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Genital Flora in Pregnancy and Its Association with Intrauterine Growth Retardation

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A study of risk factors for intrauterine growth retardation (IUGR) was conducted among a cohort of 13,914 pregnant women enrolled in the multicenter Vaginal Infections and Prematurity Study. From 23 through 26 weeks of gestational age, cultures of specimens from the vagina and cervix were done for group B streptococci, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Candida albicans*, *Gardnerella vaginalis*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, and anaerobic gram-negative rods belonging to the genera *Bacteroides*, *Porphyromonas*, and *Prevotella*. Newborns who were small for their gestational age were delivered by 1,251 women, and infants of the appropriate weight for their gestational age were delivered by 10,332 women. When controlling for ethnicity and smoking and excluding women treated with antibiotics, the Mantel-Haenszel adjusted relative risk of IUGR was 1.16 for *Bacteroides*, *Prevotella*, and *Porphyromonas* spp. (95% confidence interval [95% CI], 1.01 to 1.33), 1.16 for *M. hominis* (95% CI, 1.04 to 1.29), 1.20 for *U. urealyticum* (95% CI, 1.05 to 1.38), and 1.22 for *T. vaginalis* (95% CI, 1.05 to 1.42). There was also a strong and significant trend for an increasing risk of IUGR with the number of these four microbes recovered. Among women colonized with all four isolates, the adjusted odds ratio of IUGR was 1.79 (95% CI, 1.27 to 2.52) in comparison with women not colonized with any of these microorganisms. Group B streptococci, *N. gonorrhoeae*, *C. trachomatis*, and *C. albicans* were not significantly associated with IUGR. These results suggest that infection is associated with some cases of IUGR and that specific microorganisms, alone or in combination, are involved. Since genital isolates are highly correlated with each other, the relative contribution of each microbe is difficult to determine.

Low birth weight remains a major public health issue (19), because 10.2% of newborns weighing less than 2,500 g die before reaching 1 year of age, whereas 0.5% of infants of normal birth weight die before reaching 1 year of age (22). Although prematurity is frequently the reason for low birth weight, intrauterine growth retardation (IUGR) contributes to an additional one-third of all cases (6). At any given gestational age, a birth weight in the lower 10th percentile is predictive of an adverse outcome (36), underscoring the prognostic significance of fetal growth independent of prematurity. The currently accepted criterion for defining IUGR relies on a comparison of birth weight with a standard distribution stratified by gestational age (12, 32). Babies who are small for gestational age (SGA) are thus considered to be growth retarded, although some have raised strong arguments against this equivalence of terms (2). For the purpose of this report we considered SGA to be synonymous with IUGR.

Impaired fetal growth has been associated with genetic factors, reduced maternal blood flow, poor nutrition, smoking, and possibly, caffeine intake (10, 19, 29, 31). The classical congenital infections with rubella virus and cytomegalovirus are also known to cause IUGR, but their rarity is such that the populationwide impact on birth weight is minimal (18). The effects of more common genital microbes on fetal growth have not been studied extensively. Several reports have focused on the relationship between birth weight and the genital isolation of *Ureaplasma urealyticum* (4, 16, 21), *Chlamydia trachomatis* (14, 24, 35), *Bacteroides* spp. (13, 25), and *Neisseria gonorrhoeae* (7, 8). However, few attempts were made to distinguish between the association with prematurity versus that with growth retardation. Polk et al. (28) have recently reported that in a group of predominantly black, high-risk pregnant women, those infected with *C. trachomatis* and *Candida albicans* were at higher risk of giving birth to SGA babies, even after adjusting for other factors associated with fetal growth. The existing knowledge on the association between genital flora and IUGR is therefore limited. Furthermore, the interaction between different isolates has never been explored. A better understanding of the possible impact of genital infections on fetal growth could eventually lead to clinical interventions, such as the identification and antibiotic treatment of pregnant women at high risk for infection-related IUGR. In the study described here we examined the association between the

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genital flora in the second trimester and the occurrence of IUGR in a large and diverse cohort of pregnant women.

MATERIALS AND METHODS

From 1984 to 1989, pregnant women from 23 through 26 weeks of gestational age were enrolled in the study during a visit to a prenatal clinic. These women agreed to participate in the Vaginal Infections and Prematurity Study, which is supported by the National Institute of Child Health and Human Development and the National Institute of Allergy and Infectious Diseases. Subjects were recruited at the following seven centers: Columbia University and Harlem Hospital Center, New York, N.Y.; Louisiana State University Medical Center and Tulane University Medical Center, New Orleans; University of Oklahoma Health Sciences Center, Oklahoma City; University of Texas Health Sciences Center, San Antonio; and University of Washington Medical Center, Seattle. The standardized protocol included a personal interview, a physical examination, clinical and laboratory processing of genital specimens, and abstraction of the hospital chart, including the delivery record. Women were eligible for the study if they were older than 15 years, did not have chronic medical conditions (hypertension or kidney or heart disease requiring medication), or obstetric conditions associated with preterm delivery (erythroblastosis, multiple gestations, cervical cerclage). Women who had been taking antibiotics within 2 weeks prior to enrollment and those who used tocolytic compounds or steroids during the current pregnancy were excluded.

At the time of enrollment, genital specimens were taken and processed according to standard microbiologic methods that have been described extensively elsewhere (15). Briefly, cervical specimens were inoculated onto cycloheximide-treated McCoy cells (34) for the identification of *C. trachomatis* with fluorescent monoclonal antibody and onto Thayer-Martin and chocolate agar for the isolation of *N. gonorrhoeae*. A vaginal swab was inoculated into Diamond's medium for the isolation of *Trichomonas vaginalis* (11), which was identified by microscopically observing motile forms on wet mounts. A vaginal wash suspension obtained with sterile, prereduced saline solution was inoculated onto sheep blood agar and into a selective broth for the recovery of group B streptococci, Sabouraud agar for the recovery of *C. albicans*, human bilayer Tween agar for the identification of *Gardnerella vaginalis* and *Lactobacillus* spp. (37), and Shepard's A7B agar (33) and two selective broth media for the recovery of *U. urealyticum* and *Mycoplasma hominis*. For the isolation of anaerobes, the vaginal wash suspension was inoculated onto prereduced brucella agar or a Centers for Disease Control and Prevention anaerobic blood agar plate and a laked blood kanamycin agar plate, and the plates were incubated in an anaerobic atmosphere. Identification of anaerobes to the genus level was performed by standard methods. Gram-negative rods belonging to the genera *Bacteroides*, *Porphyromonas*, and *Prevotella* according to the current nomenclature were not differentiated and are thus presented as a single group. Specimens were reported to be positive for anaerobes only if they were found beyond the second quadrant on the streak plate.

Bacterial vaginosis was diagnosed by previously described criteria (15, 26). Briefly, vaginal smears were heat fixed, Gram stained, and evaluated for the following bacterial morphotypes: large gram-positive rods (lactobacilli), small gram-negative or variable rods (*G. vaginalis*, *Bacteroides* spp.), or curved rods (*Mobiluncus* spp.). The morphotypes were quantitated, weighed, and assigned a score of from 0 to 10 to describe the severity of the abnormal vaginal flora. Women with a score of 7 or more accompanied by a vaginal pH of greater than 4.5 were categorized as having bacterial vaginosis. Other criteria for bacterial vaginosis were not considered in the study design because of their presumed subjectivity.

Intrauterine growth was assessed by comparing the weights of the newborns with a previously published nomogram of sex-specific birth weights by gestational age (39). This nomogram was derived from a large population-based birth registry in California. SGA babies (those whose birth weights were below the 10th percentile of that reference population) were categorized as growth retarded. Babies whose birth weights were above the 90th percentile were excluded from the analyses since their birth weights might have been associated with a different group of risk factors. The remaining infants had an appropriate weight for gestational age (AGA) and were considered to have had normal intrauterine growth.

Preliminary analyses were performed by using two by k cross tabulations for the calculation of risk ratios and chi-square statistics for homogeneity and trend (9). Adjustments for confounding variables were done by using Mantel-Haenszel stratification (23) and unconditional logistic regression (5). The 95% confidence intervals (95% CIs) for the point estimates of relative risk were obtained by the Cornfield method or were verified by the likelihood ratio tests. The criteria for including a variable in the adjustment procedures were based on the magnitude of the change in the risk ratio estimates. Potential confounders considered in the analyses included the mother's age, ethnicity, marital status, gravidity, smoking, alcohol intake, income, education, pregnancy-induced hypertension, and Quetelet index before pregnancy (weight [in kilograms]/height [in square centimeters]).

RESULTS

From November 1984 to March 1989, 13,914 women were enrolled in the Vaginal Infection and Prematurity Study. Five percent (n = 629) were lost to follow-up, and for another 5% (n = 657) information was not available to categorize fetal growth. Eight percent of the women gave birth to babies who were large for gestational age (n = 1,045), and they were excluded from further analyses. Of the remaining women, 11% had SGA newborns (n = 1,251) and the remaining had AGA babies (n = 10,332). Table 1 presents the distribution of SGA infants according to various personal and demographic characteristics of the mothers. SGA was associated with younger, unmarried, primigravid, and black women. Those who smoked 3 months prior to or anytime during pregnancy were at higher risk of giving birth to SGA infants. Drinking 1 oz. (28.350 g) or more of alcohol per week was also associated with SGA babies. Finally, SGA was more prevalent in women with a lower Quetelet index and pregnancy-induced hypertension.

Figure 1 presents in ascending order the unadjusted relative risks of IUGR for various components of the genital flora as determined between 23 and 26 weeks of gestation. After adjustments for other risk factors, three species, *M. hominis*, *U. urealyticum*, and *T. vaginalis*, and the group *Bacteroides*, *Prevotella*, and *Porphyromonas* spp. were associated with a small increased risk of IUGR. Table 2 provides the crude and adjusted relative risks of IUGR for the newborns of women colonized with these isolates. Adjusted risk ratios were calculated after controlling for ethnicity and smoking. Further adjustment for other variables, including age and education, did not meaningfully change the observed associations. Between the time of enrollment in the study and delivery of the newborn, some women were prescribed antibiotics for a variety of gynecologic or other conditions. For selected microorgan-

TABLE 1. Frequency of SGA babies among women with different personal characteristics in a cohort of women delivering between 1984 and 1989

Characteristic	No. of women	No. (%) with SGA babies	Chi-square (*P* value)
Total	11,583	1,251 (10.8)	
Maternal age (yr)			
15–19	2,549	312 (12.2)	0.004[a]
20–24	4,202	458 (10.9)	
25–29	2,764	278 (10.1)	
30+	2,065	202 (9.8)	
Missing	3		
Maternal ethnicity			
Black	4,553	628 (13.8)	< 0.001
White	3,632	384 (10.6)	
Hispanic	3,398	239 (7.0)	
Missing	0		
Marital status			
Not married	6,638	806 (12.1)	<0.001
Married	4,934	443 (9.0)	
Missing	11		
Gravidity[b]			
One	3,443	450 (13.1)	<0.001[a]
Two	3,148	310 (9.8)	
Three or more	4,992	491 (9.8)	
Missing	0		
Smoking[c]			
Yes	3,962	568 (14.3)	<0.001
No	7,621	683 (9.0)	
Missing	0		
Alcohol intake[d]			
≥1 once/wk	625	84 (13.4)	0.003[a]
<1 once/wk	2,178	258 (11.8)	
None	8,780	909 (10.4)	
Missing	0		
Pregnancy-induced hypertension			
Yes	326	55 (16.9)	<0.001
No	9,552	1,034 (10.8)	
Missing	1,705		
Prepregnancy Quetelet index (kg/cm^2)			
<20.1	2,781	365 (13.1)	<0.001[a]
20.1–22.3	2,771	302 (10.9)	
22.4–25.6	2,682	270 (10.1)	
>25.6	2,595	243 (9.4)	
Missing	754		
Gestational length (wk)			
≥37	10,328	1,162 (11.3)	<0.001
<37	1,255	89 (7.1)	
Missing	0		

[a] *P* value for the chi-square statistic for trend; otherwise the *P* value is for the generalized chi-square.
[b] Including index pregnancy.
[c] Three months prior to or anytime during pregnancy.
[d] During last 3 months of pregnancy.

isms, women were classified before the analyses as having been prescribed an effective antimicrobial agent or not, depending on the antibiotics they were given. Metronidazole was considered an effective antimicrobial agent for *T. vaginalis*, and ampicillin-amoxicillin, metronidazole, or intravaginal application of triple sulfa (sulfathiazole, sulfacetamide, and sulfabenzamide) were considered effective for *Bacteroides*, *Prevotella*, and *Porphyromonas* spp. Data for women prescribed an antimicrobial agent are presented separately in Table 2 and were excluded from the calculation of adjusted relative risks. Women with positive cultures for the genital mycoplasmas were not stratified by their antimicrobial agent status since we assumed that no antibiotic regimen usually given during pregnancy is effective against these microbes.

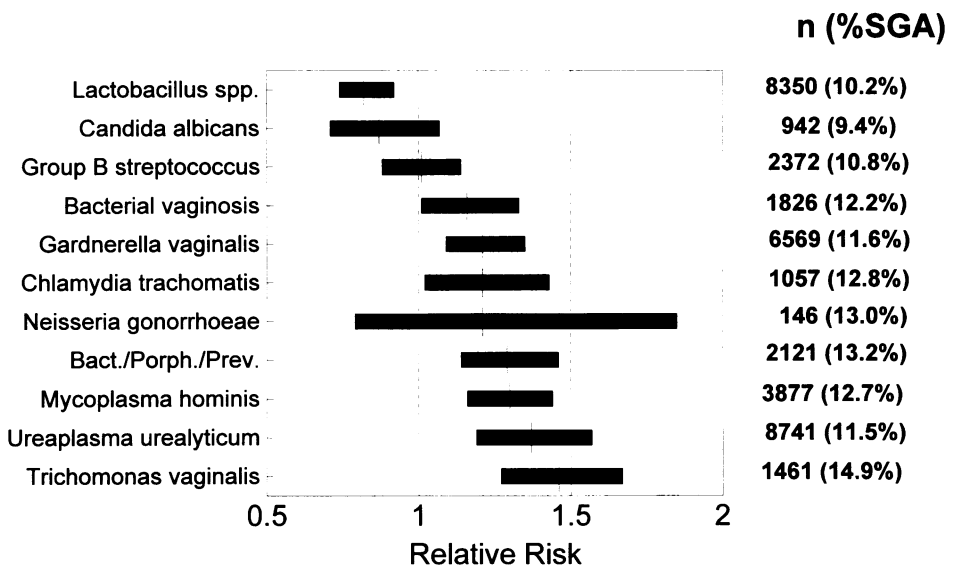

FIG. 1. Unadjusted relative risks (with 95% CIs) of IUGR in association with components of the genital flora of 11,583 pregnant women in the second trimester; *n* is the number of women with positive cultures for a given isolate, and percent SGA is the proportion of women infected with that isolate delivering an SGA infant. Bact./Porph./Prev. designates anaerobic gram-negative rods belonging to the genera *Bacteroides*, *Porphyromonas*, and *Prevotella*.

We also adjusted the association between these genital species and IUGR using multiple logistic regression. When including in a model all four microbes simultaneously and further adjusting for the mother's smoking and ethnicity, the following odds ratios were obtained: 1.14 for *Bacteroides*, *Prevotella*, and *Porphyromonas* spp. (95% CI = 0.98 to 1.33), 1.09 for *M. hominis* (95% CI = 0.95 to 1.25), 1.18 for *U. urealyticum* (95% CI = 1.01 to 1.39), and 1.18 for *T. vaginalis* (95% CI = 1.00 to 1.40).

To understand the effects of multiple species on IUGR, we calculated for each woman the number of different species recovered among *M. hominis*, *U. urealyticum*, *T. vaginalis*, and *Bacteroides*, *Prevotella*, and *Porphyromonas* spp. Figure 2 shows the unadjusted risk ratios of IUGR for the number of isolates recovered. The reference category consists of women whose specimens were culture negative for all four microorganisms (n = 2,041). After controlling for the mother's age, smoking, and ethnicity, the odds ratio of IUGR for each increment of one isolate is 1.13 (95% CI = 1.07 to 1.20) by unconditional logistic regression. This trend is statistically significant ($P < 0.001$), with no departure from linearity ($P > 0.6$). The adjusted odds ratio of IUGR in women from whom all four isolates were

TABLE 2. Unadjusted and adjusted relative risks of IUGR for individual isolates according to antimicrobial agent use[a]

Isolate[a]	No. of women	No. (%) of women with SGA babies	Relative risk		95% CI
			Unadjusted	Adjusted[b]	
Bacteroides, *Prevotella*, and *Porphyromonas* spp.					
POS[c], No Rx	1,764	227 (12.9)	1.26	1.16	1.01–1.33
POS, Rx	357	53 (14.8)	1.45		
NEG	9,390	960 (10.2)	1.00		
M. hominis					
POS	3,877	492 (12.7)	1.30	1.16	1.04–1.29
NEG	7,582	742 (9.8)	1.00		
U. urealyticum					
POS	8,741	1,005 (11.5)	1.37	1.20	1.05–1.38
NEG	2,685	226 (8.4)	1.00		
T. vaginalis					
POS, No Rx	1,281	195 (15.2)	1.49	1.22	1.05–1.42
POS, Rx	180	22 (12.2)	1.20		
NEG	10,041	1,023 (10.2)	1.00		

[a] POS, positive culture at enrollment; NEG, negative culture at enrollment; Rx, the woman was prescribed antibiotics; No Rx, the woman was not prescribed antibiotics.
[b] Adjusted for smoking and ethnicity by the Mantel-Haenszel method for obtaining estimates.
[c] Growth of 3+ to 4+ on the agar plate was considered positive, and growth of 1+ to 2+ was considered negative.

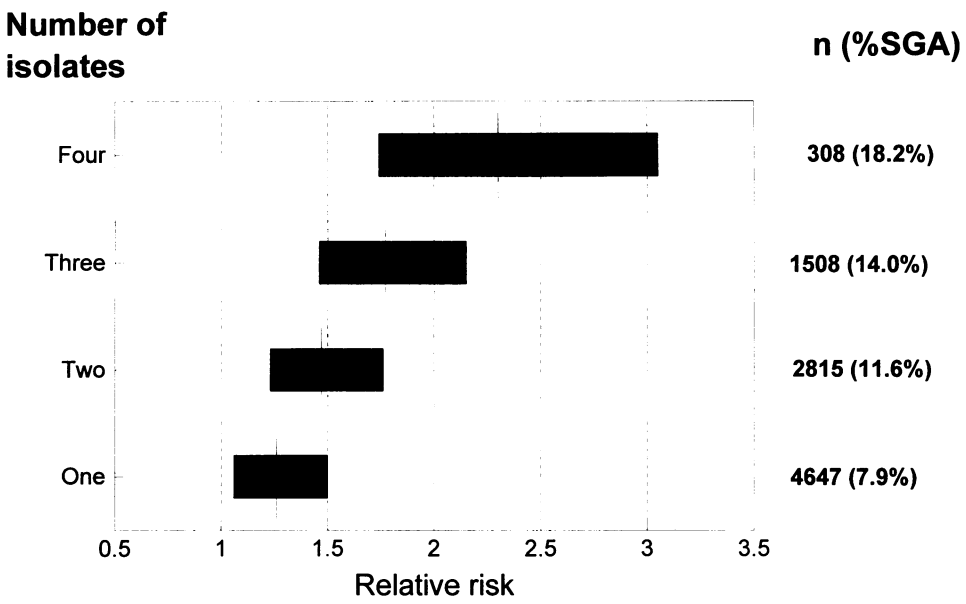

FIG. 2. Unadjusted relative risks (with 95% CIs) of IUGR for the number of the following microbes recovered in the genital flora of pregnant women in the second trimester: *Bacteroides*, *Porphyromonas*, and *Prevotella* spp., *M. hominis*, *U. urealyticum*, and *T. vaginalis*; *n* is the number of women for each level, and percent SGA is the proportion of these women delivering an SGA infant. The risk of SGA was determined by using women not infected with any of the four isolates as the reference group (n = 2,041).

recovered (n = 308) in comparison with women whose specimens were negative for all four isolates on culture was 1.79 (95% CI = 1.27 to 2.52).

The Rohrer ponderal index (17), defined as the ratio of birth weight (in grams) to the cube of the length (in cubic centimeters) × 100, was calculated for each SGA baby. We then sorted the SGA babies into two groups: the nonproportionally growth-retarded group, defined as those below the 10th percentile of the distribution of ponderal indices, and the proportionally growth-retarded group. We then compared the association between selected isolates and IUGR for the two groups of SGA babies (Table 3). Overall, there was no significant difference in the risk ratios between the proportionally or nonproportionally growth-retarded babies.

Small women tend to give birth to small babies (19). Our results confirmed this by showing an inverse association between the mother's Quetelet index and SGA status (Table 1). However, there was no relationship between the Quetelet index and genital flora, so that maternal stature and weight were not confounding the association with IUGR.

Estimation of the gestational age is the most inaccurate of the measurements used to define IUGR. We thus repeated the

TABLE 3. Unadjusted relative risks of proportional and nonproportional IUGR associated with *Bacteroides*, *Prevotella*, and *Porphyromonas* spp., *M. hominis*, *U. urealyticum*, and *T. vaginalis*

Isolate	No. of infants	SGA, N-P[a]		SGA, P[b]		Chi-square (P value)[c]
		No. (%)	Relative risk (95% CI)	No. (%)	Relative risk (95% CI)	
Bacteroides, *Prevotella*, and *Porphyromonas* spp.						
Positive	2,099	69 (3.3)	1.57 (1.20–2.05)	189 (9.0)	1.29 (1.11–1.51)	0.26
Negative	9,284	199 (2.1)		655 (7.1)		
M. hominis						
Positive	3,834	110 (2.9)	1.40 (1.10–1.78)	339 (8.8)	1.33 (1.17–1.52)	0.81
Negative	7,498	157 (2.1)		501 (6.7)		
U. urealyticum						
Positive	8,636	220 (2.5)	1.44 (1.06–1.97)	680 (7.9)	1.35 (1.14–1.59)	0.76
Negative	2,664	48 (1.8)		157 (5.9)		
T. vaginalis						
Positive	1,437	43 (3.0)	1.37 (0.99–1.88)	150 (10.4)	1.51 (1.28–1.78)	0.50
Negative	9,937	226 (2.3)		693 (7.0)		

[a] SGA, N-P, SGA infants, nonproportional IUGR (<10th percentile of ponderal index).
[b] SGA, P, SGA infants, proportional IUGR (>10th percentile of ponderal index).
[c] Chi-square statistic comparing the frequency of exposure among the nonproportionally growth-retarded infant group to that in the proportionally growth-retarded infant group.

analyses of the association between the genital flora and IUGR by restricting the analyses to newborns who had concordant gestational age (within 2 weeks) as determined by two methods, one relying on the date of the last menstrual period and the other relying on the Ballard score on the basis of a physical examination of the infant at birth. The associations between the microorganisms and IUGR remained in the restricted analyses (data not shown). Furthermore, the magnitude of the associations between genital microbes and IUGR among term babies (37 weeks of gestation or more) was similar to that among preterm babies (data not shown).

DISCUSSION

In the present study the traditional risk factors for IUGR, such as smoking, small stature, and hypertension during pregnancy, were consistently associated with SGA status. For example, the unadjusted relative risk of smoking was 1.6, which is in agreement with previous epidemiologic studies of IUGR (19). Our results also showed modest but significant associations between specific microorganisms and SGA babies. The most striking finding is that when modeling the risk according to the number of isolates recovered among the four most significant microbes, *Bacteroides*, *Prevotella*, and *Porphyromonas* spp., *M. hominis*, *U. urealyticum*, and *T. vaginalis*, there was a strong and significant trend even after adjustment for other potential confounders. The risk of IUGR when these four microbes are present is almost twice the risk when all four microbes are not present. This could suggest that some of these microbes have an additive or synergistic impact on fetal growth. The independent contribution of each microorganism and their interaction were difficult to evaluate because of the small number of women infected with each possible combination of these various species. It is possible that smaller concentrations of anaerobes in the vaginal flora might also be associated with an increased risk of IUGR. Unfortunately, the study protocol stipulated that only women infected with higher concentrations of organisms (3+ or 4+ on the streak plate) should be reported as positive, which could underestimate the true association between *Bacteroides*, *Prevotella*, and *Porphyromonas* spp. and SGA status. Furthermore, it could be argued that women treated with ampicillin or triple sulfa drugs should not be excluded from the final estimate because of the low to moderate susceptibilities of vaginal anaerobic gram-negative species to these antibiotics. However, the small number of these women is such that the change in the relative risk estimate is minimal. Finally, because of the relatively low prevalence of pathogens such as *N. gonorrhoeae* and *C. trachomatis*, the study might have been underpowered to rule out a significant impact of these microorganisms on fetal growth.

There have been few other reports on the role of genital infections in IUGR, and our study represents one of the first attempts at specifically addressing this issue. Polk et al. (28) conducted their study of IUGR and preterm delivery in a mostly black, high-risk population. They reported a relative risk of 2.4 (90% CI = 1.32 to 4.18) in women infected with *C. trachomatis* and 1.9 (90% CI = 1.2 to 3.14) in women with a positive culture for *C. albicans*. They found no significant association between IUGR and infection with *T. vaginalis*, *U. urealyticum*, *M. hominis*, and *Bacteroides fragilis*. Those results are quite different from our findings. The differences cannot be explained by the racial distribution of the study populations, since we did not observe their reported association between *C. trachomatis* infection and IUGR when restricting the analyses to black women. In our study there was a weak but consistent negative association between *C. albicans* infection and IUGR among the different ethnic groups. Other studies that reported on infection and IUGR were concerned primarily with outcomes such as low birth weight (regardless of gestational age) and prematurity. Braun et al. (4) found *U. urealyticum* infection to be associated with low birth weight for gestational age, but that observation was not verified in a more recent study (21). Ross et al. (30) even reported higher birth weights for gestational age among Caucasian women colonized with genital mycoplasmas. The resolution of these inconsistent findings may be accomplished with future studies.

We categorized IUGR on the basis of a reference distribution of birth weight by gestational age. As others have pointed out, the weight at birth is not an ideal estimate of the rate of intrauterine growth (1, 2, 38). However, the most widely available definitions of IUGR still rely on these criteria. Furthermore, follow-up studies that used this definition showed that SGA babies have an increased risk of adverse outcomes at birth and in the first 12 months of life (27, 36). The standard but imperfect definition of IUGR that we applied may have wrongly classified small or AGA babies, resulting in an underestimate of the true association between genital flora and IUGR. This is true even when assuming perfect measurement of birth weight and gestational age, which is unlikely. A further problem with the categorization of intrauterine growth on the basis of birth weight is the assessment of the duration of gestation. An estimate of gestational age that relies on the date of the last menstrual period is notoriously imprecise, especially for low-birth-weight infants (20). We examined the extent to which this estimation error may have influenced our findings in several ways. First, the measured associations were essentially unchanged when we restricted the analysis to newborns who had concordant gestational age as determined by the date of the mother's last menstrual period and by examination at birth (Ballard score). Second, our results did not suggest a weaker association between genital flora and IUGR among term babies, i.e., those for whom gestational age is presumably more accurate.

The observed association between genital flora and IUGR could be explained in several ways. One possibility is that the presence of multiple microbes reflects other incompletely measured or unmeasured risk factors, such as illicit drug use. These factors could in turn be associated with impaired fetal growth and could confound the association between infection and IUGR. Alternately, the association between genital flora and IUGR could be causal, as suggested for other conditions like preterm labor and chorioamnionitis. The ways by which these microorganisms could cause IUGR is a matter of speculation. It is unlikely that these common inhabitants of the genital flora directly infect the fetus, as is the case with the rare congenital infections with cytomegalovirus and rubella virus. More probably, they could produce a chronic, low-grade infection of the placenta, maternal decidua, or fetal membranes, impairing placental circulation. By analogy with the classical congenital infections which cause symmetrical IUGR (3), we expected to find a different association between the genital flora and SGA babies whether they were proportionally or nonproportionally growth retarded. Our results did not suggest such a differential effect, which could mean that the pathologic mechanism of IUGR is quite different from that of viral and parasitic congenital infections.

Our study is the first extensive exploration of the possible role of common genital microorganisms as causal agents of IUGR in a large and diverse population of pregnant women. The observed associations were small but significant and were consistent among all groups of women studied. Furthermore, there was evidence that some microorganisms may act syner-

gistically, as suggested by the strong inverse association between fetal growth and the number of different microbes in the genital flora. Finally, these associations persist even after controlling for other known risk factors for IUGR. Given the high prevalence of most of these microorganisms in pregnant women, the overall impact on fetal growth, as measured by the attributable risk in the population, could be substantial. Because of the known adverse prognosis for SGA infants, these results, if confirmed, might justify the consideration of antibiotic treatment trials in high-risk subgroups of pregnant women. The contribution of specific microorganisms, however, remains unclear and would need to be studied more extensively.

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