infectious partners during the observation period. This lack of precision, however, is typical of observational studies of condom use and curable sexually transmitted disease, and our approach represents an improvement over previous efforts to approximate the degree of exposure to infected partners.

There are two points that we would like to clarify. First, Mann and Stine's premise may have arisen from a misinterpretation of table 4 from our article (2) regarding the relation between the number of condom-protected exposures and infection among "condom-using" subjects. Our analysis appropriately included as "condom-using" subjects *both* consistent and inconsistent condom users. We could not determine whether inconsistent users acquired infections during protected sex or unprotected sex, and it is probable that some infections were acquired during sex acts when condoms were not used. Such infections could obscure any relation between condom-protected exposures and risk of infection. When we limited our analyses to the 33 participants who reported only consistent condom use, we still found no association between the number of condom-protected exposures and infection ($\chi^2 = 0.08$; $p = 0.77$).

Second, the fact that the adjusted odds ratio was greater than zero does not necessarily indicate that infections among consistent users were due to condom failure. Although condom failure is certainly possible, other factors that we noted (such as condom-use reporting error, infection prior to condom use, or laboratory error) might also account for some infections among consistent users. These factors could explain why infection risk did not increase with the number of condom-protected exposures among consistent users.

In our study, condom use clearly reduced the risk of infection for the group of patients who were known to have had infected partners. Although we could not measure the protective effect of condom use with precision, our results indicate that it is larger than observed in studies that are unable to control for partner infection status. Our approach, like that of Mann et al. (3), argues that condom effectiveness is best estimated by studying persons who have been exposed to infected partners. Determining the exact number of exposures to an infected partner during both protected and unprotected sex is clearly critical to this estimation. Although our measure of partner infection status represents a significant advance over previous efforts, we were still limited by an inability to measure other factors. Given that these factors likely intro-

duce bias toward the null (4, 5), what remains a matter of conjecture is how much stronger our estimate of condom effectiveness might have been had we been able to address these other sources of bias.

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RE: "PARITY AND THE RISK OF DOWN'S SYNDROME"

Although Doria-Rose et al.'s *Journal* article (1) presents convincing data that Down's syndrome livebirth increases with parity, their interpretation ignores a well-established pitfall in reproductive epidemiology. Over two decades ago, a convincing correlation between spontaneous abortion and gravidity was detected and debated at length (Wilcox and Gladen (2)). A consensus emerging from this debate held that the causative mechanism was not biologic. Rather, it was recognized that individual women always know the outcomes of their previous pregnancies and, knowingly or not, use this information in making future reproductive decisions. When a greater proportion of women with a history of

adverse pregnancy outcomes than those without such outcomes decides in favor of further attempts at reproduction, this increases the cohort of women who are attempting reproduction while at greater risk.

Risk heterogeneity is a prerequisite for the selective-fertility mechanism (2) to be operative and sufficiently account for the parity-related artifact. Evidence from the literature does, however, suggest that individual women differ intrinsically in their risk of Down's syndrome livebirth. This evidence is demonstrated by documentation that a Down's syndrome livebirth is more likely for women with a history of repeat spontaneous abortion (3). Similarly, it has

clearly been demonstrated that the recurrence risk of Down's syndrome is higher than the incidence risk (4, 5). One apparent explanation for the greater recurrence risk is that Down's syndrome occurrences include cases due to heritable mutations, including translocations, rather than trisomy 21. In addition, some occurrence of Down's syndrome may reflect germline mosaicism for trisomy 21 among oocytes (6). If this hypothesis were to prove valid, it also should enhance recurrence risk.

Could the confounding effect of selective fertility be controlled by the conditional logistic regression used by Doria-Rose et al. (1)? My answer is that this is unlikely. Although women giving birth to their first or second child may be said to have a reproductive history already, properly matching their experiences with those of more parous mothers is a very difficult task.

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Doria-Rose et al. (1) recently examined parity as a risk factor for Down's syndrome and concluded that their data support an association between parity and Down's syndrome at any age. However, as Chan (2) pointed out in the invited commentary that accompanied this *Journal* article, the Doria-Rose et al. paper suffers from some limitations, such as ascertainment of Down's syndrome births and lack of data on prenatal diagnosis.

The association between parity and Down's syndrome has been investigated in the past to identify an additional risk factor for trisomy 21. However, the results were contradictory, and it still remains unclear whether parity plays a role in determining trisomy 21. In general, major criticisms concerning studies on parity and Down's syndrome have been related to the maternal age truncation effect, different rates of accessing the prenatal diagnosis of multiparous women, and inclusion of terminations of pregnancy in the analysis.

In 1999, we conducted a study (3) on this topic with data from two congenital malformation registries operating in northeast Italy (NEI) and Sicily (ISMAC), and we used the same methodology. All liveborns and stillborns affected by Down's syndrome are registered within 7 days of birth, and, since 1988, terminations of pregnancy are registered in NEI. During the study period, an overall 716,939 consecutive liveborns and 114,726 consecutive stillborns were listed in the two registries. The study sample consisted of 1,088 consecutive newborns (1,063 (97.7 percent) liveborns and 25 (2.3 percent) stillborns) and 169 consecutive fetuses, all affected by Down's syndrome; information regarding parity and maternal age was available for 1,052 (97 percent) and 159 (94 percent) cases, respectively.

To reduce the truncation effect, we analyzed our data by 2-year and 5-year intervals, and, depending on their size, the two samples were grouped into 13 and six age classes, respectively, to estimate the effects of parity independently of the mother's age. Parity in both samples was grouped into three different classes: I (primiparous), II (multiparous; parity of two to four), and III (multiparous; parity of more than four). By definition, spontaneous abortions were not included.

To estimate birth prevalence, the number of terminations of pregnancy was multiplied by 0.74, that is, the probability that a Down's syndrome fetus will survive to birth (4). Thus, the overall termination-adjusted birth prevalence of Down's syndrome in this study was 1.46 per 1,000.

In both the NEI and ISMAC series, we found a significantly increased risk of having a Down's syndrome child for multiparas 35 years of age or older. In the ISMAC sample only, a significantly reduced risk for primiparas was found at all ages.

Our data confirm a higher risk of a Down's syndrome child limited to only those women with a parity of more than four. However, because this effect is evident for women only 35 years of age or older, its practical impact is null because these women are usually offered prenatal diagnosis in any case. However, understanding the mechanisms involved, if this association is true, is very intriguing and could stimulate scientific studies allowing better knowledge of the nondisjunction mechanisms.

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