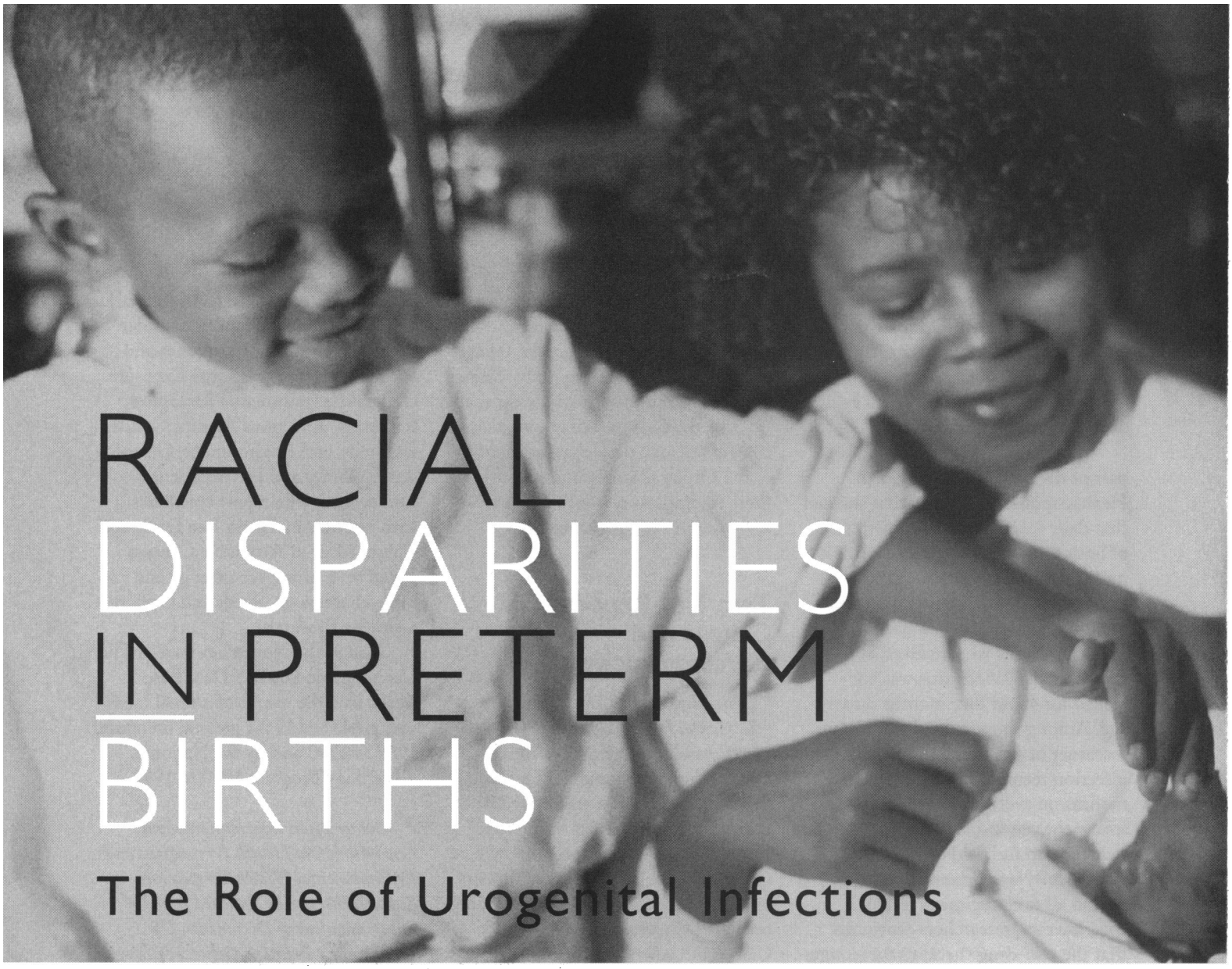


RACIAL DISPARITIES IN PRETERM BIRTHS

The Role of Urogenital Infections

Photo by Heidi Als

Kevin Fiscella, MD

Despite large reductions in overall infant mortality, the black-white gap in infant mortality has risen significantly over the past 50 years.[1] Nearly two-thirds of this gap in infant mortality is attributable to a dramatically higher rate of preterm births among black women.[2] In 1990, the rate of preterm births, defined as birth before 37 weeks gestation, was more than twice as high among black women as white women, while the rate of very preterm birth, defined as birth before 32 weeks gestation, was more than three times as high.[3]

Because the terms "race," "black," and "white" are commonly used in national birth data and in research, these terms will be employed throughout this review. However, the term "race" is used here primarily as a social convention and refers to self-identification with a particular socially defined group. The term "black" encompasses many ethnic groups. Unfortunately, research typically fail to distinguish between those who are American-born, Caribbean-born, and African-born despite the fact that each group has many different cultural heritages and despite the fact that rates of preterm birth are higher for American-born blacks than for those born outside the United States.[4,5]

Causes of the Racial Gap in Preterm Birth Rates

The causes of the racial gap in preterm births are poorly understood. Progress toward identifying potentially modifiable causes has been slow because of inadequate understanding of the causes of preterm birth among women in general.[6] Moreover, preterm birth is a complex phenomenon.[7] It can be precipitated by idiopathic preterm labor (labor occurring before 37 weeks from unknown causes), preterm premature rupture of the membranes (spontaneous rupture of the fetal membranes occurring at least one hour before the onset of labor at less than 37 weeks gestation), or by obstetrical intervention (induction of labor or delivery by caesarian section). Each of these events may, in turn, result from multiple causes. Thus it is highly implausible that a single cause will explain the entire racial gap in the preterm birth rate.

Many risk factors have been proposed to explain the gap

SYNOPSIS

Objectives: To evaluate the impact of urogenital infections on the racial gap between black and white women in preterm birth rates.

Methods: A computer-assisted search of the medical literature was conducted through MEDLINE aided by a manual bibliographic search of published articles and relevant books. Estimates of the relative risk for preterm birth were extracted from published studies for the following infections: *N. gonorrhea*, syphilis, trichomoniasis, *Chlamydia trachomatis*, Group B streptococcal vaginal colonization, asymptomatic bacteriuria, genital mycoplasmas, and bacterial vaginosis. Estimates of the prevalence among black and white women by race for each of these infections were extracted from published studies. The attributable risk for preterm birth for selected infections was then calculated for the black and white populations and the impact on the racial gap in preterm births was estimated.

Results: Only bacterial vaginosis and bacteriuria appear to be established risk factors for preterm births. Significantly higher rates of bacterial vaginosis among black women may account for nearly 30% of the racial gap in preterm births. Higher rates of bacteriuria among black women may account for roughly 5% of the gap.

Conclusion: Although these findings are limited by the reliability of published estimates of prevalence and relative risk for these infections, treatment of infections during pregnancy, particularly bacterial vaginosis, offers hope for reducing the racial gap in preterm births.

in preterm birth rates including poverty, racism, psychosocial stress,[8] substance abuse,[9] maternal weight,[10] biological differences in gestation length,[11] and birth interval.[12] Unfortunately, such risk factors generally defy clinical intervention. Although renewed societal efforts must be made to address the enormous racial disparities in income, economic opportunity, and access to health care that exist in the United States, attention must also be given to identifying clinically modifiable risk factors for preterm birth that disproportionately affect black women. One such risk factor, urogenital tract infections, is the subject of this review.

The Urogenital Infection Hypothesis

Based on findings from the Collaborative Perinatal Study, a landmark prospective study of nearly 60,000 pregnant women, Richard Naeye argued that urogenital infections represented the single largest cause of a black-white disparity in perinatal mortality.[13] However, despite Naeye's work, and despite evidence accumulated over the past decade strongly implicating urogenital tract infection as a major cause of preterm birth, and despite findings that black women have significantly higher rates of most lower urogenital tract infections, the hypothesis that urogenital tract infections represent a major contributor to black-white differences in preterm birth rates has received relatively little attention.

The evidence for the role of such infections in preterm birth has been extensively reviewed elsewhere and will not be discussed here.[14] Briefly, studies suggest that lower urogenital tract infections ascend into a women's upper reproductive tract during pregnancy, resulting in intra-amniotic infection. Although intra-amniotic infection is often subclinical, i.e., neither the women nor the fetus show typical signs of infection such as fever or rapid heart rate, such infections may result in preterm labor, preterm premature rupture of the membranes, or clinical chorioamnionitis.

Urogenital infections offer one potential explanation for the impact of various sociodemographic factors on rate of preterm births. Specifically, the observed effect on preterm births of factors such as low socioeconomic status, race, age, marital status, and substance abuse,[6] may in part be mediated through their association with urogenital tract infections.[15–18]

Racial Differences in Rates of Urogenital Tract Infections

Black women have higher rates of lower urogenital tract infections than do women from other ethnic groups.[19, 20] As seen in Table 1, black women have dramatically higher rates of sexually transmitted infections including syphilis, *N. gonorrhea*, *Chlamydia trachomatis*, and trichomoniasis. Laboratory surveillance studies and prevalence studies, unbiased by reporting practices, confirm significantly higher rates or reportable infections, such as syphilis and *N. gonorrhea*, among blacks.[21,22] Well-designed prevalence studies also confirm that rates of *Chlamydia trachomatis* and trichomoniasis are three to four times higher in black women than in white women.[15]

The causes of dramatically higher rates of preterm birth among black women are poorly understood.

The reasons for higher rates of sexually transmitted diseases (STDs) among blacks are poorly understood.[19] Racial differences in reported sexual behaviors do not account for differences in rates of infection. With the exception of earlier age of first reported coitus among black males and

Research must focus on identifying clinically modifiable risk factors for preterm birth that affect black women disproportionately.

females,[23,24] self-reported differences in sexual behavior do not appear to contribute to differences in rates of sexually transmitted diseases. For example, black women report the same number of lifetime sexual partners as do white women,[25] and black women report lower overall rates of sexual activity,[26] including coitus during pregnancy, than do white women.[27] Black men report slightly more lifetime partners,[25] more consistent use of condoms,[23,28] and higher rates of condom slippage and breakage than do white men.[29] Moreover, both black males and females report engaging in anal intercourse less frequently than do whites.[25]

Possible contributors to higher rates of sexually transmitted disease in black communities include poor access to health care, exchange of sex for drugs, historical patterns of public health neglect of endemic infections, ratios of men to women, and endemic infections in highly segregated communities.[30] However, none of these potential causes has been adequately explored through well-funded research.

Black women also experience higher rates of non-sexually transmitted urogenital tract infections (non-STDs), including bacteriuria, bacterial vaginosis, Group B streptococcal vaginal colonization, and genital mycoplasmas (*Mycoplasma hominis* and *Ureaplasma urealyticum*), though racial differences in rates of these infections are less dramatic than differences in STD rates (Table 1). Risk factors for non-STDs are less well understood than those for STDs. Although, by definition, sexual activity is not the exclusive mode of transmission for non-STDs, sexual activity does appear to play a role.[31–34] However, a recent study demonstrated that racial differences in reported sexual behavior explain little of the racial differences in rates of urogenital tract infections.[20] Controlling for the effects of

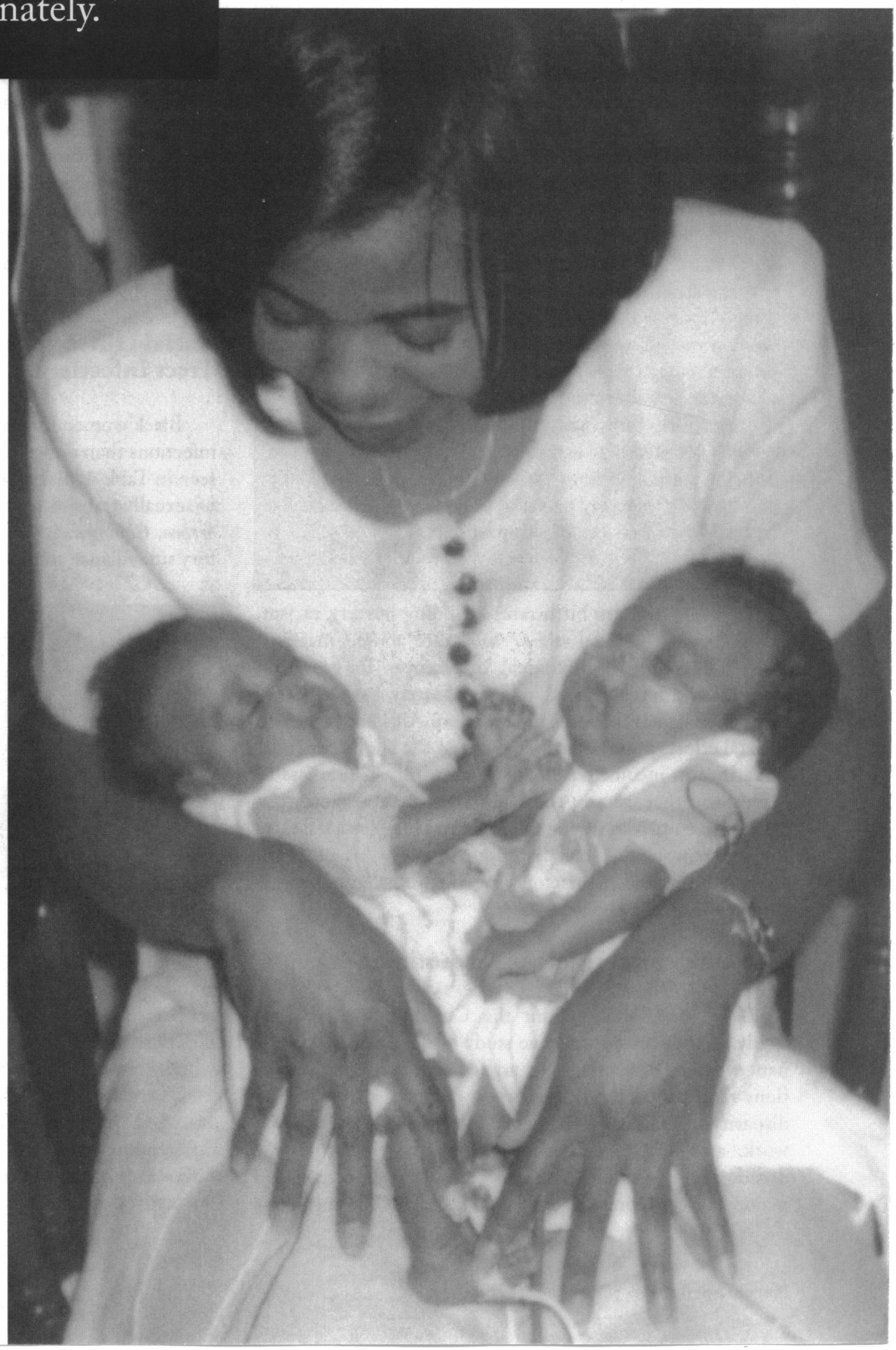


Table 1. Rates of lower urogenital tract infections in women during pregnancy

Infection	*Estimated Prevalence in Blacks*	*Estimated Prevalence in Whites*	*Black/White Relative Risk*
Syphilis[51,68,69]	0.05 – 0.1%	0.001 – 0.01%	10 – 60
N. gonorrhea[20,22,51]	1.0 – 2.5%	0.05 – 0.4%	5 – 20
Chlamydia trachomatis[20,70,71]	8 – 20%	3 – 10%	3 – 4
Trichomoniasis[72,73]	20 – 30%	5 – 8%	3 – 4
Bacteriuria[32,52,53]	4 – 10%	3 – 4%	1.5 – 5.0
Bacterial vaginosis[20,74,75]	20 – 50%	7 – 30%	1.5 – 2.5
GBS colonization[20,76]	20 – 30%	6 – 15%	1.5 – 2.0
M. hominis[20,77]	35 – 50%	15 – 30%	1.5 – 2.0
U. urealyticum[20,77]	75 – 85%	55 – 70%	1.2 – 1.5

Data comparing rates of urogenital tract infections during pregnancy by race consistently show higher rates of all infections among black women. In particular, black women have strikingly higher rates of sexually transmitted infections. Rates of syphilis are ten to sixty times higher, rates of gonorrhea are five to twenty times higher, and rates of *Chlamydia* and Trichomoniasis are three to four times higher.

age, marital status, age of first intercourse, and number of male partners had a modest impact on racial differences in rates of STDs and minimal impact on racial differences in rates of non-STDs.

Another recent study that controlled for the effects of alcohol use, smoking, gravidity (number of pregnancies), parity (number of births), and chronological and gynecological age suggested that black women may be more susceptible to bacterial vaginosis by virtue of higher vaginal pH levels.[35] However, the study did not adequately control for the effects of subclinical bacterial vaginosis infection as a potential explanation. Vaginal douching, a health behavior practiced by two-thirds of black women compared to only one-third of white women,[36] represents a potential though unexamined cause for higher rates of bacterial vaginosis among black women. Douching has been linked to alterations in vaginal flora[37] and to ascending urogenital tract infection.[38] However, a review of the literature reveals no published studies regarding the relationship between vaginal douching and bacterial vaginosis. Thus the causes of higher rates of urogenital tract infections among blacks remain unknown.

Evidence accumulated over the past decade strongly implicates urogenital tract infection as a major cause of preterm labor.

Proving Causality

Establishing that specific infections cause preterm births poses a major challenge to researchers because the relationship between infections and preterm birth is confounded by other risk factors for preterm birth. For example, women who are at higher risk for many urogenital tract infection are also at higher risk for smoking, drug use, poor nutrition, inadequate prenatal care, and other infections. Therefore, if studies fail to measure and statistically control for the effects of each of these common risk factors or confounders, any observed association between a specific infection and preterm birth may be spurious. Furthermore, many studies have used sample sizes that were too small to detect modest effects. Confounding and differences in population characteristics have also contributed to conflicting findings between studies. Even when a study is well designed, uses an adequate sample size, and controls for the effects of all known confounders, one can, nonetheless, not be certain that the effects observed are not caused by an unknown confounder. A randomized controlled trial, in which women with a particular infection are randomly assigned to treatment and placebo groups would offer the strongest evidence for a causal relationship. Obviously such a study cannot be performed for ethical reasons if that delay in treatment of a specific infection might result in harm to the mother or child.

Specific Infections Implicated in Preterm Births

To assess the evidence that specific infections cause preterm births, the author conducted an extensive review of published studies. A computer-assisted search of the medical literature for studies published between 1966 and 1995 was completed and supplemented by a manual search of references from published studies, review articles, and relevant

Table 2. Risk of preterm birth associated with lower urogenital tract infections Relative risk or odds ratio by study type+

	Case-Control	Cohort	Randomized Control Trials
Syphilis	–	4.8[40]	–
N. gonorrhea	2.9–4.7[39,78]	2.6[40]	–
Chlamydia Trachomatis	None[39]	None[40,81–85]	None[87,88+]
	3.9[79,80,42*]	1.5–2.6[57,86,87++,41*,42,*43*]	
Trichomoniasis	None[40]	None[40,44,57]	None[90]
	2.2[89]	1.5–2.7[82,27*,87++]	
Bacteriuria	2.3[91]	2.0[45**]	1.8[45**]
Bacterial vaginosis	2.1–3.8[92–94]	None[83,95,96]	2.0–2.1[46,47++***]
		1.7–6.9[44,49,97,98,99,100*,101++]	
GBS colonization	None[39,79]	None[57,102]	None[106]
		2.6–3.0[103–105]	
M. hominis	None[39]	None[41,83,107–110]	None[111*]
		2.0–5.1[57,96]	
U. urealyticum	None[39]	None[41,57,83,95,96,107–109]	None[111,112*]

None - Findings not statistically significant (95% confidence interval for relative risk or odds ratio includes 1.0).

+Randomized controlled trials represent the strongest study design (findings have more validity) followed by cohort, and case-control studies.

++ Based on preliminary findings; final results have yet to be published.

* Effects confined to a subset of women.

** Based on a meta-analysis.

***Odds ratio based only on women with bacterial vaginosis.

Findings suggest that both bacterial vaginosis and bacteriuria are associated with at least a two-fold risk of preterm delivery; and untreated syphilis and *N. Gonorrhea* are associated with a three- to a five-fold risk of preterm delivery.

books. In particular, the author reviewed observational (cohort and case-control) and experimental studies (randomized and nonrandomized controlled trials) that assessed the impact of the following infections on the rate of preterm birth: syphilis, *N. gonorrhea*, *Chlamydia trachomatis*, trichomoniasis, Group B streptococcal vaginal colonization, asymptomatic bacteriuria, bacterial vaginosis, and genital mycoplasmas (*U. urealyticum* and *M. hominis*).

The first major finding was that *N. gonorrhea* and syphilis are probable, though not definite, risk factors for preterm birth. Observational studies consistently show that syphilis and *N. gonorrhea* are associated with three to five-fold higher rates of preterm births (Table 2).[39,40] For ethical reasons, there have been no randomized controlled trials of treatment for syphilis or *N. gonorrhea*. Consequently, syphilis and *N. gonorrhea* remain presumptive, though not proven, risk factors for preterm birth.

Second, the review of the literature suggests that the following infections are probably *not* associated with a significant (twofold or higher) independent risk for preterm birth: *Chlamydia trachomatis*, trichomoniasis, Group B streptococcal vaginal colonization, and genital mycoplasmas. Although observational studies report conflicting findings regarding the impact of these infections on rates of preterm birth, randomized controlled trials have shown no benefit for treatment of these infections (Table 2). The weight of the evidence suggests that Group B streptococcal vaginal colonization, genital mycoplasmas, *Chlamydia trachomatis* colonization, and trichomoniasis are probably not risk factors for preterm birth; however, invasive *Chlamydia trachomatis* infection, as indicated by a maternal rise in IGM antibody, may be a risk factor,[41–43] and trichomoniasis may enhance the risk associated with other risk factors for preterm birth (risk modification).[27,44]

Third, the literature suggests that asymptomatic bacteriuria roughly doubles the risk of preterm birth. Although many small studies have reported conflicting findings, Romero et al. used meta-analysis to demonstrate an effect.[45] After combining the findings from published randomized controlled trials of treatment of bacteriuria during pregnancy, they found that antibiotic treatment of bacteriuria reduced the rate of preterm births by roughly 50%. These findings were corroborated by comparable findings from a meta-analysis of observational studies of bacteriuria.[45]

Last, studies suggest that bacterial vaginosis roughly doubles the risk of preterm birth. Ten of 13 observational studies show an association between bacterial vaginosis and preterm births (Table 2). These findings have been con-

firmed through two randomized controlled trials[46,47] and one large nonrandomized controlled trial,[44] which show that oral treatment with metronidazole (both with and without erythromycin) or with clindamycin reduces preterm birth rates by roughly 50%. Previous clinical trials involving ineffective systemic agents, such as amoxicillin[48] or topical clindamycin,[49] have shown no benefit. Treatment with an effective systemic agent appears to be required to reduce the risk of preterm birth.

Estimating the Contribution of Bacterial Vaginosis and Bacteriuria to the Racial Gap in Preterm Births

Epidemiology offers a methodology for estimating the population attributable risk (PAR), the proportion of a given health outcome that can be attributed to a particular risk factor in a given population.[50]

Using the methodology detailed in the side bar, the author estimated the PARs for specific urogenital tract infections in the black and white populations. Next, the theoretical rates of preterm births for the black and white population in the absence of infection were calculated. Then, these rates were used to estimate the contributions of particular infections to the racial disparity in preterm birth rates.

The respective contributions of syphilis, *N. gonorrhea*, bacterial vaginosis, and bacteriuria to the racial gap in preterm births were estimated. Neither *N. gonorrhea* nor syphilis demonstrated an appreciable impact (contribution less than 1%). This finding is a consequence of the low absolute rates of untreated *N. gonorrhea* and syphilis among black women, estimated at under 1%.[51] So, despite very high *relative* rates of *N. gonorrhea* and syphilis among black women, neither infection contributes significantly to the black/white disparity in preterm births.

However, bacterial vaginosis does appear to contribute significantly to this disparity. Based on a prevalence of bacterial vaginosis of 23% among black women and 9% among white women,[20] and a relative risk of preterm birth of 2.0, a number derived from randomized controlled trials,[46,47] bacterial vaginosis accounts for nearly 30% of the racial gap in preterm birth.

Asymptomatic bacteriuria makes a considerably smaller contribution to the gap. Based on a conservatively estimated prevalence of *untreated* asymptomatic bacteriuria among black women of 4% and among white women of 1–2%[52,53] and a relative risk of 1.8,[45] bacteriuria accounts for roughly 5% of the black-white gap in preterm births.

Discussion

Higher rates of urogenital tract infections among black women, particularly bacterial vaginosis, appear to make significant contributions to the racial disparity in rates of preterm birth. The validity of this important finding is limited by (a) the reliability of estimates of the prevalence of lower urogenital tract infections by race and (b) by the reliability of estimates of relative risk for preterm birth. Moreover, insofar as women are routinely screened, treated, and recultured for asymptomatic bacteriuria during pregnancy, estimates of the prevalence of untreated bacteriuria during pregnancy used may overstate its impact (population attributable risk) on preterm delivery. However, to the extent that black women receive less prenatal care[54] and less adequate prenatal care[55] than do white women and are as a consequence more likely to have untreated bacteriuria, estimates of the relative rates of asymptomatic bacteriuria in black and white women used here may underestimate its contribution to racial disparity in preterm birth rates.

This analysis assumed that the risk of preterm delivery associated with any urogenital tract infection is comparable among blacks and whites. However, this assumption has been recently challenged by data suggesting that bacterial vaginosis is associated with a significantly higher risk among black women (relative risk 3.3) compared to white women (relative risk 1.8).[44] Such racial differences in relative risk

Calculating the Population Attributable Risk

The potential impact of a particular lower urogenital tract infection on the racial disparity in preterm birth rates was estimated using the population attributable risk (PAR) for each infection, which was calculated using the following formula[50]: $[(P_e)(RR - 1)]/[(P_e)(RR - 1) + 1] \times 100$, where P_e = prevalence of a given lower urogenital tract infection in the population and RR = the relative risk of preterm birth in association with that infection.

The theoretical rate of preterm birth for blacks and whites in the absence of a particular lower urogenital tract infection was then estimated based on a national preterm birth rate of 18% for blacks and 8.5% whites[3]:

$EPTD_{black} = 18.0\% \times (1\text{-}PAR_{black})$, where $EPTD_{black}$ is the estimated preterm birth rate for blacks in the absence of a given lower urogenital tract infection.

$EPTD_{white} = 8.5\% \times (1\text{-}PAR_{white})$, where $EPTD_{white}$ is the estimated preterm birth rate for whites in the absence of a given lower urogenital tract infection.

The contribution of each urogenital tract infection to the racial difference in preterm birth rates was estimated using the estimated racial difference in preterm birth rates in the absence of a particular urogenital tract infection divided by the racial difference in total preterm birth rates: $100[1\text{-}((EPTD_{black} - EPTD_{white})/(18.0 - 8.5))]$. Comparable methodology has been used to estimate the contribution of very low birth weight factors to black/white differences in infant mortality[113] and to estimate the contribution of smoking to sex differences in mortality.[114]

suggest that bacterial vaginosis may contribute to as much as 60% of the racial disparity in preterm delivery. Further research is required to confirm these provocative findings.

This review assumed the absence of significant interactions (effect modification) between various risk factors for preterm birth. This assumption may also be incorrect. McGregor et al.'s study suggests that bacterial vaginosis may be associated with even higher rates of preterm birth in the presence of other urogenital infections.[44] Such an effect modification might account for the higher relative risk for bacterial vaginosis observed among black women. Moreover, this effect modification has biological plausibility. Bacterial vaginosis results in the production of mucolytic enzymes that may breach maternal defenses, thus exposing the chorioamnion to other urogenital tract infections.[49] Publication of the final results from the Vaginal Infections and Prematurity Project,[56] a national multicenter study, may begin to answer some, though certainly not all, of these important questions.

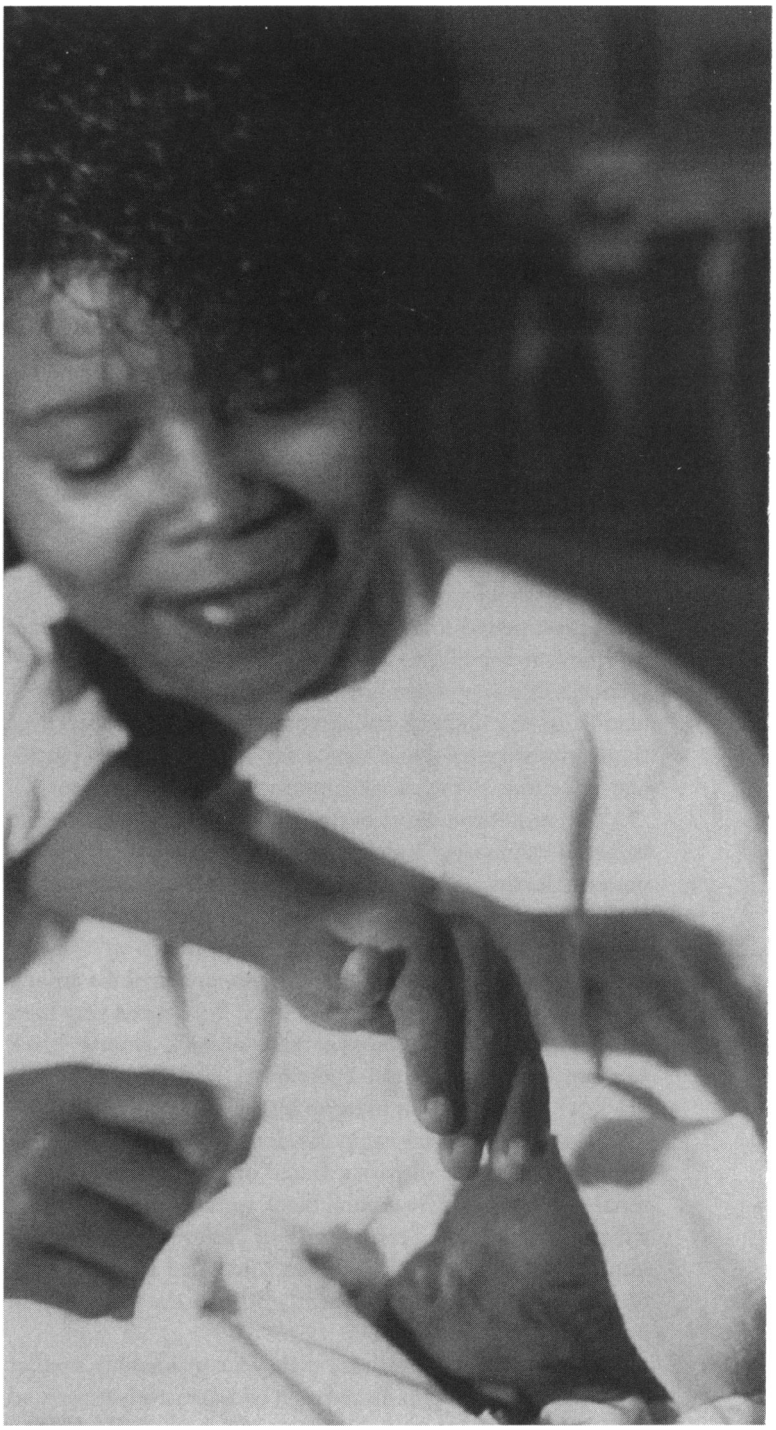
Higher rates of urogenital tract infections among black women, particularly bacterial vaginosis, appear to make significant contributions to racial disparities in rates of preterm birth.

This review focused only on the impact of urogenital tract infections; however, urogenital tract infections have also been linked to intrauterine growth retardation,[57,58] neonatal Group B sepsis,[59] and other neonatal infections.[60] Consequently, urogenital tract infections probably contribute to racial disparities in neonatal morbidity and mortality in addition to contributing to disparities in preterm birth rates.

The findings of this review have important implications for improving birth outcomes. First, this review highlights the need to provide all women with adequate prenatal care. Traditional prenatal care represents a necessary but not sufficient intervention for improving birth outcomes.[61] Prenatal care providers must begin to adopt proven interventions that target specific risk factors that disproportionately affect black women.[62,63]

This review also highlights the need for research on the causes of black/white disparities in rates of urogenital tract infections. Why are rates of syphilis,[51] *N. gonorrhea*,[51] HIV infection,[64] bacteriuria, and bacterial vaginosis higher among black women than among white women?

Last, this review underscores the potential for narrowing the racial gap in preterm birth. If early success in randomized controlled trials is confirmed through larger ongoing trials, then national recommendations for universal screening and treatment of bacterial vaginosis during pregnancy may be forthcoming. However, the potential benefits of antibiotic use during pregnancy must be carefully weighed against the potential risks.[65] Routine screening for, and treatment of, asymptomatic bacterial vaginosis necessitates exposing as many as one of 11 white women and one of four black women to systemic antibiotics during pregnancy. Although



studies suggest that clindamycin and metronidazole are relatively safe during pregnancy,[44,66,67] neither agent has been well studied through large randomized trials of pregnant women with adequate follow-up. Consequently, the long-term risks remain uncertain. Furthermore, wide-scale treatment would likely result in antibiotic resistance with unforeseen results. Therefore, universal screening and treatment of asymptomatic bacterial vaginosis should not be implemented until further data become available regarding the potential risks and benefits. These caveats notwithstanding, treatment of urogenital tract infections during pregnancy offers the hope of closing the racial gap in preterm birth rates.

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