How to Control for Gestational Age in Studies Involving Environmental Effects on Fetal Growth

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In studies on the effects 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 immediately 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, Fei et al. (2007) defined gestational age from ultrasound measurements performed 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 to 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 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 1), compared with studies using an accurately estimated date of conception. In practice, an accurate estimate of conception date may seldom be available outside the setting of *in vitro* fertilization. An alternative is reliance on LMP-based estimates, which are prone to errors due to bad recall, variability in the duration of the follicular phase of the cycle and midcycle, and 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 determine 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 estimates.

This potential bias has been recognized by Savitz et al. (2002) and was alluded to by Fei et al. (2007) in their “Discussion.” However, its consequences have probably not been fully acknowledged. When possible, researchers should 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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How to Control for Gestational Age: Olsen and Fei Respond

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As described by Slama et al., it is not a simple matter to adjust for gestational age when analyzing birth weights. Any estimate of gestational age is prone to misclassification, whether it is based on ultrasound or last menstrual period (LMP). Ultrasound measurements are based on the assumption of uniform early fetal growth or at least that the exposure under study has no impact on early fetal growth. This assumption is probably not always correct, as first demonstrated by Henriksen et al. (1995). LMP estimates are prone to large random measurement errors that may become non-random if the exposures under study affects menstrual bleeding patterns.

Although these problems are part of textbook knowledge (Olsen and Basso 2007), their impact appears to be limited in our experience. In our study (Fei et al. 2007), the analyses based primarily on LMP estimates provided a regression coefficient of –10.35 [95% confidence interval (CI), –20.6 to –0.15] between perfluorooctanoate and birth weight, compared with the regression coefficient of –10.63 (95% CI, –20.79 to –0.47) we presented in the article after adjustment for ultrasound-based gestational age. The reason is probably that large random errors of gestational age affect estimates much more than smaller systematic errors. Furthermore, perfluorinated chemicals may not impair early fetal growth.

Birth weight is a function of fetal growth and the duration of the pregnancy, but until better estimates become available, we must use these imprecise measures of gestational age to determine the duration of pregnancy. If the exposure under study slows early fetal growth, adjustment for gestational age based on ultrasound may underestimate an effect of the exposure on...
5,861,200, thereby providing 0.2 m³/person/day of available dilution. These values were used to determine the predicted environmental concentration of oseltamivir carboxylate (OC), the active antiviral metabolite of the prodrug oseltamivir phosphate (Tamiflu), in the river during an influenza pandemic.

Unlike the other rivers investigated in the study, the mouth of the LC is in Mexico. Owing to its legal requirement as per Article 15 of the U.S.–Mexican Water Treaty (U.S. Government 1944), the United States releases 1,850,234,000 m³/year of the Colorado River to Mexico (Matuska 2007; U.S. Government 1944). This flow equates to 5,069,134 m³/day, which is roughly 5-fold higher than the values used in our previous study (Singer et al. 2007). Hence, the predicted environmental concentration of OC in the LC was considerably overestimated.

Detailed characterization of pollution risks in the LC is particularly challenging because of (a) the arid environment and high evaporation; (b) water conservation efforts lending many rivers to run dry; and (c) numerous diversions for irrigation and domestic use. A survey of the rivers that join the LC indicate few, if any, significant inflows into the LC from major metropolitan areas downstream of Las Vegas (USGS 2008). Notably, the only other major city that might feed into the LC is Phoenix, which discharges into the Gila River. The daily mean discharge of the Gila River where it joins the LC is 464.8 m³/day (in 2007), thereby augmenting the LC flow by < 10% (USGS 2008). Hence, risk characterization of this catchment was focused on the sewage discharge from Las Vegas to the LC.

Las Vegas lies within Clark County, Nevada, and has a population of 1,996,542 (Clark County Department of Comprehensive Planning 2007). Wastewater treatment plants from Clark County produce approximately 757,000 m³/day, which is consistent with a population of 2,102,777, assuming 360 L/person/day, as is consistent for U.S. water usage patterns [Water Services Regulation Authority (OFWAT) 2007]. The wastewater is discharged into the Lag Vegas Wash, a reach of Boulder Basin containing Lake Mead; Lake Mead has a storage capability of 17,500,000,000 m³ of water (Matuska 2007).

In the event of an influenza pandemic with a clinical infection rate of 35%, and assuming 100% pharmaceutical coverage of the infected population, approximately 3.0 ng OC would accumulate in each liter of water in Lake Mead. Expectations are such that only 25% of the infected population will receive Tamiflu (U.S. Department of Health and Human Services 2006), resulting in < 1 ng/L in Lake Mead. Given the average 3.9-year retention time within Lake Mead (LaBounty and Burns 2005), the OC concentrations will accumulate (OC is poorly biodegradable) in the lake over the course of a pandemic—unlike in rivers, which were previously modelled (Singer et al. 2007). Hence, risk characterization of the LC indicates that the predicted environmental concentration of OC will be well below levels known to induce viral resistance (Aoki et al. 2007; Hurt et al. 2007).

One remaining concern is the poor mixing and highly stratified nature of Lake Mead; for example, the wastewater input into the lake is often slow to mix completely with the rest of the water column (LaBounty and Horn 1997), resulting in 40-times greater perchlorate levels in the thermocline (30–40 m depth), than in the epilimnion or hypolimnion (LaBounty and Burns 2005). Such observations can be used to predict that OC concentrations > 80 ng/L may be expected in the thermocline in a pandemic situation. However, because wastewater comprises only 1.5% of Lake Mead’s flow and because the water in Lake Mead is discharged through the Hoover Dam from the hypolimnion, the location of lowest pollution, there is a low risk to the environment as a consequence of OC release.

Although we are pleased that the risk to the LC is lower than originally reported, this reinterpretation does not change the overall thrust of the article (Singer et al. 2007): After an influenza pandemic, OC concentrations in rivers would be considerably greater than previously seen for any other pharmaceutical, with the actual impact varying based on dilution within a catchment.

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REASSESSING THE RISKS OF TAMIFLU USE DURING A PANDEMIC TO THE LOWER COLORADO RIVER
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We wish to highlight an error in the article “Potential Risks Associated with the Proposed Widespread Use of Tamiflu” (Singer et al. 2007) in which we predicted environmental concentrations of Tamiflu (inhalua antiviral) in several catchments in the United States and the United Kingdom. An incorrect assumption was made in the hydrology of one of these catchments, the Lower Colorado River (LC).

In that study (Singer et al. 2007), we used flow data generated by the U.S. Geological Survey (USGS) and presented in BASINS [U.S. Environmental Protection Agency (EPA) 2001], as well as watershed population statistics summarized by Anderson et al. (2004). We (Singer et al. 2007) presented the flow of the LC as 1,223,424 m³/day, serving a population of 5,861,200, thereby providing 0.2 m³/person/day of available dilution. These values were used to determine the predicted environmental concentration of oseltamivir carboxylate (OC), the active antiviral metabolite of the prodrug oseltamivir phosphate (Tamiflu), in the river during an influenza pandemic.

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Incidence of New Onset Asthma after the World Trade Center Disaster
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Wheeler et al. (2007) provided useful information on the well-recognized problem of airways disease resulting from World Trade Center (WTC) exposure, reporting a 3-year risk of 3.6% for new physician-diagnosed asthma. As a pulmonologist in New York City who has also treated many WTC workers in a dedicated program, I would like to share the perspectives that my clinician colleagues have shared with me.

The diagnosis of asthma, even if made by physicians, is often nonspecific and based on symptoms that are nonspecific, as well as common. Diagnostic clues such as chronicity, recurrence, response to therapy, and variability in pulmonary function are not available on the first visit or the first few visits. A diagnosis bias toward asthma may operate for many reasons: a) a group under surveillance has an increased awareness of the target disease; b) asthma has been widely publicized to physicians, as well as to the public, as a result of WTC exposure; c) lists of accepted diagnoses required on first visits by monitoring and treatment programs, insurance companies, and compensation systems may guide the physician’s diagnosis to asthma even if she/he is not certain that this diagnosis has been established; and d) bias may exist in specifying the start of an ongoing illness, so that patients tend to associate it with a remarkable event like the WTC disaster even if symptoms or a physician’s diagnosis preceded this event. Wheeler et al. (2007) recognized the difficulty of estimating the incidence of disease, given the propensity of patients to cite a diagnosis that may not have been substantiated and to present for care only if symptomatic.

Wheeler et al. (2007) noted that even if all exposed persons were included in the denominator, the incidence of new asthma was still high. Much weight is placed on the estimated incidence of new asthma in the general population, for which the authors cited a review article, which in turn, cited a study from rural Minnesota that ended 25 years ago (Yunginger et al. 1992). Incidence of asthma is affected by region of residence (including rural vs. inner city), occupation, smoking, temporality, and other factors.

Wheeler et al. (2007) have brought their information to public attention to be confirmed by more specific criteria for diagnosis, longer clinical follow-up, and additional estimates of incidence in relevant urban populations.

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Editor’s note: In accordance with journal policy, Wheeler et al. were asked whether they wanted to respond to this letter, but they chose not to do so.

Urinary Mercury Levels in Children with Amalgam Fillings
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Woods et al. (2007) reported on exposure to dental amalgam fillings and urinary mercury excretion in children. They stated that “urinary mercury concentrations are widely used as a measure of mercury exposure from dental amalgam fillings.” We would like to point out some caveats about interpreting the results of mercury in urine.

Clarkson and Magos (2006) and others (Mutter et al. 2007; Nilsson and Nilsson 1986; Nuttal 2004) noted that urinary mercury is a rough indicator of mercury from dental amalgams. In fact, the urinary mercury concentration is unlikely to be a robust biological indicator for prolonged exposure to mercury vapor from dental amalgam. Previous postmortem studies in humans have shown that mercury levels originating from dental amalgam surfaces and retained in tissues are higher in brain regions and thyroid than those measured in renal cortex (Guazzi et al. 2006).

These findings are consistent with the fact that kidneys are the major contributors of urinary mercury (Magos and Clarkson 2006; Nuttal 2004), and the concentrations of mercury in urine may not reflect the tissue retention of mercury in more sensitive tissues such as brain and endocrine glands. This might explain the association between an increased frequency and severity of clinical symptoms among individuals with dental amalgams and consistently reduced levels of excretion of total mercury in urine (Minoia et al. 2006; Nilsson and Nilsson 1986).

In addition, Woods et al. (2007) listed several factors that may be involved in the differences in urinary mercury concentrations between the sexes. However, they did not mention bruxism in the text. Bruxism has an important causative role in the increased concentration of mercury in urine (Barregard et al. 1995). Because various reports have suggested that bruxing behavior may increase the urinary levels of mercury (Isacsson et al. 1997), Woods et al. should have included it as a potential confounder factor.

As a result of their randomized trials, Woods et al. (2007) evaluated the influence of sex on mercury excretion rates. They found that girls have a more significant increase in the rate of mercury excreted in urine than boys. Thus, this association might confer a lower mercury toxicity risks in girls.

Our experience regarding the care and treatment of adverse mercury amalgam events among adult individuals does not support the hypothesis that males might be more susceptible than females to the adverse events caused by long-term exposure to mercury vapor from amalgams (Guazzi et al. 2005). Our findings, which were derived from an ongoing study regarding clinically significant adverse events occurred in 289 adult patients due to mercury amalgam fillings, showed that females are two to three times more susceptible than males.
times more likely to develop local (e.g., lichenoid contact stomatitis) or systemic adverse health outcomes (e.g., skin disorders) compared with males [217 of 289 were women (75.09%) with a median age of 43; 72 of 289 were men (24.91%) with a median age of 40.5; female to male ratio, 3.1:1]. Therefore, in our experience, adult females were more likely to be affected by prolonged exposure to mercury vapor released from dental amalgams.

Moreover, given that inorganic mercury [Hg^{2+}] binds mainly to thiol ligands [–SH] as homocysteine (Bridges and Zalups 2004), we suggest that future clinical trials addressing the role of sex in mercury excretion should include an evaluation of serum homocysteine, which is higher in males than in females and might account for an increased tissue retention of mercury (Novembrino et al. 2006).

Finally, Woods et al. (2007) did not consider the importance of determining whether the exposure to mercury vapor emitted from amalgams may affect the immune system of children (Pigatto and Meroni 2006). Indeed, mercury-induced immunotoxicity arises far earlier than overt toxicity in the renal and central nervous systems.

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