Letters to the Editor

Post-coital administration of levonorgestrel and post-fertilization events in the new-world monkey Cebus apella

Sir,

The paper by Ortiz et al. (2004), which concludes that ‘Post-coital administration of levonorgestrel does not interfere with post-fertilization events in the new-world monkey Cebus apella’, has no scientific basis. The conclusions are not supported by the results reported, namely, in order to demonstrate that after levonorgestrel administration there is a living embryo it is necessary to find cardiac activity in the gestational sac. The authors did not mention cardiac activity in the ultrasound examinations of gestational sacs. Were they living embryos or dead embryos? Dead embryos not yet delivered are ‘missed abortions’ as all obstetricians know.

In the human species ≥10–15% of clinical pregnancies are aborted spontaneously. Cebus apella monkeys also have spontaneous abortions. In this paper the authors did not mention any spontaneous abortion in cases or controls. Obviously, the number of cases is inadequate for a scientific demonstration of the hypothesis: only 24 treatment cycles and 24 control cycles.

In my opinion this important research should be repeated with two conditions: (i) ultrasonographic examination of cardiac activity in all gestational sacs with a longer period of observation (pregnancies were aborted too early, on day 15 or 16 of the luteal phase, without a chance to observe appearance of cardiac activity); (ii) detection of spontaneous abortion rate in Cebus apella followed by a calculation of the necessary number of treatment and control cycles in order to be able to confirm or reject the hypothesis.

His first statement is that the paper has no scientific basis. The experimental work reported was done with strict adherence to an original design in which each female was its own control, and the sequence of control and drug-treated cycles was randomized, eliminating differences in fertility between individuals and effect of procedures as confounding factors. This is obvious upon reading what is explicitly stated in the manuscript. The purpose of conducting this study was to test the widespread hypothesis found in scientific and non-scientific literature, as well as the product labelling, that one of the mechanisms of action of emergency contraceptive pills is to interfere with implantation. The proportion of control and drug-treated cycles that exhibited prolonged luteal phases, as judged by absence of menses and maintenance of elevated plasma progesterone levels (not shown), was exactly the same in both groups of cycles. The suspicion of ongoing pregnancy was confirmed in all such cases by ultrasonographic visualization of a gestational sac. Cardiac activity, which becomes visible after day 30 of development (Corradini et al., 1998), was not assessed since pregnancies were terminated on day 15 or 16 of the luteal phase.

Mating during the periovulatory period, confirmed by the presence of sperm in the vaginal smear, results in~50% of the time in pregnancy that ends in delivery of a normal fetus in our colony (M.E. Ortiz et al., unpublished data). This outcome has been constant throughout 10 years and is not different from the proportion of gestation sacs that we found on days 12–16 of the luteal phase in control and levonorgestrel-treated cycles.

Concerning the frequency of spontaneous abortion in Cebus monkey, out of 126 pregnancies diagnosed by ultrason examination on days 12–15 of the luteal phase, in our colony between 1997 and 2003, only one gestation sac (0.8%) aborted before day 30 (M.E. Ortiz et al., unpublished data). Therefore the finding of no spontaneous abortion among the 26 pregnancies diagnosed in the present study is in keeping with previous data from the same colony.

The number of cycles observed was the minimum acceptable from a statistical point of view considering the cost of the study and available resources. The assessment of number of cycles required to demonstrate a 20% decrease in the number of pregnancies with levonorgestrel with a potency of 70% at $P < 0.05$ was 26 pairs of cycles (Miettinen, 1986). Common sense and experience indicate that it is highly unlikely that repetition of a study of this nature will yield a substantially different result, but we would be very pleased to see it done in other non-human primate species. The findings we reported in Cebus are in complete agreement with the results of a comparable study done in the rat, a very different and distant species (Müller et al., 2003). Therefore, the inescapable conclusion is that the widespread hypothesis that levonorgestrel, as used for emergency contraception, interferes

References


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Patricio Mena
Universidad de los Andes, Santiago, Chile
E-mail: pmgdr@manquehue.net
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Reply: Post-coital administration of levonorgestrel and post-fertilization events in the new-world monkey Cebus apella

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