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ILLEGAL SUBSTANCE USE DURING PREGNANCY: WHAT DO WE KNOW?

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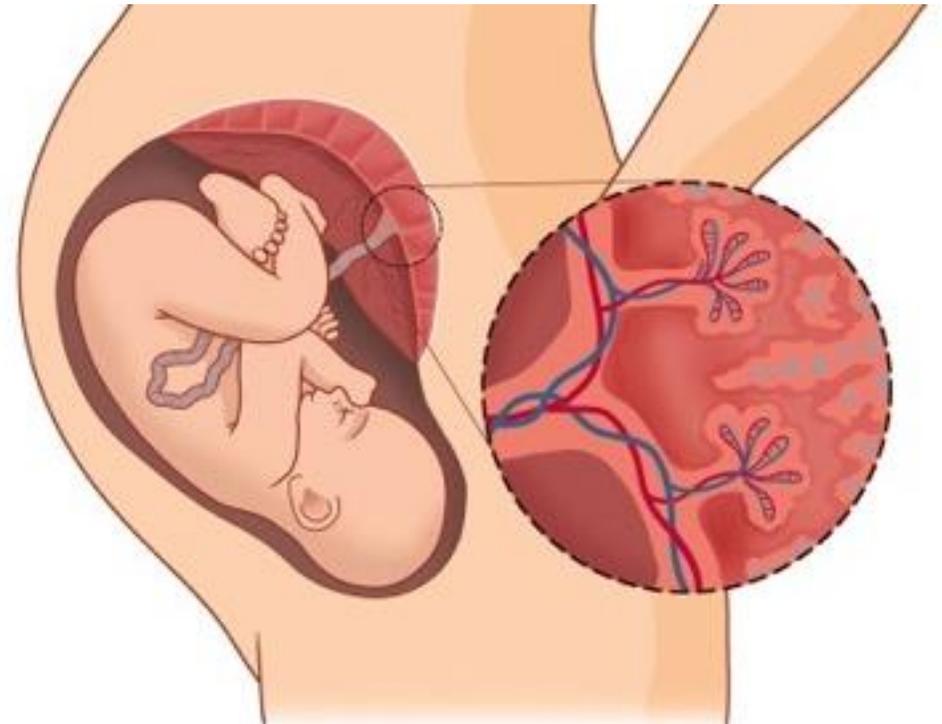
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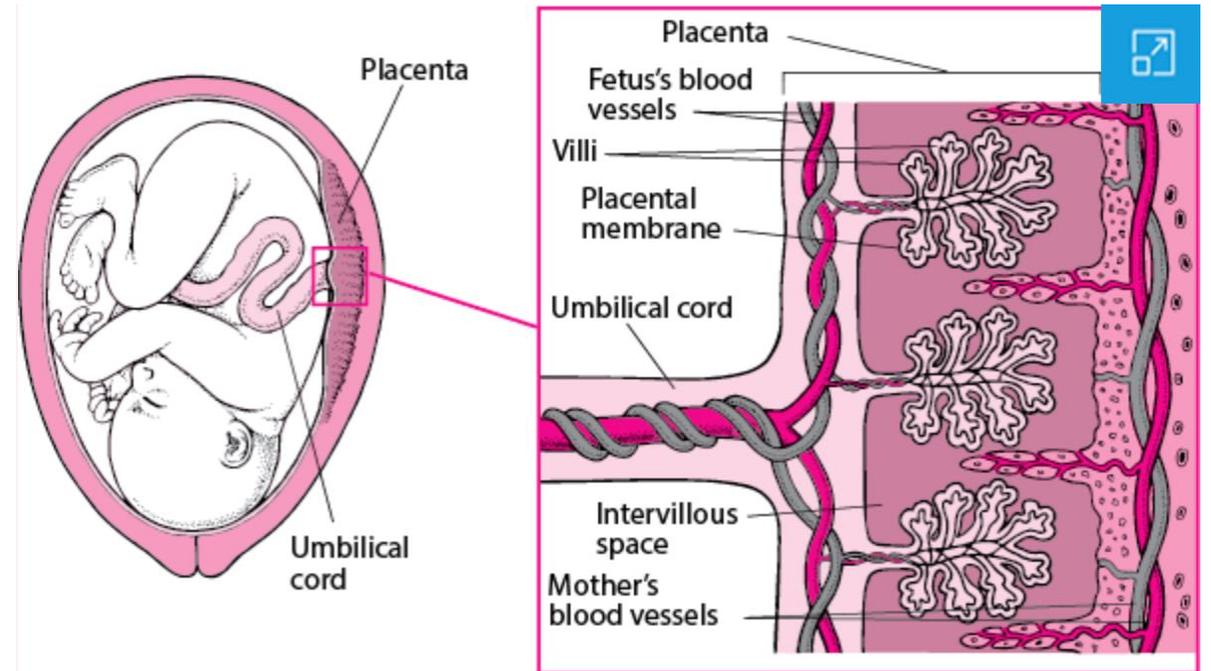
OVERVIEW

- Drug use and pregnancy
- Cocaine use during pregnancy
- Opiate use during pregnancy
- Cannabis use during pregnancy
- Amphetamine use during pregnancy



DRUG USE DURING PREGNANCY

- Most (illegal) drugs cross the placenta easily: cocaine, amphetamines, cannabis and opiates
- Direct effect of substances on the foetus
 - Congenital malformations
 - Effect on growth and later development
- Indirect effect of substances on the foetus (e.g., life-time changes associated with use)
- The earlier the use of substances during pregnancy, the larger the potential impact on the foetus

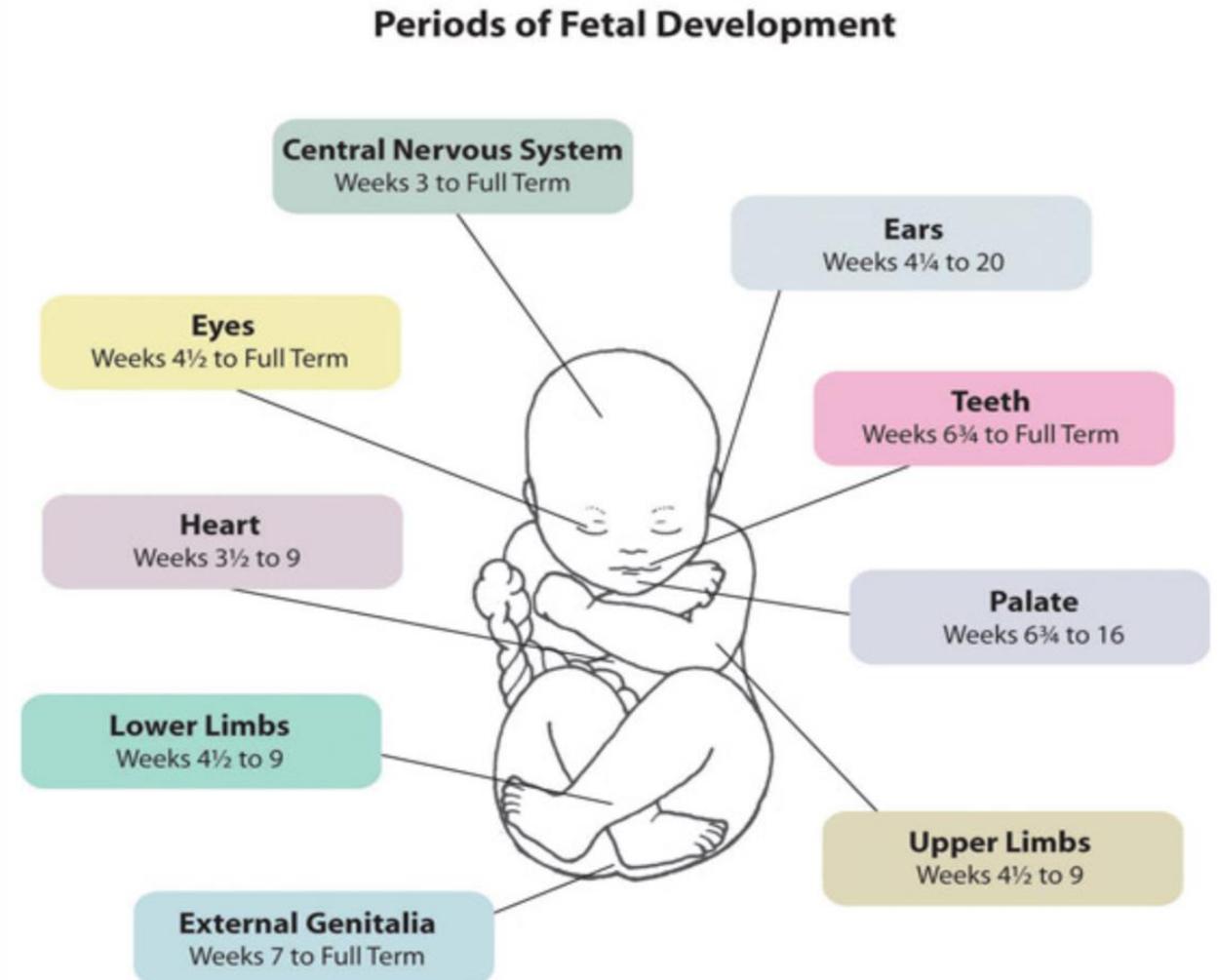


DRUG USE DURING PREGNANCY

- Cocaine:
 - 0.3% cocaine use in pregnancy population vs. 0.9% in non-pregnant population (SAMHSA, 2020)
- Opiates:
 - Heroin: 0.2% use in female population, no data in pregnant populations (SAMHSA, 2020)
 - Opioids: increased use of fentanyl use
 - Opioids: number of pregnant women with opioids at labor and delivery x4 between 1999 to 2014
- Cannabis:
 - 1.2% in first weeks of pregnancy, and 0.5% continue use during pregnancy (Scheffers-Van Schayck e.a., 2018)
 - 8% use during pregnancy for U.S.A. (SAMHSA, 2020)
- Amphetamines:
 - Increased use in non-pregnant population (SAMHSA 2020, 2021), no data of active use in pregnant population
 - 0.3% (2018)
 - 0.5% (2019)
 - 0.8% (2020)
 - x2 hospitalizations for amphetamine abuse among pregnant women 1988-2004 (cocaine -44%) (Smid e.a. 2019)

DRUG USE DURING PREGNANCY

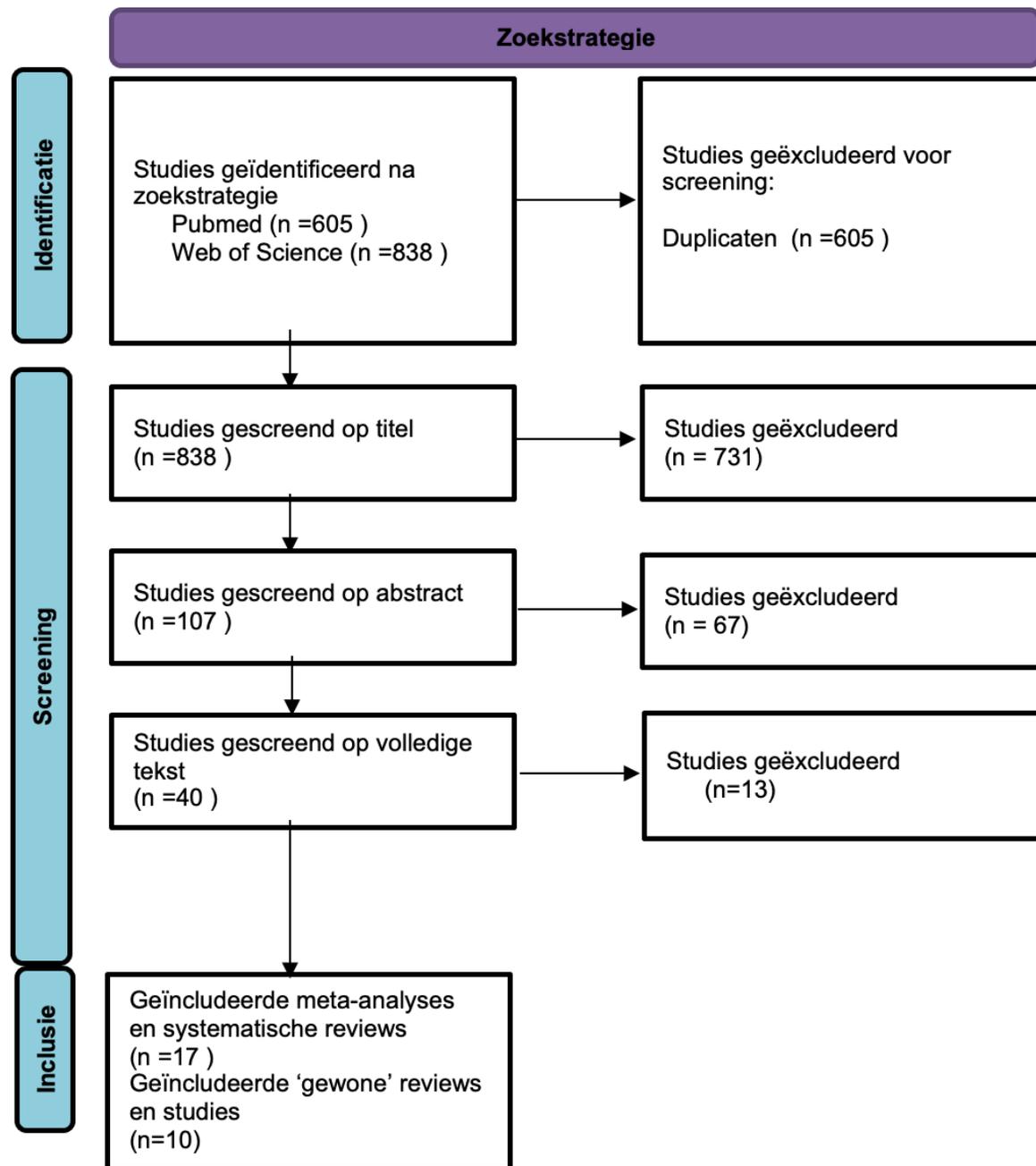
- The earlier the use of substances during pregnancy, the larger the potential impact on the foetus
- Embryonic stage:
 - teratogenic
- Fetal development stage:
 - Abnormal growth
 - Alteration in neurotransmitters and receptors
 - Brain organization
 - Altered delivery of substrates/nutrients



METHODOLOGY

- Literature review: “a review of reviews”
 - Studies of the last 30 years (1990-2022)
 - Particular focus on current meta-analyses and systematic reviews
 - Regarding risks of use on pregnancy and birth, on the newborn and in early and late child development
 - Focus on illicit use of cocaine, opiates, cannabis and amphetamines
 - Odds ratios (OR), adjusted OR (aOR), pooled OR (pOR), or RR

METHODOLOGY

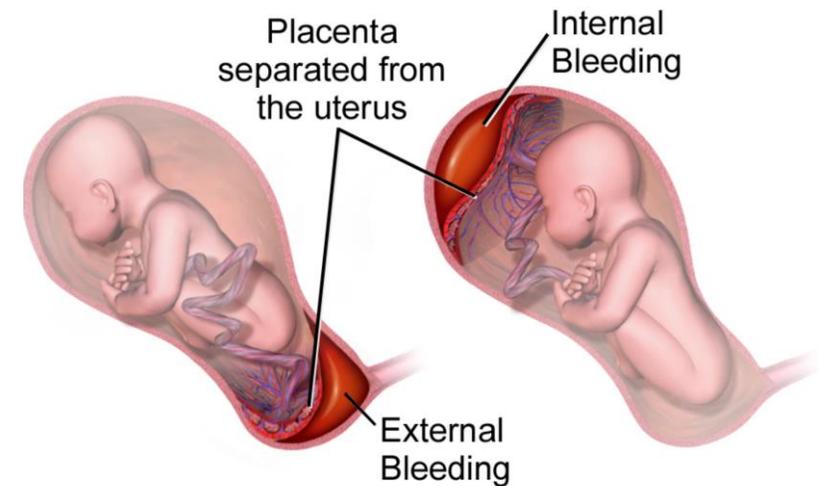


COCAINE USE DURING PREGNANCY

- × Easily passes the placenta and foetal blood-brain barrier
 - + Impact on development of neurotransmission, especially dopamine and glutamate
 - + Hypertension & vasoconstriction → reduced blood supply to the uterus and foetus (Cain e.a. 2013)
 - + Placenta metabolises cocaine: benzoylecgonine and norcocaine (De Giovanni e.a. 2012)
 - stored in myometrium and placental membrane → maintains continuous drug delivery to amniotic fluid and foetus
 - Not a barrier...

× Pregnancy & childbirth:

- + Placental abruption OR 2.03 95%CI 1.66-2.48
- + Preterm birth OR 2.22 95%CI 1.59-3.10
- + Congenital malformations ?? OR 0.91 95%CI 0.39-2.11



COCAINE USE DURING PREGNANCY

× Newborn:

- + Low birthweight OR 2.80 95%CI 2.39-3.27
- + Small for gestational age (SGA) OR 4.00 95%CI 1.74-9.18
- + Small head circumference -1,65 cm 95%CI -3.12 - -0.19
- + Little arguments for a neonate abstinence syndrome (NAS)
- + Although: (slower) reflexes, impaired autonomic regulation, difficulties focussing towards auditive and visual stimuli

× The child in later life:

- + Adolescence: cognitive dysfunctions re: EF, abstraction, impuls control, working memory, sustained attention
- + Often comorbid use with other drug use, little and sometimes contradictory evidence for cocaine

TREATMENT OF COCAINE USE DISORDER DURING PREGNANCY?

- × *“It is never too late to stop”*
- × Detoxification is advised
- × Similar as to the non-pregnant population
- × Focus on psychotherapeutic approaches, patient’s needs, reducing barriers to recovery, .. linking drug rehabilitation programs to obstetric and pediatric services

OPIATE USE DURING PREGNANCY

- × Opiates pass the placenta; resulting in exposure of mother as well as unborn child
- × Often polydrug- and I.V. use:
 - + Increased risks of infections: cellulitis, endocarditis, chorioamnionitis, HIV,...
 - + Other substances used?
- × Pregnancy & childbirth:
 - + Stillbirth RR 1.77 95%CI 1.14-2.75
 - + Congenital malformations in 17/30 studies: cleft palate, ventricular and septal defects, spina bifida and clubfoot (Lind e.a. 2017)

OPIATE USE DURING PREGNANCY

× Newborn:

- + Preterm birth RR 1.92 95%CI 1.57-2.36
- + Neonatal death RR 4.05 95%CI 2.12-7.72
- + Low birthweight RR 1.55 95%CI 1.11-2.16
- + SGA RR 2.16 95%CI 1.75-2.67
- + Longer hospital stay RR 4.39 95%CI 1.47-13.10
- + Lower APGAR -0.6 95%CI 0.2-1.4
- + NAS: symptoms of irritability, hypertonia, tremors, difficulty with feeding, emesis, respiratory problems and, in severe cases, epileptic fits
 - After 2-3 days of birth
 - Substitution therapy with tapering is sometimes necessary

× The child in later life (?):

- + Lower cognitive and perceptual functioning
- + Problems with coordination and fine motor skills
- + Difficulties with impulse control and sustained attention
- + Unsure if related to opiate or other drug use..

USE OF (SUBSTITUTION) OPIOIDS DURING PREGNANCY ?

- × With strict indication and in therapeutic dosages
 - × Opiate substitution treatment during pregnancy?
 - + To reduce the risk of (more severe) relapses
 - + No differences between methadon and buprenorphine (Minozzi e.a. 2020), or Bu/Naloxone: similar retention to treatment, similar NAS
 - + Split daily dose over several dosing moments, e.g. twice daily (due to liver enzym induction): the case for both methadone and buprenorphine; increase of methadon dosage is also an option, but do not combine slpitting and uptitration.
 - × Opioid detoxification?
 - + is NOT adviced (Ecker e.a. 2019)
 - + IS adviced ... (NICE, 2014)
 - + Safest in second trimester (Dijkstra e.a. 2017)
 - × Naloxone during pregnancy?
 - + Important to be drug-free for about a week.. → relapse in this week is likely and pernicious for foetus..
 - + No NAS
 - + If already taken before pregnancy: continue treatment during pregnancy
- Shared descision making
- + Inform patient on risk of opioid relapse (& overdose) during pregnancy
 - + Inform on risk of opioid substitution treatment

CANNABIS USE DURING PREGNANCY

- × Δ^9 -THC passes the placenta
- × Up to 30 days after use in chronic users and thus influences a sustained effect on the foetus
- × Important role of the endocannabinoid system in fetal neuronal development

- × Pregnancy & childbirth:
 - + Anemia pOR 1.36 95%CI 1.10-1.69
 - + No increased risk for gestational diabetes, abruptio placenta, hyperemesis gravidarum, weight gain, hypertension or postnatal complications
 - + Several publications on dubious effect of THC on child-related outcomes; although did not survive correction for polydrug-use (Warshak e.a. 2015)
 - + Mild to no teratogenic effect (unsure ..; Viteri e.a. 2014)

CANNABIS USE DURING PREGNANCY

× Newborn:

- + Low birth weight <2500g pOR 1.77 95%CI 1.04-3.01
- + Neonatal intensive care admission pOR 2.02 95%CI 1.27-3.21
- + No differences in neonatal length, intra-uterine growth restriction (IUGR) and APGAR score
- + Often poly-drug use (not an exclusion criteria in meta-analyses; Gunn e.a. 2016)
- + When excluding other drug use: no risk on birth weight (aOR 1.16; 95%CI 0.98-1.37) or preterm birth (aOR 1.08; 95%CI 0.82-1.43) (Conner e.a. 2016)
- + More neurological symptoms: tremor, irritability, Moro-reflex+
- + No NAS

× The child in later life:

- + Impaired cognitive functioning (Sharapova e.a. 2018), memory, intelligence and reading comprehension.
- + No increased risk of psychotic disorders in adolescence (Roncero e.a. 2020)
- + Possible link with development of ADHD and depressive disorders (Roncero e.a. 2020)
- + More cannabis use and delinquency at age 14 OR 1.76 95%CI 1.05-2.96 (El Marroun e.a. 2018)

TREATMENT OF CANNABIS USE DISORDER DURING PREGNANCY ?

- × Detoxification is advised
- × Similar as to the non-pregnant population
- × Possible at every stage of pregnancy

- × Focus on psychotherapeutic approaches
- × Possible protective effect of choline supplementation on foetus and child development? (Hunter e.a. 2021)

AMPHETAMINE USE DURING PREGNANCY

- × Amphetamines and derivatives pass the placenta
 - + Produces its effects through inhibition at 5-HT-, NE- and DA-transporters
 - + Placenta also expresses 5-HTT and NE-T: inhibition leads to elevation of 5-HT and NE and causes uterine contractions and vasoconstriction resulting in preterm delivery and decreased placental blood flow.
 - + Thus: the placenta is a direct target for the amphetamines
- × Pregnancy & childbirth:
 - + Preterm birth OR 4.11 95%CI 3.05-5.55
 - + No increased risk of pre-eclampsia RR 1.77 95%CI 0.75-4.14
 - + No increased risk of hypertensive complications RR 1.62 95%CI 0.37-7.06
 - + No meta-analyses of systematic reviews on teratogenicity, little indication from other reports (Smith e.a. 2016)

AMPHETAMINE USE DURING PREGNANCY

× Newborn:

- + Low birth weight OR 3.97 95%CI 2.45-6.43
- + SGA OR 5.79 95%CI 1.90-24.06
- + Height -0.9 cm 95%CI -0.5 cm to -1.3 cm
- + Head circumference -0.8 cm 95%CI -0.5 cm to -1.3 cm
- + Lower APGAR scores 0.94 95%CI 0.3-1.5
- + No meta-analyses of systematic reviews on NAS, but one study describes NAS in 20/170 children exposed to amphetamines in utero (Harst e.a. 2021)

× The child in later life:

- + Impairments related to social functioning, attention, heightened aggression, impaired cognitive functioning
- + At age 4: deficits in social functioning, hand-eye coordination and cognition
- + At age 7.5: learning- and concentration difficulties
- + Structural and functional brain differences: basal ganglia, thalamus, limbic system (Sanjari Moghaddam e.a. 2021)

USE OF (THERAPEUTIC & NON-THERAPEUTIC) STIMULANTS DURING PREGNANCY ?

- × E.g. methylphenidate, dexamphetamine, ... (for ADHD → risk factor for substance use)
 - + Congenital heart malformations? RR 1.28 95%CI 1.00-1.64

- × Amphetamines...
 - + Detoxification is advised
 - + Similar as to the non-pregnant population
 - + Focus on psychotherapeutic approaches

CONCLUSION

- All substances freely pass the placenta, and all have repercussions on the foetus ..
- Effects of prenatal exposure to (illegal) substances are complex and variable:
 - Depending on the (class of) substance
 - Depending on the amount and frequency/chronicity of use (often dose-dependent)

DISCUSSION

- Awareness for *underreporting* of (illegal) drug use during pregnancy
 - Fear of consequences, (legal) repercussions, inconsistent measuring and screening (self-reporting vs. biological sampling),...
- Although not the focus of this talk: do not forget about alcohol, nicotine, other drugs/medication,...
- Poly-drug use?
- Long-term effects?

CONCLUSIONS

- Illegal substance use during pregnancy is associated with risks for both mother and child, depending mainly on the substance used and the intensity and chronicity of use.
- Detoxification should always be considered in light of the available literature on risks and advantages.
- Opioid use is associated with the most severe risks, due to its teratogenicity and the risk for a neonatal abstinence syndrome.
- An important task is set for prenatal care, where in-depth anamnesis and psycho-education concerning (illegal) drugs are crucial.
- In case of prenatal exposure, follow-up is important, with attention for possible risks.

THANK YOU !

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