Are there “excess” adverse pregnancy outcomes among HIV-positive women in Dar es Salaam, Tanzania?

Dear Sir:

In a recent report in the Journal, Dreyfuss et al (1) exploited a luxurious array of measurements and variables in a longitudinal study of >800 HIV-positive Tanzanian women receiving prenatal services at a health clinic in Dar es Salaam to assess the determinants of adverse pregnancy outcomes among this population. It was not surprising that the “old standbys” of low maternal weight, primiparity, and a previous preterm birth were the robust determinants of low birth weight (LBW); the evidence of significant participation of high C8 cell counts in adverse pregnancy outcomes is a novel contribution (1).

Their inquiry, however, was predicated on the statement, “Studies from the region have reported that HIV-infected pregnant women are at increased risk of delivering LBW infants, of preterm delivery, and of intrauterine growth retardation” (1), which was based on the literature review and meta-analysis of Brockelhurst and French (2). For that cohort of women in an urban setting, the prevalences of LBW, preterm delivery, and small-for-gestational-age (SGA) birth were 11.1%, 23.5%, and 11.5%, respectively (1).

Intuitively, especially with regard to LBW, these statistics do not seem to be inordinately remarkable as developing-country populations go, especially if one looks at the rural segment of such a population. For instance, in a study from Guatemala by Lechtig et al (3) that was cited by Dreyfuss et al, among 671 infants born in 4 rural ladino villages between January 1969 and February 1973, 15.2% had birth weights <2500 g. The mean birth weight in the famous longitudinal study on the children of Santa María Cauqué by Mata (4) was 2549 ± 383 g, with a prevalence of LBW of 41.3% among 415 live, singleton births from 1964 to 1972 in that rural Mayan township. Albeit rural Guatemalan women may be much shorter in stature than urban Tanzanian women, an 11.1% rate of LBW seems by no means unreasonable. A prevalence of preterm delivery of 23.5% does indeed, however, appear to be high in urban Tanzania, but, despite the birth before 37 wk of gestation of 1 in 4 infants, most of them still came into the world weighing >2500 g.

What might be important for our understanding of gestational HIV infection in the context of urban east Africa is whether the prevalences of the 3 index adverse outcomes (LBW, SGA birth, preterm delivery) represent an excess over the rates in an HIV-negative population of pregnant women of the same social class (or attending the same health clinic). My sense is that, at least regarding LBW prevalence, the study cohort might violate the Brockelhurst and French principle (2) and not be excessive compared with unaffected pregnancies. For all one can divine, LBW and SGA birth prevalences may be even lower among births to HIV-infected women than the community background rates. Hence, I wonder whether Dreyfuss et al could share any data on the pregnancy outcome statistics for the overall community or those for HIV-negative women in Dar es Salaam to provide a perspective on any differential adverse effect of HIV on fetal health and development in the setting of their study.

Noel W Solomons

REFERENCES

Reply to NW Solomons

Dear Sir:

In our recent publication on the determinants of low birth weight (LBW) among HIV-infected pregnant women in Dar es Salaam, Tanzania, we reported incidence rates of LBW (11.1%), preterm delivery (23.5%), and small-for-gestational-age (SGA) birth (11.5%) among a cohort of women who participated in a randomized, double-blind, placebo-controlled trial of antenatal multivitamin and vitamin A supplementation (1). Multivitamin supplementation significantly decreased the risk of fetal loss, LBW, severely preterm delivery, and SGA birth in this cohort, but vitamin A supplementation had no significant effect (2). Among women who were randomly assigned to receive no multivitamins (placebo or vitamin A only), the rates of LBW, preterm delivery, and SGA birth were 15.8%, 24.5%, and 17.6%, respectively (2). This LBW rate falls within the range reported from numerous studies of HIV-infected pregnant women in sub-Saharan Africa: from 9% in Nairobi, Kenya (3), to 26% in Kigali, Rwanda (4). Most of these studies were conducted in urban settings similar to...
that of our study, but the prevalence of symptomatic HIV infection or AIDS in these cohorts varied greatly.

We recently published findings from our study cohort examining the association of HIV infection and adverse pregnancy outcomes (5). This analysis was limited to women who were randomly assigned to receive no multivitamins because of the significant effect of multivitamin supplements on the risk of adverse pregnancy outcomes previously reported in this cohort (2). We concurrently enrolled and followed 502 HIV-uninfected pregnant women in addition to our trial cohort of 1078 HIV-infected women, and we found no significant differences between these 2 groups in poor pregnancy outcomes, including the risk of fetal loss, LBW, and preterm delivery (5). However, we found significantly higher relative risks (RRs) of LBW (RR: 2.29; 95% CI: 1.34, 3.92) and preterm delivery (RR: 1.93; 95% CI: 1.35, 2.77) among symptomatic HIV-infected women than among HIV-uninfected women (5). The rates of LBW were 14.7%, 13.0%, and 26.4% in HIV-uninfected, asymptomatic HIV-infected, and symptomatic HIV-infected women (World Health Organization stage II or higher) made up 16.6% of this cohort. Braddock et al (3) reported a 17% LBW rate among women in Kenya with HIV-related diseases compared with a 6% LBW rate among women who were asymptomatic or had generalized lymphadenopathy alone (odds ratio: 3.4; P = 0.08). LBW was rare (3%) among uninfected women in the study. Ryder et al (6) reported LBW rates of 9.8%, 16.9%, and 32.9% among Rwandan women who were HIV uninfected, HIV infected without AIDS, and HIV infected with AIDS, respectively.

In the Brocklehurst and French (7) meta-analysis of HIV infection and perinatal outcomes, a modest relation was observed between HIV infection and LBW, but there was considerable heterogeneity among study results. The reported association was stronger in studies from developing countries than in those from developed countries. Compared with HIV-infected women in developed countries, infected women in developing countries are more likely to be at advanced clinical and immunologic stages of HIV-related disease, possibly because of the high prevalence of undernutrition, opportunistic infections, and poor access to treatment. These conditions increase the risk of poor pregnancy outcomes regardless of HIV status, and they may be important contributors to the high rates observed among HIV-infected women, particularly those with symptoms of HIV-related disease. Our findings support those of the meta-analysis and suggest that the increased risk of LBW and preterm delivery associated with HIV infection may be due in large part to the more advanced disease in some HIV-infected women.

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REFERENCES

Validation of air-displacement plethysmography to measure body fat

Dear Sir:

Fields et al (1) compare results obtained with the “new” method of air-displacement plethysmography (BOD POD; Life Measurement Inc, Concord, CA) with those obtained by hydrodensitometry and other reference methods to determine the fat content of human subjects. They conclude that air-displacement plethysmography is a reliable, valid, and safe technique but advocate further research to explain the differences between the estimates obtained by these methods. In a recent paper, Demerath et al (2) reached a similar conclusion.

A major problem when methods for measuring human body composition are validated by comparison with other methods is that the other methods also have quite large errors and there is no gold standard with which to compare results other than whole-body chemical analysis, which is unacceptable for living subjects. However, there are accurate (but tedious) methods for measuring change in body fat in volunteers confined to a closed metabolic ward and who consume a low-energy diet. If energy intake and output are carefully measured over several weeks and a value for the energy density of fat and fat-free mass are assumed, the proportion of fat and fat-free mass in the weight lost can be calculated. Similarly, this calculation can be made if nitrogen balance is measured and a value for the nitrogen content of fat-free mass is assumed.

Long ago we reported a study on 19 obese women studied in a closed metabolic ward for a total of 408 person-days (3). The women’s mean (±SD) initial weight was 97.55 ± 19.81 kg and in
have errors of similar magnitude to those of hydrodensitometry. Reliable than one obtained by comparison with other methods that against a change in body fat measured by metabolic balance is more desirable situation. Second, validation of air-displacement methods around the subject, the more precise the measurement of body vol-
tion. In theory this should be true; however, as stated in our review individual variations in body compartments (2–4). However more precise and accurate these may be, they still have some associated error (4–7). In addition, they may not be completely independent of the method under evaluation; such is the case when the BOD POD, which ultimately is a densitometric method, is evaluated against a 4-compartment model that also requires a measurement of densitometry. Examples of methods that could serve as independent reference methods are in vivo neutron activation analysis (8) and total-body carbon analysis (9). Neither of these methods is widely available, however; thus, the BOD POD will continue to be evaluated against commonly used techniques such as hydrostatic weighing and dual-energy X-ray absorptiometry. Because of this, when judging whether the BOD POD (or any other method) is reli-
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REFERENCES

Reply to JS Garrow

Dear Sir:

We thank Garrow for highlighting an inherent and almost unavoidable characteristic of body-composition validation studies: that the reference methods against which we compare the test methods have their own associated errors. The most common techniques against which air-displacement plethysmography (BOD POD; Life Measurement Inc, Concord, CA) has thus far been validated are hydrostatic weighing and dual-energy X-ray absorptiometry, each of which, as we point out in our review (1), has multiple inherent errors. When evaluating these studies, therefore, we must keep in mind that any differences in body-composition measurements between the reference method and the BOD POD should be attributed not only to the BOD POD but also to the reference method. Whenever possible, measurements made by any new body-composition method should be evaluated against techniques with the highest achievable accuracy and precision. These include any number of multicompartiment models that take into account individual variations in body compartments (2–4). However more precise and accurate these may be, they still have some associated error (4–7). In addition, they may not be completely independent of the method under evaluation; such is the case when the BOD POD, which ultimately is a densitometric method, is evaluated against a 4-compartment model that also requires a measurement of densitometry. Examples of methods that could serve as independent reference methods are in vivo neutron activation analysis (8) and total-body carbon analysis (9). Neither of these methods is widely available, however; thus, the BOD POD will continue to be evaluated against commonly used techniques such as hydrostatic weighing and dual-energy X-ray absorptiometry. Because of this, when judging whether the BOD POD (or any other method) is reliable and accurate, we believe it is important to keep in mind the big picture. It may be reasonable to expect and also accept that differences in measurements between methods exist. When the totality of studies shows that these differences between methods are small and randomly distributed among studies, the method under evaluation can be deemed acceptable and reasonably valid. Garrow also states in his letter that a smaller air volume around the subject will lead to a more precise measurement of body composition. In theory this should be true; however, as stated in our review (1), evidence thus far suggests that, in practice, the size of the air volume makes only a small difference in the BOD POD. Recently, Wells and Fuller (7) reported that the absolute precision for percentage body fat (%BF) measurement was 0.88%BF for adults and 0.91%BF for children aged 5–14 y. The difference in precision between adults and children increased only slightly when expressed relative to the mean %BF in each group (4.2%BF for adults and 5.8%BF for children). Additionally, there was no relation between the difference in 2 consecutive body density measurements and body volume ($r = -0.20, P = 0.14$). One major advantage of the BOD POD over hydrostatic weighing is that individuals do not need to get wet. Whereas Garrow’s plethysmograph (10), in which subjects are immersed to the neck in water, is likely a precise research tool, we feel that for everyday clinical use the gain in precision achieved by having a smaller air volume is offset by the inconvenience of the subject’s having to get wet.

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Calcium, protein, and fruit and vegetables as dietary determinants of bone health

Dear Sir:

The recent paper by Dawson-Hughes and Harris (1) suggests that an increase in dietary protein is beneficial to the skeleton, provided that dietary intakes of calcium and vitamin D meet recommended amounts (2). Because the calcium supplement used provided an alkali source (citrate and malate), a point noted by the authors, it might be prudent to examine further the relation between total potassium and alkali intakes and rates of bone loss in this data set. Frassetto et al (3) showed that the ratio of protein to potassium predicts net acid excretion and, in turn, net renal calcium loss and enables the full expression of the dietary protein-mediated anabolic drive on bone. This is supported by previous work by this group, which showed that calcium supplementation in the form of calcium citrate malate was more effective in reducing bone loss than was supplementation in the form of calcium carbonate (4).

Thus, the exciting findings of Dawson-Hughes and Harris (1) further support the arguments that maintenance of acid-base homeostasis is crucial to preserving skeletal health (15). Hence, calcium supplements may be favorable to bone health, not just through the additional mineral that they supply but also (and possibly more so) through their provision of additional alkali salts. Indeed, the challenge remains to establish the extent of any need for alkali salts in maintaining the bone matrix and the parathyroid hormone–mediated insulin-like growth factor I–mediated anabolic influences acting on the matrix and the parathyroid hormone–mediated responses to any protein-derived, acid-stimulated increased urinary calcium loss. We suggest that, in the absence of sufficient dietary alkali to neutralize the protein-derived acid, net calcium loss ensues and the anabolic drive of dietary protein on the bone matrix is ineffective in maintaining bone mineral density. However, provision of dietary alkali (either in the type of calcium supplement used in the current study by Dawson-Hughes and Harris or as fruit and vegetables) prevents urinary calcium loss and enables the full expression of the dietary protein–mediated anabolic drive on bone. This is supported by previous work by this group, which showed that calcium supplementation in the form of calcium citrate malate was more effective in reducing bone loss than was supplementation in the form of calcium carbonate (14).
for additional calcium in the presence of adequate dietary protein and fruit and vegetable intakes.

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REFERENCES

Reply to SA New and DJ Millward

Many components of the diet influence bone health. We recently addressed the association of protein intake with rates of bone loss in elderly men and women taking either supplemental calcium citrate malate and vitamin D or placebo. We found a positive association between dietary protein intake and change in bone mineral density in the supplemented group but not in the placebo group (1).

New and Millward suggest that it would have been prudent to examine the relation between total potassium and alkali intakes and bone loss in our data set. Such an examination was not a goal of our study; however, we may undertake such an examination in the future.

New and Millward’s letter does draw into focus the possibility that the different potassium and alkali intakes across the protein tertiles that we used could have influenced our results. In both the supplemented and placebo groups, the potassium intake was similar across the protein tertiles. In addition, the ratios of urinary potassium to creatinine were similar across the tertiles in both groups. These observations support our conclusion that protein intake may have a favorable effect on change in bone mineral density in elderly men and women supplemented with calcium citrate malate and vitamin D.

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REFERENCE