

principles set forth to justify vaccine mandates could easily outweigh concerns about the mode of transmission. Courts must rely on and respect the established precedent on which immunization mandates have been built.

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Dr. Stewart reports working under a contract from Merck (with the Department of Health Policy at George Washington University Medical Center, which has conducted research on access to vaccines among the underserved) to study Medicaid coverage of the HPV vaccine. No other potential conflict of interest relevant to this letter was reported.

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## Treatment of Infertility in the Polycystic Ovary Syndrome

**TO THE EDITOR:** In their report on the treatment of infertility in women with the polycystic ovary syndrome, Legro et al. (Feb. 8 issue)<sup>1</sup> do not mention lifestyle interventions, although a significant proportion of the women in their study were obese. Many studies have shown that weight reduction normalizes ovulation, improves hyperandrogenism, and ultimately increases rates of conception among women with the polycystic ovary syndrome.<sup>2</sup> In fact, ovulation rates similar to those achieved in the two recent trials with metformin<sup>1,3</sup> have been previously reported in association with lifestyle interventions.<sup>4</sup>

In addition to infertility in anovulatory women, the polycystic ovary syndrome is associated with metabolic disorders that are linked to insulin resistance and central obesity.<sup>5</sup> The administration of clomiphene alone does not target these abnormalities, and in the study by Legro et al. it actually led to increases in weight and insulin resistance. In contrast, weight loss has been associated with a significant reduction of visceral fat, leading to an improved metabolic profile.<sup>2</sup>

On the basis of this evidence, we believe that lifestyle modifications — increased exercise, a properly supervised diet, and smoking cessation — should be the first and are probably the most important steps in the therapeutic approach to the polycystic ovary syndrome in obese women.

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**TO THE EDITOR:** Legro et al. assert that the inferiority of metformin in achieving live births is inconsistent with the findings of previous studies, which show the benefits of metformin in stimulating ovulation. However, in the previous studies, subjects received metformin in an immediate-release form, whereas the subjects in the study by Legro et al. received metformin in the extended-release form, which may not be as efficacious in lowering insulin, androgen, and sex hormone-binding globulin levels.

Clinical experience with extended-release metformin suggests that it is not as effective as the immediate-release form for glycemic control. The nonsignificant decreases in the levels of glucose, insulin, proinsulin, and insulin resistance as determined by homeostasis model assessment associated with metformin in the study by Legro and colleagues provide support for this impression. In an initial study of immediate-release metformin, reported by Nestler and Jakubowicz,<sup>1</sup> sex hormone-binding globulin levels increased by 187.5% (vs. a 12.0% increase with extended-

release metformin in the study by Legro et al.), and free testosterone decreased by 44.1% (vs. a 15.2% decrease in the free androgen index). Thus, the results of the study by Legro et al. further suggest a decreased potency of extended-release metformin. If the subjects in their study had received immediate-release metformin, it might not have been inferior to clomiphene.

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1. Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome P450c17 alpha activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. *N Engl J Med* 1996;335:617-23.

**TO THE EDITOR:** The trial by Legro et al. was well designed and adequately powered, but the results contradict the findings of a meta-analysis of several earlier trials.<sup>1</sup> We are concerned about the very high rate of diarrhea in the metformin group as compared with the clomiphene group (64.9% vs. 23.0%,  $P < 0.05$ ). Although diarrhea is a known adverse effect of metformin, the proportion of subjects with this side effect was three times as high as that in previous trials involving metformin.<sup>2,3</sup> Even though the number of subjects who discontinued therapy because of adverse events was similar among the three groups in the study by Legro et al., such adverse events affect compliance and, hence, the efficacy of the drug.<sup>4</sup> Our experience with patients with type 2 diabetes for whom metformin therapy has been prescribed is that diarrhea is a major cause of poor compliance. In this study, compliance might have diminished the effect of metformin on the primary end point and insulin-sensitivity markers.

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**THE AUTHORS REPLY:** We did not conduct a weight-loss intervention either before or during our trial, as Panidis and Farmakiotis recommend. Evidence of the efficacy of weight loss as a therapy for infertility associated with the polycystic ovary syndrome rests primarily on observational studies, most of which focused on ovulation or other surrogate outcomes, not on pregnancy or live birth. The results of our study strongly suggest that successful ovulation alone does not predict fecundity. The most effective therapy for weight loss in this patient population is not known. Randomized trials in other populations suggest that combination therapies with pharmacotherapy and behavioral support are markedly more effective than lifestyle modification alone.<sup>1</sup> The risks of these therapies, including lifestyle alterations, must also be identified. In other populations of women with infertility, severe caloric restriction<sup>2</sup> and increases in the frequency of exercise<sup>3</sup> have been associated with treatment failure. Although weight loss clearly has other short-term and long-term health benefits, we believe that prospective, randomized trials of weight loss as the primary treatment for infertility in the polycystic ovary syndrome are needed rather than blanket recommendations.

Panidis and Farmakiotis also note that the previous finding that insulin resistance is the primary endocrine defect in the polycystic ovary syndrome is inconsistent with our data, which showed worsened insulin sensitivity yet improved rates of ovulation and pregnancy with clomiphene as compared with metformin. Our conclusion from these data is that perhaps other strategies are needed to guide the treatment of infertility in anovulatory women with the polycystic ovary syndrome.

Bell suggests that the extended-release metformin used in our study may be less effective than immediate-release metformin, and Geberhiwot and Jones note a high rate of side effects in our study. The Food and Drug Administration does not routinely approve extended-release preparations that have diminished efficacy, and, indeed, in type 2 diabetes, extended-release preparations have an equal or improved efficacy with respect to glycemic measures.<sup>4,5</sup> Improved efficacy with an extended-release version of metformin has been attributed to lower gastrointestinal side effects and better compliance with the medication regimen.<sup>5</sup> In our study, the two groups

taking metformin had a similarly high rate of compliance with the medication regimen; the mean compliance rate was 79.3% (interquartile range, 70.0 to 92.8) in the metformin group and 79.7% (interquartile range, 71.0 to 92.3) in the group that received metformin and clomiphene. In addition, the combination-therapy group had a rate of diarrhea (60.3%) that was similar to that in the metformin group (64.9%), although dropout, pregnancy, and live-birth rates were significantly higher and similar to those in the clomiphene group. We attribute the higher dropout rates in the metformin group to patients' dissatisfaction with the diminished rates of ovulation and pregnancy.

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## GM-CSF Autoantibodies in Pulmonary Alveolar Proteinosis

**TO THE EDITOR:** Uchida et al. (Feb. 8 issue)<sup>1</sup> report that in patients with pulmonary alveolar proteinosis, neutrophil functions are impaired because of autoantibodies against granulocyte-macrophage colony-stimulating factor (GM-CSF). Although this may be true, neutralizing GM-CSF autoantibodies are found at high levels in a small proportion (<5%) of healthy persons. The Gamma-gard immune globulin used as a "negative" control by Uchida et al. contains these autoantibodies.<sup>2,3</sup> Pulmonary alveolar proteinosis has been described in patients without autoantibodies against GM-CSF,<sup>4</sup> and pathological specimens from patients with this condition may respond to preparations of immunoglobulin containing these autoantibodies.<sup>5</sup> When primed with 10 ng of GM-CSF per milliliter, whole-blood neutrophils from patients with pulmonary alveolar proteinosis were severely impaired, presumably because most GM-CSF adhered to autoantibodies in the blood. However, without investigating whether GM-CSF at high autoantibody-saturating doses can salvage neutrophil functions in pulmonary alveolar proteinosis, one cannot exclude the possibility that neutrophil dysfunction in pulmonary alveolar proteinosis involves additional factors.

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**TO THE EDITOR:** Uchida and colleagues postulate the use of a humanized monoclonal GM-CSF antibody for the treatment of the acute respiratory distress syndrome (ARDS), which they regard as a chronic inflammatory disorder. We believe this proposal is incorrect. First, ARDS has an acute