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RESEARCH

The Roles of Formaldehyde Exposure and Oxidative Stress in Fetal Growth in the Second Trimester

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ABSTRACT

Objective: To examine the relationship between formaldehyde exposure and fetal growth in the second trimester and the potential mediating role of oxidative stress in this relationship.

Design: A cross-sectional study was conducted.

Setting: The participants were recruited from one university-related clinic and two private obstetrics and gynecology offices in the Southeastern United States.

Participants: A convenience sample of 140 healthy pregnant women in the second trimester of pregnancy was enrolled from November 2013 through June 2014.

Methods: Formaldehyde exposure was measured via vapor monitors worn by the participants for 24 hours. One-time urine samples were collected during a routine prenatal visit to measure the level of 15-isoprostane F_{2t} and cotinine as biomarkers of oxidative stress and tobacco smoking, respectively. Urine creatinine was measured to standardize the cotinine and 15-isoprostane F_{2t} levels.

Results: Eighty-eight participants (63%) returned their formaldehyde monitors. The linear regression model showed that the dichotomized level of formaldehyde exposure ($<$0.03 and $>$0.03 ppm) was a significant predictor of biparietal diameter percentile after controlling for maternal race ($p < .006$). The relationship between 15-isoprostane F_{2t} and fetal growth was nonsignificant, and the mediating role of oxidative stress in the relationship between formaldehyde exposure and biparietal diameter was not confirmed.

Conclusion: A relationship was found between formaldehyde exposure and biparietal diameter in the second trimester. Although further research is necessary to confirm the results of this study, nurses may consider advising pregnant women to limit their exposure to formaldehyde during pregnancy.

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Intrauterine fetal growth restriction (IUGR), defined as any deviation in fetal growth or failure to reach growth potential (Bernstein, Gabbe, & Reed, 2002), is associated with greater prenatal mortality and morbidity rates. Barker (1995), the author of the fetal programming hypothesis, stressed the importance of human fetal developmental experiences in determining patterns of diseases in the human life course. During the prenatal period, fetal tissues develop in a specific sequence from conception to maturity; therefore, the fetus is vulnerable to organizing and disorganizing influences on organ development (Bateson et al., 2004; Henrichs et al., 2009). Beyond the prenatal period, the long-term consequences of IUGR are associated with cognitive and developmental disabilities, metabolic disorders, and greater economic burden to family and society throughout the lifespan (Barker, 2004; World Health Organization, 2002).

Environmental exposures, such as indoor and outdoor air, are known to affect prenatal development. Air pollutants such as particulate matter, total suspended particles, sulfur dioxide, nitrogen dioxide, ozone, carbon monoxide, and polycyclic aromatic hydrocarbons have been linked to adverse pregnancy and fetal outcomes, such as small for gestational age (SGA), low birth weight (LBW), and premature birth (Dejmek, Solanský, Benes, Lenícek, & Srám, 2000; Huang et al., 2015; Langlois et al., 2014; Salam et al., 2005). Formaldehyde (FA) has been associated with abortion, congenital malformation, IUGR, and

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Limited evidence exists regarding the effect of low-level formaldehyde exposure during pregnancy on fetal growth.

preterm labor (<37 weeks gestation; Buhimschi, Buhimschi, Pupkin, & Weiner, 2003; Duong, Steinmaus, McHale, Vaughan, & Zhang, 2011; Pearson et al., 2003; Zhu, Knudsen, Andersen, Hjollund, & Olsen, 2006).

Formaldehyde, an aldehyde, is an air pollutant with the chemical formula of CH_2O. Aldehydes are organic compounds that contain a formyl group that may modify gene expression (National Toxicology Program, 2010). The International Agency for Cancer Research reclassified FA from probable human carcinogen to known human carcinogen in 2006 on the basis of sufficient evidence of its association with nasopharyngeal and nasal sinuses cancer and leukemia in industrial workers (National Toxicology Program, 2010). In addition, FA enhances oxidative stress, which is considered cytotoxic and potentially carcinogenic (Attia, Mansour, Taha, & El Dein, 2014). Furthermore, FA impairs fetal defense against allergic stimuli and infectious agents during pregnancy (Silva Ibrahim et al., 2015). Formaldehyde is defined by the Clean Air Act Maximum Achievable Control Technology standard as a hazardous air pollutant (U.S. Environmental Protection Agency [EPA], 1990). The Agency for Toxic Substances and Disease Registry (ATSDR; 2010) reported that indoor air is the dominant contributor to FA exposure through inhalation.

Indoor FA in residential dwellings is mainly emitted from building and household materials, such as paints, adhesives, wall boards, ceiling tiles, carpets, furniture, fiberglass, fabrics, household cleaners, insulation foams, and tobacco smoke (International Agency for Cancer Research, 2006). In addition, it can be produced by the blending of chemicals, such as household cleaning products, air fresheners, or perfume with ozone (Liu, Mason, Krebs, & Sparks, 2004; Uhde & Salthammer, 2007).

Although there are no standards for FA exposure level in residential dwellings (EPA, 2011), the ATSDR has established minimal risk levels of 0.040 part per million (ppm) for acute-duration inhalation exposure (14 days or less), 0.030 ppm for intermediate-duration inhalation exposure (15–364 days), and 0.008 ppm for chronic-duration inhalation exposure (365 days or more; ATSDR, 1999). Pregnant women's mean exposure level to FA is 0.040 (at the level of acute-duration inhalation), with a range of 0.003 to 0.540 ppm (Amiri et al., 2015). However, the ATSDR recommends less than 0.030 ppm for sensitive populations, including fetuses, children, the elderly, and the infirm (ATSDR, 1999).

More than 46 billion pounds of FA are produced worldwide annually and are used in building materials and household products (World Health Organization, 2010). Today, 37 companies produce FA at 40 plants in the United States in 20 states. Wood products that are imported from Malaysia and China had the greatest FA emission levels at 2.24 times the Australian standard (Ecos, 2006). In 1985, the U.S. Department of Housing and Urban Development set a maximum allowable concentration of 0.3 ppm for products used in manufactured homes (EPA, 2011); however, the EPA reported that in homes with significant amounts of new pressed wood products, FA levels can be greater than 0.3 ppm (EPA, 2011). Although 65% of the furniture sold in the United States was imported from Asian countries, and furniture imports from China increased by 166% between 2000 and 2005 (Luppold & Bumgardner, 2011), there have been no updates to the minimal risk levels or recommendations for FA exposures in sensitive populations.

Formaldehyde is absorbed through the dermis, by inhalation, or by ingestion; freely crosses the placenta to the fetus through passive diffusion; and accumulates in fetal organs (Pidoux et al., 2015). Elimination of FA is slower from fetal tissues, including brain and liver, compared with maternal tissues (Thrasher & Kilburn, 2001). The cause of this slow elimination is not clear; however, researchers showed that FA can be combined with nucleic acids and proteins and result in DNA–protein crosslinks in placental and fetal tissues (Pidoux et al., 2015). Pidoux et al. (2015) reported that FA promoted trophoblast cell fusion, decreased trophoblast hormonal functions, and increased oxidative stress in trophoblasts. Although endocrine activity of the placenta is essential for ensuring fetal growth and development, FA accumulation in the placenta may result in hormonal dysfunction in the placenta and alter its regeneration (Pidoux et al., 2015). In addition, authors of several studies showed that FA exposure during pregnancy has toxic effects on the fetal immune system, which is mediated by reduced anaphylactic antibody

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