This issue of Birth Defects Research Part C: Reviews – EMBRYO TODAY, “Prenatal Substance Use and Developmental Disorders”, features contemporary reviews of the health challenges to the conceptus resulting from prenatal substance use, including methamphetamine, cocaine, alcohol, and smoking, and associated long-term developmental disorders. This topical issue complements the Wiley-Blackwell Symposium, "Neurodevelopmental Deficits from Fetal Exposure to Methamphetamine, Cocaine, and Alcohol: Emerging Mechanisms and Human Consequences", jointly hosted by the Teratology Society and the Developmental Neurotoxicology Society and held at the 2016 Teratology Society Annual Meeting, San Antonio, Texas.

Substance use or abuse represents an increasingly significant health concern worldwide. The 2014 U.S. National Survey on Drug Use and Health (Center for Behavioral Health Statistics and Quality, 2015) reported that over 27 million individuals aged 12 and older used an illicit drug in the preceding 30 days. Among females, 7.4% of those over age of 12 and 5.3% of pregnant women 15 to 44 years of age reported current illicit drug use. Substance use among women of reproductive age is particularly concerning, as it is well documented that children of drug abusing parents are at an increased risk for Child Protective Services involvement, child abuse, and neglect, and there is a higher likelihood of caregiver depression and other co-occurring mental health disorders. In addition to drugs such as methamphetamine and cocaine, alcohol consumption and smoking during pregnancy represent additional challenges to developmental health of the fetus.

In their manuscript entitled "Fetal Oxidative Stress Mechanisms of Neurodevelopmental Deficits and Exacerbation by Ethanol and Methamphetamine", Wells et al. reviewed research findings that support oxidative stress as a principal mechanism of the effects of methamphetamine and ethanol on developmental and brain functions, specifically the formation of reactive oxygen species (ROS), resulting in altered signal transduction, and/or oxidative damages to cellular macromolecules, including lipids/proteins and DNA, the latter leading to altered gene expression, likely via non-mutagenic mechanisms. Free radicals such as ROS are highly reactive and short-lived, and antioxidative enzymes and DNA repair proteins normally serve as the body’s protective agents. Understanding the balance between oxidative and anti-oxidative mechanisms and the role of repair enzyme is critical to the development of future treatments. In "Mechanisms Involved in the Neurotoxic and Cognitive Effects of Developmental Methamphetamine Exposure", Vorhees and colleagues pointed out that 42% of pregnant women using methamphetamine continue to use throughout gestation, with the third trimester as the most susceptible period for the developing brain to prenatal exposure, resulting in a variety of higher-order cognitive deficits, such as decreased attention and working, and spatial memory impairments in exposed children. The authors reviewed studies on the impact of neonatal methamphetamine-induced neurotoxicity on behavioral outcomes, neurotransmission, receptor changes, plasticity proteins, and DNA damage.

In the paper by Smith et al., entitled "Prenatal Exposure: The effects of Prenatal Cocaine and Methamphetamine Exposure on the Developing Child", the authors reviewed the health outcomes at birth, growth, behavioral, and intellectual outcomes for children exposed to prenatal cocaine and prenatal methamphetamine. At present, there is no consistent syndrome associated with prenatal stimulant exposure, and no known withdrawal syndrome requiring pharmacologic intervention. Prenatal cocaine and methamphetamine exposure are also associated with subtle adverse growth and behavioral findings in childhood and adolescence. Some of these findings manifest in a dose-response manner and are mitigated by more responsive home environments. The authors suggest the importance of providing rapid, comprehensive drug counseling services to women actively using drugs during pregnancy, in order to optimize the long-term neurodevelopment of the exposed child. Prenatal cocaine exposure is further addressed by Stanwood and colleagues in their paper, entitled "Cocaine-Induced Neurodevelopmental Deficits and Underlying Mechanisms". Because cocaine easily crosses the placenta, its effects on the developing nervous system, before homeostatic regulatory mechanisms are properly calibrated, often differ from those on mature systems. The authors reviewed...
research findings on animal models and available clinical and image data from cross-sectional and longitudinal human studies, as well as the possibility of transgenerational transmission of altered phenotypes.

In "Impact of Fetal Alcohol Exposure on Body Systems: A Systematic Review", Jabbour and co-authors reviewed published literature on fetal alcohol spectrum disorders, fetal alcohol syndrome, prenatal alcohol exposure, and alcohol related birth defects, illustrating the brain as the most severely impacted organ of the body systems, with other abnormalities found within the heart, kidney, liver, gastrointestinal tract, and the endocrine systems. Finally, the review by Holbrook, entitled "The Effects of Nicotine on Human Fetal Development" highlights the public health concern over maternal smoking, with nicotine exposure posing an extremely harmful effect to the developing fetus, particularly at later gestational age. It is estimated that upwards of 10% of all pregnancies are exposed to nicotine. Effects on the pregnancy include premature birth, intrauterine fetal demise, placental insufficiency, and low birth weight. Conceptual health problems associated with prenatal nicotine exposure include impaired functions of the endocrine, reproductive, respiratory, cardiovascular, and neurologic systems. Poor academic performance and significant behavioral disruptions are also common, including attention deficit/hyperactivity disorder, aggressive behaviors, and future substance abuse. E-cigarettes are generally viewed by the public as safer during pregnancy than traditional cigarettes; however, solid data to support this are lacking.

With the increasing societal prevalence of substance abuse, prenatal exposure has emerged as a critical health challenge that has long term, and almost irreversible, harmful effects on the newborn and to the developing child, that often last to adulthood, with large societal costs. The disorders are largely related to brain functions, although endocrine, reproductive, respiratory, and cardiovascular systems are also often involved, particularly in the case of alcohol and nicotine prenatal exposure. Adequate and effective health education is thus vital to eliminate or reduce substance use during pregnancy. In addition, deeper understanding of the nature of the harmful effects is needed to support rigorous mechanistic science into identifying the cellular and molecular targets of the actions of these substances. The knowledge gained from these activities should elevate public awareness and the urgency on the part of both the physician and the patient to work towards a decline in substance use, and also lead to the strategic selection of druggable targets for the development of therapeutic agents for the primary and associated symptoms to improve outcomes of the pregnancy and the lifelong health of the exposed child.

References