Supplementary Table 1: Preclinical studies of stem cell therapy for POI

Stem cell origin	Model	Species	Transplantation details	Summary	References
BMSCs	Chemically induced model	Rats	4×10^6/kg BMSCs injected intraperitoneally	BMSC therapy was found to protect against germ cell apoptosis and DNA damage when it was used with chemotherapy regimens including alkylating agents	[80]
	Chemically induced model	Rats	4×10^6 BMSCs injected via tail vein	The homing and distribution of BMSCs in the ovarian hilum and medulla were greater than those in the cortex. In addition, the antral follicle count and estradiol levels increased in the BMSC treatment group	[12]
	Chemically induced model	Rats	1×10^6 BMSCs injected intravenously	After BMSCs were transplanted, E_2 and FSH levels improved. In addition, elevation of ovarian TNF-α levels and IGF-I expression in ovarian tissues may play a role in the attraction of stem cells *in vivo*	[81]
	Chemically induced model	Mice	0.5×10^6 BMSCs injected via tail vein	Hormonal levels in POI mice normalized after BMSC therapy. The ability to become pregnant after natural breeding was also observed	[18]
	Chemically induced model	Mice	1×10^4 BMSCs injected via tail vein	BMSCs could restore ovarian function following injury. Inhibiting apoptosis and promoting residual ovarian cell proliferation may contribute to the process	[82]
	Chemically induced model	Mice	1×10^6 BMDSCs or 3×10^5 $CD133^+$ cells in a volume of 100 ml injected via tail vein	BMDSC treatment promoted ovarian vascularization and cell proliferation, resulting in the production of higher numbers of preovulatory follicles and metaphase II oocytes. However, the $CD133^+$ subpopulation could not achieve the same regenerative effect as the complete BMDSC-infused group did	[99]
ADSCs	Chemically induced model	Mice	1×10^6 ADSCs injected intravenously 1×10^5 ADSCs injected directly into the bilateral ovaries	The population of follicles at different stages and ovulation significantly increased after ADSC transplantation without directly differentiating into the follicle component	[91]
	Cell culture	Human patient	1×10^4, 2×10^4, and 1×10^5 cells/well	Combined treatment with ADSCs and estrogen played an immunomodulatory role by promoting Treg proliferation, thereby alleviating impaired ovarian function	[108]
	Surgical model	Mice	5×10^4 ADSCs were directly injected into the center of grafted ovaries	The ability of ADSCs to reduce oxidative stress and inflammation might play a significant role in improving the structure and function of autografted ovaries	[119]
	Chemically induced model	Rats	2×10^6 ADSCs with or without 20 ml collagen injected via intraovarian route	The transplantation of ADSCs on soluble collagen scaffolds exerts a potent therapeutic effect in a rat model of POI induced by TG	[9]
MenSCs	Chemically induced model	Mice	1×10^4 HuMenSC sphere injection	HuMenSCs could survive within POF mouse ovaries for at least 14 days. Moreover, the HuMenSC-transplanted group expressed higher levels of ovarian markers, such as AMH and FSHR, and the proliferative marker Ki67	[25]
	Chemically induced model	Mice	2×10^6 MenSCs injected via tail vein	MenSC transplantation could improve the ovarian microenvironment by reducing apoptosis in GCs and the fibrosis of ovarian interstitium and secreting FGF2 for reparative effects on damaged ovaries	[24]
	Chemically induced model	Rats	1×10^6 MenSCs injected intravenously	HuMenSCs can induce upregulation of Bax and Bcl2 genes and anti-apoptotic effects on GCs	[27]
	Chemically induced model	Rats	1×10^6 MenSCs injected intravenously	Migration and localization of HuMenSCs were detected in the GC layer of immature follicles. In addition, HuMenSCs can differentiate into GCs in POF to help follicle formation and ovulation	[26]
	Chemically induced model	Mice	1×10^6 MenSCs injected via tail vein	MenSCs combined with BSTCR improved the ovarian function in POF mice, which might be related to the inhibition of GADD45b expression and the promotion of cyclin B1 and CDC2 expression	[83]
	Chemically induced model	Mice	1×10^6 MenSCs injected via tail vein	MenSCs participated in the activation of ovarian transcriptional expression in the ECM-dependent FAK/Akt signaling pathway and thus restored ovarian function to a certain extent	[139]

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Supplementary Table 1: Contd...

Stem cell origin	Model	Species	Transplantation details	Summary	References
OSSCs	Chemically induced model	Rats	4×10^6 BMSCs or 4×10^6 OSSCs via intraperitoneal injection	OSSCs exert more potent protective effects on follicle maturation than BMSCs in cyclophosphamide-induced ovarian damage	[31]
FGSCs	Chemically induced model	Mice	2×10^4 FGSCs injected via intraovarian route	Mice with CTx possessed FGSCs, which played a role in restoring ovarian function, producing offspring, and avoiding immune rejection from exogenous germline stem cells	[140]
hAD-MSCs	Chemically induced model	Rats	4×10^6 hAD-MSCs or LUPUS-pretreated hAD-MSCs injected via the tail vein	LIPUS-pretreated hAD-MSCs are more advantageous for reducing inflammation, improving the local microenvironment, and inhibiting GC apoptosis because of enhanced paracrine ability	[93]
	Naturally aged model	Mice	Intraovarian injection	hAMSCs improve ovarian function in natural aging by secreting HGF and EGF to improve the proliferation rate and inhibit apoptosis	[76]
	Chemically induced model	Rats	4×10^6 hAD-MSCs injected via the tail vein	hAD-MSCs secreted FGF2, IGF-1, HGF, and VEGF to improve ovarian function in rats with chemotherapy-induced POI	[28]
	Chemically induced model	Mice	1×10^6 hAD-MSCs injected intraperitoneally	hAMSC transplantation can improve injured ovarian tissue structure in oxidatively damaged POF mice by improving the local microenvironment of the ovary	[77]
hAECs	Chemically induced model	Mice	2×10^6 hAECs injected via tail vein	hAEC transplantation promotes ovarian function by inhibiting TNF-α-mediated cell apoptosis and reducing inflammation in chemotherapy-induced POF	[84]
	Chemically induced model	Mice	2×10^4 hAECs injected into the unilateral ovary hAECs-CM (from a total of 2×10^4 cells) injected into the unilateral ovary	hAECs significantly inhibited chemotherapy-induced apoptosis and activated the TGF-β/Smad signaling pathway within primary granulosa-lutein cells in a paracrine manner. Moreover, 109 cytokines in hAECs-CM might participate in a variety of biological processes	[78]
hAD-MSCs hAECs	Naturally aged model	Mice	Di-labeled hAMSCs and hAECs tail vein injection	hAMSCs are a more effective cell type to improve ovarian function than hAECs because of the biological characteristics of hAMSCs (telomerase activity, pluripotent markers, cytokine, and collagen secretion)	[35]
hUC-MSCs	Chemically induced model	Rats	(100 μL, at a concentration of 1×10^6/ml) hUC-MSC injected intravenously	UCMSC transplantation recovered disturbed hormone secretion and folliculogenesis in POF rats without obvious proliferation	[36]
	Chemically induced model	Rats	2×10^6 hUC-MSC injected into the bilateral ovaries	UCMSCs can trigger an effect on the ovarian epithelium or indirect enrichment of the ovarian niche by regulating tissue expression of CK8/18, TGF-β, and PCNA to suppress CASP-3-induced apoptosis	[85]
	Surgical model	Mice	UC-MSCs or collagen/ UCMSCs injected via intraovarian route	UC-MSCs on a collagen scaffold (collagen/ UC-MSCs) can activate primordial follicles via phosphorylation of FOXO3 and FOXO1	[127]
	Chemically induced model	Mice	2×10^5 UC-MSC with or without degradable collagen injected via intraovarian route	Collagen/UC-MSCs significantly promoted ovarian angiogenesis and GC proliferation with increased expression of CD31 and Ki67, respectively	[128]
	Autoimmune-induced model	Mice	1×10^6 hUMSCs injected via tail vein	The ovarian function and endometrial receptivity in POF mice were regulated by the Th1/Th2 cytokines and uNK cells following hUMSC transplantation	[109]
	Chemically induced model	Rats	5×10^6 UCMSCs injected intravenously	UCMSCs could reverse ovarian failure via the NGF/ TrkA signaling pathway	[87]
	Chemically induced model	Mice	hUCMSCs-CM (cell-derived conditioned medium) injected intraperitoneally	G-CSF/PI3K/Akt pathways play important roles in protecting GCs following hUCMSC-CM transplantation	[86]

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Supplementary Table 1: Contd...

Stem cell origin	Model	Species	Transplantation details	Summary	References
hPMSCs	Autoimmune-induced model	Mice	1×10^6 hPMSCs injected intravenously	The recovery of ovarian function in POF mice following hPMSC transplantation occurs via the PI3K/Akt signal pathway to change the ratios of Th17/Tc17 and Th17/Treg cells as well as production of associated cytokines	[106,107]
	Chemically induced model	Mice	2×10^6/kg CP-MSCs injected via the tail vein	MSCs derived from the chorionic plate can alleviate CTX-induced ovarian dysfunction	[39]
	Autoimmune-induced model	Mice	1×10^6 hPMSCs injected intravenously	hPMSC transplantation can inhibit excessive follicular atresia and GC apoptosis by increasing the expression of AMH and FSHR in ovaries	[38]
	Autoimmune-induced model	Mice	1×10^6 hPMSCs injected via the tail vein	Transplantation of hPMSCs in POF mice inhibited the ER stress-induced activation of the IRE1 alpha signaling pathway, thereby suppressing GC apoptosis	[88]

MSCs: Mesenchymal stem cells; BMSCs: Bone marrow-derived MSCs; ADSCs: Adipose-derived MSCs; hAD-MSCs: Human amnion-derived MSCs; UC-MSCs: Umbilical cord MSC; hPMSCs: Human placenta-derived MSCs; MenSCs: Menstrual blood-derived stem cells; OSSCs: Oogonial stromal stem cells; FGSCs: Female germline stem cells; hAECs: Human amniotic epithelial cells; POF: Premature ovarian failure; GC: Granulosa cell; HGF: Hepatocyte growth factor; TG: Tripterygium glycoside; IGF1: Insulin-like growth factor-1; CTX: Cyclophosphamide; TNF-α: Tumour necrosis factor-α; AMH: Anti-Müllerian hormone; FSHR: Follicle-stimulating hormone receptor; ER: Estrogen receptor; ECM: Extracellular matrix; hUC: Human umbilical cord; CM: Conditioned medium; IRE1: Inositol-requiring enzyme 1

Supplementary Table 2: Clinical studies of stem cell therapy for POI

Category	Actual enrollment	Year	Location	Stem cell origin	Methods	Phase	Transplantation details	Clinical trial number	References
Completed	14	2018	Nanjing, China	UC-MSCs on a collagen scaffold (collagen/ UC-MSCs)	Randomized controlled trial	1, 2	Intraovarian injection (both), 800 μL of the UC-MSC fraction (a total number of 10×10^6 cells, 5×10^6/400 μL for unilateral ovarian injection) or of the collagen/UC-MSCs (5×10^6/400 μL for unilateral ovarian injection, collagen concentration, 5 mg ml)	NCT02644447	[127]
	10	2015	Cairo, Egypt	MSC, OCT4 marker measured	Randomized controlled trial, single-group assignment	1, 2	Intraovarian injection	NCT02372474	https:// clinicaltrials.gov/
	60	2016	Giza, Egypt	Autologous BMSCs	Randomized controlled trial, single-group assignment	1, 2	Intraovarian injection (one side), 3-5 million MSCs injected into ovarian tissue of patients with idiopathic and drug-induced POI	NCT02043743	https:// clinicaltrials.gov/
	9	2018	Tehran, Iran	Autologous ADSCs	Parallel assignment	1, 2	Intraovarian injection, 5, 10, or 15 million MSCs	NCT02603744	https:// clinicaltrials.gov/
Recruiting	4	2015	Nanjin, Jiangsu, China	CD29+/CD44+ human ADSCs	Single group assignment	4	Intraovarian injection; the ADSCs were transplanted directly into bilateral ovaries when cells reached a density of $5\text{-}10\times10^6$	NCT01853501	https:// clinicaltrials.gov/
	28	2019	Zhengzhou, China	MSCs	Sequential assignment, nonrandomized controlled trial	1	Intraovarian injection, groups 1, 2, 3: low (0.2×10^7), medium (0.5×10^7), and high dosage (1.0×10^7), respectively, of cell injection for each ovary	NCT03877471	https:// clinicaltrials.gov/
	40	2014	Shenzhen, China	hUCMSCs and hCBMNCs	Randomized controlled trial	1, 2	Groups 1, 2 ,3, and 4: HRT plus hUC-MSCs treatment; HRT plus hCB-MNCs and hUC-MSCs therapy; HRT plus hCB-MNCs; HRT treatment, respectively	NCT01742533	https:// clinicaltrials.gov/
	60	2014	Cairo, Egypt	Autologous MSCs treatment + OCT4 marker measured	Single-group assignment	1, 2	Intraovarian injection 3-5 million autologous MSCs	NCT02062931	https:// clinicaltrials.gov/
	320	2018	Beijing, China	hUC-MSCs	Randomized controlled trial, parallel assignment	1, 2	Intraovarian injection	NCT03033277	https:// clinicaltrials.gov/
	20	2015	Shandong, China	Autologous ADSCs	Observational study, sequential assignment	1	Intraovarian injection	ChiCTR-ONB-15007411	http://www.chictr.org.cn/index.aspx
	50	2018	Amma, Jordan	Autologous BMSCs and MSCs	Single-group assignment	1, 2	Intraovarian transplantation of autologous purified BMSCs and MSCs	NCT03069209	https:// clinicaltrials.gov/

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Supplementary Table 2: Contd...

Category	Actual enrollment	Year	Location	Stem cell origin	Methods	Phase	Transplantation details	Clinical trial number	References
Active	3	2020	Illinois, US	BMSC treatment directly to ovary	Single group assignment	-	Intraovarian injection of BMSCs into the right ovary	NCT03816852	https://clinicaltrials.gov/
	10	2016	Qena, Egypt	Autologous BMSCs	Single-group assignment	-	Intravenous infusion. Bone marrow aspiration of 10 ml/kg was done from the posterior iliac crest. The sample was put in a sterile container with an appropriate amount of heparin and then filtered to remove bone spicules, fat, and cellular debris. The filtered sample was injected unprocessed into a peripheral vein	NCT02779374	https://clinicaltrials.gov/

MSCs: Mesenchymal stem cells; UC-MSCs: Umbilical cord mesenchymal stem cells; ADSC: Adipose-derived MSCs; BMSCs: Bone marrow stromal cells; POI: Premature ovarian insufficiency; hCB: Human cord blood-mononuclear cells; MNCs: Mononuclear cells; HRT: Hormone replacement therapy; hUC: Human umbilical cord

Supplementary Table 3: Next-generation stem cell-based therapy for POI

Category	Cell origin	Model	Optimization/modification process	Summary	References
iPSCs	-	Chemically induced model	MiR-17-3p, a microRNA, was transfected into iPSCs to help differentiate into OSE-like cells	The ovarian weight and plasma E_2 level increased over time in the transplantation with OSE-like cells derived from iPSCs	[45]
		Chemically induced model	iPSCs differentiate into OGLCs according to a multistage protocol using cell growth factors and hormones	OGLCs transplanted into POF mice exhibited substantial growth in murine ovarian tissues	[46]
Engineered stem cells	BMSCs	Chemically induced model	MSCs were transfected with miR-21 lentiviral vector	miR-21-MSCs can decrease apoptosis in GCs by downregulating PTEN and PDCD4 expression	[50]
	BMSCs	Chemically induced model	MSCs were placed in a water bath for heat shock pretreatment	HS pretreatment enhanced the repair effect of MSCs because of the further vitality enhancement of MSCs, which led to a greater inhibition of apoptosis of GCs	[52]
	ADSCs	Chemically induced model	ADSCs were transfected with plasmids, pVEGF, and pGFP-N plus PRP	The addition of PRP to VEGF (+) MSCs further increased CXCL12, BMP-4, TGF-β, and IGF-1 expression and blood estradiol levels	[51]
EVs	AFSCs	Chemically induced model	5×10^5 AFSCs or 125 μg exosomes proteins injected via intraovarian route	The delivery of microRNAs miR-146a and miR-10a in exosomes may be critical to apoptosis of CTx-damaged GCs	[59]
	ADSCs	Chemically induced model	Injection of exosomes (an approximate amount produced by 1×10^6 cells)	The mechanism by which exosomes derived from hADSCs improved ovarian function via regulation of the SMAD signaling pathway	[58]
	BMSCs	Chemically induced model	125 μg exosomes injected into the tail vein	miR-644-5p carried by BMSC-derived exosomes inhibited the apoptosis of ovarian GCs by targeting p53 in cells	[90]
	BMSCs	Cell culture	HOVECs were treated with BMSC-conditioned media	MSC secretomes induced significantly higher expression of several angiogenic markers such as VEGF, Tie2/Tek, and VE-Cadherin in HOVECs	[105]
	hAECs	Chemically induced model	Exosomes and proteins injected via the intraovarian route	hAEC exosomes inhibited chemotherapy-induced GC apoptosis by transferring functional miRNAs such as miR-1246	[57]
	hUC-MSCs	Chemically induced model	150 mg EVs proteins injected via tail vein	After EV treatment, the ovarian function of POI mice was found to be recovered and fertility was increased, with a reduced time to get pregnant	[60]
	hUC-MSCs	Chemically induced model	Injection of hUMSC-Exos at 10^{11}, 5×10^{11}, or 10^{12} particles/ml	Exosomal miR-17-5P and its downstream target mRNA SIRT7 in hUMSC transplantation therapy are critical to the anti-apoptotic process	[61]
Engineered tissues	Primary ovarian cells	Surgical model	Scaffolds were created from decellularized bovine medulla sections with 2×10^6 cells seeded	The ovary made of primary ovarian cells on a decellularized matrix provides a niche for steroid hormone production, which initiates puberty in ovariectomized mice	[131]
	Enzymatically isolated follicles	Surgical model	Encapsulation of enzymatically isolated follicles in PEG-VS hydrogels	The functioning graft activates a small cohort of follicles each estrous cycle and helps restore the HPG axis	[130]
	Ovarian granulosa and theca cells	Surgical model	Bioengineered ovarian constructs were fabricated by encapsulation techniques into several layers	These constructs ameliorate previous adverse effects of hormone deficiency, including bone health, uterine health, and body composition in this rat model	[123]
	Multilayer secondary follicles	Surgical model	3D printed microporous hydrogel scaffolds (30°/60°/90°) with four follicles	Follicle-seeded scaffolds become highly vascularized, and ovarian function is fully restored, specifically in 60° scaffolds with wider through-pores	[124]
	Primary ovarian cells	Surgical model	2.0×10^6 cells seeded in each SLES-treated decellularized scaffold	A human ovary-specific scaffold based on an SLES-decellularized protocol can be an ideal scaffold used to reconstruct the ovary	[132]

Supplementary Table 3: Contd...

Category	Cell origin	Model	Optimization/modification process	Summary	References
	Porcine primordial follicles	SCID model	2×10^6 cells seeded in macroporous alginate scaffolds with affinity-bound BMP-4	After xeno-transplantation of the follicle devices supplemented with additional angiogenic factors, the follicles reached antral size and secreted hormones at normal levels	[129]
	BMSC	Surgical model	2500 BMSC (1250 in inner compartment and 1250 in outer compartment) encapsulated in multilayered microcapsules	Tissue-engineering constructs with BMSCs achieved estrogen secretion levels greater than constructs without BMSCs, while also regulating pituitary hormones	[125]

iPSCs: Induced pluripotent stem cells; EVs: Exosomes; secretomes; extracellular vesicles; MSCs: Mesenchymal stem cells; BMSCs: Bone marrow stromal cells; ADSCs: Adipose-derived MSCs; pVEGF: Phospho-vascular endothelial growth factor; PRP: Platelet-rich plasma; HOVECs: Human ovarian endothelial cells; POF: Premature ovarian failure; GCs: Granulosa cells; SLES: Sodium lauryl ester sulfate; POI: Premature ovarian insufficiency; AFSCs: Amniotic fluid stem cells; hAECs: Human amniotic epithelial cells; hUC: Human umbilical cord; OSCs: Oogonial stem cells; OGLCs: Ovarian granulosa_like cells; pGFP-N: GFP transfection with plasmids; HPG axis: Hypothalamic pituitary gonadal axis; PEG-VS: poly (ethylene glycol) vinyl sulfone; TNF-α: Tumour necrosis factor-α; PTEN: Phosphatase and tension homologue