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Title:

How to control for gestational age in studies of effects of environmental factors on fetal growth?

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In studies about the effect of environmental factors on fetal growth, birth weight is usually corrected for gestational age. With the generalized use of ultrasound examinations in many countries, gestational age is often defined or corrected from the ultrasound measurements performed during or right after the first trimester of pregnancy, which are compared to a reference growth curve. As an illustration, in a cohort study investigating the association between exposure to perfluorinated chemicals and fetal growth and gestational age, Fei et al. (2007) defined gestational age from ultrasound measures done before 24 gestational weeks and, if this information was missing, from the date of the last menstrual period (LMP).

The superiority of ultrasound measurements over other approaches to predict the date of delivery (Lynch and Zhang 2007) does not imply that ultrasound-based gestational age leads to an unbiased estimate of the effect of environmental factors on fetal growth. The use of ultrasound-based gestational age assumes that fetal ultrasound measurements at a given gestational week during the first trimester have very little variability. However, there is some evidence of the contrary (Bukowski et al. 2007). Part of this variability might be due to exposure to environmental pollutants. If the environmental pollutant considered can restrict fetal growth as early as from the first trimester, correcting gestational age using first trimester ultrasound measurements will erroneously shorten the gestational age of these small-for-gestational-age fetuses. This may lead to underestimating effects of environmental pollutants on birth weight or size controlled for gestational age (Figure), compared to studies with an accurately estimated date of conception. In practice, an accurate estimate of conception date may be hardly available outside the setting of *in vitro* fertilization and an alternative is to rely on LMP-based estimates. These are prone to errors due to bad recall, variability in the duration of the follicular phase of the cycle

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and midcycle or early pregnancy bleeding (Lynch and Zhang 2007). Moreover, using the LMP-based estimate of gestational age would be problematic if, as already reported for specific environmental pollutants (Windham et al. 2003), the environmental factors considered could influence the duration of the menstrual cycle. Therefore, detailed studies may be needed to cautiously make the balance between the possible biases in the estimated effect of the environmental factor entailed by the use of ultrasound-based measurements and LMP-based estimate.

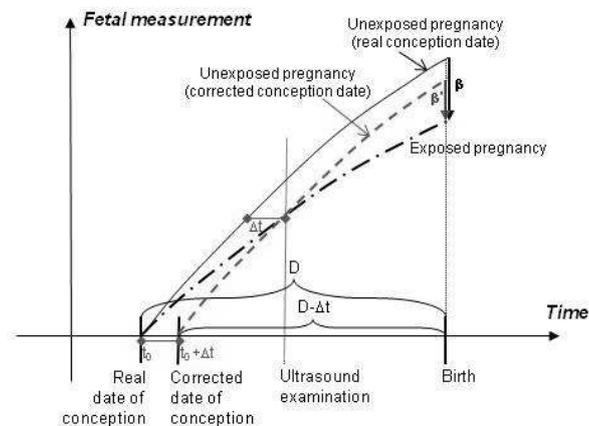
This potential bias has already been recognized (Savitz et al. 2002) and was alluded to by Fei et al. (2007) in their discussion. However, its consequences have probably not fully been acknowledged yet. When available, authors could conduct sensitivity analyses using different measures of gestational age, to help quantify the potential for bias. The same approach could also be used when gestational duration is the studied outcome (Lynch and Zhang 2007).

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## References

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**Figure:** Hypothetical evolution of a fetal measurement (e.g. fetal length) during pregnancy, for a pregnancy exposed or unexposed to an environmental factor affecting fetal growth from early pregnancy. The ultrasound examination leads the obstetrician to correct the date of conception of the exposed pregnancy by  $\Delta t$ , so that this exposed pregnancy is not compared to unexposed pregnancies with the same gestational age  $D$  (solid curve) as should be the case but with gestational age  $D - \Delta t$  (dashed blue curve). Consequently, the estimated difference in the gestational age-specific fetal measurement at birth between exposed and unexposed pregnancies is not the correct value  $\beta$  but a smaller value  $\beta'$ .



**Figure:** Hypothetical evolution of a fetal measurement (e.g. fetal length) during pregnancy, for a pregnancy exposed or unexposed to an environmental factor affecting fetal growth from early pregnancy. The ultrasound examination leads the obstetrician to correct the date of conception of the exposed pregnancy by  $\Delta t$ , so that this exposed pregnancy is not compared to unexposed pregnancies with the same gestational age  $D$  (solid curve) as should be the case but with gestational age  $D - \Delta t$  (dashed blue curve). Consequently, the estimated difference in the gestational age-specific fetal measurement at birth between exposed and unexposed pregnancies is not the correct value  $\beta$  but a smaller value  $\beta'$ .

