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MINI REVIEW

The impact of phthalate on reproductive function in women with endometriosis

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Abstract

Background: Endometriosis is a common gynecological condition in which stromal or glandular epithelium is implanted in extrauterine locations. Endometriosis causes detrimental effects on the granulosa cells, and phthalate interferes with the biological and reproductive function of endometrial cells at a molecular level.

Methods: This article retrospectively reviewed the studies on phthalate exposure and its relationship with endometriosis. A literature search was performed for scientific articles using the keywords "phthalate and endometriosis," "endometriosis and granulosa cells," "phthalate and granulosa cells," and "phthalates and endometrial cells."

Results: Endometriosis can affect cytokine production, steroidogenesis, cell cycle progression, expression of estrogen receptor-α (ER-α)/progesterone receptor (PR), and cause endoplasmic reticulum stress, senescence, apoptosis, autophagy, and oxidative stress in the granulosa cells. Mono-n-butyl phthalate (MnBP) alters the expression of cytokines, cell cycle-associated genes, ovarian stimulation, steroidogenesis, and progesterone production. Several in vitro studies have demonstrated that phthalate caused inflammation, invasion, change in cytokines, increased oxidative stress, viability, resistance to hydrogen peroxide, and proliferation of endometrial cells.

Conclusion: This might provide new insights about the impact of phthalate on the pathogenesis of endometriosis and its consequences on the ovarian function.

KEYWORDS

endometrial cells, endometriosis, granulosa cells, phthalate, reproductive function

1 | INTRODUCTION

Endometriosis represents a common gynecological condition in which the stromal or glandular epithelium gets implanted in extrauterine locations.[1-3] The prevalence of endometriosis is estimated to be 10% among women of reproductive age, which is approximately 190 million women worldwide.[4] Some women with endometriosis are asymptomatic; however, most of them suffer from chronic pelvic pain, dysmenorrhea, deep dyspareunia, and infertility.[5] Although the hypotheses about the etiopathology of endometriosis have been reported for almost one century, the etiology remains unknown.[6] Several evidences suggested that environmental pollutants might be involved in the pathogenesis of endometriosis.[7-11] These endocrine-disrupting chemicals interrupt hormonal homeostasis and result in estrogen signaling changes.[11-23]

Phthalate is diesters of phthalate, which are commonly used in several plastic products, and solubilize other agents.[24-26] Ingestion and inhalation are the common routes of phthalate exposure.[27-29] After entering the body, phthalates are hydrolyzed by the digestive tract into monoesters, then absorbed, oxidized, and excreted in the urine.[28,30-32] Several reports have suggested a link between phthalates and human reproductive health through their influence on spermatogenesis in males.[33] Previous studies have demonstrated that sexually mature female rats exposed to di (2-ethylhexyl) phthalate (DEHP) and its metabolite, mono (2-ethylhexyl) phthalate (MEHP) showed a decrease in serum progesterone, delayed ovulation, and smaller preovulatory follicles with high levels of serum follicle-stimulating hormone (FSH).[17,19,34,35] Many studies demonstrated that phthalate exposure is significantly associated with endometriosis.[10,36-40]

Kim et al. demonstrated the effects of DEHP on endometrial cells, including cell invasion, viability, proliferation, and oxidative stress through mitogen-activated protein kinase (MAPK)/ extracellular regulated protein kinase (Erk), and nuclear factor-κB (NF-κB) pathways.[10,41] Endometriosis is harmful to granulosa cells, because it affects steroidogenesis and cell cycle progression, lowers aromatase activity, and alters the mitochondrial gene expression in human granulosa cells.[38,42-47] This article retrospectively searched the keywords "phthalate and endometriosis," "endometriosis and granulosa cells," "phthalate and granulosa cells," and "phthalates and endometrial cells" on PubMed. This review aims to evaluate the exposure of phthalate and the risk of endometriosis, and its impact on the granulosa cells based on current data.

2 | PHTHALATE EXPOSURE AND THE RISK OF ENDOMETRIOSIS

Several studies and meta-analyses have suggested an association between phthalate exposure and the risk of endometriosis (Table 1). In 2003, Cobellis et al.[48] found a positive correlation between plasma DEHP and endometriosis. DEHP and MEHP were detected in the peritoneal fluid. Reddy et al. published two papers about higher levels of butyl benzyl phthalate (BBP), DEHP, di-n-butyl phthalate (DnBP), and di-n-octyl phthalate (DnOP) in women with endometriosis compared to those in the control group, which were also significantly associated with stage I-IV of endometriosis.[49,50] Nazri et al. also reported that DEHP was increased in the serum of women with endometriosis.[51] In Taiwan, two studies demonstrated an increased level of urinary mono-n-butyl phthalate (MnBP) in women with endometriosis.[38,52] In Korea, Kim et al. reported that women with endometriosis had higher levels of DEHP and MEHP in the plasma, and the presence of mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), Log mono-2-ethyl-5-carboxyphentyl phthalate (MECPP), Log MEHHP, Log MEOHP in the urine.[41,53] In the United States, 14 phthalate metabolites were analyzed in both, population cohort comprised women matched on age and residence (n = 131) and operative cohort comprised women undergoing laparoscopy (n = 495). The study found that MnBP, mono-2-carboxymethyl hexyl phthalate (MCMHP), MECPP, MEHP, MEHHP, MEOHP were higher in the population cohort in women with endometriosis. Moreover, MEHP and monooctyl phthalate (MOP) were increased in the operative cohort in women with endometriosis.[8] Upson et al.[54] showed an inverse association between MEHP and the risk of endometriosis. However, some studies have reported a reverse correlation or no association between endometriosis and some phthalate metabolites, which might be due to non-adjustment for other covariates or small sample size.[54-57]

Recently, two meta-analyses reported about the association between endometriosis and phthalate metabolites. The most commonly used phthalate, DEHP, showed a significant risk of endometriosis (OR = 1.42; 95% CI: 1.19-1.7).[39] Another meta-analysis analyzed five phthalate metabolites from eight studies and reported that only MEHHP was associated with endometriosis in Asia but not in the USA.[58]

These studies and meta-analyses strengthen the evidence that phthalate metabolites might play an important role in the occurrence of endometriosis. More studies on urine samples of women with endometriosis should be conducted to prove the association between phthalate exposure and endometriosis.

3 | GRANULOSA CELLS IN WOMEN WITH ENDOMETRIOSIS

Endometriosis might affect the granulosa cell steroidogenesis, change the cell cycle progression, cytokine expression (interleukin-6 [IL6], interleukin-8 [IL-8], interleukin-12 [IL-12], and tumor necrosis factor-α [TNF-α]), alter the mitochondrial gene expression, decrease the aromatase activity, and vascular endothelial growth factor (VEGF) and growth differentiation factor-9 (GDF-9) in human granulosa cells.[42-46,59-63] These reports suggest that endometriosis might be harmful to granulosa cells making them less sensitive to luteinizing hormone stimulation.[47,64] Moreover, the expression of progesterone receptor (PR) and estrogen-α in granulosa cells was higher in women with endometriosis than in those with tubal infertility.[65] Sreerangaraja Urs et al.[66]demonstrated that decrease in steroidogenic acute regulatory protein (StAR) and 3β-hydroxysteroid dehydrogenase (3β-HSD), mitochondrial dysfunction, and apoptosis were found in the granulosa cells of women with endometriosis. Sanchex et al.[67] reported that dysregulation of the wingless-related integration site (WNT) pathway and down-regulation of survivin were found in the granulosa cells of women with endometriosis.

Recently, Sirtuin 2 (silent information regulator proteins; SIRT2) and kisspeptin receptor (KISS1R) were found to be increased in the granulosa cells of women with endometriosis.[68,69] The granulosa cells from women with endometriosis had higher NF-κB binding activity, increased expression of inhibitor of NF-κB kinase subunit β (IKKβ) and NF-κB inhibitor α (IκBα), which decreased the telomerase activity and human telomerase reverse transcriptase (hTERT).[70] Moreover, intrafollicular TNF-α might decrease the telomerase

TABLE 1 Epidemiological studies and meta-analysis of the association between Phthalate or and endometriosis

Author	Study design	No. of Endometriosis/ control	Samples	Metabolites	Outcomes of endometriosis	Reference
Cobellis et al. 2003	Case-control	35/24	Blood Peritoneal fluid	DEHP, MEHP	Higher plasma DEHP Detectable peritoneal fluid DEHP and/or MEHP	48
Reddy et al. 2006	Case-control	49/38	Blood	BBP, DEHP, DnBP, DnOP	Higher BBP, DEHP, DnBP, DnOP	50
Reddy et al. 2006	Case-control (stage I-IV)	85/135	Blood	BBP, DEHP, DnBP, DnOP	Higher BBP, DEHP, DnBP, DnOP	49
Itoh et al. 2009	Case-control	57/80	Urine	MBzP, MEHHP, MEHP, MEOHP, MEP, MnBP	No significant association	57
Weuve et al. 2010	Case-sectional	87/1020	Urine	MnBP, MBzP, MEHHP, MEHP, MEOHP, MEP	Higher MnBP, Lower MEHP	56
Huang et al. 2010	Case-control	28/29	Urine	MMP, MEP, MnBP, MBzP, MEOHP, MEHHP	Higher MnBP	52
Kim et al. 2011	Case-control	97/169	Blood	DEHP, MEHP	Higher DEHP, MEHP	53
Buck Louis et al. 2013	Cohort (Population) Cohort (Operative)	14/113 190/283	Urine Urine	MnBP, MBzP, MCHP, MCMHP, MCPP, MECPP, MEHHP, MEHP, MEOHP, MEP, MIBP, MMP, MNP, MOP	Two fold higher MnBP, MCMHP, MECPP, MEHP, MEHHP, MEOHP Higher MEHP, MOP,	8
Upson et al. 2013	Case-control	95/195	Urine	MEHP, MEHHP,MEOHP, MECPP, DEHP, MBzP, BzBP, MEP, MiBP, MnBP, DBP	Lower MEHP	54
Kim et al. 2015	Cohort	55/33	Urine	MBzP, MECPP, MEHHP, MEOHP, MnBP	Higher MEHHP, MEOHP, Log MECPP, Log MEHHP, Log MEOHP	41
Nazri et al. 2018	Case-control	50/50	Blood	DEHP	Higher DEHP	51
Cai et al. 2019	Meta-analysis	8 studies		MEHHP, MEHP, MEP, MBzP, MEOHP	Higher MEHHP	58
Wen et al. 2019	Meta-analysis	6 studies		PAEs	Higher DEHP	39
Moreira Fernandez et al. 2019	Case-control	30/22	Urine	MMP, MiBP, MnBP, MCHP, MiNP, MOP, MBzP, MEHP	No significant association	55
Chou et al. 2020	Case-control (Operative)	123/82	Urine	MnBP, MEHP, MBzP, MEOHP, MEHHP	Higher MnBP	38

Abbreviations: BBP, butyl benzyl phthalate; DEHP, di-2-ethylhexyl phthalate; DnBP, di-n-butyl phthalate; DnOP, di-n-octyl phthalate; MBzP, monobenzyl phthalate; MCHP, monocyclohexyl phthalate; MCMHP, mono-2-carboxymethyl hexyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MECPP, mono-2-ethyl-5-carboxyphentyl phthalate; MEHHP, mono-2-ethyl-5-hydroxyhexyl phthalate; MEHP, mono-2-ethylhexyl phthalate; MEOHP, mono-2-ethyl-5-oxohexyl phthalate; MEP, monoethyl phthalate; MIBP, mono-2-isobutyl phthalate; MMP, monomethyl phthalate;MNP, monoisonoyl phthalate; MnBP, mono-n-butyl phthalate; MOP, monooctyl phthalate; PAEs, phthalate esters.

activity and hTERT through NF-κB activation.[70] Li et al.[71] found that down-regulation of the long non-coding RNA MALAT1 decreased the granulosa cell proliferation in women with endometriosis through an increase in the p21 expression via the MAPK/Erk activation pathway. In women with peritoneal endometriosis, the expression of bone morphogenetic protein 6 (BMP6) and mothers against decapentaplegic homolog 6 (SMAD6) were decreased in the granulosa cells.[72] Moreover, Ding et al.[73] demonstrated the increased Beclin-1 (BECN1) and provoked autophagy in the late follicular progesterone elevation in the granulosa cells of women with ovarian endometriosis.

There are many evidences about increased oxidative stress in the granulosa cells of women with endometriosis, who when compared to women with normal ovaries showed higher 8-hydroxydeoxyguanosine and lipid peroxidation (4-hydroxy-2-nonenal).[74-76] Lin et al. reported that the granulosa cells from women with endometriosis had excessive reactive oxygen species, which provoked senescence through endoplasmic reticulum (ER) stress,

decrease in mitochondrial membrane potential, and reduction in ATP production.[77] ER stress is significantly associated with oxidative stress. Treating the oxidative stress inducer caused upregulation of the unfold protein response (UPR)-associated genes and apoptosis in human granulosa cells.[78] Moreover, the granulosa cells from women with endometriosis expressed several transcripts associated with UPR and increased the phosphorylation of ER stress sensor proteins, including inositol-requiring enzyme 1 and double-stranded RNA-activated protein kinase-like ER kinase (PERK). These results suggested that high oxidative stress in the granulosa cells in women with endometriosis provoked ER stress and apoptosis.[78] These studies illustrated that endometriosis is harmful to the granulosa cells and might lead to ovarian dysfunction (Figure 1).

4 | EFFECTS OF PHTHALATE ON GRANULOSA CELLS

Phthalates are common synthetic chemicals with ubiquitous exposures in our daily life. Till now, several epidemiologic evidences have reported that phthalates might be toxic to the male and female reproductive system.[37] Studies from laboratory examinations showed that phthalates interacted with the female reproductive system in animal models; these findings support the potential hazardous effects of phthalates in women. Granulosa cells play an important role in the ovarian follicular growth and steroidogenesis. The first study from Treinen et al.[79] reported that MEHP decreased FSH-induced cyclic adenosine monophosphate (cAMP) accumulation in the granulosa cells. Furthermore, MEHP also inhibited FSH-induced progesterone production by a protein kinase-C-independent mechanism.[80] Davis et al. found that MEHP-related decrease in estradiol concentration might be due to decreased aromatase independent of the cAMP-stimulated pathway in granulosa cells.[17,19,81] Lovekamp-Swan et al. demonstrated that MEHP stimulated peroxisome proliferator-activated receptor-α (PPAR-α) and peroxisome proliferator-activated receptor-γ (PPAR-γ) to inhibit aromatase and decreased cAMP stimulation to alter the metabolism- and differentiation-associated genes.[82,83] MEHP stimulated basal steroidogenesis and StAR expression in primary cultures of Leydig cell progenitors and immature granulosa cells in rats.[84] It induced ovarian toxicity by inhibition of follicular development and abnormal steroid hormone synthesis in cultured rat ovarian follicles.[85] It also inhibited the rat granulosa cell viability, increased apoptosis through caspase-3 activation and Bcl-2-associated x protein (BAX) expression, stimulated steroid hormone secretion, and induced the expression of key enzymes in progesterone expression and sex hormone receptors.[86-88]

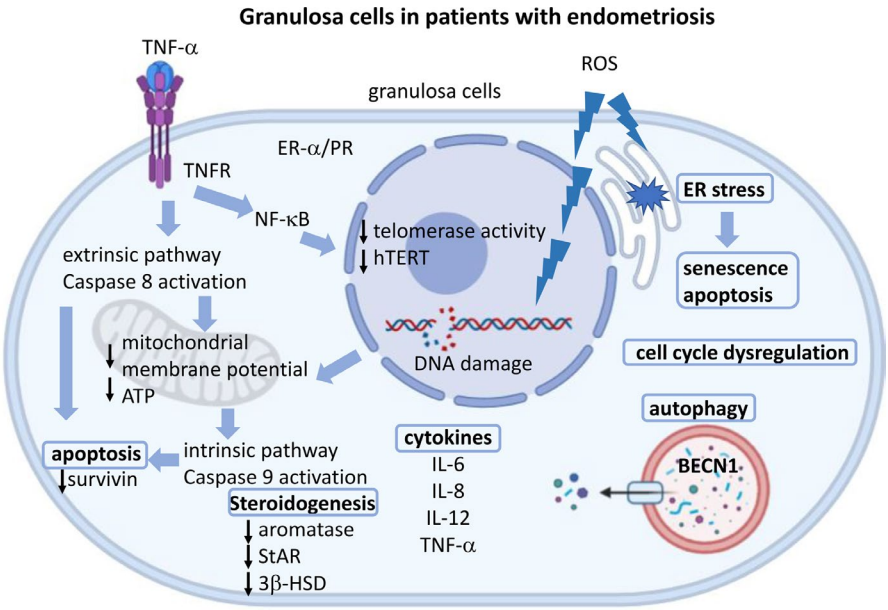

FIGURE 1 The potential effects of endometriosis on granulosa cells. Endometriosis might affect steroidogenesis (aromatase, StAR, 3β-HSD), cytokine production (IL6, IL-8, IL-12, TNF- α), cell cycle progression, ER-α/ PR, oxidative stress, ER stress, apoptosis, senescence, and autophagy in granulosa cells. The granulosa cells in women with endometriosis showed increased oxidative stress, which induced DNA damage, and decreased the mitochondrial membrane potential and ATP production and induced apoptosis. The increased TNF-α activated NF-κβ to decrease the telomerase activity and hTERT. TNF-α also induced extrinsic and intrinsic apoptosis pathway and decreased survivin expression. The increased oxidative stress in the granulosa cells in women with endometriosis stimulated senescence and apoptosis through ER stress. StAR, steroidogenic acute regulatory protein; 3β-HSD, 3β-hydroxysteroid dehydrogenase; IL-6, interleukin-6; IL-8, interleukin-8; IL-12, interleukin-12; TNF-α, tumor necrosis factor α; ER-α, estrogen receptor- α ; PR, progesterone receptor; NF-κB, nuclear factor-κB.; hTERT, human telomerase reverse transcriptase, ER stress, endoplasmic reticulum stress; BECN1, beclin-1. This figure was created with BioRender.com [Colour figure can be viewed at wileyonlinelibrary.com]

In DEHP-fed rats, the estrous cycles were prolonged, delayed, or ovulation was suppressed; moreover, smaller preovulatory follicles were found, suggestive of polycystic ovaries and hypoestrogenic anovulatory cycles.[34] PPARs are the crucial regulators of cell differentiation and lipid metabolism. DEHP had a dual effect on the pituitary-gonadal axis including stimulation of the hormonal effects of the pituitary gland and inhibition of steroidogenesis in granulosa cells at the same time.[89] The DEHP exposure induced apoptosis and increased the production of reactive oxygen species (ROS) in horse granulosa cells.[90] DEHP also provoked oxidative stress by increasing the ROS levels and mitochondrial membrane potential, and the levels of apoptotic markers (BAX and cytochrome c).[91] Furthermore, DEHP arrested the cell cycle progression in G_0/G_1 phases and increased the proportion of apoptosis in rat granulosa cells.[92] Chen et al.[93] found that benzyl butyl phthalate (BBP) stimulated necrosis through aryl hydrocarbon receptor (AhR) and cytochrome-P450 (CYP)1B1 in HO23 cells (immortalized human granulosa cells). In KGN cells (human granulosa cell lines), DEHP reduced estradiol production and induced AhR expression to regulate the function of granulosa cells.[94] DEHP also induced several microRNAs (miRNAs), including let-7b, miR-17-5p miR-181a, and miR-151, to inhibit the proliferation of follicular granulosa cells. Moreover, DEHP affected the anti-apoptosis function of KIT ligand (KITL) and growth differentiation factor-9 (GDF-9) and increased the BAX/ BCL2 expression ratio to promote apoptosis of the granulosa cells.[95] Recently, Li et al.[88] demonstrated that quails fed on DEHP showed mitochondrial damage and decreased thickness of the ovarian granulosa cell layer, along with oxidative stress.

DBP is ubiquitous in our daily life and might affect the health in humans. Wang et al.[96] reported that DBP reduced FSH-induced KIT ligand G (KITLG) expression and hypoxia-inducible factor 1-α (HIF1-α) to suppress estradiol and progesterone production and proliferation of the granulosa cells. From global gene expression analysis, expression of the cell cycle, mitosis, Rho GTPases, polo-like kinase-1 (PLK1), Aurora B signaling pathways, and E2F-mediated regulation of DNA replication, steroidogenic, angiogenic, and epidermal growth factor-like growth factor genes, including CYP11A1, CYP19A1 (aromatase), VEGF-A, betacellulin (BTC), StAR and epiregulin (EREG) were associated with DBP exposure in the granulosa cells.[97,98] Li et al.[99] reported that DBP reduced oocyte germinal vesicle breakdown (GVBD) and polar body extrusion (PBE) rate in mice, damaged oocyte cytoskeleton, and disrupted the cortical granule-free domains (CGFDs), and induced early apoptosis of the oocyte and granulosa cells. In the human granulosa cell line KGN, treatment with DBP upregulated the expression of aromatase, estradiol, and FSH receptors.[100] Moreover, Mei et al.[101] found that dimethyl phthalate (DMP) increased the apoptotic rate of ovarian granulosa cells and interfered with the pituitary-ovary axis. These studies proved that phthalate interferes with the biological and reproductive function.

The effects of MnBP on granulosa cells are shown in Figure 2. With a low dose of MnBP, the expression of progesterone, vimentin,

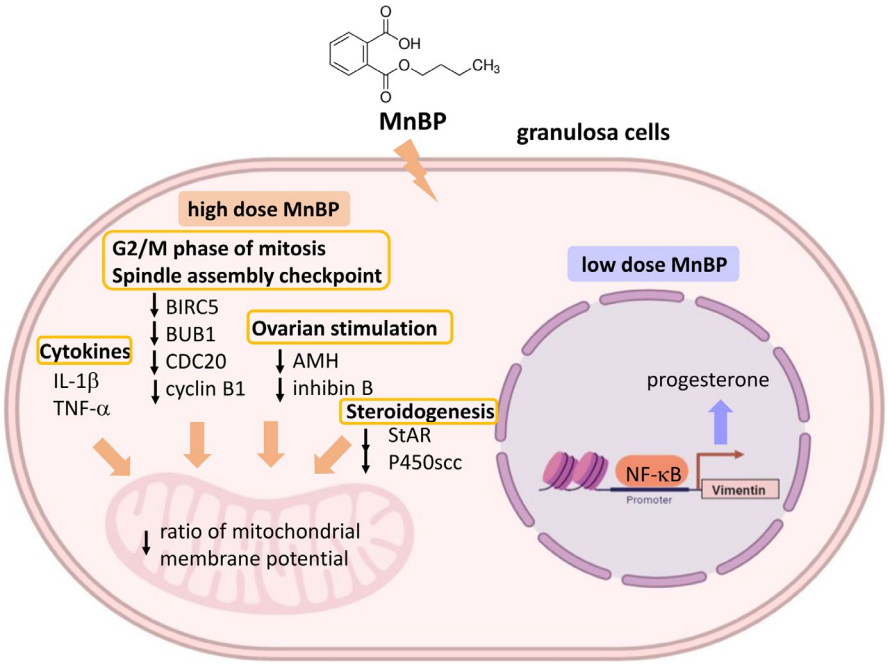

FIGURE 2 Potential mechanisms of MnBP on human granulosa cells. A high dose of MnBP, it stimulates IL-1β and TNF-α cytokine expression. MnBP also affects the G2/M phase of mitosis and spindle assembly checkpoint, including BIRC5, BUB1, CDC20, and cyclin B1 gene expression. These changes cause decrease in AMH, inhibin B, StAR, and P450scc, which affect ovarian stimulation and steroidogenesis. The affected gene expressions result in poor health of the cells. A low dose of MnBP stimulated NF-κB binding to vimentin promoter and induced progesterone production. MnBP, Mono-n-butyl phthalate; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor α; BIRC5, baculoviral inhibitor of apoptosis repeat-containing 5; BUB1B, budding uninhibited by benzimidazoles 1 homolog beta, mitotic checkpoint serine/threonine kinase beta; CDC20, cell division cycle 20; AMH, anti-Mullerian hormone; StAR, steroidogenic acute regulatory protein; P450ssc, cytochrome cholesterol side-chain cleavage enzyme; NF-κB, nuclear factor-κB. This figure was created with BioRender.com [Colour figure can be viewed at wileyonlinelibrary.com]

and phosphorylated p65 was significantly increased in the mouse granulosa cells. Further experiments found that MnBP stimulated the binding of p65 to vimentin promoter to induce progesterone production.[102] Recently, Chou et al. demonstrated that MnBP attenuated the ratio of the mitochondrial membrane potential and affected the gene expression levels of baculoviral inhibitor of apoptosis repeat-containing 5 (*BIRC3*), budding uninhibited by benzimidazoles 1 homolog beta, mitotic checkpoint serine/threonine kinase beta (*BUB1B*), cell division cycle 20 (*CDC20*), cyclin B1, IL-1β, and TNF-α in human granulosa cells. Moreover, MnBP also decreased the steroidogenesis genes and hormones, including anti-Mullerian hormone (AMH), inhibin B, StAR, and cytochrome cholesterol side-chain cleavage enzyme (P450ssc), and expression of human granulosa cells.[38]

5 | EFFECTS OF PHTHALATE METABOLITES ON ENDOMETRIAL CELLS

The first report of the effects of phthalate on endometrial cells showed that DEHP and MEHP stimulated the secretion of prostaglandin F2-α (PGF2-α) and inhibited the secretion of prostaglandin E2 (PGE2).[103] Kim et al.[104] also found that DEHP results in increased viability of the endometrial stromal cells in the serum-free condition with exposure to hydrogen peroxide. Another study demonstrated that DEHP induced the expression of IL-1β, IL-8, matrix metalloproteinase-2 (MMP2), intercellular cell adhesion molecule-1 (ICAM-1), cyclooxygenase-2 (COX2), and PPARγ to stimulate the inflammatory response, and it might be mediated by PPARγ.[105]

The effects of DEHP on human endometrial cells include increased ROS generation and decreased expression of superoxide dismutase (SOD), glutathione peroxidase (GPX), heme oxygenase (HO), and catalase (CAT), phosphorylated-Erk/ phosphorylated-p38 and NF-κB-mediated transcription, and estrogen receptor-α (ER-α) expression.[106] In DEHP-treated mice, the volume of peritoneal endometriotic lesion increased, with higher expression of MMP-2, MMP-9, and p21-activated kinase-4 (Pak-4). Increased cell invasion and phosphorylation of Erk were observed in DEHP-treated endometrial cells.[41] Human endometrial cells from the eutopic endometrium of endometriosis showed upregulation of aldo-keto reductase (AKR) 1C1, AKR1C2, AKR1C3, and AKR1B10 after DEHP exposure, while AKR1C3 continuously increased in the endometrial cells of the ectopic endometrium in patients of endometriosis both before and after DEHP exposure.[107] Under conditions of hypoxia, DEHP decreased the ER-α protein and VEGF secretion in Ishikawa endometrial adenocarcinoma cells.[108] In chronic, low-dose DEHP feeding mice, the endometrial stromal cells were significantly increased and changed the localization of steroid hormone receptors.[109] These studies are illustrated in Figure 3.

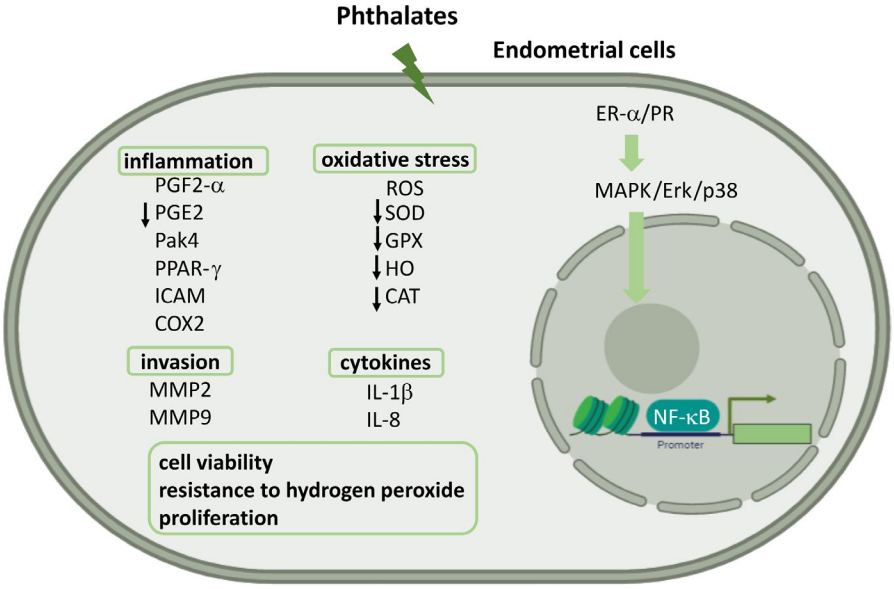

FIGURE 3 The effect of phthalates on endometrial cells. After phthalate stimulation, the endometrial cells showed inflammation, invasion, change of cytokines, increased oxidative stress, cell viability, resistance to hydrogen peroxide, and proliferation. The inflammatory effects stimulated the secretion of PGF2-α, Pak-4, PPARγ, ICAM-1, COX2, cytokine (IL-1β and IL-8), and inhibited the secretion of PGE2. Phthalate also increased ROS generation and decreased the expression of SOD, GPX, HO, and CAT. In DEHP-treated mice, the endometrial cell might show increased migration through MMP-2 and MMP-9. Increased ER-α/PR activated p-ERK/p-p38 and NF-κB. Exposure to phthalate induced endometrial cell viability, resistance to hydrogen peroxide and proliferation. PGF2-α, prostaglandin F2-α; IL-1β, interleukin-1β; IL-8, interleukin-8; Pak-4, p21-acticvated kinase-4; PPARγ, peroxisome proliferator-activated receptor-γ; ICAM-1, intercellular cell adhesion molecule-1; COX2, cyclooxygenase-2; prostaglandin E2, PGE2. ROS, reactive oxygen species; SOD, superoxide dismutase, GPX, glutathione peroxidase; HO, heme oxygenase; CAT, catalase; MMP2, matrix metalloproteinase-2; MMP9, matrix metalloproteinase-9; ER-α, estrogen receptor-α; PR, progesterone receptor; NF-κB, nuclear factor-κB. This figure was created with BioRender.com [Colour figure can be viewed at wileyonlinelibrary.com]

From these studies, it is evident that phthalate exposure might affect gene regulation, invasion, cell viability, and proliferation of endometrial cells to influence the development of endometriosis.

6 | CONCLUSION

In this review, the interaction between phthalate exposure and granulosa cells in women with endometriosis has been discussed based on the evidence from several studies. A thorough understanding of the effects of phthalate on granulosa cells and endometrial cells might provide new insights into the pathogenesis of endometriosis and its biological effects on ovarian function. More studies are necessary to understand the detailed mechanisms of the interplay between phthalate, granulosa cells, and endometriosis.

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DISCLOSURES

Conflict of interest: The authors declare no conflict of interest. *Human and Animal Rights*: This article does not contain any study with human or animal participants that have been performed by any of the authors.

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