Neuropharmacology of drugs and alcohol in mother and fetus

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Summary Epidemiological evidence suggests that an adverse prenatal environment can have profound long-term health consequences throughout postnatal life. This chapter discusses the underlying mechanisms implicated in the consumption of mood-altering recreational drugs and teratogenicity in the fetus. The way metabolic parameters in pregnancy influence the pharmacokinetic characteristics of drugs and alcohol and the developmental stage of neurotoxicity are reviewed. The general underlying mechanisms that link multifaceted interactions between drug characteristics, gene polymorphisms, dietary deficiencies, changed endocrine indices and fetal programming are outlined, with specific examples throughout the text. As developmental injury is of significant social concern, the final section questions whether society provides adequate support for making appropriate and informed lifestyle choices to alleviate preventable transgenerational harm.

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Introductory background

Teratology, from the Greek word teras meaning abnormal form, is that branch of science dealing specifically with the biological, genetic, biochemical and behavioural causes of maldirected development and spans the period from germ-cell differentiation to the termination of functional...
development in the postpartum individual. The term "teratogen" broadly includes any reproductive and/or developmental toxicant that induces structural malformations, metabolic or functional deficits, growth retardation or psychological/behavioural anomalies in the offspring, whether at birth or in any defined postnatal period.\(^1\) Functional deficits refer to physiological or systems deficits that could result in hormonal, immunological or neurological/behavioural anomalies. Epigenetic influences (i.e. all the external environmental variables that regulate gene activity) modulate normal developmental processes. Harmful epigenetic influences can derail development by triggering intrinsic gene defects (mutations) or adversely modifying normal gene expression resulting in impaired growth and development. Neurotoxicity is generally defined as a structural or a functional alteration of the nervous system resulting from exposure to a chemical, biological or physical agent.

The term used to refer to a substance that is foreign to the living system is ' xenobiotic '. Drugs, by their very nature, are xenobiotics—they alter biological processes and so the potential for harm is almost always present. Whereas the protective blood—brain barrier of the adult central nervous system (CNS) prevents entry of many potentially harmful xenobiotics into the brain, the developing CNS is distinguished by the absence of a blood—brain barrier, rendering it particularly vulnerable to toxic insults. Because of the many chemicals that have been shown to cause deleterious morphological/behavioural changes in the developing CNS, developmental neurotoxicology is of major social concern.

Despite a continuum of fresh insights, many neurological anomalies in humans are still not well understood.\(^2\) That uncertainty persists is normal because a particular type of anomaly—cleft palate, for example—can be caused by diverse agents and mechanisms and a particular pathogenesis can result in very different outcomes depending on factors such as dose, duration of exposure, embryonic/fetal age and genetic susceptibility. Silent neurotoxicity, where exposure to certain chemicals during brain development causes subtle morphological/biochemical changes that are not apparent until the individual grows, matures or is exposed to additional epigenetic challenges, is also of concern.\(^3\) It is difficult, therefore, to ascertain with confidence the underlying aetiology and pathogenesis of a given developmental anomaly based on the final outcome. For this reason, it is important to look early in the developmental process to determine which tissues, or cell populations, were initially affected; whether the early effects were maternally or paternally mediated and what the effects on these targets were.

As epigenetic effects can be operative at any time during the differentiation of the gametes, the health and living conditions of both parents from the time of gamete formation to the conception of the offspring are crucial, as is the mother's situation during pregnancy and lactation. Male reproductive function can be altered by chronic exposure to bioactive compounds capable of crossing the Sertoli cell barrier following systemic absorption. Components in tobacco smoke, alcoholic beverages, selected 'recreational' drugs and narcotics including marijuana, cocaine, heroin/methadone and amphetamines have a detrimental effect on male reproductive hormones and on semen quality.\(^4\)\(^–\)\(^7\) Moreover, adverse paternal drug effects on offspring parallel the continuum of maternal effects and range from early spontaneous abortion (which might be perceived as infertility), to delayed miscarriage and stillbirth, malformations, preterm delivery, delivery of small-for-gestational age infants, childhood cancer, altered postnatal behaviour and changes in reproductive function.\(^8\) Importantly, genetic and epigenetic influences have profound lasting effects on progeny outcome and either drug-exposed parent can influence pregnancy loss, alterations in growth, malformations and overall well-being that ultimately identifies the conceptus, newborn infant and adult. The remainder of this chapter focuses specifically on the neuropharmacology of drugs and alcohol abuse in women, but we need to bear in mind the ways in which 'momma' and 'poppa' can compromise the developmental outcomes and subsequent well-being of their children and grandchildren.\(^9\)

There are two important concepts when interpreting complex neuropharmacological effects. First, statistical associations between specific exposures and reproductive outcome do not necessarily prove causality because they might be due to unidentified or uncontrolled confounding variables, to genetic bias or to chance. Second, epidemiological studies can never prove a lack of reproductive toxicity; they can only show that the risk is below a certain level. A low risk might not initially be detectable but could subsequently represent a major cause of behavioural or other adverse effect in the affected population. For example, the nervous system possesses reserve capacity that can compensate for damage, but the resulting reduction in reserve capacity needs to be regarded as an adverse effect. It is, therefore, important to re-emphasize that the heritability of complex systems; such as behavioural and personality characteristics, are the result of genetic and epigenetic influences interacting as one integrated system.

By studying transgenic animals, scientists have been able to gain a clearer idea of the influence of specific genetic predispositions on behaviour. A genetic predisposition involves inherent physiological factors that influence behaviour. These include brain chemistry—the neurological structure with which we are born—where the combined action of several different genes, each with small but cumulative effects, produces a certain genetic predisposition. A genetic predisposition directs, but does not necessarily control, behaviour. Some genetic predispositions remain latent until a triggering event or set of circumstances occurs. For instance, a particular predisposition might be activated by distress, illness or lifestyle, such as smoking. Positive and negative experiences have the power to alter our brain's chemistry and function—permanently in extreme cases.\(^10\)

**Pharmacokinetics and neurotoxicology**

Classic pharmacokinetics quantifies the absorption, distribution, metabolism and elimination characteristics of a drug in the context of that drug's mechanism of action. For example, some compounds require bioactivation to the active molecule, whereas others can generate new but different bioactive molecules. Caffeine is a drug in the
latter category; bioreactive dimethylxanthine metabolites—theophylline and theobromine—are generated during hepatic disposition of caffeine. For this reason, a drug’s toxic potential might be confounded when the parent molecule alone is considered but a metabolite also mediates toxicity. Because chemical interaction between different substances might affect their individual toxicity, the biological effects of two or more toxins—or drugs—administered together can be very different in kind and degree to the effects of the substances alone. For example, cognitive impairment, learning disabilities and behavioural disorders are CNS manifestations of prenatal alcohol exposure and become especially manifested in the child who also exhibits subtle cognitive, speech and language development disabilities following prenatal cocaine exposure. When two substances have similar physiological functions, their effects might be simply additive or they might be synergistic; that is, the total effect is greater (sometimes by many orders of magnitude) than the sum of the effects of each separately.

Potentiation occurs when an inactive substance enhances the action of an active one; antagonism occurs when an active substance decreases the effect of another active one. Should there be no lasting harmful effects from a particular toxic exposure, the effect is said to be reversible, whereas permanent effects are termed irreversible. Irreversible effects of toxic exposure remain after the substance is eliminated from the body. A major consideration when prescribing drugs during pregnancy is to establish a dose that has adequate therapeutic efficacy without unacceptably high side effects. For example, women with epilepsy need to continue their medication to control their seizures but exposure of the offspring to anticonvulsant drugs risks developmental neurotoxicity. However, the present discussion does not concern itself with predetermined supervised medication; rather it deals with voluntary, unsupervised behaviour causing preventable disability in children. Physiological changes in pregnancy affect maternal metabolism and, as a consequence, influence the pharmacokinetic characteristics of drugs and other reactive xenobiotics. Appropriately, the logical extension of pharmacokinetics is its application in toxicity assessment where it plays a critical role in developmental and reproductive toxicology.

There are many pathways by which the embryo or fetus can be exposed to neurotoxic drugs during development. Initially, the preimplantation blastocyst is freely exposed to solutes within the uterus, where embryonic exposures can be rapid and extensive. Subsequently, during gestation, the predominant interface is the placenta and maternal–placental–fetal interactions drive the developmental processes. The major determinant of intrauterine growth is the placental nutrient supply, which, in turn, depends on the size, morphology, blood supply and nutrient transporter abundance of the placenta. The placenta plays a crucial role in the synthesis and metabolism of hormones that direct appropriate signals to the placenta itself and to maternal and fetal targets driving the succession of endocrine event and the timing of parturition. Because the placenta is both active and selective in the transport of nutrients and xenobiotics, it also plays a significant role in metabolizing compounds that, depending on the compound, might create reactive metabolites or assist in detoxification. Hydroxylation of xenobiotics increases their solubility and is an initial step in their metabolism and excretion. The hepatic cytochrome P450 oxygenases comprise a gene superfamily of enzymes responsible for the biotransformation of a large variety of endogenous compounds, such as steroid hormones, pharmacological agents and many environmental xenobiotics. It is interesting to note that microsomal P450 oxygenases are essentially absent in the placentas of non-smoking women but that P450 oxygenation activity is significantly induced as a result of maternal cigarette smoking. The human fetal liver also has significant capability of metabolizing xenobiotics using its cytochrome P450 enzymes; thus actively participating in feedback loops across the maternal–placental–fetal metabolic divide.

**Teratogenesis and developmental stage susceptibility**

The environment encountered from preconception to birth exerts a profound influence on physiological function and risk of disease in adult life. Development in utero can be divided into three periods with regard to susceptibility to toxic insult. These are: (1) predifferentiation; (2) the embryonic period; and (3) the fetogenic period. During the predifferentiation stage of development the damaged embryo characteristically either repairs the damage or dies. However, repair might not be complete in all instances, as is the case for ionizing radiation or exposure to highly genotoxic chemicals. The embryonic period, when the organ primordia (foundations for later development) are laid down, is the most complex stage of development. Each organ or organ system has a critical, or vulnerable, period during pregnancy when it is being formed. During early organogenesis the embryo is most susceptible to induction of malformations and once the basic structures are formed it becomes increasingly difficult to alter them structurally. The fetogenic, or advanced organogenesis, period is the period largely devoted to body growth, histocytological differentiation and functional maturation of organs and organ systems. Insults during this period predominantly cause growth retardation, developmental delay and functional deficits particularly neurobehavioural as the brain matures relatively late in development. Different organs not only grow at different times and rates, but different constituents within the same tissue can undergo different developmental changes. Thus, depending on timing and mechanism of action, teratogens produce characteristic syndromes of structural, functional and/or neurobehavioural abnormalities. However, any given developmental toxicant might act by more than one mechanism at the same time in the same conceptus, although one, or more, mechanisms might predominate.

Human brain development is exceptional and multiphasic, extending over the entire prenatal period and through the first 2–3 years of postnatal life. To summarize: the growth of the brain after organogenesis follows two somewhat overlapping phases. The first phase is one of neuronal multiplication and is followed by the second phase, which is of glial-cell proliferation. This is also a time
when axons grow, dendrites branch extensively, synapses form, neurotransmitter systems develop and myelination proceeds. Neurons multiply in the first trimester of intrauterine life but the major growth phase is during the third trimester and continues after birth. Brain growth in weight is approximately a quarter complete by birth but attains about three-quarters of its adult weight by 2 years. There is a finer-grained chronology within the above overview as, within a single brain region, subpopulations of neurons develop at different rates and at different times. Importantly, different parts of the CNS form at different stages of development and there is not one but many critical periods where neuroteratogens can exert their deleterious effects.\(^3\) Which distinct brain region is differentially affected depends on certain specifics. For example, cocaine readily crosses the placenta and has been associated with alterations in the developing monoaminergic neurotransmitter systems with both structural and functional implications.\(^4\) However, the degree of damage and how this might influence selective attention and information-processing abilities across the developmental continuum is greatly influenced by factors such as the timing and pattern of fetal exposure, as well as individual differences in genetic susceptibility of the conceptus and variable cocaine biodegradation (see the section Gene polymorphism and drug teratogenicity, below).

Brain-targeting teratogens, like alcohol, cause primary damage during prenatal life; this can be amplified by a cascade of secondary effects after birth (Fig. 1). Neurotoxic exposure of multiplying neuronal cell populations during the structural phase of brain development can result in localized lesions. The primary consequence is microcephaly or a permanent reduction in the total number of cells present in the mature brain. In postnatal life, further brain damage continues during the phase of neurological organization. Primary reduction of nerve cell density correspondingly reduces the normal network of possible synaptic transmissions connecting other target-dependent areas of the brain. Further, abnormal neurotransmitter concentration at synaptic transmission sites can initiate a cascade of secondary effects. In attention deficit hyperactivity disorder (ADHD), for example, subthreshold dopamine levels are responsible for a cascade of multiple, heterogeneous secondary effects in fine-tuning of functions scattered throughout the cerebral cortex. Thus, as a result of primary prenatal brain growth restriction, a self-reinforcing cycle of secondary injury is initiated in one or more target-dependent systems controlling cognition, behaviour, somatic sensation, vision and movement, in children originally genetically robust but drug damaged.\(^10\)

**Drug teratogenicity, genetic predisposition and fetal programming**

It is well known that susceptibility to teratogens depends on the genotype of the conceptus, especially if the level of exposure is near the threshold of a particular adverse effect. Developmental outcome is also influenced by the maternal genotype as a determinant of, for example, the rate of biotransformation of the toxicant, its peak level in the maternal blood and the half life of the parent compound and its reactive metabolite(s). The term ‘multifactorial causation’ is used when the combination of environmental insults(s) and a particular susceptible genome in the conceptus is required for adverse effects to be apparent. Research identifying functional interactions between specific gene polymorphisms that contribute to genetic vulnerabilities is recent and falls within the new field of ecogenetics.

Ecogenetics reinforces the urgent need to upgrade more vigorously social, economic and political responsibility, and where better to start than with an in-depth understanding of the neurotoxic effects of alcohol and the fetal alcohol syndrome (FAS)? The teratogenic effects of FAS include, but are not confined to, prenatal and postnatal growth deficiencies, microcephaly, distinct craniofacial features, cardiac defects, limb deformities and a variety of genitourinary/musculoskeletal abnormalities. Common behavioural effects of FAS are attention deficit hyperactivity disorder (ADHD), learning difficulties, delays in psychomotor and language development, poor visual memory and psychosocial maladjustment.\(^15\) Of all the characteristics of FAS, intellectual disability is the most damaging and consistent consequence, yet this continues undiminished although the detrimental consequences of alcohol consumption during pregnancy have been known for centuries. Aristotle warned that ‘women drunkards’ often gave birth to abnormal children and the consumption of alcoholic beverages by young married couples was prohibited in ancient Greek and Old Testament writings.\(^1\) Despite a plethora of scientific publications concerned with the medical, social and economical aspects of alcoholism, the problem of alcohol abuse in present-day society remains alarming. Inappropriately managed alcohol consumption places a heavy burden on society through productivity losses, traffic deaths and morbidity, violent crime and alcohol-related illnesses. Less obvious are the transgenerational burdens, which might be of an even greater magnitude because excessive drinking by either sex rarely renders the woman incapable of conceiving.

Alcohol is not the only well-recognized drug posing serious neurodevelopmental effects. Many drugs of potential abuse, such as nicotine, marijuana, cocaine and ecstasy, adversely affect brain development, and behavioural teratologists are kept fully occupied debating how best to characterize complex symptoms resulting from prenatal exposure to different drugs and drug combinations. CNS dysfunction is revealed by a continuum of symptoms variously attributable to reduction in intelligence, genetic potential, learning capacity, social adaptation, self-sufficiency and a multiplicity of other physical and psychological problems. Tobacco and marijuana smoking are two of the most commonly abused substances in pregnancy and both have been associated with adverse effects in animal and human studies. Overall these studies reveal a dose-dependent association between prenatal exposure to cigarettes and reduced global intelligence scores based on a variety of performance tasks. By contrast, prenatal marijuana exposure is associated with impaired executive functions that require impulse control, visual mapping and analysis/hypothesis testing.\(^16\) Specifically, prenatal marijuana exposure in the first and third trimesters significantly increases hyperactivity, inattention
and impulsive symptoms in affected children, which might explain increased behavioural problems and delinquency. A recent epidemiological study using functional magnetic resonance imaging (fMRI) established long-lasting damage resulting from in-utero exposure to marijuana. 

Intellectual functions are highly heritable and modern genomics is increasingly providing clues as to the finer molecular mechanisms driving neurodevelopment and cognitive ability, particularly those relating to the multifaceted interactions among drug characteristics, gene polymorphisms and dietary deficiencies. Normal development can be disrupted by harmful environmental influences and, for those individuals who survive their prenatal challenges, the cost can be a struggle with long-term health consequences. Much has been learned since David Barker and colleagues first proposed that suboptimal intrauterine growth might alter fetal development in ways that predispose the offspring to a range of diseases in adulthood. As nutrition directly or indirectly influences epigenetic processes that fine-tune DNA function, the nutrient supply to the fetus is a prime determinant in establishing the offspring’s long-term health prospects. The phenomenon variously referred to as ‘fetal programming’ or ‘developmental programming of adult health and disease’ or just ‘programming’ occurs when the normal pattern of fetal growth is disrupted in response to unfavourable intrauterine conditions. 

Fetal growth can be disrupted by a drug; ionizing radiation; an environmental shift, such as hyperthermia or hypoxia; disease or by a micronutritional imbalance, as in dietary folate (vitamin B9) deficiency, which increases neurological anomalies such as neural tube defect. Essentially, programming takes place when normal placental signalling is disrupted. However, little is known about the mechanisms whereby variable stressful challenges programme the future trajectory of development. Hormones regulate fetal growth and tissue development,
so changed endocrine indices are believed to have a central role in intrauterine programming. Hormones such as insulin, insulin-like growth factors, thyroxin and, particularly, glucocorticoids act as nutritional and maturational signals and adapt fetal development to the prevailing intrauterine conditions.20 The strongest candidates in the saga of fetal tissue programming are the glucocorticoids, because they are growth inhibitors able to affect the development of any organ system, and their concentrations in utero are elevated by all nutritional and other stressful challenges known to have programming effects.20 Glucocorticoids can act directly on genes and indirectly through changes in the bioavailability of other hormones and have persistent differential effects on the hypothalamic–pituitary–adrenal (HPA) axis, which, in turn, can influence physiological function throughout the course of life.21 Indeed, the HPA axis—responding to stress as is its function—is highly susceptible to programming during fetal development22 and there is evidence that programming of HPA activity might underlie some of the long-term behavioural and cognitive deficits that are observed following prenatal ethanol exposure.22 It is believed that fetal programming is an adaptive evolutionary strategy in mammals that confers some survival advantage in utero, albeit at an increased risk of adult-onset degenerative diseases.23 Impaired fetal growth is a strong predictor for diseases of adaptation, such as cardiovascular disease, hypertension, cancer, asthma, type II diabetes, schizophrenia and depression.24 Diseases of adaptation can be exacerbated further by environmental risk factors such as drug abuse, obesity, physical inactivity, prolonged anxiety and increasing age.

Endocrine changes might be both the cause and the consequence of intrauterine programming but how is such programming implemented? Epigenetic marking, including DNA and histone methylation, are considered likely mechanisms to induce long-term programming effects.24 Methylation is a process whereby marks are set in chromatin to differentially programme gene expression. DNA methylation is generally associated with transcriptional silencing, whereas histone methylation can induce either gene activation or repression.25 Because methylation enforces the heritability of lineage-specific modifications, changes in gene expression or repression last throughout the course of fetal and adult development and, by implication, across generations. Folate functions as a major methyl donor for nucleic acid synthesis; it is thus influential in methyl-group availability for DNA synthesis and normal tissue growth, integrity and repair, including the proliferation of neuronal progenitor cells in the developing brain.26 Significantly, xenobiotic-perturbed changes affect specific functional polymorphisms of genes involved in nutrient metabolism and variably modulate gene expression through DNA methylation patterns.26 However, methylation might not be the only method of chromatin remodelling and future studies might uncover a much wider range of epigenetic programming mechanisms.

**Gene polymorphism and drug teratogenicity**

The previous section provided an overview of the relationship between fetal growth restriction brought about by the presence of reactive xenobiotics such as alcohol, and altered neurodevelopment in the drug-exposed offspring. This section summarizes the genetic contribution to fetal alcohol teratogenesis in humans derived from studies of the polymorphisms of enzymes responsible for elimination of alcohol from the body. Fetal alcohol spectrum disorders (FASD), including fetal alcohol syndrome (FAS), depend on the maternal and fetal genotypes interacting with ethanol to produce significant damage in some fetuses and not so obvious effects in others. The term “fetal alcohol spectrum disorders” was first proposed in 2001 by Barr and Streissguth27 to describe the full range of adverse craniofacial, neuroanatomical, neurodevelopmental and organ abnormalities associated with prenatal alcohol exposure. The range of responses to developmental toxicants such as alcohol are due to differences in inherent susceptibility of the conceptus and/or differences in maternal physiology and drug pharmacokinetics, including biotransformation and disposition kinetics.

The major pathway of ethanol elimination is by the liver’s oxidative enzymes, in particular alcohol dehydrogenase (ADH), which metabolizes 90–95% of the consumed ethanol to acetaldehyde. The acetaldehyde is further oxidized by aldehyde dehydrogenase (ALDH) to acetate, which, in turn, is degraded into carbon dioxide and water. Several distinct classes of human alcohol dehydrogenase exist but the majority of ethanol is metabolized by isozymes encoded by three members of the ADH class 1 family: ADH1A, ADH1B and ADH1C. Other enzyme systems, such as the microsomal oxygenases, are also capable of metabolizing ethanol and a small amount is eliminated unchanged through the breath, sweat, urine and faeces. Because of low fetal hepatic ADH activity, it is the maternal pattern of ethanol elimination that determines the fetal exposure and is the rate-limiting step. Following maternal ‘binge’-type drinking, the amniotic fluid retains a reservoir of ethanol and acetaldehyde over relatively long periods. As ethanol stimulates catecholamine release, the umbilical vessels respond by contracting and, in cases of chronic drinking, placental villus deterioration follows repeated vasoconstriction. In this way, ethanol-linked changes in placental physiology and structure adversely affect nutrient transport and gas exchange between the mother and her fetus, further accentuating the teratogenic effects of ethanol.

Polymorphic variants of the ADH genes that encode enzymes with altered kinetic properties can fundamentally alter the potential teratogenic effects of ethanol. For example, inheritance of the gene encoding for the high-activity ADH variant increases the rate of ethanol oxidation and elimination, whereas inheritance of the gene encoding for the low-activity ADH variant associated with decreased catabolism results in an increased risk of FASD.28 The complete identification of specific polymorphisms contributing to FASD is ongoing but it is interesting to note that polymorphisms of one of the genes for the alcohol dehydrogenase enzyme family (ADH1B) contributes to FASD vulnerability whereas another candidate gene (ADH1B*2) reduces risk for FASD in a mixed ancestry South African population.29 Subsequent research has highlighted another variant (ADH1B*3), which seems to provide protection for FASD in African–American populations.29
Other factors that frequently accompany alcoholism can contribute to FASD; in particular multiple or polydrug abuse, which can include cigarettes, marijuana and cocaine reinforced by poor nutrition. Nicotine readily crosses the placenta and the fetal system is exposed to relatively higher nicotine concentrations than the maternal system. It is well established that smoking during pregnancy is causally associated with pregnancy complications, including placental abruption, intrauterine growth retardation and fetal death. Further, epidemiological studies support an association between maternal smoking and cognitive deficits, attention deficit hyperactivity disorder, conduct disorder and criminality in the offspring and a predisposition to smoke and abuse alcohol in adulthood.30

Disruptions in metabolic activation and detoxification pathways attributable to maternal genetic polymorphisms also provide for variable adverse impacts of tobacco smoke on fetal growth. It has been established that the extent of birth-weight reduction among infants born to smoking mothers significantly correlates with polymorphic forms of the aryl hydrocarbon receptor gene, which mediates the detoxification of xenobiotic chemicals; such as the highly genotoxic/carcinogenic polycyclic aromatic hydrocarbons found in tobacco smoke.31 It is also likely that prenatally drug-exposed infants will experience suboptimal postnatal growth and neuroanatomical development over the period of breast-feeding due to a combination of nutritional deficit and drug-contaminated breast milk.

Concluding remarks: social and ethical concerns

The developing brain is extremely vulnerable to toxic insults because complex developmental processes take place over an extended period. The lack of a protective fetal blood–brain barrier gives drugs free access to the developing brain and can exert a range of deleterious effects, depending on drug characteristics and times of exposure. Indeed, neural developmental damage with physical, intellectual and behavioural consequences occurs, typically, at lower doses than is necessary to induce disruption of other organ systems.32 The neurological effect of low-dose exposure to drugs such as alcohol, nicotine and cocaine might, therefore, be of considerably greater concern in the absence of identifiable physical malformations. Further, although the effects of xenobiotic exposure might be subclinical in nature, they might have profound long-term consequences on aging and reproductive function. Nicotine and alcohol dependency in pregnancy have received much research attention and, thanks to a well-tried series of risk-assessment protocols, the deleterious effects of less well known drugs are also being recognized. To have a sufficient assessment of potential developmental neurotoxicity, end-point evaluations of drugs have to include motor development and function, cognitive function, sensory function and social behaviour.33 In the light of the above, it might be prudent to apply the precautionary principle and to flag-up ignorance about the safety of all psychoactive drugs when administered during critical phases of CNS neurogenesis, neural migration and synaptogenesis. A willingness to make decisions despite uncertainty is supported by ethical responsibility to the next and subsequent generations.

Epigenetic factors (including drugs) can impose specific changes in DNA sequence (mutation), chromatin packaging or DNA methylation patterns influencing gametogenesis and the preimplantation conceptus. They also alter the support system linking placental function to fetal programming with glucocorticoid involvement.34 The importance of epigenetic influences in the application of the more invasive assisted reproductive technologies (ART) to treat infertility must also be considered. A recent study reported that total lifetime marijuana use adversely affects fertility chances when undergoing IVF/GIFT treatment procedures in men and women.35 Sadly, an estimated one-third of all patients referred for fertility treatment have a significant history of drug exposure, reinforcing the view that drug exposure is an important consideration in all at-risk groups.

Varying combinations of addictive substances such as alcohol, nicotine, marijuana and cocaine with poverty, poor nutrition and lack of prenatal care are just some of the high-risk conditions certain infants are forced to suffer. It is crucial to recognize that prevention of avoidable harm requires that—as a society—we take responsibility and establish programmes that go far beyond the drug education of pregnant women. Only by evaluating the addiction problem from a broad social and economic perspective will we be able to develop strategies that can alleviate trans-generational neural and growth-related disabilities.9

Practice points

- Impaired fetal growth is a strong predictor for diseases of adaptation.
- Neuroteratogens can exert deleterious effects over an extended series of overlapping critical developmental phases.
- The fetal HPA axis—implicated in fetal programming—is considered functional by the beginning of the second trimester.
- Developmental-stage neurotoxicity is modulated by gene polymorphism, inducibility of gene expression and variable enzyme activity.
- Information brings responsibility, so the burden of proof is to demonstrate lack of harm before remedial action is necessary.

Research directions

- Gene–xenobiotic interaction and fetal programming.
- The role of prenatal drug influence on sexual orientation.
- Disease susceptibility genes, disease management and personalized drug therapies.
- Support cross-disciplinary research.
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