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Title: The intimate connection between maternal health and fetal development

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Human development depends on a complex interplay between genetics and environment. The fetoplacental unit does not grow in an isolated chamber, but is intrinsically connected to maternal physiology and all of its associated perturbations. In this special topic issue of *Prenatal Diagnosis*, we turn our focus to the important maternal health conditions and environmental exposures that have short and long term consequences for the developing fetus.

The intrauterine environment has been long recognised as having a far-reaching impact on an individual's health. Last century, the British epidemiologist David Barker first drew attention to the associations between low birthweight and adult-onset cardiovascular disease and diabetes.¹ Today, we now grapple with the intergenerational consequences of maternal overnutrition, not undernutrition. In this issue, Edlow and colleagues synthesize the growing body of epidemiological, clinical, and animal studies on the relationship between maternal obesity and adverse cardiometabolic and neurodevelopmental outcomes in offspring.^{2,3}

The global increase in maternal obesity has also driven a rise in gestational diabetes mellitus. Murray and Reynolds review the consequences of gestational diabetes mellitus (GDM), and examine emerging concerns with use of the oral glucose-lowering drugs, metformin and glibenclamide.⁴ Maternal pre-existing diabetes can have much more profound effects on

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fetal development than GDM. Shub and Lappas review the mechanisms by which congenital anomalies and disorders of fetal growth occur in women with pre-existing diabetes, including the epigenetic modifications, changes in gene expression in critical developmental pathways, and the role of oxidative stress.⁵

Advances in treatment of monogenetic disorders has led to more women with significant health conditions reaching reproductive age and contemplating motherhood. While pregnancy can have a significant impact on a woman's health when there is an underlying genetic disorder, there can also be fetal effects, including embryopathy, fetal growth restriction and brain injury. Mardy, Chetty and Norton review several maternal genetic conditions with important fetal risks, including inborn errors of metabolism, tuberous sclerosis, myotonic dystrophy, cystic fibrosis, and Turner syndrome.⁶ Additional articles in this issue cover other key maternal medical conditions with implications for fetal health including systemic lupus erythematosus, thyroid disease, and maternal Rhesus alloimmunization.⁷⁻⁹

Maternal contributors to adverse fetal outcomes may be iatrogenic. Maternal medication-related embryopathies, antenatal corticosteroids and diagnostic radiology are also included in this issue, providing clinicians with up-to-date advice on clinical management of short and long term risks to the fetus/child and current controversies and knowledge gaps.¹⁰⁻¹² While the use of medications during pregnancy will always raise concerns, there is hope that new concepts in the fetal blood brain barrier may usher in a more rational approach to future drug development and safety testing.¹³

This issue also addresses the impact of two of the most common legal recreational substance exposures. While it is widely accepted that cigarette smoking and alcohol consumption during pregnancy is harmful, the need to understand the mechanisms of their impact on the fetus and placenta has not abated. Our cover image comes from a review on the genetic and epigenetic mechanisms involved in fetal alcohol spectrum disorders from Kaminen-Ahola.¹³ She advances the case for improving our understanding of the molecular mechanisms of prenatal alcohol exposure so that we can devise better approaches for prevention or treatment of the alcohol-induced developmental disorders. Similarly, understanding the cellular and subcellular effects of nicotine and tobacco exposure on the placenta is particularly relevant with the rise of electronic nicotine delivery systems over the past decade. Suter and Aagard summarize the latest research on the placenta and tobacco smoke or nicotine exposure, including both histologic, epigenetic and molecular modifications to the placenta.¹⁴

Finally, one of the great success stories in the prevention of fetal abnormalities is folic acid supplementation and neural tube defects (NTDs). Although NTDs remain among the most debilitating of all human developmental anomalies, there is still much to understand about the gene-environment interactions, particularly with regard to folic-acid resistant NTDS. Rick

Finnell, our opening keynote speaker at the 23th international conference on Prenatal Diagnosis and Therapy held in 2019, contributes a comprehensive review with his colleagues, using NTDs as an exemplar of new approaches to studying the genomic architecture of complex birth defects.¹⁵

As a multidisciplinary readership, we are united by our collective interest in the developing fetus, gene-environment interactions, and clinical care of the pregnant woman. This special topic issue of *Prenatal Diagnosis* brings together contributions from a broad range of clinical and research experts in maternal fetal medicine and human development, and I trust, will deliver something of interest to each of our readers.

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