

“NO ONE ASKED THE BABY” – AN ETHICAL ISSUE IN PLACEBO-CONTROLLED TRIALS IN PREGNANT SMOKERS

Peter Selby, Bhushan M. Kapur, Richard Hackman and Gideon Koren

The Motherisk Program, Division of Clinical Pharmacology & Toxicology, The Hospital for Sick Children and University of Toronto

Corresponding Author: gkoren@sickkids.ca

ABSTRACT

This case report involving a placebo-controlled nicotine patch trial illustrates the difficult issue of conducting placebo studies in pregnancy, when one of the two patients involved cannot be asked to consent.

Key words: Ethics, placebo-controlled trial, consent, nicotine

A 23-year-old G4P2A1 at 24 weeks gestation with a 10-year history of heavy smoking was enrolled in a 12-week double-blind placebo-controlled nicotine patch trial. She had tried to quit 3 times in the past and had been successful for 9 months after using the transdermal nicotine patch (TNP) but eventually relapsed to smoking. At the outset of the study she smoked 25 cigarettes a day with a corresponding plasma cotinine of 519ng/ml. Her first cigarette was within 5 minutes of waking up and most of her smoking occurred in the morning. She felt guilty about smoking while pregnant and wanted assistance with quitting. She understood the potential risks and benefits of TNP in pregnancy. On her quit date, the subject applied the patch as instructed as part of the double-blind placebo-controlled study. Within an hour she noticed increased fetal movement accompanied by mild abdominal cramping.

Her own symptoms were similar to withdrawal she had experienced in the past when she tried to stop smoking. The excess fetal movements continued for an hour, when she removed the patch and started smoking again. Almost immediately, fetal movement slowed down and the cramping disappeared completely. The patient was examined in the labour suite. Her vital signs were stable, and she appeared to be

comfortable. The cervical os was closed and no uterine contractions were noted. An electronic fetal heart tracing was normal for gestational age and the sonogram was normal. Her plasma cotinine was 380 ng/ml. She chose to withdraw from the study because she was convinced she had been given a placebo. The safety review committee broke the study code and confirmed that she had been randomised to the placebo arm of the study.

This case has led the team to suspend the study before its completion and to plan a dose-escalating study, which is now in its development phase. The dose escalating study will allow for a safe increase in the dose of nicotine and ensure that the increased clearance rate of this xenobiotic in late pregnancy does not lead to subtherapeutic dosing schedules.¹

Randomised placebo controlled trials are the gold standard required to validate the efficacy of any new treatment.² The safety of NRT (Nicotine Replacement Therapy) in pregnancy has not been established and pregnancy itself may lead to decreased smoking.³ Therefore, a placebo arm was deemed to be reasonable to quantify the efficacy of TNP. Blinding of both the subject and the investigator is necessary to prevent bias in the response to treatment. In a recent review of 27 studies, subjects in 65% of studies guessed drug

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allocation correctly.⁴ Therefore, it is important that participants are not unmasked based on properties of either placebo or active drug. The placebo should be identical to the active drug in appearance and taste. The subjective effects produced by the placebo should also be similar to prevent unmasking by the subject especially with psychoactive medications.⁵ In conducting studies in addicted patients, it is necessary that neither the active treatment nor placebo precipitate or worsen withdrawal symptoms that might cue the subject. This presents a special challenge in nicotine dependent pregnant smokers who might get cued not only by their own symptoms but those produced by the fetus.

In this case, no alternate aetiology has been identified for the fetal reaction and its resolution after smoking resumed. This case suggests that abrupt discontinuation of smoking in pregnancy during placebo exposure may adversely affect the fetus who, like the mother, is nicotine dependent. Alternate methodology should be considered to ensure fetal safety and maintain blindness between the two arms of the study.⁶ Moreover, heavy smokers in the latter half of pregnancy may require pharmacological assistance while quitting rather than being advised to quit “cold-turkey.”

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