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Potential latent effects of prenatal cocaine exposure on growth and the risk of cardiovascular and metabolic disease in childhood[☆]

Sarah E. Messiah^{a,*}, Tracie L. Miller^{a,b}, Steven E. Lipshultz^{a,b}, and Emmalee S. Bandstra^c

^aDivision of Pediatric Clinical Research, Department of Pediatrics, University of Miami Leonard M. Miller School of Medicine, Miami, FL, USA

^bDepartment of Epidemiology and Public Health, University of Miami Leonard M. Miller School of Medicine, Miami, FL, USA

^cDivision of Neonatology, Department of Pediatrics, University of Miami Leonard M. Miller School of Medicine, Miami, FL, USA

Abstract

The literature strongly suggests that prenatal exposure to certain medications and substances does not cause major malformations in early childhood. However, these exposures may have far-reaching latent health effects, such as restricted growth, hypertension, and cardiovascular events in adulthood. We reviewed the literature to identify the effects of prenatal cocaine exposure on growth and the risk of cardiovascular and metabolic disease in late adolescence and early adulthood by examining studies that were published in peer-reviewed English-language journals from 1990 through 2009 and indexed in MEDLINE. We found that animal and clinical studies of the influence of prenatal cocaine exposure on child and adolescent growth and the subsequent development of myocardial and cardiometabolic disease risk factors are few and inconclusive. Studies support the hypothesis that vascular and hemodynamic functions are partially programmed in early life and thus substantially influence vascular aging and arterial stiffening in later life. Sub-optimal fetal nutrition and growth may increase blood pressure and the development of cardiovascular and metabolic disease in late life. How prenatal cocaine and other drug exposure effects this relationship is currently unknown. Despite high rates of cocaine and other drug use during pregnancy (up to 18% in some studies), little is known about the health effects of prenatal cocaine exposure in adolescence and early adulthood. The few studies of early growth deficits persisting into adolescence are inconclusive. The literature provides little information on how exposed children grow into adulthood and about their subsequent risk of cardiometabolic and vascular disease.

Keywords

Prenatal; Drug exposure; Cardiovascular disease; Pediatric; Growth; Metabolic disease

* All work originated from the University of Miami, Miller School of Medicine, Department of Pediatrics, Division of Neonatology and Division of Pediatric Clinical Research.

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[☆]Corresponding author. University of Miami, Miller School of Medicine, Department of Pediatrics, Division of Clinical Research, Batchelor Children's Research Institute, Room 541, 1580 NW 10th Avenue (D820), Miami, FL 33101, USA. Tel.: +1 305 243 1943, +1 305 778 5309 (cell); fax: +1 305 243 8475. smessiah@med.miami.edu. .

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1. Introduction

Prenatal drug exposure, and cocaine use in particular, has been linked to several cognitive, language, neurodevelopmental, and behavioral deficits in infancy and childhood [1-5]. Much less is known about how this exposure affects the cardiovascular or metabolic system in the later years of adolescence and young adulthood, including whether prenatal drug exposure may affect the development of cardiometabolic and vascular disease risk factors. Heart disease and diabetes are both major causes of mortality (ranked first and sixth, respectively) in the United States accounting for over 700,000 deaths per year [6].

The belief that events in the perinatal period have latent effects throughout the life course has become increasingly accepted. The literature on this “fetal-origins hypothesis” strongly suggests that while exposure to certain medications and substances, maternal malnutrition, and poor maternal health might not cause major malformations in childhood, such exposure can nevertheless have enduring, or latent effects such as restricted growth, hypertension, cardiovascular events, and altered renal function in adulthood [7]. The fetal-origins literature also describes intergenerational transmission of the mother’s own gestation and life into the prenatal and child-rearing environments of her offspring [8]. These environments are physiological (e.g., maternal metabolic regulation), psychobehavioral (e.g., stress, smoking, mother’s continued substance use), and ecological (e.g., poverty, unstable food supply). How these environments affect the long-term growth and health of the child as they develop into adulthood is largely unexplored, however.

We reviewed the literature to identify the effects of prenatal cocaine exposure on the fetus, infant and mother as well as on growth and the risk of cardiovascular and metabolic disease in late adolescence and early adulthood by examining studies that were published in peer-reviewed English-language journals from 1990 through 2009 and indexed in MEDLINE.

2. Effects of prenatal cocaine exposure on the fetus

The fetal heart is fully functioning only 55 days after conception. Further development occurs through cell division, maturation of cardiomyocytes, development of the conduction system, formation of gap junctions, and calcium handling that enables optimal myocyte function and appropriate ventriculo-vascular coupling. The maturation of baroreceptor function and the growth of arteries and peripheral vascular beds and their regulation are determined during the prenatal and early postnatal months. These processes can all be permanently altered by environmental assaults in the womb, such as insufficient nutrition and oxygen uptake and the introduction of toxins. These exposures can have potent effects that last a lifetime. For example, people who were small at birth tend to remain biologically different from those who were larger [9]. The differences include an increased susceptibility to hypertension and type 2 diabetes mellitus: two disorders closely linked to coronary heart disease [10]. Additionally, birth weight is associated with differences in blood pressure and insulin secretion within the normal ranges [9].

Knowing the mechanisms involved in the association between fetal growth and, in particular, latent cardiovascular disease risk, might allow the development of new strategies to lower the prevalence of diabetes and coronary artery disease, although the pathophysiological links are still unclear. Several hypotheses have been proposed [9,11]. Each likely represents a different piece of the same puzzle and may explain some of the implications of prenatal cocaine use.

One process associated with disproportionate fetal growth is the redistribution of blood flow to the brain, heart, and adrenal glands from other organs such as the liver and kidneys [11]. This redistribution involves altered responses to vasoconstrictors and vasodilators in

different organs and the shunting of blood to bypass certain regions. The two main shunts are the ductus arteriosus and the ductus venosus. In fetal animals, the response to hypoxemic and other adverse influences is to shunt highly oxygenated blood in the umbilical veins through the ductus venosus and into the inferior vena cava [12,13]. This shunting benefits cerebral circulation but deprives the liver and impairs its growth. Less is known about the immediate and long-term consequences of redistributed blood flow in the human fetus and among those exposed to cocaine in particular.

Studies of the general population indicate that in a nutritionally compromised uterine environment, certain organs, such as the brain, tend to be spared at the expense of others [14-17]. Specifically, fetal and early postnatal undernutrition can invoke metabolic adaptations that affect variables such as hepatic enzyme profiles [18], lipoprotein profiles [19], and clotting factor production [20]; anatomical adaptations that affect processes such as end-organ glucose uptake [21] and renal solute handling [22]; and endocrine adaptations that affect the hypothalamic–pituitary–adrenal axis [23], insulin signaling [24], and leptin levels [24]. These changes affect adult health outcomes, such as coronary heart disease, stroke, type 2 diabetes, and metabolic syndrome, all of which are more common in individuals with low-birth-weight. Over-nutrition (obesity) in later life, however, can overwhelm the physiology, causing disease [9]. This hypothesis was later expanded to include the proposal that pathological changes after undernutrition in early life also greatly depend on other factors, notably obesity, aging, and physical inactivity [25].

3. Effects of prenatal cocaine exposure on the infant

The most common problems in babies born to mothers using cocaine while pregnant include low birth weight and reported abnormalities in the liver, lungs, genitals, and neurological system [26]. Cardiac malformations reported to be associated with prenatal cocaine exposure include atrial and ventricular septal defects, hypoplastic right or left side of the heart, and absent ventricle [27]. In addition, associations with coarctation of the aorta, peripheral pulmonary stenosis, patent ductus arteriosus, aortic valve prolapse, and arrhythmias have also been documented [28,29]. In some children, these cardiovascular abnormalities are associated with congestive heart failure, cardiorespiratory arrest, and death [30,31].

4. Maternal effects of cocaine use during pregnancy

According to the 2007 National Survey on Drug Use and Health conducted by the US Substance Abuse and Mental Health Services Administration, approximately 2 million Americans aged 12 years and older are regular cocaine users [32]. More than 3% of women are reported to be using an illicit drug, including cocaine, during pregnancy [32], resulting in potentially tens of thousands of cocaine-exposed infants born every year.

Pregnancy is associated with increased sensitivity of the cardiovascular system to cocaine, and in turn the cardiovascular toxicity of cocaine is substantially increased in pregnancy. Cocaine is rapidly transferred across the placenta to the fetus by simple diffusion and may cause marked vasoconstriction of fetal blood vessels [33]. Additionally, maternal vasoconstriction can indirectly affect the fetal effects of cocaine. Because uterine blood flow is not autoregulated, decreased uteroplacental blood flow may lead to uteroplacental insufficiency, acidosis, and fetal hypoxia.

Pathophysiologically, by blocking the presynaptic uptake of sympathomimetic neurotransmitters (including norepinephrine, serotonin, and dopamine), cocaine produces prolonged adrenergic stimulation and feelings of euphoria by prolonging dopamine's activity in the limbic system and cerebral cortex [34,35]. It is well known that ingesting

cocaine causes life-threatening cardiovascular events, including hypertension, tachycardia, malignant arrhythmias, myocardial ischemia, and infarction [36,37]. Mechanisms of cocaine-induced myocardial ischemia or infarction include thrombosis, vasospasm, or both, and direct myocardial depression [38]. Further direct maternal complications of cocaine ingestion during pregnancy include premature labor, placental abruption, uterine rupture, cardiac dysrhythmias, hepatic rupture, cerebral ischemia or infarction, and death [39-41].

5. Latent health effects and growth in prenatally cocaine-exposed children

Whether any early growth deficits related to cocaine exposure will persist from infancy into childhood is unclear: some studies report that prenatal cocaine exposure has a detrimental effect on growth [42-46] and others report no detrimental effect [47-52].

A few investigators have explored the effects of prenatal cocaine exposure on growth into the preschool- and school-age periods. Hurt et al. [53] found reduced weight and head circumference at 2 and 2.5 years in prenatally cocaine-exposed infants, although these analyses did not control for alcohol, marijuana, or tobacco use; Minnes et al. [54] found relationships between a cocaine metabolite in infant meconium and height-for-age and weight-for-height z scores at age 6 years, after controlling for correlates of prenatal cocaine exposure; and Covington et al. [55] reported associations among prenatally cocaine-exposed children with reduced height at age 7 years in offspring of women over 30 years of age, after controlling for prenatal alcohol and tobacco use. Moreover, in a longitudinal growth-curve analysis by Richardson et al., children exposed to cocaine during the first trimester of pregnancy grew at a slower rate through 10 years of age than did unexposed children, even when controlling for exposure to other drugs [56]. In contrast, other studies have found no pronounced effects on the growth of cocaine-exposed preschool- and school-aged children [53,57].

In an investigation of birth size and subsequent growth through age 6 years, Shankaran et al. reported significant differences in birth weight, length, and head circumference of exposed infants; however, these differences disappeared by 2 years of age for weight and head circumference and by 3 years of age for height [58]. Thus, the literature on the long-term effects of prenatal cocaine exposure on growth is limited, has had conflicting results, and has not assessed growth past 10 years of age.

Additional factors that might influence growth must also be considered. For example, prenatal alcohol exposure has been associated with long-term growth deficits in some studies [59-61] but not in others [62,63]. In addition, growth is influenced by sex, race, and age [64-66]; parental size [67]; demographic and environmental variables [68,69]; and maternal nutrition [70] and smoking [71,72]. These characteristics must be considered when investigating the relationship between prenatal cocaine exposure and growth.

Several studies have reported, with few exceptions, that maternal smoking during pregnancy is associated with higher body mass index (BMI) and type 2 diabetes in the offspring during childhood [73,74]. Smoking in pregnancy has also been reported to be associated with lower birth weights [75]. Just as higher birth weights tend to be associated with later obesity, lower birth weights have been associated with increased adiposity and central fatness in later life [76]. Metabolic adaptations linked to maternal smoking may retard prenatal growth through pathways that may increase the risk of obesity after birth [77-81]. Despite the promotion of smoking cessation for women planning to conceive, a substantial proportion of women continue to smoke in early pregnancy [82]. Therefore, studies are needed to determine whether smoking in early pregnancy *combined with other drug use* may affect later health outcomes in children as well.

6. The importance of “catch-up” growth

When discussing the topic of pediatric growth it is important to mention the importance of postnatal “catch-up” growth (when an infant experiences such rapid weight gain shortly after birth that weight and/or height changes from a percentile well below the mean to one at or even above the mean) and its potential to modify the association between birthweight and cardiovascular disease. Some researchers propose that the metabolic adaptations permitting survival for growth-retarded infants are a liability in childhood and result in a higher-than-expected risk of type 2 diabetes in adulthood [83]. Increases in the percentage of body fat, insulin resistance, and central obesity were greatly enhanced when low birth weight was followed by rapid postnatal catch-up growth [84,85]. Further-more, several studies report that catch-up growth may have particularly adverse effects on later metabolic health among small-for-gestational-age babies [8-10,20-25,86-93]. However, the period after birth in which accelerated growth may be disadvantageous is unknown, with some studies pointing to the immediate postnatal period [89,90] and others suggesting that low weight at age 1 year or low weight gain in the first year of life may contribute to the risk of metabolic and cardiovascular disease associated with low birth weight [8-10].

Several studies indicate that accelerated growth in childhood further increases the risk of cardiometabolic disease [9,10]. Nevertheless, a potential confounder in many studies may be the lack of correction of catch-up growth for low-birth-weight infants. Given the fact that small-for-gestational-age infants at the time of birth are shifting from an adverse and sparsely nutritional intrauterine environment into a presumably healthier one, not correcting for catch-up growth may be important. In other words, the potential state of cellular hunger in small-for-gestational-age infants at the time of birth may by itself facilitate a more efficient nutritional uptake and energy metabolism and thereby a greater postnatal growth rate. Furthermore, the statistical phenomenon, “regression toward the mean,” may theoretically result in an apparently more rapid growth in these infants.

Unfortunately, only a few long-term prospective studies have reported precise measurements of early infant growth and later metabolic health. In one study blood pressure was measured at 6 to 8 years in 153 of 299 (51%) of a cohort of children born small for gestational age and randomly assigned at birth to receive either a standard or a nutrient-enriched formula. The enriched formula contained 28% more protein than standard formula and promoted weight gain. Diastolic and mean (but not systolic) blood pressure was significantly lower in children assigned to standard compared with nutrient-enriched formula (unadjusted mean difference for diastolic blood pressure, -3.2 mm Hg; 95% CI, -5.8 to -0.5 ; $P=0.02$) independent of potential confounding factors (adjusted difference, -3.5 mm Hg; $P=0.01$) [91].

Another study reported that infant weight gain from birth to 6 months was positively associated with metabolic risk at 17 years of age, partly independent of birth weight z-scores.[90] Specifically, clustered metabolic risk at age 17 years was predicted by weight gain during infancy (standardized beta = 0.16; $P<0.0001$) but not during early childhood (standardized beta = 0.10; $P = 0.23$), adjusted for birth weight, gestational age, current height, maternal fat mass, and socioeconomic status at age 17 years. Further adjustment for current fat mass and weight gain during childhood did not alter the significant association between infancy weight gain with the metabolic risk score (standardized beta = 0.20; $P = 0.007$).

Although prenatal cocaine exposure is linked with height deficits at age 7 [55], to date no catch up growth patterns have been consistently reported among this population. However, we found no information on children exposed to cocaine *prenatal* beyond the age of 10.

7. Fetal and early postnatal programming of vascular function

Vascular alterations appear early in life. Myocardial responses to prenatal exposures may permanently alter the limits of myocardial compensation and reduce overall adaptive ability (a process called “programming”), resulting in heart failure in adult life [94]. To date there have been no human studies linking prenatal cocaine exposure and altered vascular function later in life. However, evidence of early alterations in vascular function has been described in children and adolescents with low birth weight [95]. These alterations are indicated not only by high blood pressure but also by an increase in blood pressure variability, pulse pressure, and the impact of reflecting waves on central pulse pressure. Children with the lowest birth weights tend to have not only the lowest systolic blood pressures but also the highest heart rates. These intermediate phenotypes are the expression of functional or structural abnormalities that have been solidified *in utero*.

Vascular performance is described in terms of its elastic modulus (coefficient of elasticity) and characteristic resistance modulus, which vary by vessel caliber and dispersion [94]. In turn, vessel caliber and dispersion may restrict growth by reducing peripheral vascular beds both in size and vascularity [96]. As vascularity and peripheral vascular beds enlarge and subdivide, the peripheral vascular and dynamic impedance moduli fall. The vascular modeling responses seen in altered flow states enable the vessel wall to maintain an optimal shear stress [97].

In the human fetus, elastin deposition does not occur at the same rate as increases in aortic length. Deposition is largely driven by increasing hydrodynamic forces and the pressure of fetal circulation, so much so that elastin distribution decreases with increasing distance from the ascending aorta. However, elastin is rapidly deposited during the second half of pregnancy and the first months of life, a fact supporting the hypothesis that abnormal nutrition at this time may in some way affect elastin deposition, altering the natural increase in distensibility of the aorta and thus accounting for later cardiovascular pathophysiology [94].

8. Endothelial function

The endothelium is integral to vascular growth and modeling and thus influences the size of vessels and tissues and organ perfusion, as well as immune responses, vascular permeability, and tissue metabolism. Programming the vascular endothelium has implications beyond the cardiovascular system and how prenatal cocaine exposure effects the growth and development if the endothelium is largely unknown. Changes to the normal development of vascular endothelial function increase the incidence of hypertension, atherogenesis, diabetes, coronary heart disease, and metabolic syndrome [94].

9. Arterial baroreceptor function

Human and animal studies have shown that the arterial baroreflex is active and more responsive during early development than later in pregnancy. Tilt testing to assess baroreceptor function in babies and in those with apparently life-threatening events has shown an imbalance between the inhibitory parasympathetic and stimulatory sympathetic activity [98]. Heart rate variability appears to be set by early environmental influences, and neonatal studies report that the normal progressive decrease in the low-to-high-frequency power ratio in the normal fetus is altered in fetuses with restricted growth [97]. This alteration suggests that the increase in vagal tone associated with normal maturation is delayed in fetuses that have experienced an adverse environment and that this delay may result in persistent elevation of basal sympathetic tone, which may also reduce arterial compliance [99,100].

10. The influence of growth restriction on vascular development

Growth-restricted fetuses remain significantly lighter and shorter than normal until the end of the first year of life [101]. This reduced size is not generally reflected in altered cardiac size, although the left ventricle may be smaller and thus does not adequately prepare the fetus for the catch-up in somatic growth that occurs during infancy. The growth-restricted fetus shows marked vascular pathophysiology, as indicated by reductions in mean flow velocity, aortic pulse amplitude, and other measures of vascular distensibility [101]. The reduced relative pulse amplitude reported in studies of growth-restricted fetuses may reflect altered vascular responses to the distending pulse pressure. In hypertensive adults, this response is an important independent predictor of cardiovascular complications.

These abnormalities of aortic physiology may be explained by augmented pressure waves in the descending aorta that result from the rapid reflection of waves produced by increased placental impedance. Despite this increased impedance the volume of blood flow (corrected for fetal weight) does not differ greatly in growth-restricted infants, and cardiac output is usually maintained unless there is marked hypoxemia. However, flow is redistributed to the fetal brain, increasing left ventricular output, which may be why the aortic valve diameter is increased in growth restriction. Growth velocity rate in the descending thoracic aorta is reduced after birth in studies that have corrected for weight and for gestation, suggesting that cardiac growth velocity is proportional to somatic growth velocity and that both are reduced [101].

In summary, epidemiological and mechanistic studies support the hypothesis that vascular and hemodynamic function are at least partially programmed in early life and thus substantially influence vascular aging and arterial stiffening in later life. Suboptimal fetal nutrition and growth may increase blood pressure and the development of cardiovascular and metabolic disease in late life through several mechanisms. Specifically, the structure of the arterial wall may be permanently altered by sub-optimal fetal nutrition (such as a reduced elastin content), resulting in reduced arterial impedance and increased loading conditions on the heart. Secondly, abnormal fetal blood flow patterns may alter vascular shear stress and endothelial function and reset baroreceptors, thus permanently altering an individual's response to changes in flow. Additionally, renal mechanisms may alter the response of the renin angiotensin system, altering the vascular responses that accompany myocardial hypertrophy and fibrosis. A combination of these mechanisms and additional neuroendocrine responses are likely to act together to determine an individual's later cardiovascular responses. Exposure to cocaine and other drugs during fetal development has been largely unexplored, however, in terms of these latent effects.

11. Type 2 diabetes

To date no studies have examined prenatal cocaine exposure's effect on the latent development of insulin resistance, glucose intolerance and type 2 diabetes in late childhood or adulthood. However, this is an intriguing paradigm given that the majority of type 2 diabetes cases result in obesity and increased caloric intake may take place to compensate for stress in many of these situations. Whether children exposed to cocaine *prenatal* are more vulnerable to eating as a stress coping mechanism compared to non-exposed children remains to be determined.

Both animal and human studies consistently support a positive association between insulin resistance and/or insufficient insulin production as mechanisms and the onset of type 2 diabetes and obesity in offspring of mothers who were hyperglycemic while pregnant [102]. Animal models have shown that not only is the risk for adult onset diabetes increased via in-utero exposure to high maternal glucose concentrations, but that this risk may be

transmitted to further generations [103] suggesting that *prenatal* exposure to maternal diabetes has an epigenetic impact.

Type 2 diabetes is now a leading cause of morbidity and mortality in the world, and among developed countries in particular. Lifestyle changes, namely increased nutrition/caloric intake and decreased physical activity have been major etiological factors in the explosion of this chronic disease. Although there are a multitude of potential mechanisms for both cardiovascular disease and diabetes risk factors that are as yet poorly understood, the literature that is available shows that both cardiovascular physiology and metabolism systems have similar vulnerable time periods during development that occur very early in pregnancy.

For example, one study recently showed that endothelial progenitor cells from the offspring of diabetic mothers displayed altered angiogenic functions [104]. Such early endothelial dysfunction consisted of reduced colony formation and self-renewal capacity, and capillary-like tube formation, due to reduced proliferation and accelerated senescence. High glucose concentrations in vitro were responsible for similar effects. Concentrations of circulating soluble markers of endothelial function, such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin, have been found to be increased in offspring of type-1 diabetic mothers compared with offspring from non-diabetic pregnancies [105].

Animal studies that report poor adult insulin sensitivity among offspring of diabetic mothers typically are manipulated to induce severe maternal hyperglycemia [104]. As such, this restriction results in restricted fetal growth and low birth weight. Interestingly, these studies report that in adulthood the size of the endocrine pancreas and the beta cell mass are increased, and the in-vitro insulin response to glucose is augmented via a reduction of insulin action.

The literature often identifies hyperinsulinism as the precursor to impaired glucose tolerance. Animal studies have shown that early exposure to elevated levels of insulin and leptin alter the long term orexigenic and anorexigenic neuron function in the arcuate nucleus of the hypothalamus. The regulation of appetite then becomes malprogrammed in the offspring, with increased immunopositivity of orexigenic neuropeptide Y and agouti-related peptide, and decreased positivity of the anorexigenic melanocyte-stimulating hormone, both contributing to excess food intake and overweight (the “functional teratogenesis” hypothesis) [105,106].

It is now well accepted that prenatal cocaine exposure is associated with neurobehavioral, autonomic and neurochemical alterations [107-111] as well as cardiovascular alterations including diastolic function [112,113], heart rate variability [114] and transient myocardial ischemia [115]. While clinical teratogenesis may be absent at birth latent decrease in behavioral response to stressful stimuli has been found. Although neural compensations occurring after prenatal cocaine exposure may permit some functional recovery, the cost of reorganization may be a dramatic decrease in the animal’s ability to adapt to stress [116]. Studies have shown that behavioral deficits following exposure to cocaine remain latent until the offspring is exposed to cognitive or environmental demands (stressors), at which time, the animals exhibit a number of behavioral alterations, including diminished performance on stress tests [117], altered dopaminergic activity [118], and heightened hypothalamic–pituitary–adrenal (HPA) axis activity [118].

12. Challenges to studying latent health effects among prenatally cocaine-exposed children

Several methodological limitations are intrinsic to the study of prenatal drug exposure, including the non-experimental nature of this research and the difficulty of separating the influences of such exposures from those of a myriad of other factors that may impact child outcomes. Although there is interest in the potential teratogenic effects of these drugs (and although efforts are made to control for potential confounding variables statistically), isolating the effects of prenatal drug exposure may not be entirely meaningful, given the multiple factors that shape the vascular outcomes of drug-exposed children.

The fetal origins hypothesis may not consider all the possible risk and protective factors pertinent to drug involvement in prenatally exposed children. We do not yet know the candidate genes or functional polymorphisms that affect the development of vascular disease. The end result may be a mis-specified hypothesis in which an apparent effect of prenatal drug exposure actually should be attributed to an underlying but as yet undiscovered genetic susceptibility trait (e.g., undiscovered combinations of functionally important genes).

13. Public health implications of latent effects of prenatal cocaine exposure

There is a paucity of research on the influence of prenatal cocaine exposure on the development of child and adolescent growth and subsequent development of cardiovascular disease risk factors in particular, yet many of those children who were prenatally exposed to cocaine are also at high risk for cardiovascular and metabolic disease due to both genetic and environmental factors. As such, longitudinal case-control studies on large cohorts of children from birth to adolescence are needed to quantify potential cardiovascular and metabolic disease risk, identify the critical time windows, and determine the effects of other risk factors, such as abnormal growth and the onset of obesity.

Given the current childhood obesity epidemic occurring at increasingly younger ages and the tendency of cardiovascular and metabolic disease risk factors to track into adulthood it is critical to identify potential environmental risk factors as early in life as possible. If these risk factors can be identified early in life, appropriate interventions can be implemented to prevent the future onset chronic disease. This is particularly relevant among girls as they enter their reproductive years. To ensure as healthy a pregnancy as possible, these women should be identified as having risk factors for gestational diabetes and/or elevated blood pressure.

14. Conclusions

Recognition of the fetal origins of health problems in adulthood has drawn increased attention to gestational processes. There is a paucity of research on the influence of prenatal cocaine exposure on the development of child and adolescent growth and on the subsequent development of vascular disease risk factors in particular. Large, longitudinal cohort studies of children from birth to adolescence are needed to quantify potential vascular disease risk, identify critical time windows, and determine the effects of other risk factors, such as abnormal growth and the onset of obesity.

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