

didates for allogeneic stem-cell therapy or for clinical trials of potentially better drugs, including newer and more selective JAK inhibitors.

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## Nicotine Replacement for Smoking Cessation during Pregnancy

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Cigarette smoking during pregnancy increases the risk of delivering a low-birth-weight or preterm infant, as well as the risks of pregnancy complications (premature rupture of membranes and placental abruption) and perinatal and infant death.<sup>1</sup> Despite these risks, 10 to 12% of pregnant women in the United States<sup>2</sup> and 6 to 22% of pregnant women in high-income countries<sup>3</sup> smoke, making cigarette smoking a major modifiable cause of adverse pregnancy outcomes in high-income countries.

Behavioral counseling is recommended for pregnant smokers, increasing quit rates in this population by 6% to 10% over usual care<sup>4,5</sup>; other than counseling, however, it is not clear how best to treat pregnant smokers. Nicotine-replacement therapy increases quit rates among nonpregnant smokers,<sup>5</sup> but its efficacy during pregnancy is uncertain.

In this issue of the *Journal*, Coleman and colleagues report the results of a controlled trial of nicotine-replacement patches in pregnant women.<sup>6</sup> Pregnant smokers were randomly assigned to receive behavioral counseling and either a standard course of nicotine patches (at a dose of 15 mg per 16 hours) or a visually identical placebo. The study treatment was administered for 4 weeks, followed by an additional 4 weeks of treatment that was contingent on biochemical evidence of abstinence from smoking. Although the quit rates at 1 month were higher in the nicotine-

replacement group than in the placebo group, prolonged quit rates (to the end of pregnancy) were similar in the nicotine-replacement and placebo groups (9.4% and 7.6%, respectively). However, overall adherence to therapy was low; only 7.2% of women in the nicotine-replacement group and 2.8% of those in the placebo group used the treatment for more than 4 weeks.

The finding that nicotine-replacement therapy did not improve long-term quit rates in pregnancy is consistent with two other, smaller, placebo-controlled studies of nicotine gum<sup>7</sup> or patches<sup>8</sup> in pregnant smokers. In these studies, adherence to therapy was also low with respect to dose (number of pieces of gum per day<sup>7</sup>) and duration of treatment<sup>7,8</sup>; the average duration of use of nicotine-replacement therapy was less than 20% of the recommended duration for the patch<sup>8</sup> and less than 50% of that recommended for gum.<sup>7</sup>

Adherence to therapy is a well-recognized determinant of efficacy. With low adherence rates in placebo-controlled trials of nicotine-replacement therapy in pregnant smokers,<sup>6-8</sup> it is difficult for clinicians to counsel their patients regarding whether such treatment would be efficacious or safe if used as directed. In the current study, the higher abstinence rate at 1 month in the nicotine-replacement group than in the placebo group (21.3% vs. 11.7%) indicates the efficacy of the medication<sup>6</sup>; however, the majority

of women who quit smoking for a short time did not use the patch for more than 4 weeks. A central question is whether participants stopped the study treatment before or after a smoking relapse; the former would suggest that future trials should focus on adherence to therapy, whereas the latter would suggest that the medication is not efficacious for smoking cessation. Elucidating reasons for the low adherence among pregnant smokers in this and other trials (i.e., lack of efficacy, concern about medication use during pregnancy, nicotine-withdrawal symptoms, adverse effects, or other factors) would also increase our understanding of the potential usefulness of nicotine-replacement therapy for smoking cessation during pregnancy and would inform the design of future pharmacotherapy trials. Adverse events did not appear to be a major factor in the low adherence to therapy in the current study, given that the 8.8% rate of discontinuation that was attributed to adverse events in the nicotine-replacement group is only slightly higher than the rate reported among nonpregnant smokers (1 to 5%).<sup>9</sup> The present article does not include data on other factors that could predict adherence to therapy.

The clearance of nicotine is accelerated during pregnancy,<sup>10</sup> and it has been suggested that, to optimize efficacy, higher doses of nicotine-replacement therapy may be needed in pregnant smokers.<sup>6,10</sup> However, given that nicotine is a neuroteratogen in animals,<sup>11</sup> it would be important, particularly in any studies using higher doses, to monitor the overall exposure to nicotine (i.e., cotinine concentrations) in order to ensure that exposure during the use of nicotine-replacement therapy did not exceed baseline exposure (i.e., cotinine concentrations during smoking). Ultimately, the goal of nicotine-replacement therapy should be not only to facilitate cessation of smoking but also to reduce overall exposure to nicotine. In a study in which cotinine levels were monitored to guide the adjustment of the nicotine-gum dose,<sup>7</sup> birth weight and gestational age were significantly higher in the nicotine-replacement group than in the placebo group.

Although placebo-controlled trials of nicotine-replacement therapy in pregnancy have been negative, two randomized but not placebo-controlled studies of the effectiveness of nicotine-replacement therapy in pregnant smokers showed that

nicotine replacement increased quit rates.<sup>12,13</sup> In one of these studies,<sup>12</sup> adherence to therapy was reported to be a predictor of treatment response. The behavioral counseling in these studies was relatively intensive, in terms of the length of the initial counseling visit and the number of subsequent visits, which may have influenced the response rates to medication.

In summary, the study by Coleman et al., like previous placebo-controlled trials, showed that nicotine-replacement therapy was not efficacious for smoking cessation during pregnancy, but adherence to therapy was low. Pending more data on the efficacy and safety of nicotine-replacement therapy during pregnancy, this therapy cannot be recommended with any clinical certainty.

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