Reviewer’s report

Title: Childhood and adolescent phenol and phthalate exposure and the age of menarche in Latina girls

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Reviewer: Jean-Pierre Bourguignon

Reviewer's report:

In this study, 26 phenol and phthalate urinary biomarkers were measured in 200 Chilean girls before the onset of breast development and at Tanner B4 stage. The data were correlated with menarcheal age after adjusting for different factors including adiposity.

General comment: The approach followed by the authors is consistent with that used so far in clinical studies aiming at possible EDC effects on pubertal timing. I wish however to bring some issues that were not addressed in the manuscript and suggest that the authors consider those issues in the discussion and, whenever possible, in data analysis.

1. It is generally agreed that 60-80% of the variance in menarcheal age is determined by genetic factors. The environmental contribution is thus comparably minor. A relatively reliable reflection of the genetic background of pubertal timing is the mother's menarcheal age that is known as being directly correlated with the daughter's menarcheal age. Along this observation, a girl apparently early (menarche at 11) whose mother had menarche at 10 may actually be late for her genetic background. Obviously, confounding factors (nutrition, life setting, ...) may also have influenced menarcheal age in the mothers. Do the authors have data on mother's menarcheal age and could they adjust the results accordingly? For instance, showing that mother's menarcheal age is not significantly different among the mothers in the studied tertiles for each chemical could reinforce a possible environmental influence.

2. BMI increases at puberty, depending on pubertal timing. Calculation of BMI Z scores based on average timing of puberty (Line 102) can account for a bias if not corrected for early or late timing. When referred to BMI in girls with average timing, an early or a late maturing girl will have adiposity overestimated or underestimated, respectively. Then, I would expect that a higher proportion of girls qualifies for BMI > 85th centile among the early maturing subjects than among the late. In the whole study population, 31.5% girls had a BMI above the 85th centile at B4, i.e. twice as many for an expected proportion of 15%. (Note the misspelling line 24 of table 1: B1 should be B4). My comment is in accordance with the observation reported in the 1980's by Tanner et al (J Pediatr 1985;107:317-29) who proposed reference height and height velocity curves corrected for pubertal timing (early, average and late). I am not quite sure a similar approach has been used for BMI references.
though it would be justified. I wonder whether such a bias could contribute to the increased adiposity in the subjects with earlier menarche as illustrated in Fig. 3.

3. Among the reasons for discordant observations as discussed lines 85-89, the role of environmentally relevant complex mixtures of EDCs should be considered. This includes persisting pollutants that are not addressed in the present study. A huge number of chemicals can possibly affect pubertal timing and the possible interactions among those chemicals at low doses remain unknown. Moreover, there are different periods in life when EDCs could affect pubertal (as rightly mentioned in the discussion). Considering all these aspects, what is the likelihood that a single measurement of a non-persisting chemical reliably reflects the burden of EDCs on a given endpoint i.e. pubertal timing? The authors could expand on this issue in the introduction or the discussion.

4. I find difficult that the authors argue on the association between menarcheal age and health outcomes for substantiation of their study (abstract, introduction, discussion and conclusion) though they did not study any health outcome. As an example, the concluding statement (abstract) on implications for future health is speculative (based on the data in the manuscript) and implies causality. My suggestion would be that this issue is only addressed in a paragraph in the discussion with emphasis on association not meaning causality. Line 62 is confusing in this respect: Early menarche does not increase the risk… It is associated with increased risk of… The authors could discuss that exposures could independently affect menarcheal age and cardiovascular/metabolic outcomes or cancer risk. Finally, the psychosocial consequences of early or late pubertal timing (risk-taking behaviors) could also be mentioned as a concern about changes in pubertal timing.

Specific comments:

5. Line 55: EDC impact on pubertal timing modified by BMI Z score: unspecific statement. Please be more specific.

6. Line 66-68: recent secular changes have been more towards earlier onset of breast development than earlier menarche. There is some confusion among a secular trend towards earlier menarche that started back in the late 18th century (Scandinavian countries) and a much more recent trend towards earlier onset of breast development and, to a lesser extent, earlier menarche. B2 stage is usually considered as the gold standard to evaluate the timing of onset of puberty. As a matter of fact, the recent secular changes are more important for B2 than for menarche. Thus, the average time period between B2 and menarche may have increased during the past 2-3 decades. What was the rationale for using B4 instead of B2?
7. Line 77-78: Also, effects can occur at different places including the neuroendocrine system (so-called central puberty), the pituitary gland, the ovaries and tissues such as the breasts (peripheral puberty).

8. Line 85-89: Ref 39 also falls into the longitudinal study in relation with puberty.

9. Line 97: Since the studied EDCs are not chemicals persisting in the human body fluids, what was the rationale for collecting samples at B4 and not at B2?

10. Line 123-128: The method used for timing of menarche is thus the so-called "recall" method as opposed to the "status quo" method. If data are available, the interval between menstrual episodes could provide most interesting information since regular intervals are meant to reflect ovulatory cycling and this developmental stage could be reached after a time period that can show secular changes (Hum Reprod 2002;17:228-232) and is a potential endpoint for EDC effects.

11. Line 174: Body size: Do you mean adiposity?

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