Teratogenic agents in man

1) Chemical
2) Physical
3) Infectious
4) Maternal diseases
5) Immunologic
6) Placenta mediated
7) Mechanical
8) Vascular disruption due to hypertension
9) Agents causing epigenetic changes
10) Paternal

What determines teratogenicity

1) Developmental stage at exposure (gestational age)
2) Duration of exposure
3) Concentrations of a teratogen
4) Single or multiple dose exposures
5) Organ specificity
6) Maternal metabolic changes
7) Single or multiple teratogens
8) Teratogens may have a specific “time window” for their damage
9) Genetic susceptibility
**Sensitive periods of brain development; brain plasticity**

- First half of pregnancy
- Second half of pregnancy
- First two years of life
- Many neurons die after birth and only the functioning connection persist
- Survival is competitive and environmentally regulated
- Nutritional factors, sensory input, emotional factors, chronic diseases (control) may affect neuronal survival, sprouting, synaptogenesis, myelinization

**FDA Classification of Drugs**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No fetal risk; proven safe for use during pregnancy (vitamins)</td>
</tr>
<tr>
<td>B</td>
<td>Fetal risk not demonstrated in animal or human studies (many drugs)</td>
</tr>
<tr>
<td>C</td>
<td>Fetal risk unknown; no adequate human studies (most drugs)</td>
</tr>
<tr>
<td>D</td>
<td>Some evidence of fetal risk. May be necessary to use the drug (AEDs)</td>
</tr>
<tr>
<td>X</td>
<td>Proven fetal risk. Contraindicated for use during pregnancy (methotrexate, retinoids, contraceptives)</td>
</tr>
</tbody>
</table>

As of this year, these categories will be replaced by text.

Adapted from the Federal Drug Administration

**Substances which may cause addiction or brain damage (Cat. X)**

- Alcohol (ethanol)
- Cannabinoids (marijuana, hashish)
- Heroin and opioids: methadone, meperidine, naloxone, buprenorphine, Cocaine, Crack (free base), Ecstasy (MDMA)
- LSD, pencyclidine (PCP), Toluene
- Cigarette smoking (tobacco-nicotine)
- Lactation is generally contraindicated

**Pharmacology of cocaine**

- Local anesthetics.
- CNS stimulant.
- Euphoria and excitement.
- Reduces reuptake of catecholamines.
- Vasoconstriction, hypertension.
- Reduced heart beats.
- Pyrexia.
- Addiction.
Cocaine induced fetal damage during pregnancy

- Intrauterine death
- Abruptio placentae
- Placental infarcts
- Intracerebral hemorrhage and infarcts
- Neonatal neurological damage
- SGA
- Prematurity
- SIDS

Cocaine: Pattern of neonatal (postnatal) neurological effects

- Somnolence
- Tremor
- Feeding problems
- Hypotonia
- Vomiting, sneezing

Cocaine: Mechanism of damage

- Increased oxidative stress
- Hemorrhages and edema resulting from vasoconstriction and hypertension
- Decreased placental blood flow
- Interference with Dopamine synapses
- Maternal malnutrition caused by cocaine
- Effects of environment versus exposure

Cocaine induced anomalies in the human fetus

- Some increase in anomalies in animals: ocular, skeletal and distal limbs
- Slight increase in anomalies of: Urinary tract
  Cardiovascular
  Respiratory
  Microcephaly; brain infarctions
- Reduction limb defects?
Cocaine: Pattern of postnatal neurological damage and anomalies

- Neonatal withdrawal
- Poor neonatal adaptation
- Early neurodevelopmental delay: language, social
- Decreased cognitive function
- Memory problems
- Increased ADHD and learning difficulties
- Behavioral changes

Cocaine: summary

- Intrauterine death prematurity SGA
- Neonatal withdrawal symptoms and poor adaptation
- Intracerebral and placental bleeding with consequences
- Prenatal and postnatal death (SIDS)
- Neurobehavioral problems: dependent on the early environment
- Lactation is contraindicated

Pharmacology of opioids

- Analgesia.
- Alteration of mood, euphoria.
- Mental clouding.
- Autonomic N.S. symptoms: respiratory depression, constipation, vomiting, constriction of pupils, increased muscle tone.
- Addiction.

Heroin and opiates: physiology

- 1. Endorphins, enkephalins and dynorphins are endogenous opioids (proencephalins)
- 1. Connects to different opioid receptors
- 2. Potent analgetics; also cause euphoria and depression of CNS and autonomic functions
- 3. In high doses cause respiratory depression which may lead to death
- 4. Cross the human placenta
- 5. Chronic high dose use may lead to infertility, especially in males (oligospermia)
**Types of heroin dependent parents in Israel**

- 1. Using mainly heroin
- 2. Strictly on methadone maintenance programs
- 3. On methadone maintenance but also use heroin
- 4. Mostly use other psychoactive drugs (benzodiazepines, barbiturates)
- 5. Most addicts smoke cigarettes

**Effects of heroin on the fetus**

1. Teratogenic in some animals (NTD, cardiovascular but not in man)
2. Intrauterine death
3. Prematurity
4. SGA
5. Increase perinatal mortality
6. Poor neonatal adaptation including visual maturation delay
7. SIDS

**Postnatal effects of heroin**

Withdrawal syndrome: hyperactivity, diarrhea, fever, abnormal sleep, respiratory distress
Early developmental delay
Hyperactivity, inattention
Learning difficulties
Behavioral disorders
Increased dependency?

**Objectives: study the development of children born to heroin dependent parents from preschool age to adolescence**

- To assess the role of the environment vs. heroin-induced damage in utero
- By studying the cognitive development
- The rate of learning difficulties
- The rate of behavioral problems
- The rate of ADHD
- The neurological status
- Carried out on children from 0.5-17 years
Groups of children in the heroin study: all in regular education: preschool, early school age and adolescents

- Controls, normal SES
- Low SES, environmental deprivation
- Drug dependent fathers
- Drug dependent mothers, raised at home
- Drug dependent mothers, adopted at infancy
- Non drug using parents, adopted at infancy (only adolescents)
- There were 30-50 children in each group of the 3 different age groups, altogether about 450.

Birth weight of children born to drug dependent parents and controls

- Fathers: 3135
- Mothers: 2928
- Low SES: 3070
- Controls: unknown
- Adopted: 2410*

* significantly lower than other groups, p<0.01

Gestational age of children born to drug dependent parents and controls

- Fathers: 39.2
- Mothers: 34.9*
- Low SES: 37.4
- Controls: 38.6
- Adopted: unknown

* significantly lower than other groups, p<0.01
**Psychological evaluation: children of heroin addicted mothers raised at home or adopted**

- **Raised at Home (42)**  
  - MDI  
    - Bayley  *96.4 ± 9.7*  
  - PDI  
    - McCarthy GCI  *95.9 ± 10.3*  

- **Adopted (40)**  
  - MDI  
    - 108.8 ±17.7  
  - PDI  
    - 97.0 ±14.1  

* significantly lower than adopted, p<0.05

About 50% of children born to drug dependent mothers at home have behavioral problems; only 20% of adopted

**WISC R performance (blue) and verbal (red) tests of early school age children born to drug dependent parents and controls**

* significantly lower than controls, p<0.05
# significantly lower than adopted, p<0.05

**Arithmetic’s evaluation of school age children of drug dependent parents**

* significantly lower than controls, p<0.05
# significantly lower than adopted, p<0.05

**Reading evaluation of school age children of drug dependent parents**

* significantly lower than controls, p<0.05
# significantly lower than adopted, p<0.05
Conner’s average score (blue) and % failed score > 21 (red) of drug dependent parents and controls

* significantly higher than controls, p<0.01
# significantly higher than adopted and low SES, p<0.05
& significantly higher than addicted fathers, p<0.05

Externalizing (blue) and internalizing (red) parental Achenbach in children of drug dependent parents and controls

* significantly higher than controls, p<0.01
# significantly higher than adopted and low SES, p<0.05

Maternal Wender’s questionnaire

*significantly higher than all other groups, p<0.001
**significantly higher than controls, p<0.05

Summary: early school age children of heroin dependent parents

- Normal growth in children of all groups
- Reduced WISC-R (verbal and performance), reading and arithmetic in drug dependent parents and low SES compared to controls
- Normal verbal WISC-R, reading and arithmetic in children of heroin dependent mothers-adopted, but reduced WISC-R performance
- High rate of ADHD in children of heroin dependent mothers, even if adopted
- High rate of ADHD among heroin dependent mothers; no correlation with their children
Description of Research Groups: Adolescents

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Number contacted</th>
<th>% participation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-exposed Addicted Father</td>
<td>35</td>
<td>57</td>
<td>61</td>
</tr>
<tr>
<td>Exposed Addicted Mother</td>
<td>31</td>
<td>51</td>
<td>61</td>
</tr>
<tr>
<td>Non-exposed - Low SES</td>
<td>28</td>
<td></td>
<td>61</td>
</tr>
<tr>
<td>Exposed Adopted</td>
<td>28</td>
<td>41</td>
<td>66</td>
</tr>
<tr>
<td>Non-exposed High SES</td>
<td>51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-exposed Adopted</td>
<td>23</td>
<td>31</td>
<td>74</td>
</tr>
</tbody>
</table>

Parental education, years in adolescents

*significantly lower than adopting parents and controls

WISC-R: Similarities, Vocabulary and Arithmetic’s in adolescents

*Significantly lower than controls and non exposed adopted

WISC-R: picture arrangement & Block Design in adolescents

*Significantly lower than controls, p<0.05
Results of Conner’s & Life attitude in adolescents

* significantly higher than controls and low SES, p<0.05

Parental CBCL of adolescents: general, externalizing and internalizing

*Significantly lower than other groups, p<0.05

Results of maternal Wenders’-adolescents

* Significantly higher than controls, p<0.05

Drug use Questionnaire-adolescents
**Summary: children of heroin dependent parents at adolescence**

- Normal growth in children of all groups
- Reduced WISC-R in adolescents of drug dependent parents whether adopted or not, and low SES compared to controls.
- Adoption does not reduce cognitive function
- High rate of severe ADHD in adolescents of heroin dependent mothers, even if adopted
- High rate of ADHD among heroin dependent mothers
- No difference among adolescents in tendency for drug use or in self esteem and competence

**Intrauterine heroin exposure**

- Induces specific, slight brain damage, behavioral and learning difficulties
- More severe with environmental deprivation
- Controlled intake of opioids (Methadone) less injurious to the fetus

- Abusing and neglecting environment induces postnatal stress & developmental problems + ADHD
- May further affect cognitive, emotional and social development & learning
- Early intervention (adoption) may reduce “damage”, but some problem may reappear at adolescence, mainly due to poorly treated ADHD

**Genetic factors related to the etiology of ADHD**

- Hereditary factors are responsible for about 60% of ADHD
- Abnormal dopamine receptor (DRD$_3$, DRD$_4$, DRD$_5$) and dopamine and serotonin transporter genes.
- Abnormal serotonergic and adrenergic mechanisms (genes) i.e. MAO alleles- long MAO A allele
- Increased breakdown of dopamine in synapses (that is reduced by Ritalin, dextroamphetamine ext).
- Different genetic markers in different families with ADHD
- Strong interrelation between ADHD and drug dependency. In the USA, about 50% of “dependent” youth (alcohol, heroin, cocaine ext) have ADHD

**Genetic studies carried out on index and control children**

- DNA samples were obtained from mouth washings from the adolescents and their parents
- We studied polymorphism for the following genes: DRD$_3$, DRD$_4$, DRD$_5$, DAT$_1$, dopamine and serotonin transporter genes, MAO A and COMT
- Results are correlated with the presence and severity of ADHD in the parents and offspring
- Specific changes in polymorphism of some genes
**MESSAGE:** Society’s responsibility

- In infants with slight brain damage (heroin exposure) the early environment has a crucial role and we should do our best to improve it in all “high risk” infants
- Cognitive development, attention span and learning are affected more than motor functions

**Maternal Methadone**

1) Opioid analgesic; in high doses similar to heroin
2) Is used as alternative to opioids (heroin addicts)
3) Generally no increased anomalies in animals
4) No increased risk for congenital anomalies
5) High rate of withdrawal syndrome
6) Apparently no adverse effects on the fetus if continued at low doses during pregnancy
7) In high doses may affect the fetus: FGR, prematurity, decreased head circumference, cardiac arrhythmias; neurodevelopmental problems
8) Similar to the effects of heroin

**Maternal naltroxone (naloxone)**

- An opioid receptor blocker
- Higher levels of free drug in the fetus
- No increased risk for congenital anomalies in animals even with very high doses
- High doses may induce behavioral effects
- Withdrawal syndrome is rare
- No data in human pregnancies, but no contra-indication to use low doses
- Is the effect similar to that of Methadone?

**Maternal Buprenorphine**

1) Opioid analgesic with agonist antagonist properties
2) Is used together with naloxone as an alternative to methadone (Subutex)
3) No increased anomalies in animals
4) Most probably no increased risk for congenital anomalies.
5) Low rate of withdrawal syndrome - lower than with methadone
6) Apparently no adverse effects on the fetus
Maternal cannabis, ecstasy and other substances

1) Most probably no increased risk for congenital anomalies.
2) Withdrawal syndrome is rare.
3) Rarely: early developmental delay; apparently dependent on home environment.
4) Hyperactivity, inattention, behavioral disorders and possibly slight cognitive impairment.

Maternal alcohol drinking during pregnancy

Heavy drinking (>100 g/d) high teratogenicity.
Moderate drinking (>50 g/d) low or no teratogenicity.
Binge drinking - low teratogenicity.
Genetic differences are an important factor in outcome.
Various degrees of neurocognitive deficits.

Fetal alcohol (abuse) syndrome:
in 4-6% of heavy drinkers (>100 gr)
Prenatal and postnatal growth restriction deficiency
Microcephaly and CNS dysfunction
Mental retardation, developmental delay
Behavioral changes (severe hyperactivity and inattention); intellectual deficits persist
Smoking aggravates the effects of alcohol drinking
Fetal alcohol abuse syndrome (>100g/day)

Increased first trimester miscarriage
Short stature, microcephaly
Facial anomalies: short palpebral fissures, flat mid-face, thin upper lip, flat philtrum.
Various congenital anomalies: brain, cardiovascular, urogenital, cleft palate
Often only some of the symptoms

Fetal alcohol effects 30-60g/day

No typical facial dysmorphism; growth deficiency.
Increased minor anomalies
Intellectual deficits, decreased reaction time, decreased memory
Behavioral abnormalities (ADHD)
Learning difficulties; numeric and language skills; deficiency persist into adolescence
Increased childhood leukemia
Children of alcoholic parents are at greater risk to develop alcoholism. High concordance among MZ twins
Beer drinking is more dangerous

Fetal alcohol effects Binge drinking

Five drinks or more at once (over 100 gr. ethanol)
May cause brain structural anomalies: Purkinje cell loss, small vermis and microcephaly, especially during brain growth spurt – from week 15 of pregnancy
In animals – increased neuronal death
Intellectual deficits (5-7 point decrease in IQ)
Behavioral abnormalities (ADHD)
Learning difficulties; numeric and language skills deficiency persist into adolescence
Breast feeding in heavy drinkers

Ethanol passes to the human milk with the same concentrations as in the blood.
Mothers who are heavy drinkers should, generally, not nurse their infants.
Infants may have developmental delay, mainly motor.
Paternal drinking has no effect on the embryo or fetus but cause impotence, sperm damage and infertility.

Cigarette composition: tobacco-derived chemicals

- Lighting a cigarette creates over 4000 harmful chemicals with hazardous adverse effects on almost every organ in the body.
- The common constituents of cigarette smoke are:
  - In the particulate phase: tar, nicotine, hydrocarbons, phenol, cresol, trace elements - cadmium (carcinogens), indole, carbazole (tumor accelerators), and 4-aminobiphenyl.
  - In the gas phase: carbon monoxide (impairs oxygen transport and utilization), hydrocyanic acid, acetaldehyde, acrolein, ammonia, formaldehyde and oxides of nitrogen nitrosamines, hydrazine and vinyl chloride (carcinogens).

Smoking in pregnancy

Heavy smoking (over 20 cigarettes/day) may cause an increase in Cleft Palate, cardiovascular anomalies and perhaps other major anomalies.
May cause IUGR perinatal and neonatal complications, respiratory distress; the rate correlates with the number of cigarettes/day.
May increase the effects of other teratogens (alcohol, SSRI’s, lithium?)
Mechanism: increased oxidative stress.
Less than 10 cigarettes/day are apparently safe.
Women should quit smoking in pregnancy.

Smoking in pregnancy: mechanism

Heavy smoking (over 20 cigarettes/day) may interfere with placental perfusion causing hypoxia and malnutrition (IUGR).
Nicotine stimulates nicotinic acetylcholine receptors and induce abnormalities in neuronal proliferation and differentiation.
Nicotine affects fetal neurotransmitters: reducing the response of dopaminergic and noradrenergic systems - a problem existing in ADHD; increased release of norepinephrine.
Mechanism: increased oxidative stress.
Maternal smoking in pregnancy and brain Development

- Effects are dose dependent.
- Observed from 10 cigarettes/day and more
- Reduced birth weight, perinatal and neonatal complications, more respiratory distress
- Higher rate of mental illness among smoking pregnant mothers that do not quit smoking
- Slightly reduced IQ in the offspring;
- Smoking adolescents if exposed in utero to cigarettes have more problems in listening and in word recognition; if they do not smoke as adolescents, their performance is better but not as in controls

Environment and brain Development Hypothesis

- Parental education and profession (SES) are known to affect postnatal brain development
- Children with minor brain damage (diabetic or drug dependent mothers, very low birth weight infants) will be more affected by poor environment
- This is based on results of many developmental studies: drugs of abuse, prematurity, twins discordant for birth weight and children of diabetic mothers

THANKS