Table S1. A summary of the main findings concerning the physiological role of the ECS in the early pregnancy processes (as discussed in paragraph 4).				
Oviductal transport	***Species***	***Tissue, cells***	***Main findings***	***Ref.***
	Mus musculus (C57BL/6J)	oviduct, uterus, embryo	FAAH deficiency increases oviductal embryo retention by CB1-dependent signaling	[1]
	Mus musculus (C57BL/6J)	oviduct, uterus, embryo	CB1 deficiency and Meth-AEA increase oviductal embryo retention by CB1-dependent signaling	[2]
	Mus musculus (C57BL/6J)	oviduct, uterus, embryo	CB1/adrenergic signaling dysregulations increase oviductal embryo retention	[2]
	Mus musculus (C57BL/6J)	oviduct, uterus, embryo	Δ9-THC, but not CBD or CBN, increases oviductal embryo retention by CB1-dependent signaling	[1]
Blastocyst development	***Species***	***Tissue, cells***	***Main findings***	***Ref.***
	Mus musculus (C57BL/6J)	oviduct, uterus, embryo	FAAH deficiency impairs embryo development by CB1-dependent signaling	[1]
	Mus musculus (129/C57Bl6)	oviduct, uterus, embryo	CB1 and FAAH deficiency impairs embryo development	[3]
	Mus musculus (CD-1)	oviduct, uterus, embryo	CB1, CB2 and CB1/CB2 deficiency impairs embryo development	[4]
	Mus musculus (C57BL/6)	uterus, embryo	CB1/CB2 deficiency does not affect embryo development	[5]
	Mus Musculus (CD-1)	embryo culture	AEA and 2-AG inhibit the synchronous embryo development by CB1-dependent signaling.	[6]
	Mus musculus (C57BL/6J)	oviduct, uterus, embryo	Δ9-THC, but not CBD or CBN, impairs embryo transition to blastocyst by CB1-dependent signaling	[1]
	Mus Musculus (CD-1)	embryo culture	AEA, Δ9-THC, WIN55-212, CP 55,940, but not AA and CBD, impair embryo transition to blastocyst in a dose-dependent manner	[7]
Implantation	***Species***	***Tissue, cells***	***Main findings***	***Ref.***
	Mus musculus (CD-1)	uterus	AEA level is lower in receptive than non-receptive uteri	[4]
	Mus musculus (129/C57Bl6)	uterus	AEA and 2-AG levels are lower in IS than inter-IS	[8]
	Mus musculus (CD-1)	uterus	AEA level is lower in IS than inter-IS	[9]
	Mus musculus (CD-1)	uterus	NAPE-PLD activity is lower, while FAAH activity is higher, in IS than inter-IS	[10]
	Mus Musculus (CD-1)	uterus	NAPE-PLD activity and AEA levels are lower in IS than inter-IS and regulated by sex steroid hormones and blastocyst state.	[11]
	Mus musculus (CD-1)	embryo culture	AEA reduces blastocyst hatching by CB1-signaling	[9]
	Mus musculus (C57BL/6J)	uterus, embryo	FAAH deficiency impairs blastocyst implantation by CB1-dependent signaling	[1]
	Mus musculus (C57BL/6J)	uterus	CB1/CB2 deficiency impairs luminal epithelial organization and increases edema in the PDZ	[5]
	Mus musculus (CD-1)	embryo culture	CB1 is higher in dormant than activated blastocysts	[4]

	Mus musculus	embryo culture	CB1 is higher in dormant than activated blastocysts	[12]
	Mus musculus	embryo culture	AEA regulates blastocyst competency by differently modulating MAPK signaling and Ca^{2+} channel activity trough CB1-dependent mechanisms.	[12]
	Mus musculus (129/C57Bl6)	embryo, TSC culture	CB1 and FAAH deficiency affects cell migration-related genes in blastocysts and cell mobility in TSCs.	[3]
	Mus musculus (CD-1)	uterus, embryo	Δ9-THC impairs blastocyst implantation by CB1/CB2-dependent signaling	[4]
	Mus musculus (C57BL/6J)	uterus, embryo	Δ9-THC, but not CBD or CBN, impairs blastocyst implantation by CB1-dependent signaling	[1]
	Mus Musculus (CD-1)	uterus	Δ9-THC impairs blastocyst implantation by CB1-dependent signaling	[6]
	Mus musculus (CD-1)	uterus, embryo	CP 55,940 inhibits blastocyst implantation by CB1-dependent signaling	[9]
Decidualization	***Species***	***Tissue, cells***	***Main findings***	***Ref.***
	Homo sapiens	St-T1b cells and primary HdF cells	AEA impairs human ESC proliferation and differentiation, but not viability, by CB1-dependent signaling	[13]
	Homo sapiens	St-T1b cells and primary HdF cells	AEA impairs decidualization and reduces COX-2 level and PGE2 production by CB1-dependent signaling	[14]
	Homo sapiens	St-T1b cells	AEA induces apoptosis, ROS production, loss of ΔΨm, ER stress and reduces cell viability and proliferation partly by induction of COX-2 activity	[15]
	Homo sapiens	placental microsomes, St-T1b cells and primary HdF cells	AEA shows anti-aromatase activity and regulates aromatase expression and E2 secretion partly by CB1-dependent signaling	[16]
	Homo sapiens	ESC cells, BeWo cells, HTR8-SV/neo cells	Δ9-THC, CBD, CBN impair ESC decidualization, trophoblast-endometrium interaction and invasion	[17]
	Homo sapiens	placental microsomes, St-T1b cells and primary HdF cells	CBD, but not Δ9-THC, shows anti-aromatase activity and impairs decidualization in ESCs	[18]
	Homo sapiens	primary ESC and HdF cells	WIN55,212 inhibits decidual fibroblasts and ESC decidualization. WIN55,212 induces apoptosis and reduces intracellular cAMP levels	[19]
	Homo sapiens	St-T1b cells and primary HdF cells	WIN55,212, JWH-122 and UR-144 induce ROS/RNS production and ER stress. WIN55,212 reduces cell viability and proliferation, induces apoptosis and loss of ΔΨm partly by CB1-dependent signaling	[20]
	Homo sapiens, Mus musculus (*C57BL/6*)	uterus, primary mESCs, HdF	CB1/CB2 deficiency impairs decidualization, vascular remodeling and formation of avascular PDZ. CB1 deficiency impairs decidualization in mESCs and HdF.	[21]
	Rattus norvegicus (Wistar)	primary decidual cells	AEA induces apoptosis, loss of ΔΨm and ROS production by induction of COX-2 activity	[22]
	Rattus norvegicus (Wistar)	primary decidual cells	AEA reduces cell viability and induces apoptosis in decidual cells by CB1-dependent signaling	[23]
	Rattus norvegicus (Wistar)	primary decidual cells	AEA induces ROS production, loss of ΔΨm, and apoptosis in decidual cells by ceramide synthesis	[24]
	Rattus norvegicus (Wistar)	primary rat ESC; in vivo deciduoma model	AEA reduces cell viability and impairs differentiation of primary ESCs. AEA impairs decidualization and downregulates α2-MG, COX-2 and VEGF expression *in vivo*	[25]
	Rattus norvegicus	primary decidual cells	2-AG reduces cell viability and induces apoptosis in decidual cells by CB1-dependent signaling	[26]

	(Wistar)			
Placentation	***Species***	***Tissue, cells***	***Main findings***	***Ref.***
	Homo sapiens	BeWo cells	2-AG induces apoptosis, loss of ΔΨm, ROS/RNS production and reduces proliferation in BeWo cells by CB1 and/or CB2-dependent signaling.	[27]
	Homo sapiens	hCTs, BeWo cells	2-AG induces apoptosis, ROS/RNS production and ER stress partly by CB2-dependent signaling	[28]
	Homo sapiens	hCTs	2-AG impairs cAMP/PKA, p38 and ERK1/2 signaling, endocrine functions and placental protein expression, but not cell viability, in syncytiotrophoblasts by CB1 and/or CB2-dependent signaling	[29]
	Homo sapiens	hCTs	AEA induces apoptosis, loss of ΔΨm, ROS/RNS production, and intracellular Ca^{2+} level increase in hCTs by TRPV1-dependent mechanisms.	[30]
	Homo sapiens	BeWo cells	Meth-AEA impairs the syncytialization in Fsk-treated BeWo cells	[31]
	Homo sapiens	hCTs, BeWo cells	AEA reduces cell viability in hCTs and BeWo cells. AEA induces apoptosis, loss of ΔΨm and ROS/RNS production in BeWo cells by CB1 and/or CB2-dependent signaling	[32]
	Homo sapiens	HTR8-SV/neo cells	AEA and 2-AG modulate angiogenic factors partly via CB receptors. AEA and 2-AG promote HTR8-SV/neo tube formation, and 2-AG increase HTR8-SV/neo cells migration	[33]
	Homo sapiens	BeWo cells	JWH-018, JWH-122, UR-144 and Δ9-THC affect cell viability and cell proliferation. JWH-018, UR-144, JWH-122 induce ROS/RNS production; Δ9-THC, UR-144, JWH- 122 induce loss of ΔΨm. The effects on apoptosis are mediated by CB1 and/or CB2 dependent (for JWH-018, UR-144, Δ9-THC) or independent mechanisms (for JWH-122)	[34]
	Homo sapiens	hCTs, BeWo cells	WIN55,212 reduces cell viability in hCTs and cell viability and proliferation in BeWo cells. WIN55,212 reduces ΔΨm and increases apoptosis by CB1-dependent mechanisms in BeWo cells.	[35]
	Homo sapiens	BeWo cells	Δ9-THC impairs syncytialization and biochemical differentiation, endocrine secretion, mitochondrial dynamics partly by CB1 and CB2-dependent signaling. Δ9-THC increases stress responses, intracellular defenses, ROS production and reduces ΔΨm and oxygen consumption	[36]
	Homo sapiens	HTR8-SV/neo cells	Δ9-THC impairs trophoblast invasive capacity and mitochondrial dynamics through CB1 and/or CB2 receptors. Δ9-THC increases ROS production and stress responses, and decreases mitochondrial respiration and ΔΨm.	[37]
	Homo sapiens	BeWo cells	Δ9-THC induces ER stress through CB1 and CB2 receptors. Δ9-THC reduces mitochondrial respiration and ATP-coupling efficiency.	[38]
	Homo sapiens	chorionic villous explants cultures, BeWo cells	Δ9-THC upregulates aromatase and ERα expression by CB1 and CB2-dependent signaling	[39]
	Homo sapiens	BeWo cells	Δ9-THC reduces GLU1 and GR expression in BeWo cells.	[40]
	Homo sapiens	placenta, HUVECs	*Cannabis* exposure leads to placenta vascular defects. Δ9-THC reduces HUVEC proliferation, migration, tube formation capacity. Δ9-THC inhibits RhoA/MLC signaling pathway affecting cell migration and tube formation.	[41]
	Homo sapiens	BeWo cells, HTR8-SV/neo cells	CBD reduces cell viability, proliferation, ΔΨm, and increases apoptosis in BeWo cells and HTR8-SV/neo cells. No effects on ROS/RNS production. CBD increases autophagy by HIF1α and impairs migration in HTR8-SV/neo cells.	[42]
	Homo sapiens	placenta, hCTs	hCTs express CNR1 and show higher levels of 2-AG than AEA. CB1 is involved in hCT invasion	[43]

Homo sapiens	BeWo cells	AEA and Δ9-THC modulate FA uptake in time, dose and pH-dependent manner. The acute modulatory effects of AEA and Δ9-THC are not mediated by CB1 or CB2-dependent signaling	[44]
Homo sapiens	placenta, BeWo cells	AEA downregulates syncytialization-related genes and BCPR transporter expression by CB2/cAMP signaling. AEA is not a substrate or inhibitor of BCRP in BeWo cells.	[45]
Homo sapiens	placenta, BeWo cells	CBD inhibits the BCRP efflux activity both in BeWo cells and perfused placentas as *ex vivo* models. CBD does not affect placental tissues viability.	[46]
Macaca mulatta (rhesus macaque)	placenta	Δ9-THC reduces the amniotic fluid volume, maternal perfusion of the IVS and fetal oxygen availability. Δ9-THC alters histology and gene expression profile in placenta, with DEGs enrichment in cytokine binding, regulation of cell migration, cell-substrate adhesion, angiogenesis, and vascular development	[47]
Rattus norvegicus (Wistar)	placenta	Δ9-THC exposure results in symmetrical IUGR, increased placental weights, and reduced fetal:placental weight ratio. Δ9-THC exposure results in an increased labyrinth layer areas, maternal/fetal blood space ratio and number of pericytes. Δ9-THC reduces GLU1 and GR expression.	[40]
Mus musculus (C57BL/6)	placenta	Δ9-THC attenuates placental angiogenesis by inhibiting RhoA/ MLC signaling pathway	[41]
Mus musculus (C57BL/6)	uterus, TS cells	PCP signaling in cooperation with CB1 receptors regulates trophoblast migration in placentation	[48]
Mus musculus (C57BL/6J)	oviduct, uterus, placenta	CB1 deficient mice show compromised placentation, reduced fetal trophoblast proliferation and invasiveness	[49]

Abbreviations: 2-AG, 2-arachidonoylglycerol; AEA, anandamide; BCRP, Breast cancer resistance protein; cAMP/PKA, cyclic Adenosine monophosphate/protein kinase A; CB, G protein-coupled cannabinoid receptors; CBD, cannabidiol; CBN, Cannabinol; COX-2, Cyclooxygenase-2; DEG, differentially expressed genes; E2, estradiol; ECS, endocannabinoid system; ER, endoplasmic reticulum; ERα, estrogen receptor α; ESC, endometrial stromal cells; FA, acid folic; FAAH, fatty acid amide hydrolase; Fsk, forskolin; GLU1, glucose transporter 1; GR, glucocorticoid receptors; hCTs, human cytotrophoblast cells; HdFs, human decidual fibroblasts; HIF1α, hypoxia-inducible factor; hTS, human trophoblast cells; HUVECs, human vein endothelial cells; IS, implantation sites; IUGR, intrauterine growth restriction; IVS, intervillous space; MAPK, mitogen-activated protein kinase; Meth-AEA, methanandamide; NAPE-PLD; N-acylphosphatidylethanolamine specific phospholipase d-like; PCP, planar cell polarity; PDZ, primary decidua zone; PGE, prostaglandin E; RhoA/MLC, Ras homolog family member A/myosin light chain; ROS/RNS, reactive oxygen species/reactive nitrogen species; St-T1b, human immortalized endometrial stromal cell line; TRPV1, transient receptor potential vanilloid 1; TSC, trophoblast stem cells; VEGF, vascular endothelial growth factor; α2-M, α2-macroglobulin; Δ9-THC, Δ9-tetrahydrocannabinol; ΔΨm, mitochondrial membrane potential.

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