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Fetal Effects of Psychoactive Drugs

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There has been a longstanding concern with the fetal effects of psychoactive drug use by pregnant women. In this article we describe the effects of three drugs with similar molecular targets that involve monoaminergic transmitter systems. These stimulants include the illegal drugs cocaine and methamphetamine and the class of selective serotonin re-uptake inhibitors (SSRIs) used to treat maternal depression during pregnancy. We discuss the mechanisms of action of each drug, including a possible common epigenetic mechanism for their effects on the developing child. We also discuss fetal neurobehavioral techniques that may be useful in the early detection of the effects of in utero drug exposure.

In the past three decades, the concept of behavioral teratology[1] expanded the field of teratology to examine behavioral effects in the neonate due to acute exposure to substances in utero, including environmental, nutritional, and drug exposures.[2,3] The developmental consequences of prenatal exposure to a toxic substance may include central nervous system (CNS) insult related to the period during gestation of the exposure. In contrast to the effects of drugs on the adult brain, which result in deformation of the developed brain, fetal effects are more likely to produce malformation in which the developing brain is prevented from forming normally.[4] The effects of exposure during the first half of gestation will impact processes related to cytogenesis and histogenesis whereas effects during the second half of gestation relate to brain growth and differentiation. During this organizational phase in the second half of gestation, progressive events (neuroblast proliferation and migration, axonal projection, and

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synaptogenesis) and regressive events (programmed cell death and selective elimination of processes) affect the maturation of brain circuitry. Thus toxic influences during this period may dramatically alter brain development but may also alter the regressive events that underlie the capacity of the developing brain to compensate for injury.[4]

Recent years have seen further expansion of the principles of behavioral teratology to examine exposure effects on the human fetus at the time of the exposure. Epigenetic and organismic models of developmental theory suggest that true understanding of a developing system can occur with the study of its organization of form and structure as it moves toward a teleological state.[5,6] This study includes examination of the mutual influences of genes, physiology, and behavior as well as the physical, cultural, and social environments of the organism.[6]

Increasing evidence from preclinical, prospective clinical and epidemiological studies suggests that many biological factors acting during prenatal life are associated with adult disease as well as long term neurobehavioral abnormalities[7–17] and behavioral disorders.[18–21] The notion that the development of common adult cardiovascular and metabolic disorders are linked to factors during prenatal development was originally known as the “Barker” or “fetal origins hypothesis”.[7,9,10] Although these early studies related low birthweight to adult disease, it is generally accepted that low birth weight per se is not at the heart of these disorders, but that there are common factors that influence intrauterine growth as well as adult physiological systems.[22] The “fetal origins” observations are due, in part, to environmental factors acting early in life that affect developing systems, altering structure and function. It has been suggested that the biological purpose of this “programming” is to alter the set-points or “hard-wire” physiological systems to prepare the fetus for optimal adaptation to the postnatal environment.[23]

Common factors arising from prenatal exposure to psychoactive drugs could include mechanisms related to “fetal origins” and may also contribute to more long-term outcomes. Longitudinal study of the organism and contexts beginning before or at the time of exposure, as well as of long-term outcomes, is essential to understanding developmental trajectories related to substance exposures.

Cocaine

In the 1980s, cocaine became one of the most frequently abused illicit drugs during pregnancy and also one of the most studied with regard to its potential teratologic and neurodevelopmental effects on the developing fetus and child. While early catastrophic predictions about the long-term outcome of prenatally cocaine- exposed children were exaggerated, concern remains about more “subtle” effects[24] that may affect development, particularly in childhood and adolescence.

The neurochemical and vasoconstrictive effects of cocaine have been well documented. Cocaine acts primarily at the presynaptic level to block reuptake of the monoaminergic neurotransmitters dopamine, norepinephrine and serotonin[25,26] by specific, presynaptic plasma membrane transporters.[27] These transporters are expressed in discrete pathways of the CNS, on postganglionic sympathetic neurons and in the adrenal medulla. These pharmacologic actions lead to elevated circulating catecholamine levels and exaggerated sympathetic responses including hypertension, tachycardia, vasoconstriction, agitation, euphoria, and excitation. These effects are particularly profound in the fetus in which elevated sympathetic tone has been demonstrated.[28–31] Cocaine affects neuronal formation, proliferation and early connectivity,[32–34] and disrupts neuronal migration and resulting cortical architecture.[35–38] Cocaine also affects the expression of transcription factors (IEGs or immediate early genes) along dopaminergic[39,40] and serotonergic pathways.[41] Because monoamine neurotransmitter receptors (NA, 5-HT, and DA) are present early in corticogenesis, areas highly expressing

these neurotransmitter systems may be especially susceptible to elevated synaptic monoamine neurotransmitter levels secondary to cocaine's main effect of blocking catecholamine reuptake at the presynaptic level.[42–44] Also, because monoamine neurotransmitters play a key trophic role in brain development,[45] prenatal cocaine may alter normal mechanisms that modulate neuronal growth.[42]

The effects of cocaine on fetal development have also been attributed to vasoconstrictive mechanisms. Uptake inhibitors such as cocaine (as well asamphetamines and SSRIs), which block catecholamine transport[28,46] and decrease placental blood flow, reduce the supply of oxygen and nutrients to the fetus. Fetal hypoxemia and possibly ischemic injury can compromise brain development. Blood flow to the developing brain can also be reduced by cocaine-related noradrenergic effects on the developing fetal vasculature.[47,48] Norepinephrine and particularly the monoamine serotonin (5-HT) exert vasoconstrictive effects on the umbilical vein, thereby reducing blood flow from the placenta to the fetus.[49,50] Furthermore, the vascular response to 5-HT is potentiated by uptake inhibition.[51,52] Vasoconstriction at the uteroplacental complex coupled with anorexic effects of cocaine could explain the increase in intrauterine growth retardation (IUGR) that has been reported in cocaine-exposed infants.[53]

In addition to neurochemical and vasoconstrictive effects, cocaine may also act as an intrauterine stressor that alters "fetal programming" through epigenetic mechanisms that might alter the offspring's developmental trajectory.[54] In this model, cocaine alters the expression of key candidate genes and gene networks important to placental function in late gestation, specifically the norepinephrine transporter NET [55] and a steroid metabolic enzyme, 11β-HSD-2. Placental NET and 11β-HSD-2 protect the fetus from excess catecholamines and glucocorticoids, which have harmful effects on the fetus.[56] 11β-HSD-2 in particular converts maternal cortisol to inert cortisone, protecting the developing fetus from exposure to maternal cortisol.[57] Placental expression of 11β-HSD-2 is downregulated by norepinephrine, which is in turn regulated by NET.[58] Prenatal cocaine exposure is associated with downregulation of NET,[59,60] which leads to increased circulating catecholamines, downregulation of 11β-HSD-2, and chronic fetal hypercortisolism. These changes in placental gene expression may be due to epigenetic mechanisms including DNA methylation, as suggested by the findings in Figures 1 and 2.[54] Figure 1 shows decreased 11β-HSD-2 expression in mothers who used cocaine (n=4) or cigarettes (n=4) or were depressed (n=3), compared with 17 controls. The altered expression of these two key candidate genes is likely associated with changes in networks of genes involved in critical placental functions that maintain physiological homeostasis *in utero* and otherwise promote intrauterine growth, development and preparation for postnatal life. Figure 2 suggests that these changes inplacental gene expression are associated with methylation of placental genomic DNA, particularly in promoter regions. These findings in Figure 2 are based on the same group of subjects with pregnancies complicated by cocaine, nicotine, and depression, and controls, shown in Figure 1. The relative incorporation of cytosine used to measure methylation was comparable in promoter and genomic DNA in the cocaine and nicotine exposed subjects, suggesting hypermethylation of the promoter regions of DNA that contain CpG islands. This hypermethylation of DNA suggests gene silencing related to *in utero* cocaine exposure.

There is a substantial literature on the effects of cortisol on children[61] including infants with prenatal cocaine exposure.[62–64] Preclinical studies suggest effects of prenatal cocaine exposure on the developing monoaminergic system, resulting in both structural and functional changes to circuitry subserving functions such as arousal, regulation, and reactivity.[43,65] Human infant studies show effects of prenatal cocaine exposure on arousal, hypertonicity and excitability, acoustic cry characteristics,[66] and auditory brain response.[67] At school age these children show more behavior problems[68] and they are more likely referred for special education services.[69] On functional neuroimaging (fMRI) they show differences in the right inferior frontal cortex

and caudate during response inhibition, suggesting cocaine effects on brain systems involved in the regulation of attention and response inhibition.[70] This set of cognitive abilities is referred to as executive function and is particularly important as children reach school age. A recent review of 42 follow-up studies of cocaine-exposed children suggested that executive function and behavior problems were major domains affected by prenatal cocaine exposure.[71] Thus, fetal programming effects that alter the intrauterine neuroendocrine environment may be a marker for long-term behavioral consequences of prenatal cocaine exposure.

Methamphetamine

Methamphetamine (MA) is the dominant drug problem in the Western and Midwestern portions of the United States, second only to alcohol and marijuana,[72] and is the most widely abused drug worldwide.[73,74] The number of adults age 12 and over who have tried MA once in their lifetime has increased to 5.3% in 2007 from 4.3% in 1999 and 2.5% in 1997.[75] This increase has led to the concern that MA is the growing drug of choice for adults in the United States, including pregnant women.[76–78]

Although there is controversy about the nature and extent of the MA problem in the U.S., including exaggerations reminiscent of the cocaine “epidemic,” there is little argument that MA is a dangerous drug that substantially challenges policymakers, health care professionals, social service providers, and the law enforcement community,[79] and there is little information about MA use by pregnant women.

MA is a CNS stimulant of the sympathetic nervous system with neurotoxicpotential for developing monoaminergic systems. As the “first cousin” of amphetamine with the addition of a methyl radical, MA exerts its action by releasing dopamine and serotonin, blocking monoamine reuptake mechanisms, and inhibiting monoamine oxidase.[80] The mechanism of action most likely occurs by increasing synaptic concentrations of the neurotransmitters dopamine and norepinephrine[80] either by direct release from storage vesicles or by inhibition of reuptake.[81,82] MA may enhance synaptic catecholamine levels by inhibiting monoamine oxidase, the enzyme responsible for the oxidation of norepinephrine and serotonin.[83] MA acts on the dopamine transporter (DAT) that mediates the inward transmission of dopamine in the neuron. The action of MA on DAT releases dopamine and inhibits reuptake of dopamine from the presynaptic terminals, thus increasing dopamine activity.[84] MA also decreases serotonin (5HT) uptake and densities of binding sites.[85] MA has been shown to be neurotoxic to mature dopaminergic and serotonergic axons and axon terminal arbors,[86] and potentially neurotoxic to mature glutaminergic axons.[87] The cellular and molecular mechanisms implicated in the neurotoxicity induced by MA on mature neurons include the production of reactive oxygen species and nitric oxide, p53 activation resulting in apoptosis, and mitochondrial dysfunction.[88] Less is known about the mechanisms involved in MA-induced toxicity in the developing CNS; however, the early and widespread influence of serotonergic, dopaminergic and glutaminergic systems on neuronal growth and connectivity suggests that prenatal exposure to MA may result in alterations in developing neural circuitry.[87]

Amphetamines are considered noncatecholamine sympathomimetics because they lack catecholamine structure yet have sympathomimetic actions.[89] These structural characteristics are important because they account for the wide distribution and long duration of action of amphetamine. MA also has vasoconstrictive effects[90,91] resulting in decreased uteroplacental blood flow and fetal hypoxia.[92] In addition, MA has anorexic effects on the mother. These maternal/placental effects could affect fetal development to the above monoaminergic effects. Weight control may also help explain the popularity of MA with women, including pregnant women.

Unfortunately, the scant human literature that is available on the effects of prenatal MA exposure is beset by methodological problems.[93] Recent, more reliable findings showed that MA-exposed infants, although born at term, are more likely to be small for gestational age.[94] Newborn neurobehavioral effects were reminiscent of cocaine-exposed infants showing effects on arousal and physiological stress.[95] In addition, these findings showed a dose response relationship between amphetamine metabolites in meconium and newborn neurobehavior.

In preclinical work, administration of MA to laboratory animals results in profound and long-lasting toxicity to the developing CNS. Brain studies in the ovine model have found MA increases fetal blood pressure and decreases fetal oxyhemoglobin saturation and arterial pH.[96,97] In rodents, MA is toxic to dopaminergic and serotonergic neurons.[98,99] Damage to dopamine (DA) terminals[100,101] are thought to reflect irreversible terminal degeneration.[102] Positron emission tomography (PET) studies in abstinent MA users demonstrated decreased dopamine transporters, suggesting long-lasting neurotoxicity due to MA abuse.[103]

Neurotoxic effects of prenatal MA exposure on serotonergic neurons produce neurochemical alternations in the CNS[104,105] thought to be associated with learning impairment, behavioral deficits,[105] increased motor activity,[106] enhanced conditioned avoidance responses,[107] and postural motor movements[108] seen in MA-exposed animals. Rhesus monkeys showed reduced brain monoamines 4 years after the last drug exposure.[109]

Administration of MA to laboratory animals also results in motor[110] and learning and memory impairment.[111] Studies with rats have shown a range of physical, motor, neurotransmitter, and behavioral effects in MA-exposed offspring. These include increased maternal and offspring mortality, retinal eye defects,[106,112,113] cleft palate and rib malformations,[113] and decreased rate of physical growth and delayed motor development.[107,112] MA exposure to pregnant dams showed effects on spatial learning in their adult offspring.[108] Spatial learning and attenuated corticosterone response was found in rats with prenatal MA exposure.[114] In pregnant mice, MA caused dopaminergic nerve terminal degeneration and long-term motor deficits in offspring.[115]

Consistent with the “fetal programming” model described above, the human placenta may also be a direct target for MA. MA causes inhibition of the norepinephrine and serotonin transporters, suggesting cellular mechanisms by which MA could affect the developing fetus.[116] Blockage of these transporters would increase the concentrations of norepinephrine and serotonin, resulting in constriction of blood vessels and decrease blood flow to the placenta. Also, placental norepinephrine transporter (NET) downregulation resulting from MA could lead to increases in circulating catecholamines, downregulation of 11β-hydroxysteroid dehydrogenase-2 (11β-HSD-2), and chronic fetal hypercortisolism,[59,117] which could affect behavior through alteration of the HPA axis, especially arousal regulation and attention.[43]

SSRIs

Each year at least 600,000 infants born in the United States are exposed to maternal Major Depressive Disorder (MDD) during gestation, which is associated with newborn medical and neurobehavioral deficits and long-term emotional, behavioral, and social problems in the child. Pharmacological treatment of MDD during pregnancy remains the most common form of treatment. The current first-line choice of clinicians for somatic therapies during pregnancy is selective serotonin reuptake inhibitors (SSRIs) and dual-action serotonin and norepinephrine reuptake inhibitors (SNRIs)(referred to collectively here as SRIs) due to their lower side-effect profiles and relatively low risk to the fetus.[118,119] Over the past two decades, the use of newer antidepressants has dramatically increased over the use of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors. A survey of national patterns of antidepressant medication prescribed by physicians from 1987–2001 reported that SRIs were prescribed in 69% of office

visits for depression in 2001.[120] Similarly, another study reported that in 2000, 65% of all antidepressants prescribed by primary care providers were SSRIs (fluoxetine, sertraline, paroxetine, fluvoxamine and citalopram), and newer antidepressants, including SNRIs such asvenlafaxine, comprised an additional 17% of antidepressants prescribed.[121] A recent study examining antidepressant treatment rates during pregnancy found that at least 37% of depressed pregnant women choose to take antidepressant medications during pregnancy.[122] Another large study conducted retrospectively from 1993 to 2007 showed the use of SRIs during pregnancy to have a steady increase from 0.44% in 1993 to 6.61% of all pregnant women in 2007.

SRIs block the presynaptic reuptake of serotonin (5-HT) by binding to theserotonin transporter SERT. Some of the SRIs also bind to the norepinephrine (NE) transporter gene, NET. SERT and NET are responsible for the reuptake and transport of 5-HT and NE out of the synapse. Inhibition of SERT and NET activity by SRIs prolongs neurotransmitter signaling. Fluoxetine has also recently been found to antagonize 5-HT_{2c} receptors. The antidepressant mechanisms of SRIs and many other psychoactive drugs remain unclear, but are presumed to be a result of the enhanced serotonergic neurotransmission at postsynaptic receptors, the effect on intracellular signal transduction cascades, and the modulation of other neurotransmitters.[123]

SRIs and their metabolites have been detected in both umbilical cord blood and amniotic fluid. The potency of serotonin placental passage, expressed as a ratio of medication concentration in cord blood to maternal serum, ranged from 0.29 (sertraline and paroxetine) to 0.89 (citalopram and fluoxetine).[124] A study of cord:maternal serum levels found roughly equivalent values for fluoxetine, sertraline, and paroxetine and their metabolites (.52–67), while the concentration for the SRI venlafaxine was 1.1.[125] SRIs have also been found in amniotic fluid, representing another source of exposure as the fetus swallows an increasing amount of amniotic fluid throughout pregnancy.[126] Administration of fluoxetine to pregnant ewes was associated with a transient decrease in uterine artery blood flow, perhaps due to serotonin activity following administration.[127] Immediately following fluoxetine administration, there is an increase in plasma serotonin concentrations. However, with prolonged exposure, plasma serotonin levels decline. Serotonin acts as a vasoconstrictor; therefore, elevations in serotonin followed by a decline might explain the uterine artery blood flow findings. Decreases in serotonin levels in exposed offspring may be one mechanism by which SRI medication influencesadverse effects.

The serotonergic system develops early in gestation and is likely to be influenced by serotonin levels in all trimesters of pregnancy.[128] Serotonin is widely distributed throughout the central and peripheral nervous systems and is involved in the development of multiple brain areas.[128–131] Alterations in the 5HT system during development are associated with changes in somatosensory processing, motor output, and emotional responses.[132,133] Recent evidence suggests that components of the serotonin system are critical to the development of neurobehavioral systems involved inmood, anxiety, aggression, and substance abuse.[133,134]

The serotonin system includes at least 14 receptors, multiple enzymes, and transporter proteins that exert influence on 5HT metabolism, release, and reuptake. The serotonin transporter gene, or 5-HTT (SLC6A4), encodes for the transporter protein. The promoter region of the gene contains two common polymorphic alleles, a short or “S” allele with 14 repeated elements, and a long or “L” allele with 16 repeated elements. The variant region has been labeled the serotonin transporter linked polymorphic region (5-HTTLPR).[135] Functionally, the deletion polymorphism (“s”, or short allele) appears to cause a reduction in basal and stimulated transcription activity, 5-HTT mRNA, and 5-HT binding and uptake.[136] Individuals with the S allele (S/S or S/L) have been more susceptible to stress, depression, anxiety, suicidal ideation, and irritable temperament. Longitudinal research suggests a gene × environment interaction,

in that those with the S allele are more susceptible to depression given stressful conditions.[137] Allelic differences have also been linked to responsiveness to antidepressant medication.[138]

The most recent meta-analysis of the effects of SRIs on pregnancy and fetalphysical development included published reports from 1995 through August of 2005.[139] The findings of the meta-analysis are in agreement with most of the previous reviews that did not find an increased risk of major, cardiovascular or minor malformations, but did find an increased risk of spontaneous abortion.[140,141] The findings are in disagreement with reports of a higher rate of major cardiac malformations and persistent pulmonary hypertension of the newborn for infants exposed to SRIs compared with other antidepressant medications and controls.[142,143]

Lower birth weight, younger gestational age at birth, and lower Apgar scoreshave been reported with SRI exposure.[144] Similar results were seen with third trimester exposure of fluoxetine but not with first or second trimester exposure.[140] Lower birth weight has been associated with higher doses of fluoxetine compared with lower doses or other SRIs,[145] while other studies failed to find birth weight differences between early and late SRI exposed infants[146] or between SRI exposed and nonexposed infants.[147,148]

Recent evidence supports acute effects of SRI exposure on neonatal neurobehavior. Several reviews were published in 2005 looking at recent case reports, database analyses, and cohort studies on the effects of SRI exposure on neonatal outcomes.[149–152] In general, a cluster of symptoms was observed in newborns who were prenatally exposed to SRIs. These symptoms include irritability, tremors, jitteriness, trouble feeding, agitation, respiratory distress, and poor sleep. Other symptoms reported include convulsions, abnormal posturing, and shivering.[153,154] These symptoms have been reported most often in infants exposed to paroxetine, but all SRIs have been indicated,[140,151,152] and the symptoms were originally described as a syndrome called “poor neonatal adaptation” which included respiratory difficulties, jitteriness, poor motor tone, hypothermia, hypoglycemia, weak or absent cry, and trouble feeding.[140] Since that time, frequent reports of “poor neonatal adaptation” have been seen in the literature. Data from a 2006 review suggest that 30% of SRI–exposed neonates have symptoms consistent with “neonatal abstinence syndrome,” a condition often described in newborns withdrawing from other (mostly opioid) prenatal drug exposures.[155–158] The long-term outcomes associated with these apparently transient symptoms following delivery have only just begun to be studied. The few empirical studies have shown SRIs related to increased active sleep[159] and decreased facial and behavioral responses to acute pain in the first week postnatally and at 2 months of age, suggesting a blunting of pain reactivity.[160,161] SRI-exposed infants were found to have decreased basal cortisol levels in the early evening compared with non-exposed infants at 3 months of age, although this effect was not related to prenatal exposure level or current SRI level measured in infant plasma.[162] A related paper suggested that third trimester maternal mood, rather than SRI exposure, is related to increased infant HPA reactivity and that this effect is mediated by increased methylation of NR3C1 (human glucocorticoid receptor gene).[163] In a recent review of studies on the long-term development of children with prenatal SSRI exposure, 11 studies (306 children) suggested no impairment with exposure, and 2 studies (81 children) suggested mild adverse effects.[150]

It is also possible that SRIs affect fetal neurobehavior. Studies of SRI effects on sleep state development in the fetus are limited to the work of Morrison et al., who examined fetal sheep after fluoxetine exposure and found a significant decrease in fetal rapid eye movement (REM) sleep.[164] By contrast, a study of sleep state in the first 2–3days postnatally reported more active sleep, more arousals, and more activity during sleep in SSRI-exposed newborns.[159] It is possible that the increase in REM sleep reported after birth by Zeskind et al.[159] was compensatory following REM sleep deprivation based on the fetal sheep data.[165] This finding

could be due to the fact that serotonergic neurons in the dorsal raphe nucleus appear to be involved in the "turning-off" of active sleep and are a central monoamine involved in the regulation of ultradian rhythms.[166] The initial action of antidepressant medications is to enhance postsynaptic transmission of serotonin. Therefore, it is reasonable to expect that SRI exposure wouldinitially decrease the amount of active sleep. Another possibility is that the newborn effects are related to the discontinuation of the SRIs following delivery.

The effects of SRIs on fetal neurobehavior can be studied by incorporating fetal actocardiography with ultrasound observations of fetal behavior.[167–170] The **FE**tal **N**eurobehavior coding **S**ystem (FENS) is a method of fetal neurobehavioral observation and scoring that includes measurement of fetal heart rate, motor activity, behavioral state, and responsiveness to external or extra-uterine stimuli.[171] A fetal actocardiograph provides measurement of fetal heart rate, fetal heart patterns, and motor activity. The use of ultrasound technology enables visualization of the fetus to observe specific fetal action patterns, quality and amplitude of movements, and eye movements. Thus, ultrasound technology coupled with fetal actocardiography allows for a comprehensive assessment of fetal neurobehavior. Table 1 presents the behavioral variables coded in the FENS coding system.

Effects of SRIs on FENS neurobehavioral measures are shown in Figures 3 and4. Fetal behavioral and physiological data were collected simultaneously by a research nurse certified in obstetrical ultrasound and fetal heart rate monitoring. The data were obtained using a Toshiba ultrasound machine model SSA-340A with a 3.75 MHz transducer and a Toitu MT325 actocardiograph. The time of the recordings was standardized to between 12 and 5:00 pm to account for possible variability in fetal activity levels at different times of the day.[172] The participants were asked to fast for at 1 ½ hours before their scheduled appointment to increase their appetite. Upon arrival to the appointment, the participants were given a small meal, standardized for calories andcontent, to standardize the immediate nutritional influence on fetal activity. Participants were asked about their smoking as well as nutritional and caffeine intake on the day of the observation to account for the potential acute effects of caffeine and nicotine on fetal behavior. Baseline behaviors and heart rate were collected for the first 40 minutes. A single, 3-second single vibroacoustic stimulus (VAS) (Toitu) was applied to the maternal abdomen during the first quiescent period following the 40-minute baseline period. Recording continued for 20 minutes post VAS presentation. Additionally, a VAS-stimulus control trial was conducted in the baseline period to control for maternal reaction to the VAS. Research assistants trained on the FENS and blinded to maternal condition conducted the coding of fetal behaviors. Coders use the Mangold Interact Video Coding Software to score digital recording files for fetal movements and behaviors in 10-second epochs. The presence or absence of isolated limb and head movements, gross body movements, and behavior patterns were scored within each 10-second epoch. All movements were categorized as smooth, jerky, or indeterminate, with high inter-rater reliability. The actocardiograph data were scored for mean fetalheart rate (FHR), FHR accelerations, and fetal movement measures.[169,173]

In Figures 3 and 4, the data are shown for fetuses (n=60) exposed and unexposed to SRIs, with maternal depression scores used as a covariate. Fetuses in both groups demonstrated the expected developmental decrease in jerky movements from 26 to 36 weeks' gestational age; however, fetuses exposed to SRIs had more jerky movements at both gestational ages (Figure 3). The SRI-exposed fetuses did not show the anticipated developmental increase in fetal breathing movements at 36 weeks' gestational age, and they had significantly fewer fetal breathing movements than nonSRI fetuses (Fig. 4).

Biogenic amine transporters

Some of the adverse effects on the fetus of the three uptake inhibitors that we have reviewed--cocaine, methamphetamine and SRIs--may be due to their action on blocking catecholamine transport, especially serotonin (5-HT). Catecholamines also exert vasoconstrictive effects on the umbilical vein, thereby reducing blood flow from the placenta to the fetus.[49,50] Furthermore, the vascular response to 5-HT is potentiated by uptake inhibition.[51,52] As the umbilical cord is not innervated, transporter-dependent uptake by the placenta is also protecting the umbilical-placental circulation from deleterious effects of these neurotransmitters.[174,175]

Nonetheless, regulation of the placental capacity for catecholamine uptake should not be viewed solely in the context of protecting the fetus from exaggerated elevations in catecholamines and/or serotonin. Endogenous catecholamines are critical to fetal and neonatal growth, development, and survival. This conclusion is supported by studies inmice in which the gene for either tyrosine hydroxylase[176,177] or dopamine beta-hydroxylase[178,179] has been disrupted. The majority of fetuses homozygous for the disruption of either gene die during embryonic development. Small proportions (5–10%) of fetuses survive, suggested to be rescue of the lethal phenotype by passage of maternal catecholamines across the placenta. Serotonin (5HT) is also important at critical stages of development. 5HT is present in early embryos and has been suggested to be maternal in origin.[180] Mouse embryos grown in the presence of high concentrations of 5HT or serotonin uptake inhibitors develop cranio-facial and cardiac abnormalities of the 3rd-5th brachial arches.[181] Similar abnormalities have been seen in rat and chick embryos.[182] Thus, highly regulated mechanisms control the concentration of intrauterine biogenic amines, which are central to fetal growth and development. Administration of uptake inhibitors to mouse dams in early to mid-gestation during placentation and embryogenesis leads to a high incidence of fetal/placental resorption.[183] In survivors, there is a significant reduction in birth weight and delay in maturational milestones (ear opening).[183] Thus, the capacity for placental biogenic amine uptake and/or transport has a significant impact on intrauterine growth and development. Understanding the ontogeny and regulation of placental biogenic amine transport is important in understanding the way in which the intrauterine neuroendocrine milieu programs develop.

Previous studies on the regulation of monoamine transporters suggest that drugs as well as maternal mood and anxiety are able to alter transporter activity.[184] Male rats exposed to stress in early gestation were shown to have behavioral manifestations similar to major depression, including maladaptive behavioral reactivity and anhedonia with subsequent increased sensitivity to SRI medication. These rats were found to have decreased SERT in the hippocampus. The authors state that a potential mechanism could be increased 5-HT output and decreased reuptake by SERT. This mechanism may explain increased sensitivity to acute postnatal SRI administration.[185]

Other drugs that affect transporters, such as cocaine, given during fetal rat brain development have been related to increased norepinephrine turnover rate in older animals[186] and altered cerebral glucose uptake.[187,188] Interestingly, the cocaine-treated animals had enhanced acoustic startle responses to selective serotonin agonists whichwere attenuated by the fluoxetine exposure.[188] This finding is consistent with our observations on the effects of antenatal cocaine exposure on auditory brain stem responses, newborn cry, fetal heart rate, and arousal responses.[189,190] In other work, we showed that disorders linked to chronic intrauterine stress, including cocaine exposure and/or intrauterine growth retardation, are associated with decreased placental NET expression, directly proportional to the elevation in umbilical arterial plasma norepinephrine concentrations.[59] The decreased placental NET gene expression we have observed, and resultant increases in circulating catecholamines, may explain the adverse

effects on the fetus of drugs such as cocaine and methamphetamine, which block catecholamine transport and render the fetus more vulnerable to other physiologic derangements.

As described above, 11β-HSD is expressed in the placenta and converts biologically active cortisol to cortisone.[191,192] 11β-HSD-2 expression in the placenta is widely considered to protect the fetus from maternal hypercortisolism during pregnancy. We also know that placental 11β-HSD-2 is downregulated by norepinephrine and thatchronic intrauterine stress leads to downregulation of placental NET gene expression and increased circulating catecholamine levels in the fetus and the placental microenvironment. Dysregulation of norepinephrine levels in the placental microenvironment in turn leads to alterations in the placental neuroendocrine milieu. One potential mechanism for neurobehavioral effects of drugs such as cocaine, methamphetamine and SRIs involves the alteration of fetal placental monoamine transporter expression and the resulting alterations in neuroendocirne and neurotransmitter system development. As an example of how placental geneexpression may be related to substance exposure and maternal health conditions, we present in Figure 5 placental SERT data from 33 mothers. These data demonstrate an interaction for MDD/SRI use on SERT expression in the placenta. The MDD-exposed fetuses (no SRI exposure) had lower SERT levels than controls and MDD+SRI-exposed fetuses, but were not different from those of SRI-exposed fetuses whose mothers no longer met criteria for MDD. These data highlight how maternal diagnosis might change the outcome of substance exposure-related outcomes. We have also shown this same type of alteration in neurobehavioral outcomes in cocaine-exposed infants whose mothers were depressed in the first month of pregnancy.[193]

Fetal Origins

The developmental trajectories of fetuses exposed to psychoactive substances may be altered by multiple factors. However, we suggest that drugs such as cocaine, methamphetamine and SRIs can be stressors that affect fetal programming, disrupt fetal placental monoamine transporter expression, and alter neuroendocrine and neurotransmitter system development. Stress hormones such as catecholamines and glucocorticoids can alter regulation of the neuroendocrine environment by acting on the hypothalamic-pituitary-adrenal (HPA) axis, which results in an altered set point for physiologic, metabolic, and behavioral outcomes.[194] Because they are an important feature of the stress response, glucocorticoids have become prominent candidates as mediators of the effects of “programming.” Effects on gene expression through epigenetic mechanisms such as DNA methylation or chromatin remodeling could result in altered developmental trajectories.

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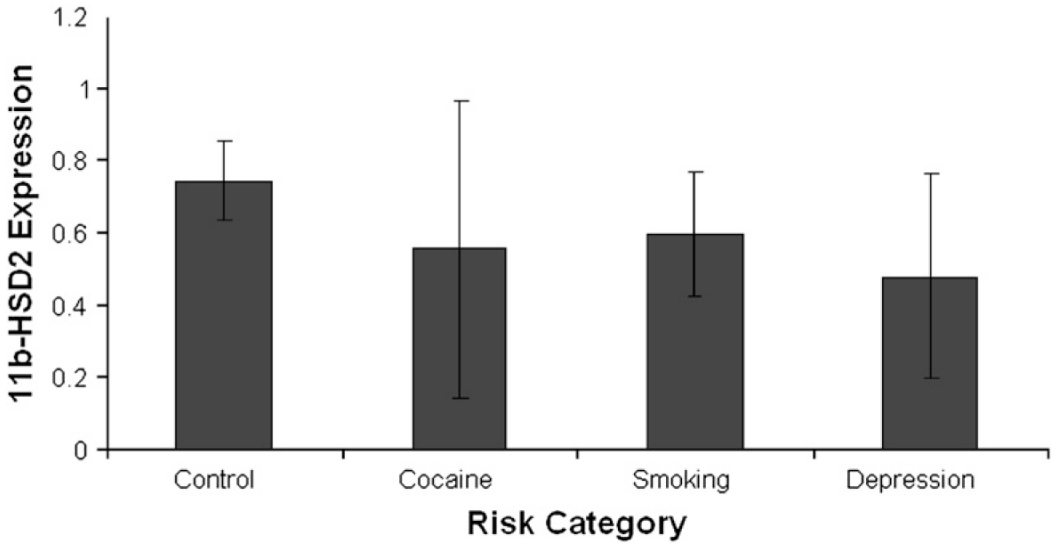

Figure 1.
Mean 11β-HSD-2 expression in risk groups.

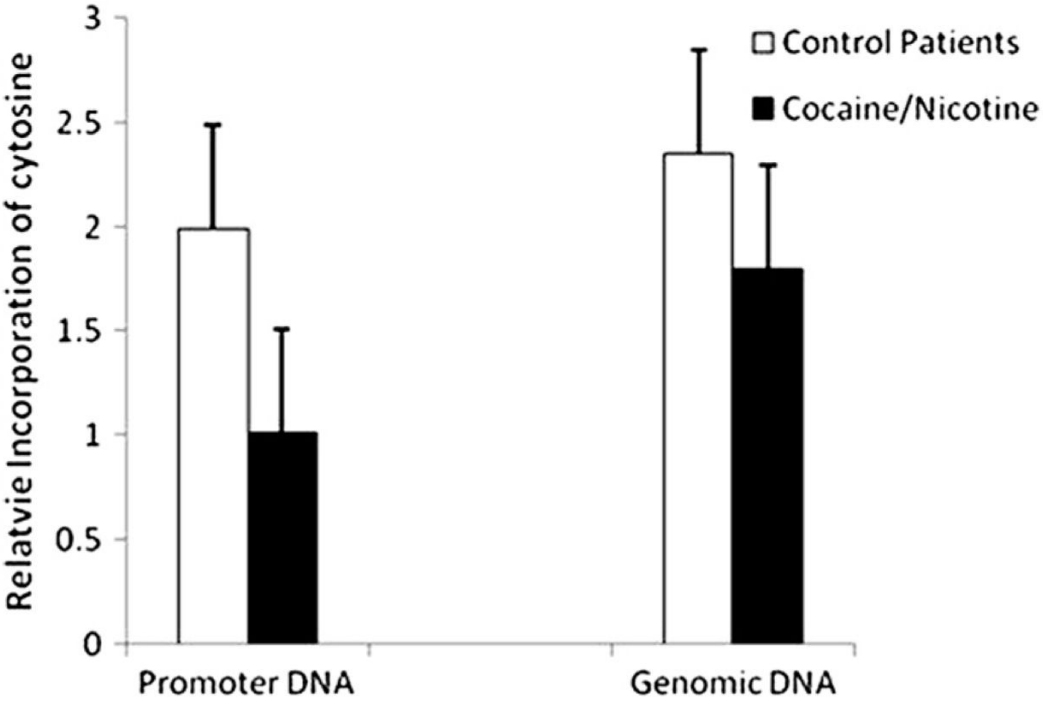

Figure 2.
Hypermethylation of DNA in placentas from cocaine/nicotine exposed.

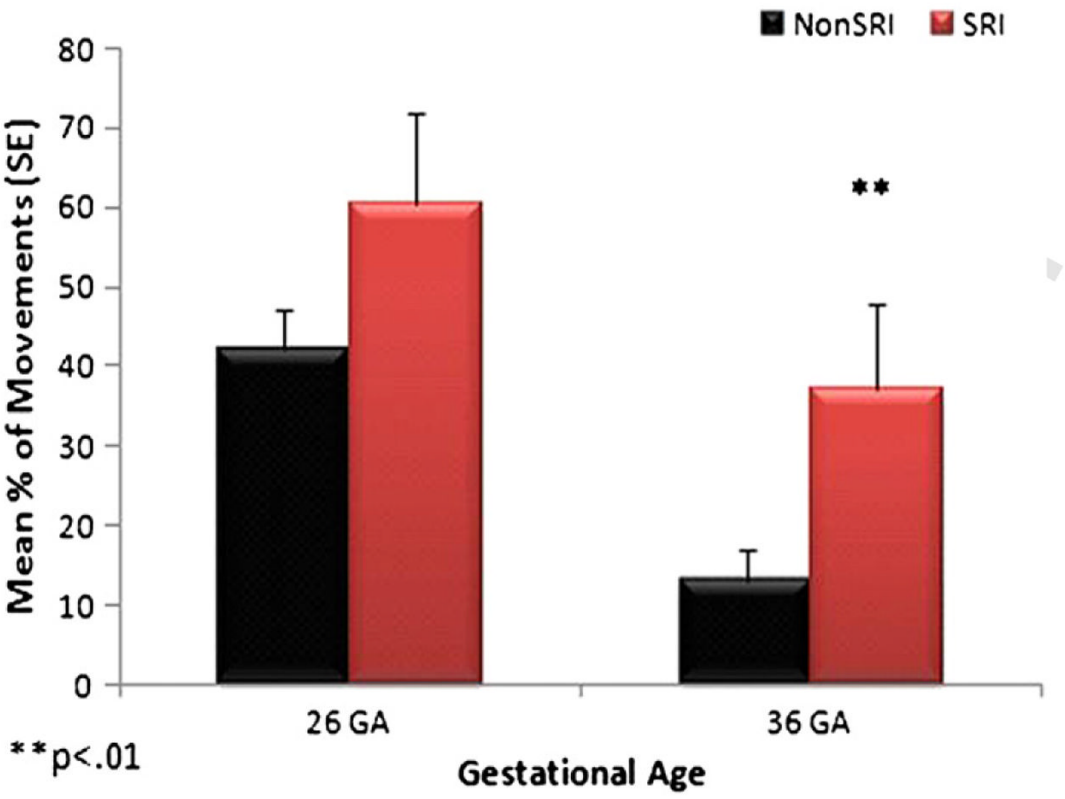

Figure 3.
Fetal jerky movements.

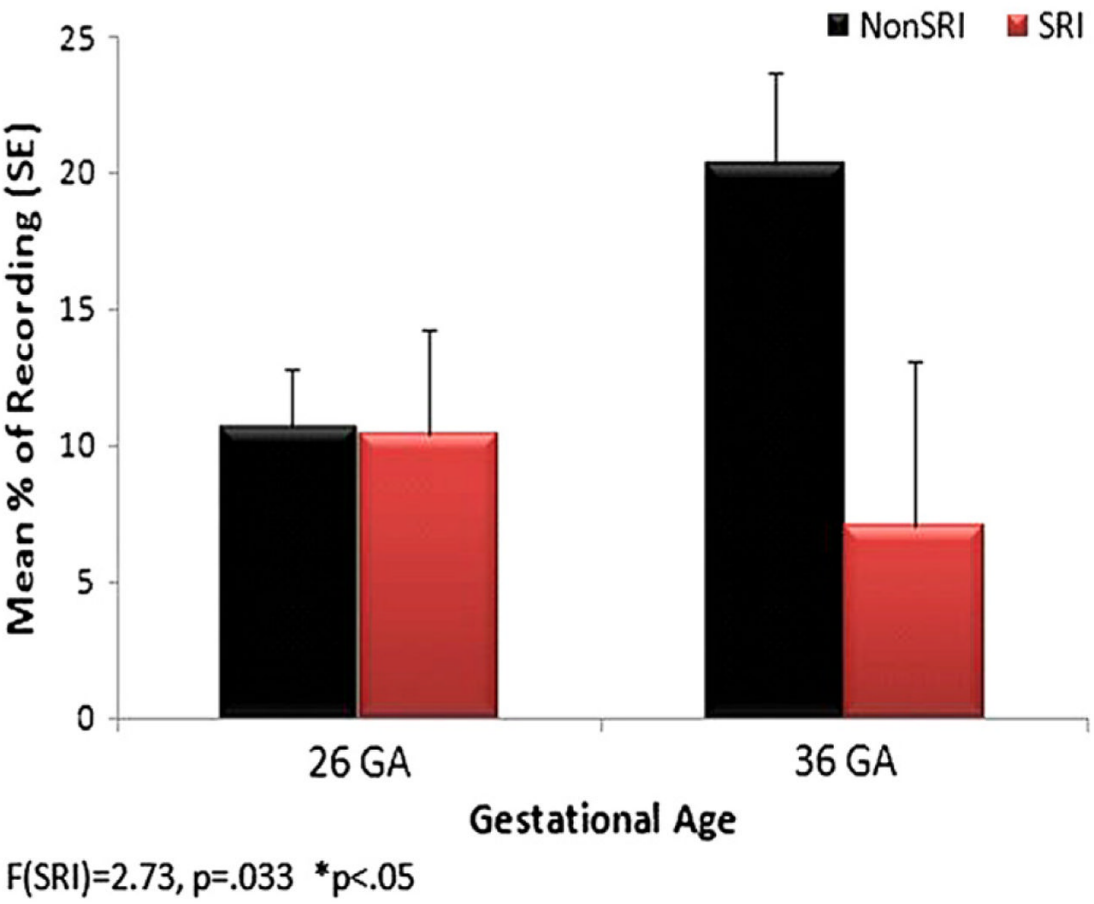

Figure 4.
Fetal breathing movements.

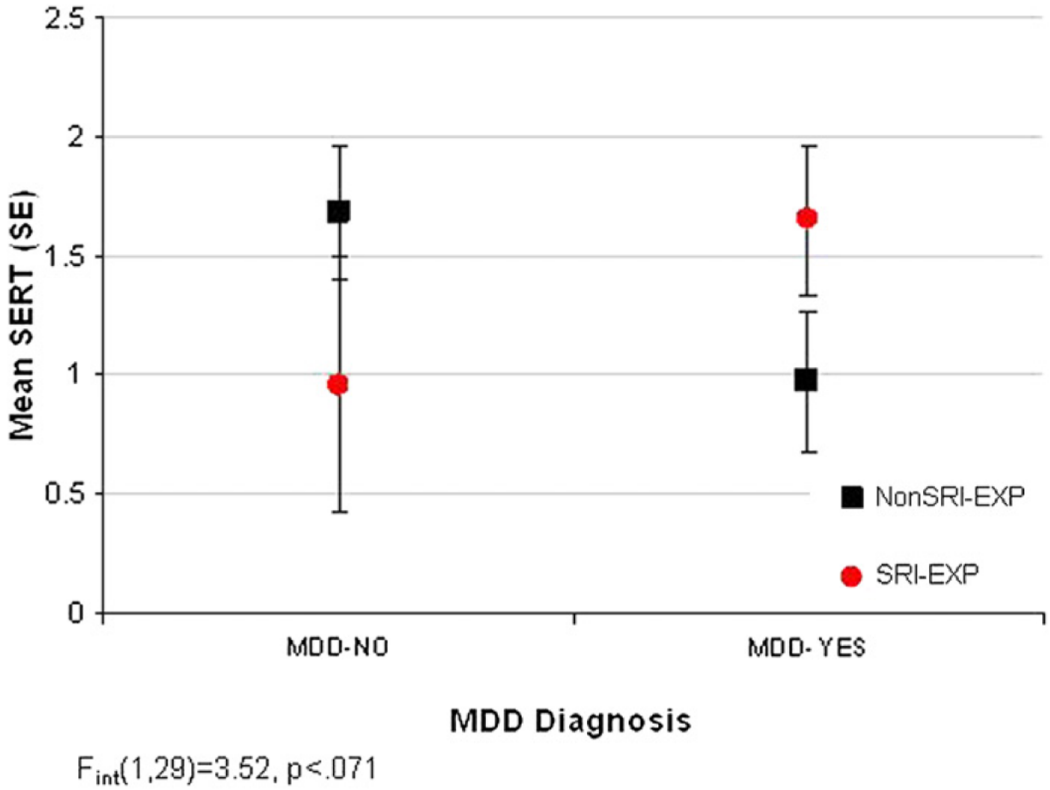

Figure 5.
Placental SERT levels.

Table 1

Fetal Behaviors Coded from Ultrasound Recordings in the FENS System

Summary Variable	Variable	Description
Fetal Eye Movement	Present	Clear movement of the pupil or eyelid
	Absent	A clear view of the eye is obtained and there is no movement
Fetal Breathing Movements	Regular	Displacement of the diaphragm with outward movement of the abdomen
	Vigorous	FBM's that are large enough to move the entire fetus' body
	Hiccup	Consists of a jerky, repetitive contraction of the diaphragm
General Body Movements	Smooth	Pattern of movement involving smooth, simultaneous movement of a limb, trunk and head that results in a change in plane
	Jerky	GBM that involves jerky movements of limbs or entire body
	Incomplete	GBM that is not fluid or coordinated and does not result in change
	Flexion	Flexion of the trunk
Patterned Body Movements	Stretch	A single event including a back extension or upward movement of the shoulder with retroflexion of the head Typically includes a pause at the movement with subsequent relaxation
	Backarche	Extension of the trunk and maintenance in this position for greater than 1 second
	Startle	A quick, generalized movement, involving abduction or extension of the limbs with or without movement of the trunk and head, followed by a return to a resting position.
	Fidget	Nearly continuous limb movements that are not part of a GBM or other patterned movement
Head Movements	Rotation	Movement of the head in the lateral plane for at least a 30 degree angle from starting position
	Extension	A small movement of the head that extends upward in the vertical plane
	General	Small Movement of the head that is not an extension or rotation
Mouthing Movements	Rhythmic	Rhythmical bursts of jaw opening and closing at least 4 times in 5 seconds (sucking)
	NonRhythmic	Mouth opening and closing that is isolated or limited to less than 4 at one time, often with tongue protrusion or lapping (drinking)
	Yawning	The timing of a yawn is similar to a stretch that includes prolonged wide opening of the jaws followed by relaxation. Often accompanied by a stretch or a subsequent GBM.
Limb Movements	Smooth	Limb(s) moves from origin to destination without backtracking
	Jerky	Limb movement is interrupted by backtracking
	Indeterminate	Unable to determine quality of movement
	Lower Limb	Lower limb is moving but unable to determine quality of movement
	Multiple	Repetitive limb movement in the same plane in a single epoch.
	Hand to Face	The hand slowly touches the face or mouth
	Tremor	Small rhythmic, jerky movement of an extremity