Invited Commentary

Invited Commentary: Interpreting Associations Between Exposure Biomarkers and Pregnancy Outcome

David A. Savitz*

* Correspondence to Dr. David A. Savitz, Brown University, 37 George Street, 3rd Floor, Room 302, Providence, RI 02912 (e-mail: david_savitz@brown.edu).

Initially submitted September 22, 2013; accepted for publication October 8, 2013.

Levels of exposure biomarkers vary among individuals because of differences in both environmental exposure and metabolism. However, the ultimate interest is in providing information about the impact of modifying environmental exposures through regulation or behavior change. Using these levels in studies of pregnancy outcomes, as nicely illustrated by the study of Kadhel et al. in this issue of the Journal (Am J Epidemiol. 2014;179(5):536–544), has the usual strength of being integrative across multiple pathways but may reflect reverse causality, in which the underlying disease alters biomarker levels or shared physiological determinants of the biomarker level and the health outcome. Specifically, biomarkers may vary because of spatial differences in exposure, behavioral differences affecting exposure, and metabolic differences across members of the study population. Proper interpretation of such studies calls for a clearer understanding the sources of variation in exposure to more fully consider confounding and reverse causality due to metabolic differences within the study population.

biomarkers; fetal growth; pregnancy; preterm birth; reverse causality

A research paradigm for studies of environmental toxicants and pregnancy outcome has become well established, as nicely illustrated in the study by Kadhel et al. (1): Women are recruited during pregnancy, biospecimens are obtained for assaying the agents of interest (conveniently in the course of prenatal care), and the outcomes of pregnancy, most commonly gestational age and birth weight, are examined. The toxicants may be persistent or transient, may be studied in urine or blood, and are generally measurable to varying degrees in all study participants. Such studies do not examine variation in environmental exposure but rather variation in measured biomarkers. The reasons for interindividual variation in biomarker levels within the study population are often poorly understood and result from both differences in environmental exposure and differences in metabolism. The relative contribution of these 2 sources of variation is rarely known.

Chlordecone, the focus of the study by Kadhel et al., is plausibly a reproductive toxicant. The investigators collected biospecimens in a time window of etiological interest, the laboratory analyses were carefully done, and several other potential reproductive toxicants were assayed and controlled for as potential confounders (1). The agent was widely used in agriculture and is persistent in the environment in Guadeloupe, resulting in contamination of certain foods that resulted in elevated exposure in the study population. A log$_{10}$ increase in measured chlordecone was associated with shortened gestation (by approximately 2 days on average) and an increased risk of preterm birth (adjusted odds ratio = 1.6, 95% confidence interval: 1.1, 2.3), with an apparent dose-response gradient across biomarker quintiles. Although these data suggest that higher levels of chlordecone exposure may cause preterm birth, the key question is whether modifying the levels of environmental exposure to chlordecone would result in increased duration of gestation and lower risk of preterm birth.

The intent of such studies is to inform decisions regarding environmental regulation or behavior change to reduce exposure, not to decide whether biomarker levels should be manipulated. In fact, biomarker levels are not subject to direct manipulation, other than perhaps by enhancing excretion or diminishing uptake. The fundamental question is, “If the women with greater environmental exposure had received lower levels of environmental exposure, would their pregnancy outcomes have been different?” This easily drifts into the less interpretable question, “Had their measured biomarker levels been different, would the pregnancy outcome have been different?” Just as we can manipulate diet or physical activity level but not directly alter obesity, we can modify...
the environment or behavior but generally cannot directly alter the biomarker levels.

The use of pregnancy biomarkers of environmental toxicants is both the great strength and the pitfall of such studies. Ideally, the biomarker serves as an integrated measure of environmental exposures that are difficult to measure directly, capturing subtle variation in the location and behavior of women, the levels of contaminants in their home, yard, and neighborhood, and what they eat and what consumer products they use, as well as the levels of contaminants in those sources. Given the well-known limitations in the accuracy of dietary assessment, the decision to use a biomarker of chlordecon has great appeal relative to assessing levels of chlordecon in specific foods and querying the patterns of dietary consumption. However, in addition to reflecting the desired differences in exposure, the biomarker levels reflect differences in metabolism—volatile uptake, excretion, deposition, and transformation. Even if every individual in the population of the study by Kadhel et al. ate exactly the same foods with exactly the same concentrations of chlordecon, biomarker levels would undoubtedly vary. These concerns apply to some extent to all environmental biomarkers, but pregnancy raises some distinctive concerns because of the close proximity of biomarker measurement and health outcome and the physiological impact of pregnancy itself. An additional challenge is that abnormalities in pregnancy, such as preeclampsia or fetal growth restriction, may differentially affect biomarker levels relative to normal pregnancy. The ambiguous meaning of exposure biomarkers has made it difficult to reach resolution on the causal impact of many widely studied environmental toxicants on pregnancy outcome, despite a large number of well-done studies that support an association. Biomarkers vary among individuals for different reasons, and each is susceptible to differing biases and therefore has differing implications for causality.

BIOMARKER LEVELS MAY VARY AS A RESULT OF DIFFERENCES IN SPATIAL PATTERNS OF EXPOSURE IN THE COMMUNITY

The familiar challenge in this scenario is with the potential for spatial confounding due to neighborhood characteristics, most notably socioeconomic factors and correlated toxicants that follow the same spatial pattern as the one of interest. Measuring and statistically adjusting for those factors is challenging, given the difficulty of fully capturing constructs such as socioeconomic status and the feasibility and appropriateness of measuring and controlling for the other potential toxicants correlated with the exposure of interest.

BIOMARKER LEVELS MAY VARY BECAUSE OF VARIATION IN BEHAVIORS THAT RESULT IN EXPOSURE

Behaviors may include differences in occupation, dietary choices, use of consumer products, and hobbies. For each of these, there is a challenge in isolating the impact of environmental toxicant variation associated with the behavior from other correlated consequences of that behavior. Dietary choices affect nutrition as well as exposure to toxicants, occupation is associated with aspects of lifestyle that can affect health, etc.

BIOMARKER LEVELS MAY VARY BECAUSE OF INTERINDIVIDUAL DIFFERENCES IN METABOLISM

This possibility poses a less familiar challenge to inferring causality that is distinctive for biomarkers. With biomarkers, the outcome of interest may affect the measured biomarker level (reverse causality), or there may be shared biological determinants of the exposure measure and pregnancy outcome. A well-established example in pregnancy is the role of plasma volume expansion. Lesser amounts of expansion are known to be associated with pregnancy complications and related reductions in birth weight and increases in risk of preterm delivery (2, 3), and depending on the nature of toxicant storage, they may result in greater measured concentrations resulting from less hemodilution. Another concern is the role of renal function in pregnancy; the proteinuria associated with preeclampsia (4) or subclinical microalbuminuria (5) is predictive of unfavorable pregnancy outcomes but is also a potential source of variation in biomarker levels related to renal clearance. The environmental toxicant itself may alter metabolism, further complicating the interpretation of biomarkers and pregnancy outcome.

The question to be asked in studies of exposure biomarkers and pregnancy outcomes is how closely the situation approximates a controlled trial with exposure to the environmental exposure across individuals effectively randomized. In order to answer that question and assess the study’s implications for causality, we need to:

1. Be explicit about the hypothesized reasons for variation in biomarker concentrations across individuals within the study population and provide as much empirical evidence as possible to address the reasons that they vary, because susceptibility to confounding or reverse causality is entirely dependent on the source of interindividual variation. Although the average levels of chlordecon in Gaultrele relative to other geographic settings are undoubtedly elevated because of the use of the pesticide in that locale, the reasons that levels vary within that population are not so clear, potentially reflecting spatial variation in food production and dietary choices, as well as individual differences in metabolism. Repeat biomarker measures can help to quantify the contribution of some of these potential influences (6).

2. Examine other toxicants that may suggest nonspecific effects of interindividual variation in metabolism: Substantial correlation across a wide range of agents with presumably differing sources but shared metabolism suggests that the biomarker levels are driven by physiological variation and not differences in environmental exposure. Although it is possible that all of the associated agents have similar effects on the same outcome, that scenario is generally less plausible than a nonspecific correlation between metabolism and outcome. The modest correlations of chlordecon with dichlordiphenyl dichloroethylene and polychlorinated biphenyls, which are likely to vary primarily because of metabolic variation in the absence...
of a clear environmental source, provides some reassurance that chlordecone levels do not simply reflect metabolic tendencies.

3. Take into account the events in pregnancy that are likely to have a substantial impact on biomarker levels, including timing of biospecimen collection in gestation, renal function, plasma volume expansion, and proteinuria, and consider whether those same physiological traits may be related to the health outcome of interest. The consistency of findings for spontaneous and medically indicated preterm births provides some assurance that recognized pregnancy complications, such as severe preeclampsia (which leads to induced preterm birth), that affect renal function were not key contributors to the association found by Kadhel et al. (1).

The recognized virtue of biomarkers as integrative measures of exposure remains, but it needs to be reconciled with their potential shortcomings on a case-by-case basis. Although the association of serum levels of chlordecone with duration of gestation and preterm birth seems clear, the meaning of that association is not, and it can only be elucidated with better understanding of the reasons for exposure variation and perhaps with replication in complementary study designs in which exposure varies for different reasons than in Guadeloupe.

ACKNOWLEDGMENTS

Author affiliation: Department of Epidemiology, Brown University School of Public Health, Providence, Rhode Island; and Department of Obstetrics and Gynecology, Brown University Alpert Medical School, Providence, Rhode Island.

I thank Dr. Joseph Braun for helpful comments and suggestions on the manuscript.

Conflict of interest: none declared.

REFERENCES