

**Table S1** – Summary of Key Clinical and Preclinical Outcomes Regarding the Effects of Gestational Cannabis Exposure on Birth, Placental and Metabolic Outcomes

Study	Model/Organism	Drug and/or Dosage	Birth Outcomes	Placental Outcomes	Offspring Metabolic Outcomes
(English et al., 1997)	Clinical	Cannabis	↓ BW	N/A	N/A
(Gunn et al., 2016)	Clinical	Cannabis	↓ BW ↑ NICU admission	N/A	N/A
(Conner et al., 2016)	Clinical	Cannabis	↓ BW, except when controlled for tobacco use ↑ Preterm delivery, except when controlled for tobacco use	N/A	N/A
(Carter et al., 2016)	Clinical	Cannabis	N/A	↑ Placental weight	N/A
(Bailey et al., 2020)	Clinical	Cannabis	↓ BW ↑ NICU admission ↑ Preterm delivery ↓ Apgar score	N/A	N/A
(Singh et al., 2020)	Clinical	Cannabis	↓ BW ↑ NICU Admission	N/A	N/A

↑ pre-term delivery					
<b>(Brar et al., 2019)</b>	Clinical	Cannabis	↓ BW	↑ Placental vascular resistance	N/A
<b>(Maia et al., 2019)</b>	Preclinical ( <i>ex vivo</i> w/ human placentae)	Δ9-THC (10-40 μM)	N/A	↑ Placental NAPE-PLD ↓ Placental FAAH ↑ Placental AEA	N/A
<b>(Neradugomma et al., 2019)</b>	Preclinical ( <i>in vitro</i> w/ THESC)	Δ9-THC, CBD, CBN (0.2, 2 and 20 μM)	N/A	↓ Decidualization ↓ Trophoblast-endometrial stromal cell interactions ↓ Trophoblast invasion	N/A
<b>(Chang et al., 2017)</b>	Preclinical ( <i>in vitro</i> w/ BeWo cells, <i>in vivo</i> w/ mice and human placenta)	Δ9-THC (0.3 to 30 μM) <i>in vitro</i> ; Δ9-THC (5 mg/kg <i>i.p.</i> ) GD5.5-18.5 <i>in vivo</i> ; human cannabis smoker controlled for tobacco and alcohol	↓ BW ↓ Litter size	↓ Trophoblast migration and invasion <i>in vitro</i> ↓ CB1 and CB2 in humans and animals	N/A
<b>(Khare et al., 2006)</b>	Preclinical ( <i>in vitro</i> )	Δ9-THC (15 μM)	N/A	↓ Trophoblast proliferation	N/A
<b>(Walker et al., 2020)</b>	Preclinical ( <i>in vitro</i> )	Δ9-THC (20 μM)	N/A	↓ Syncytialization ↑ Oxidative stress	N/A

				↓ Fetal growth hormones ↓ Mitochondrial respiration	
<b>(Almada et al., 2020)</b>	Preclinical ( <i>in vitro</i> w/ THESC (St-T1b) cells)	Δ9-THC (10 μM) and/or CBD (2 μM)	N/A	↓ Decidualization by CBD but not Δ9-THC ↓ Differentiation by CBD but not Δ9-THC ↓ mRNA levels of CYP19A1 and estradiol by CBD but not Δ9-THC	N/A
<b>(Chang et al., 2018)</b>	Preclinical ( <i>in vitro</i> w/ HUVECs; <i>in vivo</i> w/ mice and human placenta)	Δ9-THC <i>in vitro</i> (0–20 μM); Δ9-THC (5 mg/kg <i>i.p.</i> ) <i>in vivo</i> w/ mice; Cannabis inhalation in humans controlled for alcohol and tobacco	N/A	↓ HUVEC migration and tube formation ↓ Placental angiogenesis in mice ↓ Placental angiogenesis in humans	N/A
<b>(Natale et al., 2020)</b>	Preclinical ( <i>in vivo</i> w/ rats and <i>in vitro</i> w/ BeWo cells)	Δ9-THC <i>in vivo</i> (3 mg/kg <i>i.p.</i> from GD6-22) and <i>in vitro</i> (15 μM)	↓ BW No changes in litter size, maternal	↑ Placental weight ↓ Fetal:placental weight ratio ↑ Placental	N/A

			weight gain and food intake ↓ Liver:body weight ↓ Brain:body weight	labyrinth area ↓ EPCAM expression ↓ Fetal blood space ↑ Pericytes recruitment ↓ Glut1 & GR	
<b>(Benevenuto et al., 2017)</b>	Preclinical ( <i>in vivo</i> w/ mice)	200 mg of Cannabis sativa 5 min of inhalation daily from GD5.5–GD17.5	↓ BW	↑ Placental weight ↓ Fetal:placental weight ratio	N/A
<b>(Lojpur et al., 2019)</b>	Preclinical ( <i>in vitro</i> w/ BeWo cells)	Δ9-THC (3 -30 μM)	N/A	↑ ER stress via CB1 and CB2 ↓ Mitochondria respiration	N/A
<b>(Oke et al., 2021)</b>	Preclinical ( <i>in vivo</i> w/ rats)	Δ9-THC (3 mg/kg i.p. daily from GD5.5-22)	↓ BW ↓ Liver:body weight	N/A	↑ Catch-up growth at PND21 ↑ Markers of hepatic lipid synthesis at PND21 and 6 months ↑ Hepatic triglycerides at 6 months

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					↑ Hepatic mitochondrial dysfunction and oxidative stress ↑ Epigenetic (microRNA) markers associated with dyslipidemia ↑ Visceral adiposity
<b>(Gillies et al., 2020)</b>	Preclinical ( <i>in vivo</i> w/ rats)	Δ9-THC (3 mg/kg i.p. daily from GD5.5-22)	↓ BW ↓ Pancreas: body weight ↓ β-cell mass	N/A	↓ Pancreatic total and small islet density at PND21 & 5 months ↑ Catch-up growth at PND21 ↑ Glucose intolerance at 5 months ↓ β-cell mass at 5 months ↓ Peripheral insulin signalling
<b>(Lee et al., 2021)</b>	Preclinical ( <i>in vivo</i> w/ rats)	Δ9-THC (3 mg/kg i.p. daily from GD5.5-22)	↓ BW ↓ Heart: body weight ↓ Stroke volume ↓ Heart rate		↑ Catch-up growth at PND21 ↓ Stroke volume ↓ Cardiac output ↑ Left ventricular wall thickness

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↑ Cardiac protein expression of collagen type I & 3

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Summary of key clinical and preclinical studies in this present review as it pertains to maternal cannabinoid exposure and its effects on the placenta, neonatal and postnatal metabolic outcomes. This table primarily focuses on cannabis and its constituents with an emphasis on preclinical findings. Δ9-THC: Δ9- tetrahydrocannabinol; AEA: anandamide; BW: birth weight; CB1: cannabinoid receptor type 1; CB2: cannabinoid receptor type 2; CBD: cannabidiol; CBN: cannabinol; EPCAM: epithelial cell adhesion molecule; ER: endoplasmic reticulum; FAAH: fatty acid amide hydrolase; GD: gestational day; Glut1: glucose transporter 1; GR: glucocorticoid receptor; HUVEC: Human umbilical vein endothelial cells; NAPE-PLD: N-acylphosphatidylethanolamine-specific phospholipase D; PND: postnatal day; THESCs: telomerase-immortalized human endometrial stromal cell line

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