variant accounts for a small proportion of the total *S. milleri* group. However, one mannitol-positive isolate was recovered from the placental membranes of one patient.

*S. sanguis* II was the most frequently observed species from placenta and amniotic fluid, followed by *S. intermedius*, *S. acidominimus*, *S. morbillorum*, *S. sanguis* I, *S. mitis*, *S. constellatus*, *S. mutans*, unclassified viridans group streptococci, mannitol-positive *S. intermedius*, and *S. uberis*. In two separate studies of amniotic fluid, 4 of 18 women with intact fetal membranes and 5 of 13 women with ruptured membranes were colonized with viridans group streptococci, but the streptococci were never recovered in pure culture (20, 21). A study of the subchorionic fibrin of the placenta (1) reported 4 of 224 placentas were colonized with viridans group streptococci, one of which was the only isolate. In these studies, viridans group streptococci from sterile sites were not identified to the species level, nor was the frequency of viridans group streptococci in the vagina and sterile sites compared.

Studies that have identified the viridans group streptococci from patients with endocarditis have found that *S. sanguis* II accounts for a larger percentage of endocarditis infections than does *S. intermedius*. Parker and Ball observed in a study of 317 patients with viridans group streptococcus-associated endocarditis that *S. sanguis* II, *S. sanguis* I, *S. mitis*, and *S. mutans* were all isolated more frequently (>10%) than *S. intermedius* and the other viridans group streptococcus species (<10%) (23). A more recent study by Sussman et al. of 36 patients with endocarditis caused by viridans group streptococci also found *S. sanguis* I and *S. sanguis* II to be in higher frequency than *S. intermedius* (33). These three organisms are more likely to produce dextrans than are the other species of viridans group streptococci (8). The role of dextran production by viridans group streptococci as a virulence factor in subacute bacterial endocarditis was studied by Scheld et al. (30), who found that the amount of dextran produced directly corre-

lated with the ability of the organisms to adhere to fibrin and fibrin plus platelets.

In this study, we found that three dextran-producing viridans group streptococci (*S. sanguis* I, *S. sanguis* II, and *S. mutans*) were recovered more frequently from the sterile sites than from the vagina (35% versus 16%,  $P = 0.004$ ). The placenta, which has a high fibrin content (10), yielded more dextran-producing species than did vaginal secretions (52% versus 18%,  $P = 0.001$ ) or amniotic fluid (52% versus 13%,  $P = 0.12$ ). This study suggests that the subchorionic fibrin of the placenta, like the platelet-fibrin deposits on heart valves, may be susceptible to infection by the dextran-producing viridans group streptococcal species.

Our data support the concept of viridans group streptococci being part of the normal vaginal flora. In this study, we demonstrate that the overall frequency of viridans group streptococci in the genital tract of pregnant women is 30% at 23 to 26 weeks gestation and 44% at the time of delivery. Early in pregnancy, women with BV are more likely to be colonized with viridans group streptococci than are women who have a normal microflora. *S. acidominimus*, previously considered to be a relatively rare isolate, was detected in 6% of all pregnant women and was associated with a diagnosis of BV. The dextran-producing species of viridans group streptococci were more frequently isolated from the placenta than *S. intermedius*, which was the most frequent vaginal isolate. However, some dextran-producing species appear to be able to preferentially colonize or infect the fibrin-rich tissues of the placenta.

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