

Effects of Substance Use on Fetal Development

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6/1/2022

General Disclosures

The UW Department of Psychiatry gratefully acknowledges receipt of Cambia Health Foundation's support for this activity – working to expand access to perinatal behavioral health services throughout Washington State.

Speaker Disclosures

I have no disclosures to report

Learning Objectives

- Briefly review the process of embryonic and fetal development
- Reflect on the timing of events of embryonic/fetal development and how this influences the risks of substance use
- Describe the effects of substances on fetal development

Definitions

- Pregnancy is 38 weeks from conception to birth
- Gynecologic timing is from LMP, so 40 weeks “gestational” age
- Embryonic period is the first 8 weeks; all major organs formed
- Fetal period is the remaining 30 weeks; organs grow larger and become more complex

Definitions

- SAB = spontaneous abortion
- IUFD = intrauterine fetal demise, stillbirth
- FGR = fetal growth restriction
- LBW = low birth weight
- SGA = small for gestational age
- PTB = preterm birth
- PTL = preterm labor
- PPROM = preterm, premature rupture of membranes

GA by LMP = 4 wks

6 wks

8 wks

10 wks

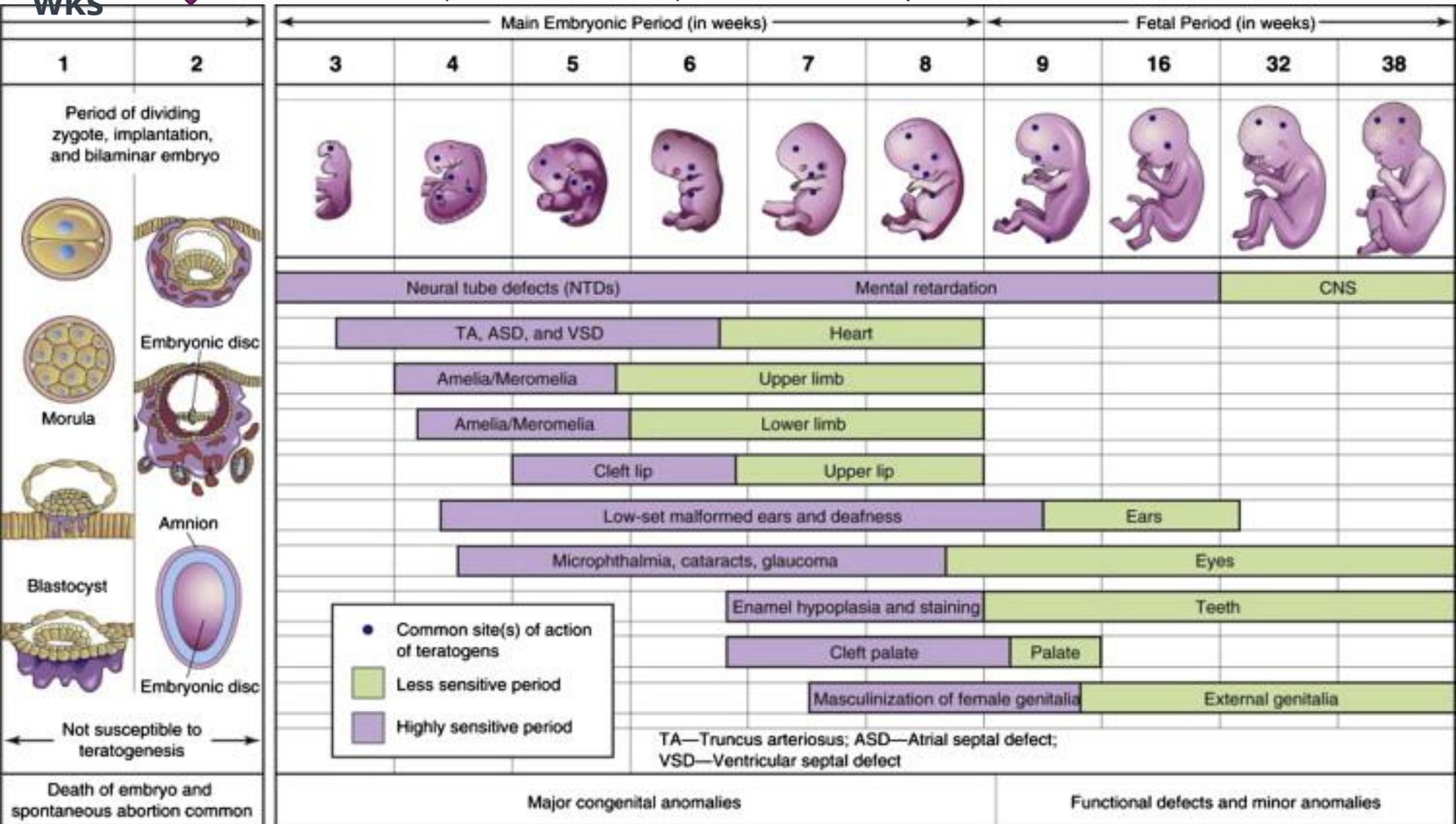


Photo Credit: Moore and Persaud. Before We Are Born: Essentials of Embryology, 2020.

Teratogens

- When considering possible teratogenicity, consider:
 - Period of development
 - Dose of drug or chemical
 - Genotype (genetic constitution) of the embryo
- The most critical period in development is when cell differentiation and morphogenesis are at their peak
- Disturbances in 1st 2 wks may interfere with cleavage or implantation, causing miscarriage
- During the organogenesis period (4-8 wks) the development of the embryo is most easily disrupted

Alcohol Use

- > Alcohol use disorder affects 1-2% of women of childbearing age
- > 5.2% of pregnant adults reported binge drinking in the prior 30 days and 13.5% reported current alcohol consumption



Gosdin 2022

Photo Credit: <https://www.cnn.com/2018/11/30/health/fetal-alcohol-syndrom-gbr-scli-intl/index.html>

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Alcohol Use: Risks

- > Increased risks of miscarriage, IUFD, LBW, and FASD
- > Fetal alcohol spectrum disorder (FASD) in 1-2 infants/1000
 - Characterized by growth deficiency, unique facial features, CNS abnormalities
- > No known safe amount or time to drink during pregnancy

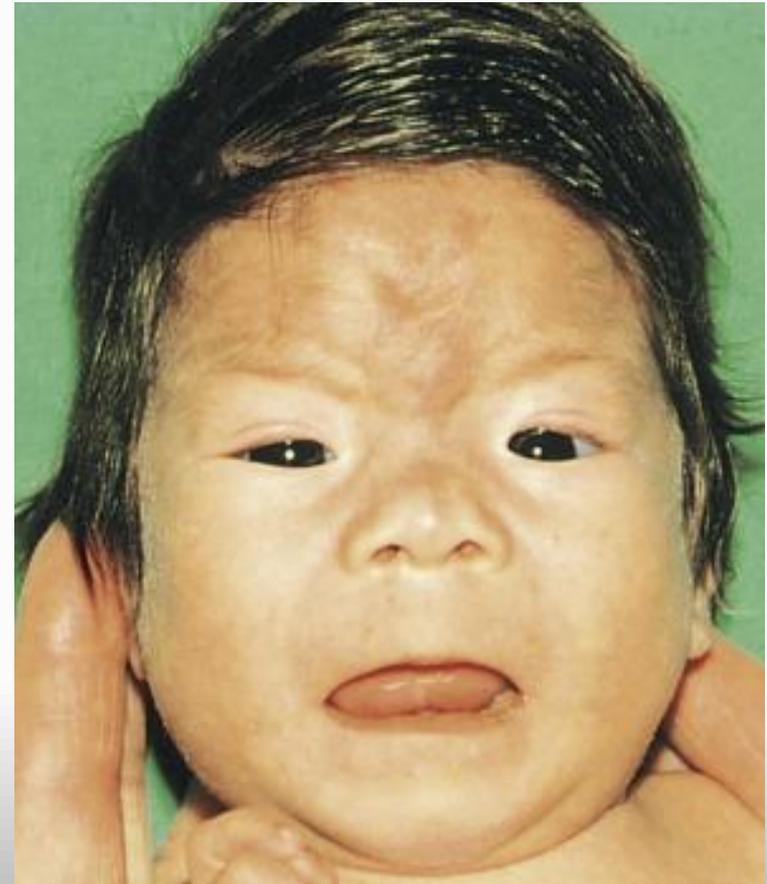


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Tobacco Use: Risks



- > ~7% of pregnant patients smoke
- > Pregnancy is motivating: 46% of pregnant people quit smoking directly before or during pregnancy

Smoking is one of the most important modifiable causes of poor pregnancy outcomes in the US!

- > Increased risks of FGR, premature delivery, PPRM, placenta previa, placental abruption, LBW
- > 5-8% of preterm deliveries, 13-19% of LBW in term infants, 23-34% of SIDS, and 5-7% of preterm-related infant deaths can be attributed to maternal smoking
- > Children born to mothers who smoke have increased risks of asthma, infantile colic, childhood obesity

ACOG 2020, Crum 2019, Dietz 2010. Drake 2016

Photo Credit: <https://www.loyolamedicine.org/about-us/blog/8-best-tips-to-quit-smoking-for-good>

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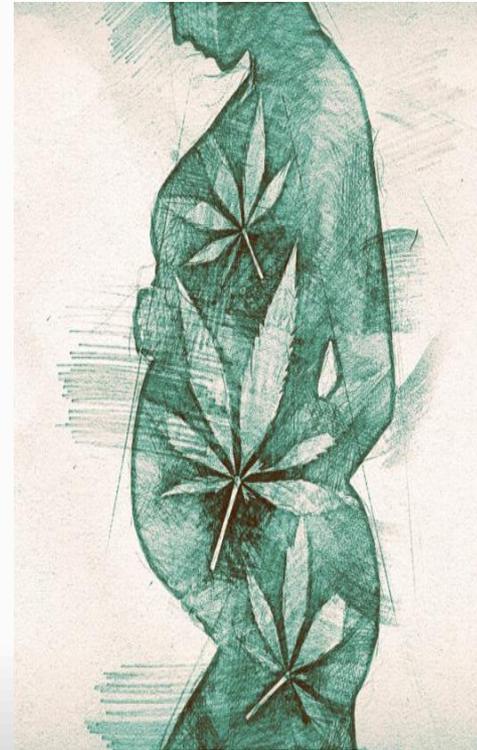
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Cannabis Use

- > Marijuana is the most commonly used illicit substance (federally) during pregnancy
- > Self reported prevalence during pregnancy is up to 7%
- > 19% believed it was of no risk during pregnancy



ACOG 2017; Volkow 2019; Jarlenski 2017
Photo Credit: <https://www.statnews.com/2019/12/23/pregnant-women-providers-how-to-talk-marijuana/>

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Cannabis Use: Risks



- > THC has been shown in animal studies to cross the placenta
 - Fetal levels ~10% of maternal levels (higher with repetitive exposures)
- > Limited data also shows it in breast milk up to 6 days after last use

Hutchings 1989; Bertrand 2018

Photo credit: <https://www.womenshealthmag.com/life/a19994105/is-it-okay-to-smoke-weed-while-breastfeeding/>

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Cannabis Use: Risks

- > Uncertain risks
- > May be associated with increased risk of SGA and PTB
- > Associated with increased risk of neonatal morbidity
- > Increased risk of autism spectrum disorder and other neurodevelopmental disorders

Stimulant Use

- > Prevalence of cocaine use in pregnancy is 2-4%
- > Prevalence of methamphetamine use in pregnancy is 1-5%



Bhuvanewar 2008; Wright 2015

Photo Credit: <https://teens.drugabuse.gov/drug-facts/methamphetamine-meth>

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Cocaine Use: Risks

- > Crosses the placenta and fetal blood-brain barrier
- > Vasoconstriction is likely the mechanism for fetal and placental damage
- > Associated with maternal HTN
- > Increased risks of PTB, LBW/SGA
- > Mixed data on long term risks. May have negative effects on cognitive, motor and language development
 - Review of 36 studies did not find this association

Methamphetamine Use: Risks

- > Amphetamines and byproducts cross the placenta
- > No congenital anomalies have been reported
- > Increased risks of FGR, GHTN/preeclampsia, abruption, PTB, IUFD, neonatal death
- > Newborns may develop jitteriness, drowsiness and respiratory distress. Increased rate of NICU admission
- > Long term outcomes
 - IDEAL Study: Heavy meth exposure associated with anxiety/depression and attention problems by age 3 and 5 yo

Jones 2009; Nguyen 2010; Gorman 2014, Derauf 2011; LaGasse 2012

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Opioid Use: Risks

Fetal

- > No consistent increase in congenital anomalies
- > Increased risks of FGR, abruption, PTL, IUFD
- > Impact on in-utero fetal behavior
 - Decreased fetal heart rate variability, lower baseline, fewer accelerations, less motor activity and breathing
 - Higher incidence of non-reactive non-stress tests

Data may be confounded by comorbid medical complications, obesity, nutritional and socioeconomic status, alcohol, tobacco or other substance abuse, medication-assisted treatment

Opioid Use: Risks

Neonatal

- > Risk of NAS/NOWS, longer hospitalization at birth
- > Postnatal feeding difficulty in opiate exposed infants
 - Altered sucking patterns
 - May affect development of brainstem respiratory and swallow centers

Neonatal Abstinence Syndrome

- > Neonatal Abstinence Syndrome (NAS)
 - Infant born to a mother with substance use during pregnancy may experience physiologic withdrawal
 - Variably expressed, unique to each infant, changes over time
 - Continuum of signs of neonatal neurobehavioral dysregulation
- > Neonatal Opioid Withdrawal Syndrome (NOWS)
 - Opioid-only drug withdrawal symptoms
 - Often used interchangeably with NAS

Neonatal Abstinence Syndrome

> Timing of NAS

- Short acting opiates have earlier onset of NAS symptoms than methadone or long-acting opiates
- Can occur from the first 24 hours to day 14 of life
- Usually within first 72 hours

Neonatal Abstinence Syndrome

> Maternal Dose and NAS

- Neither the incidence or severity of NAS directly correlate with maternal methadone dose, although trend toward higher rates with higher doses
- Buprenorphine is associated with a lower incidence and shorter duration of NAS than methadone

Neonatal Abstinence Syndrome

Complex Predictors of NAS

- Maternal history of opioid or other drug misuse
- Exposure to psychotropic medications
- Smoking
- Substance use: alcohol, benzodiazepines
- Genetic contributions to NAS
- Neonatal: gestational age, birth weight

Desai 2015; Kaltenbach 2012; Stover and Davis 2015

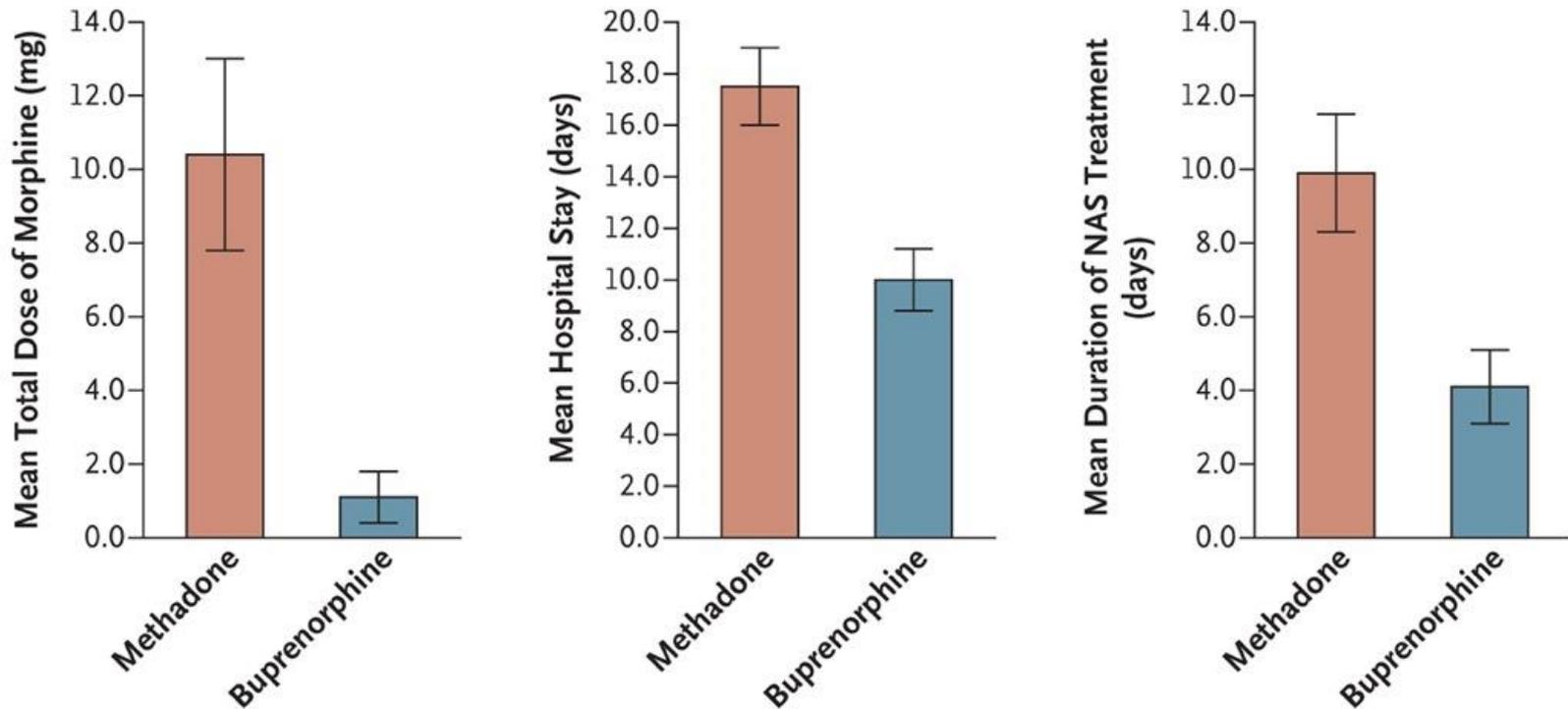
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Opioid Use Disorder: Treatment

- > Medication Assisted Treatment:
 - Methadone
 - Buprenorphine (*Subutex*® or *Suboxone*®)
- > No increase in congenital anomalies
- > Compared to methadone, buprenorphine associated with:
 - Modest reduction in treatment for NAS (*this was not significant after adjusting for possible unmeasured confounding by indication)
 - Modest reduction in mean hospital length of stay
 - Higher mean gestational age, weight, length, and head circumference at birth

Brogly, 2014

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MOTHER Study: Neonates of those on BUP used less morphine, had shorter hospital stays, and shorter duration of treatment for NAS. Those on methadone had higher retention rates.

Jones, 2010

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OD: Treatment

Medically Supervised Withdrawal (*not recommended)

Risks:

- > Acute maternal withdrawal -> ? fetal withdrawal
 - Maternal catecholamine surge, uterine contractions, reduced placental blood flow/oxygen supply
 - Elevated amniotic fluid catecholamines, fetal corticosteroid surge, fetal motor hyperactivity, increased fetal O₂ demand
- > Preterm birth, stillbirth, miscarriage, meconium
- > Stress related epigenetic fetal programming -> ? short/long term risks on brain development
- > Rates of relapse are higher
- > No decrease in NAS

Opioids and Lactation

American Academy of Pediatrics supports breastfeeding in patients on opioids including methadone (with no dose limitation)

- > Infants receive 2-3% of weight adjusted maternal dose via breast milk
- > Short acting opioids commonly prescribed after cesarean section without concern for lactation
- > Breast/chestfeeding is beneficial in lactating people taking methadone or buprenorphine and reduces the severity of NAS, need for pharmacotherapy, shortens length of hospital stay, facilitates attachment and skin-to-skin care
- > Not recommended if ongoing illicit drug use or codeine use

AAP, 2001

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Hallucinogens



- Lysergic acid diethylamide (LSD)
 - Mixed data in animals, with some studies suggesting teratogenicity
 - May increase risk of SAB (McGlothlin 1970)
- Ayahausca
 - Rat study suggests increased risks of SAB, FGR, and occurrence of fetal anomalies, including fetal soft tissue and skeletal anomalies (Gueiros da Motta 2018)
- Psilocybin
 - No data

Photo Credit: <https://www.scientificamerican.com/article/psilocybin-therapy-may-work-as-well-as-common-antidepressant/>

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MDMA (Ecstasy, Molly)

3,4-Methylenedioxyamphetamine



- Limited data
- MDMA is known to generate increase in stress hormone cortisol
- DAISY study found significant delay in psychomotor development in child of MDMA-using mothers (Singer 2012a, Singer 2012b, Singer 2013)
- May be associated with congenital anomalies, especially cardiovascular and musculoskeletal (McElhatton 1999)

Photo Credit: <https://www.mentalhelp.net/depression/can-ecstasy-cause/>

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