Reviewer’s report

Title: Prenatal exposure to antifungal medication may change anogenital distance in male offspring: A preliminary study

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Reviewer: Angelo Moretto

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This paper reports on the ano-genital (scrotal - AGDas - and base of penis - ADGap) distance and penile width in three months old boys in relation to mother's exposure to antifungal medication with special attention to conazoles.

The authors base their conclusion on 4 (four) boys born from mothers who had a single 150 mg intake of fluconazole during the sensitive masculinization programming window (MPW). These boys had a mean AGDas (but not AGDap or penile width) lower that the mean of controls or of boys born from mother who used vaginal tablets and/or vaginal creams containing miconazole or cotrimazole. However, the AGDas of these boys were within the range of values of boys born from mothers not treated with antifungal medication.

The authors also state (from line 397) that the use of antifungal agents during the MPW was associated with larger reduction than the use outside the MPW. This is not consistent with the data presented in table 2. Of note also, that the penile width is reduced in boys born from mothers who were treated with unspecified (or "unspecific") antifungal medicines, but this is not commented by the authors.

There is also a lengthy discussion on possible pharmacokinetics explanations for the apparent (no statistically significant difference) lower AGDas in boys born from mothers using vaginal tablets as compared to those using vaginal cream; however, no data are presented to support this hypothesis.

The authors describe a number of weaknesses of the study that outweigh the (few) strengths. In any case, no meaningful conclusion can be based on four cases, though statistically significant.

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