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REVIEW

Roles of lipid mediators in early pregnancy events

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Abstract

Background: Early pregnancy events, including embryo implantation, are critical for maintaining a healthy pregnancy and facilitating childbirth. Despite numerous signaling pathways implicated in establishing early pregnancy, a comprehensive understanding of implantation remains elusive.

Methods: This paper provides a comprehensive review of the current research on lipids in the context of early pregnancy, with a particular focus on feto-maternal communications.

Main Findings: Embryo implantation entails direct interaction between uterine tissues and embryos. Introducing embryos triggers significant changes in uterine epithelial morphology and stromal differentiation, facilitating embryo implantation through communication with uterine tissue. Studies employing genetic models and chemical compounds targeting enzymes and receptors have elucidated the crucial roles of lipid mediators—prostaglandins, lysophosphatidic acid, sphingosine-1-phosphate, and cannabinoids—in early pregnancy events.

Conclusion: Given the high conservation of lipid synthases and receptors across species, lipid mediators likely play pivotal roles in rodents and humans. Further investigations into lipids hold promise for developing novel diagnostic and therapeutic approaches for infertility in humans.

KEYWORDS
embryo implantation, lipids, mice, pregnancy, uterus

1 | INTRODUCTION

Infertility is associated with social and health problems experienced by approximately 15% of couples worldwide.[1] Decades after the first childbirth by in vitro fertilization-embryo transfer (IVF-ET) was reported, the demand for artificial reproductive technologies (ARTs) has been increasing, especially in developed countries. However, 10–15% of couples undergoing IVF-ETs suffer recurrent failures in implantation, and women fail to get pregnant at least three times, even using good-quality embryos,[2] which indicates the crucial role of feto-maternal circumstances in accepting and nourishing healthy embryos; however, the underlying mechanisms remain unclear owing to ethical and technical limitations associated with investigation of early pregnancy events in vivo.

Embryo implantation is a process in which the embryo and receptive endometrium interact intimately.[3–6] Rodents have been utilized to investigate the mechanisms underlying embryo implantation because of the similarity in female hormonal regulation and the responses of the endometrium to blastocysts between rodents and humans.[3] Gene deletions or chemical treatments in mouse models

have revealed the mechanisms underlying the communication between uterine cells and embryos.[3,6] In this review, we describe previous reports of early pregnancy events focusing on the uterine functions of lipid mediators.

2 | PROCESSES OF EMBRYO IMPLANTATION

Peri-implantation embryos mainly comprise cells of fetal and placental origins. Implantation-competent embryos, blastocysts, contain inner cell mass (ICM) that develops to the fetal body and is surrounded by trophoblasts that invade the endometrium to form the placenta.[7] The uterus, where embryos develop, comprises several types of cells: the endometria contain luminal/glandular epithelial cells and fibroblastic stromal cells.[3] Endothelial and immune cells in the endometria are considered to have both protective[8,9] and detrimental effects[10,11] during pregnancy. The myometrium surrounds the endometria and contributes to uterine contraction.[12–14] After fertilization, blastocysts enter the uterine cavity for spacing and apposition.[3] In mice, this event occurs between the morning and afternoon of day 4 (day 1 = plug-positive day), corresponding to embryonic day 3.5 (E3.5) and E3.8. Subsequently, embryos attach to luminal cells at midnight on day 4. In humans and rodents, the luminal cells facing the embryos detach from the basal layers and are eliminated,[15–18] which promotes invasion of the trophoblast into the stromal area and placentation. Stromal cells around the attached embryos undergo cell differentiation (decidualization),[19] and key steps of this process have been well elucidated in rodents.[16–18,20,21] In the mouse uterus, stromal cells near the attached blastocysts differentiate into epithelial-like cells from day 5 afternoon onward, forming a tight barrier to protect embryos from maternal immune cells and pathogens present in the circulation.[20–22] This multi-layered epithelium-like structure is called the primary decidual zone (PDZ),[20,23] which disappears by day 8. Stromal cells outside the PDZ differentiate into polyploid cells (forming secondary decidual zone, SDZ), which support embryonic growth via increased transcriptions.[24–26] On day 8, the cells in the SDZ reach terminal differentiation[27] and are shed with the placenta after delivery (Figure 1).

3 | LIPID MEDIATORS IN EARLY PREGNANT UTERUS

Considering the adequate advances in rodent-based research and the similarity of murine and human systems,[3,28] we focused on the studies in rodent models to demonstrate the uterine functions of bioactive lipids (lipid mediators) during early pregnancy. Lipids comprise a major component of the human body. Cells use lipids, such as triacylglycerols, for energy storage,[29] and phospholipids and steroids, to form cellular and organellar membranes.[30] Lipids also serve as a permeability barrier in the skin to protect against infections and inflammations.[31] Furthermore, accumulating evidence has revealed bioactivities of lipids.[32] Bioactive lipids, known as "lipid mediators," are locally synthesized in response to extracellular stimuli, activating specific G protein-coupled receptors in an autocrine or paracrine manner.[32] Here, we summarize the uterine functions of lipid mediators revealed by recent advances in mass spectroscopy, genome editing, and chemical treatments targeting synthesizing enzymes and receptors.

3.1 | Prostaglandins

Prostaglandins (PGs) are lipid mediators synthesized from arachidonic acid (AA) by cyclooxygenases (COXs: COX-1 and COX-2) serving as rate-limiting enzymes.[33,34] Each PG performs various cellular functions through specific G protein-coupled receptors (GPCRs)[34,35] (Figure 2).

Phospholipase A_2 (PLA_2) influences the production of AA by cleaving the *sn*-2 fatty acid chain of phospholipids.[33] Four kinds of PLA_2s are reported in mammals: cytosolic ($cPLA_2$), secretory ($sPLA_2$), $Ca2+$−independent ($iPLA_2$), and platelet-activating factor (PAF) hydrolase. In the mouse uterus, $cPLA_2$ is crucial for early pregnancy events.[36] $cPLA_2\alpha$, a $cPLA_2$ isoform, is highly expressed in the epithelial layer and stroma on days 4 and 5 of pregnancy, respectively, which coincides with Cox-1 and Cox-2 expression. Deletion of this enzyme causes delayed implantation and embryo crowding, accompanied by lowered PG levels. These abnormalities

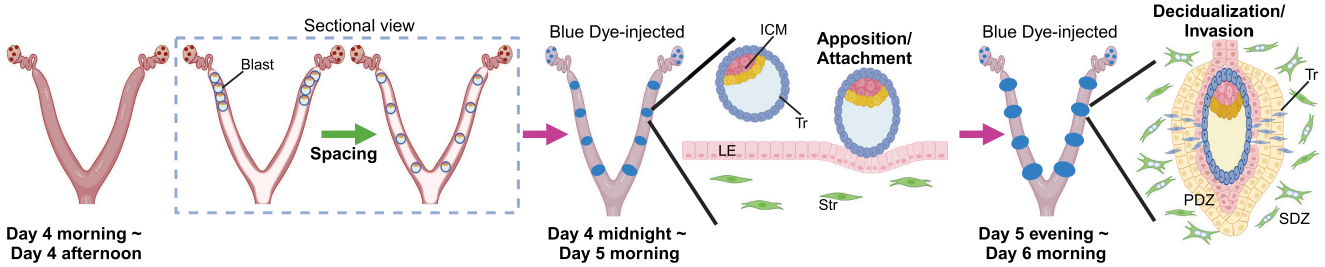

FIGURE 1 Time course of embryo implantation in mice. On the morning of day 4 after coitus (day 1 = plug positive), blastocysts arrive to the uterine cavity and evenly space with each other. Once embryos make an apposition and attach to the endometria, surrounding endometria show increased vascular permeability so that each implantation site can be visualized by intravenous injection of blue dye. On day 5, evening onward, the implantation sites become evident due to decidualization, and trophoblasts initiate the invasion of the primary decidual zone (PDZ) and secondary decidual zone (SDZ). Blast, Blastocyst; ICM, Inner cell mass; LE, Luminal epithelia; Str, Stroma; Tr, Trophectoderm/trophoblast. The image was prepared by Biorender.com.

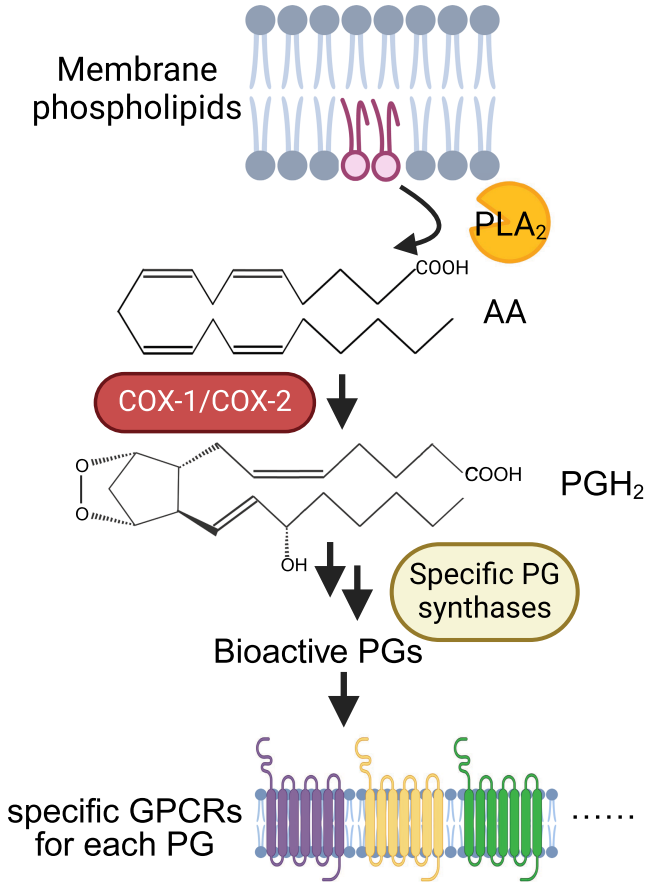

FIGURE 2 Prostaglandins (PGs) pathway. To synthesize PGH_2, cyclooxygenases (COX-1 and COX-2) utilize a substrate arachidonic acid (AA), which is cleaved from membrane phospholipid by phospholipase A_2 (PLA_2). Each PG species produced by specific synthases exert bioactivities via activation of GPCRs. The image was prepared by Biorender.com.

in embryo implantation cause defective fetoplacental development, hemorrhage, shared placentae, and fewer pups.[36,37] Treatment with PGE_2 and cPGI (a PGI_2 analog) can rescue the deferred implantation but not the embryo spacing in *cPLA*$_2\alpha$ knockout (KO) females,[36] which indicates a potential involvement of other PG species in spacing.

In *Cox-2* KO females, severe infertility is associated with multiple anomalies in processes ranging from ovulation to parturition.[34,38] Although previous reports demonstrate the significant correlation of PG receptors with ovulation, fertilization, and parturition,[39–41] the receptor playing key roles in peri-implantation processes remains unidentified. During early pregnancy in mice, several PG receptors have been detected in different types of cells in the uterus.[42,43] However, no single knockout of any prostaglandin receptor has been reported to disrupt uterine functions during early pregnancy. This suggests that multiple PG receptors may act concurrently in the uterus. A pharmacological analysis revealed that PGI_2 plays a critical role in embryo implantation via activating a nuclear receptor PPARδ rather than GPCRs.[44] PPARδ is highly induced in stroma and decidua from day 4 evening onward. Additionally, treatments of PGI_2 analog or PPARδ agonist improved the implantation rate in *Cox-2* KO females after embryo transfer; however, decidual tissue weights were smaller than the control one.

A recent transcriptome-wide comparative study indicated the importance of COX-2 in early pregnancy in marsupial to eutherian mammals.[45,46] In eutherian mammals, pro-inflammatory gene expression is induced upon embryo attachement, while anti-inflammatory signals are upregulated after implantation.[45] Contrastingly, marsupials have no anti-inflammatory phase and exhibit a shorter pregnancy period. COX-2 upregulation after attachment is highly conserved among these species. Furthermore, PGE_2 treatment induces decidualization in stromal cells derived from pregnant opossums.[46] These results indicate that the COX-2-PGs pathways are evolutionarily conserved and are crucial in pregnancy events.

Although the role of intrauterine COX-1 expression in early pregnancy remains unclear, it is highly expressed in the mouse uterine luminal epithelia on day 4.[36] *Cox-1* KO mice exhibit normal pregnancies except for defective parturition because of the compensatory induction of Cox-2 expression in the early pregnant uterus.[13] However, Cox-2 inhibition alone cannot induce noticeable abnormalities in the implantation which were observed in *cPLA*$_2\alpha$ or *Cox-2* KO,[47] reflecting the potential role of Cox-1 in early pregnancy. Moreover, Cox-1 expression in the SDZ on days 7 and 8 suggests that Cox-1 was involved in decidual reactions.[36] Li et al. demonstrated the possible roles of Cox-1 during early pregnancy by utilizing mice with one-by-one substitution of Cox-1 and Cox-2 loci with knock-in alleles reciprocally, which exhibited reduced fertility and defective embryo implantation.[48]

As *cPLA*$_2\alpha$ KO showed a normal decidual reaction, the PLA_2 molecule responsible for decidualization has not been identified.[36] Studies in mice have shown that multiple PLA_2 enzymes are expressed within the uterus during pregnancy,[36] suggesting cooperative roles in uterine function. Further research using pharmacological tools or conditional knockout systems could help address the remaining gaps in our understanding of the PLA_2-COXs-PGs pathways within the pregnant uterus.

Furthermore, COX-PGs are critical not only for uterine health but also for uterine pathology. In the uterine-specific KO (uKO) mice with *p53* KO, decidual senescence caused spontaneous preterm birth, which was associated with the upregulation of Cox-2 and $PGF_{2\alpha}$, which can enhance myometrial contractility.[27] The preterm birth phenotype in *p53* uKO was suppressed by a selective inhibitor of Cox-2. Excessive Cox-2 induction has also been observed in a preeclampsia-like mouse model (BPH5).[49] In BPH5 mice, decidual Cox-2 levels increased on day 6; however, the attachment reaction downregulated Cox-2 levels compared to control mice. The upregulation of Cox-2 disrupts the accumulation of decidual natural killer (NK) cells, which are critical for blood vessel remodeling at the feto-maternal interface. Similar to preterm birth model mice, a Cox-2 selective inhibitor repressed pathological conditions in BPH5, indicating the significance of properly regulated Cox-2 and PG levels.

3.2 | Lysophosphatidic acid (LPA)

Lysophosphatidic acid (LPA) is one of the simplest glycerophospholipids with a fatty acid chain and a phosphate group in the polar head.[32,50,51] LPA evokes various cellular processes, including cell proliferation, prevention of apoptosis, and cell migration, through activating six G-protein-coupled receptors (LPAR1-6). LPA is mainly produced by a membrane-binding enzyme called phosphatidic acid-specific phospholipase $A_1\alpha$ (PA-$PLA_1\alpha$)[52] and a secreted enzyme called autotaxin (ATX) that exhibits lysophospholipase D activity[53,54] (Figure 3). Among the six LPA receptors, Lpar3 was reported to crucially influence early pregnancy events.[55-59] In mice, the expression of *Lpar3* peaks on day 4 of pregnancy in a female sex hormone-dependent manner.[55,56] It is expressed only in the luminal epithelial layer, directly interacting with the embryo.[55] Deletion of Lpar3 in female mice induces deferred embryo implantation and abnormal embryo spacing, resulting in reduced litter sizes and shared placenta[55,57,59]; these outcomes are comparable to those observed in *cPLA*$_2\alpha$ KO dams.[36,37]

We previously reported that a Lpar3 agonist activates luminal Lpar3, contributing to decidual reactions.[59] Intrauterine injection of T13, a specific and potent agonist of Lpar3,[60] on day 4 caused robust decidual reactions throughout the uterine horns, which was induced by the sequential upregulation of early pregnancy event-associated genes,[59] such as HB-EGF and Cox-2 expressed in the epithelia,[19,25,38,61,62] and Bmp2 and Wnt4 expressed in the stroma.[19,63,64]

In contrast to this Lpar3 agonist-induced decidualization throughout the uterine horns,[59] physiological decidualization occurs locally around attached embryos.[19,25] This outcome reflected that LPA synthesis and the subsequent activation of Lpar3 immediately in the vicinity of the embryos. Female mice missing PA-$PLA_1\alpha$, an LPA-synthetic enzyme, are fertile, which indicates no significant association of PA-$PLA_1\alpha$ with pregnancy processes.[65] Contrastingly, previous reports demonstrate potential roles for ATX in female reproduction.[53,66,67] However, the actual contribution of ATX to pregnancy is unclear because systemic deletion of ATX results in embryonic lethality,[68] making it difficult to study ATX functions in adults. Previously,[59] we demonstrated the localization of ATX in the apical surface of the luminal epithelium and detected lysophosphatidylcholine (LPC), a major substrate for ATX, in blastocysts.[54,69] Furthermore, pharmacological inhibition of ATX causes defective embryo implantation similar to that in *Lpar3* KO mice.[59] These results suggest the importance of the ATX-LPA-Lpar3 axis at the blastocyst–epithelial boundary in inducing decidualization during early pregnancy.

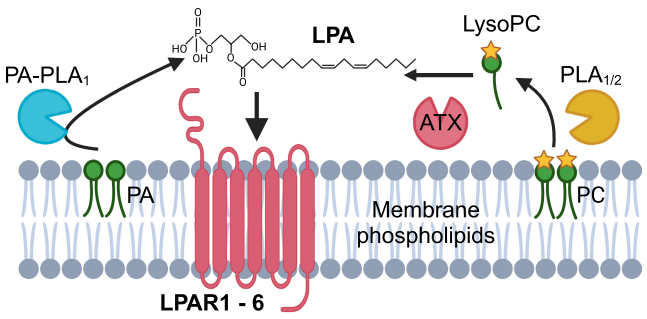

FIGURE 3 Lysophosphatidic acid (LPA) pathway. LPA is majorly synthesized by either PA-PLA_1 or autotaxin (ATX), activating GPCRs named LPAR1-6. LysoPC, Lysophospatidyl choline; PA, Phosphatidic acid; PC, Phosphatidylcholine; $PLA_{1/2}$, Phospholipase $A_{1/2}$. The star icons represent choline. The image was prepared by Biorender.com.

All six LPA receptors were detected in the uteri of pregnant mice and primary cultured uterine stroma.[58,70] However, only Lpar3 was identified critical for early pregnancy in vivo.[55–57,59] Lpar1 is the most abundant LPA receptor in the uterus; however, neither single KO nor double KO of *Lpar1* and *Lpar2* receptors affect embryo implantation processes.[58] However, in our in vitro culture model of primary uterine stromal cells, inhibition of the ATX – Lpar1/3 axis dramatically suppressed cell proliferation.[70] These results suggest that Lpar1 plays a critical role in uterine cell growth. In human endometrial stromal cells cultured in vitro, LPA treatment induces IL-8 expression via p38 MAP kinase and NF-κB pathways.[71] Conditioned media derived from LPA-treated stromal cells stimulate the migration of endothelial cells in vitro, indicating a possible role for LPAR1 in uterine angiogenesis.

Similar to *cPLA*$_2\alpha$ KO,[36] *Lpar3* KO mice exhibit flawed embryo spacing[55,57]; however, the underlying mechanism remains unclear. Histological analyses revealed embryo spacing occurring from morning to evening on day 4 in the wild-type (WT) uteri, whereas it is compromised in *Lpar3* KO mice.[57] In an organ bath culture assay, T13 treatment caused uterine muscle contractions, which is potentially associated with uterine spacing.[57] Lpar3 is localized in luminal cells; some secretory molecules may act downstream of Lpar3 and cause uterine contractions. Nonetheless, activation of the PGE_2/PGI_2 axis, which is downregulated in *Lpar3* KO uteri, only recovers the timing of attachment of the embryo, but not embryo spacing.[55] Moreover, comparable outcomes are recorded in *cPLA*$_2\alpha$ KO,[36] suggesting that other PG species might contribute to embryo spacing.

Most LPA receptors are highly expressed throughout the body and are critical for fetal development,[50,51] making it difficult to validate the specific roles of LPA receptors expressed in pregnant uteri. Uterine-specific KO mice and specific agonists/antagonists of each LPA receptor can facilitate further investigations.

3.3 | Sphingolipids

Sphingosine-1-phosphate (S1P), a lysophospholipid with a phosphate head and sphingosine backbone,[72,73] is mainly produced in the cytoplasm by two sphingosine kinases (SPHK1 and SPHK2) via the phosphorylation of sphingosine. S1P lyase or S1Pase mediates intracellular degradation of S1P in the ER membrane and contributes to glycerophospholipid or ceramide synthesis. After extracellular release mediated by a specific transporter SPNS2, S1P functions as a lipid mediator through activation of GPCRs (S1pr1–5) (Figure 4).

Previous reports demonstrate the function of SphKs in decidualization.[74–76] Despite normal ovulation, fertilization, and embryo attachment *in SphK1*$^{-/-}$/*SphK2*$^{+/-}$ females, they are completely infertile[74].

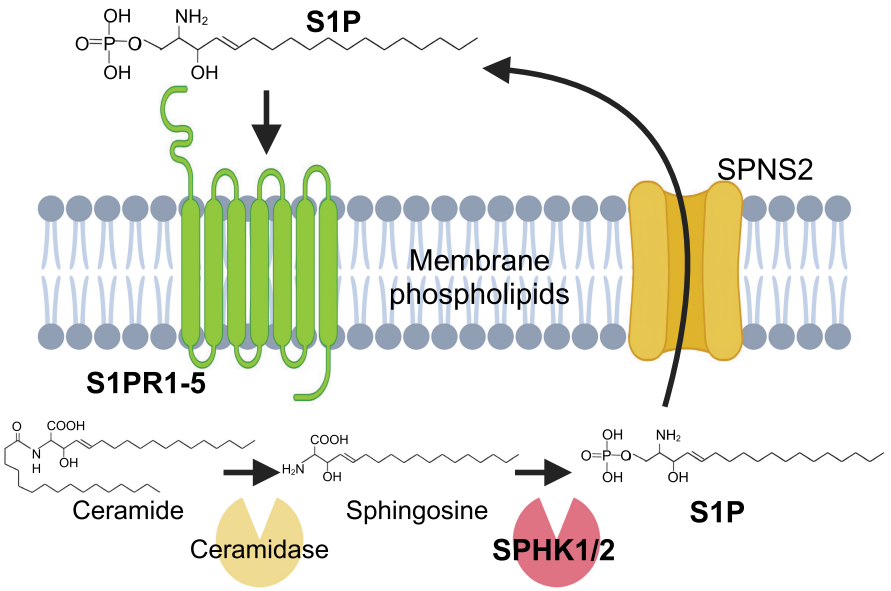

FIGURE 4 Sphingolipid pathway. Sphingosine is synthesized by cleavage of a fatty acid from ceramide, and then phosphorylated by sphingosine kinase 1/2 (SPHK1/2) to produce S1P. S1P is transported by spinster homolog 2 (SPNS2) and then activates GPCRs called S1PR1-5. The image was prepared by Biorender.com.

Further detailed analyses revealed the correlation between decidualization failure and their infertility.[75] *SphK1*$^{-/-}$/*SphK2*$^{+/-}$ uteri exhibit reduced proliferation/differentiation and increased death of the stromal cells. These stromal defects cause poor decidualization, allowing neutrophil infiltration into the feto-maternal interface, which causes tissue injury through the excessive neutrophil extracellular traps (NETs) formation.[75,76] NETs are neutrophil-derived DNA/protein fibers that kill pathogens in the extracellular regions.[76] Pharmacological inhibition of chemoattractant signaling and NET formation partially rescues abortion in mutant mice.[76] Therefore, sphingolipids significantly impact decidualization and maintenance of pregnancy.

Mizukishi *et al.* also focused on exploring which sphingolipid molecule is critical for decidualization downstream of SphKs. In *SphK1*$^{-/-}$/*SphK2*$^{+/-}$ uteri, the S1P level remains unaltered despite a lack of SphK activity,[74] whereas other sphingolipids, including sphingosine, are dramatically increased with reduced levels of phosphatidylethanolamine; these results suggest that the total balance of lipid compositions may influence decidual reactions. This notion was validated by a report that demonstrated highly expressed serine palmitoyltransferases (SPT; Sptlc1-3), the first key enzymes for de novo sphingolipid synthesis, in the decidua and impairs decidualization induced by inhibition of SPT.[77]

While it is still unclear whether S1P has any rolles in early pregnancy, Ye *et al.* reported that all S1P receptors are highly expressed in pregnant uteri.[58] Moreover, females with a single KO of *S1pr2* and double KO of *S1pr2*/*S1pr3* showed reduced litter sizes[78]; however, the number of embryo implantation sites was comparable to that of WT on day 5 immediately after embryo attachment.[58] Hence, we propose that S1P signaling plays an important role in post-implantation events, including decidualization.

3.4 | Cannabinoids

Cannabinoids comprise a class of lipids that exert psychoactive effects by activating two GPCRs: CNR1 and CNR2.[79,80] In early pregnant mice, Cnr1 is found in trophoblasts and broadly throughout the endometria.[81-83] The expression of Cnr2 is evident in the inner cell mass of blastocysts, blood cells, and endothelial cells; however, it is not detected in uterine cells.[81,84,85] In the 1990s, endogenous ligands for CNR1/CNR2 (endocannabinoids) were identified.[86,87] Among endocannabinoids, anandamide (arachidonoylethanolamide; AEA) and 2-arachidonoylglycerol (2-AG) have been well explored. AEA is produced by N-acyl phosphoethanolamine phospholipase D (NAPE-PLD) activity and degraded by fatty acid amide hydrolase to generate AA and ethanolamine (FAAH).[79,88] Contrastingly, 2-AG is produced by sn1-diacylglycerol lipase (DAGL) and is degraded mainly by monoacylglycerol lipase (MAGL) to form AA and glycerol.[79,89] In early pregnant mice, NAPE-PLD and DAGLα are highly expressed in the epithelial layers (Figure 5).[90,91]

Previous genetic and pharmacological analyses have revealed the vital roles of cannabinoids in the murine female reproductive system of mice.[82,84,85,91-98] Both upregulation and suppression of cannabinoid signaling via Cnr1 were reported to compromise proper embryonic development. A single deletion of Cnr1 can cause a 50% reduction in pregnancy rate.[84] Double deletion of *Cnr1* and *Cnr2* further reduces female fertility, leading to an 80% reduction in pregnancy rates. FAAH is found in the uterine stroma of humans as well as mice, and *Faah* KO females exhibit increased levels of anandamide and reduced fertility.[94] These findings indicate that the strictly regulated cannabinoid signaling significantly impacts pregnancy.

Here, we have focused on the functions of cannabinoids at the feto-maternal interface during early pregnancy, although cannabinoid pathways are also involved in oviductal transport[84] and protection from preterm birth.[95,98] Recently, Cnr1/Cnr2 has been reported as important factors regulating PDZ formation.[85] In the uteri of females with *Cnr1*/*Cnr2* double KO (DKO), poorly formed PDZ causes excessive infiltration of macrophages near the attached blastocysts. Hif2α, a critical transcriptional factor expressed in PDZ to promote trophoblast invasion,[17] is downregulated in the PDZ of *Cnr1*/*Cnr2*

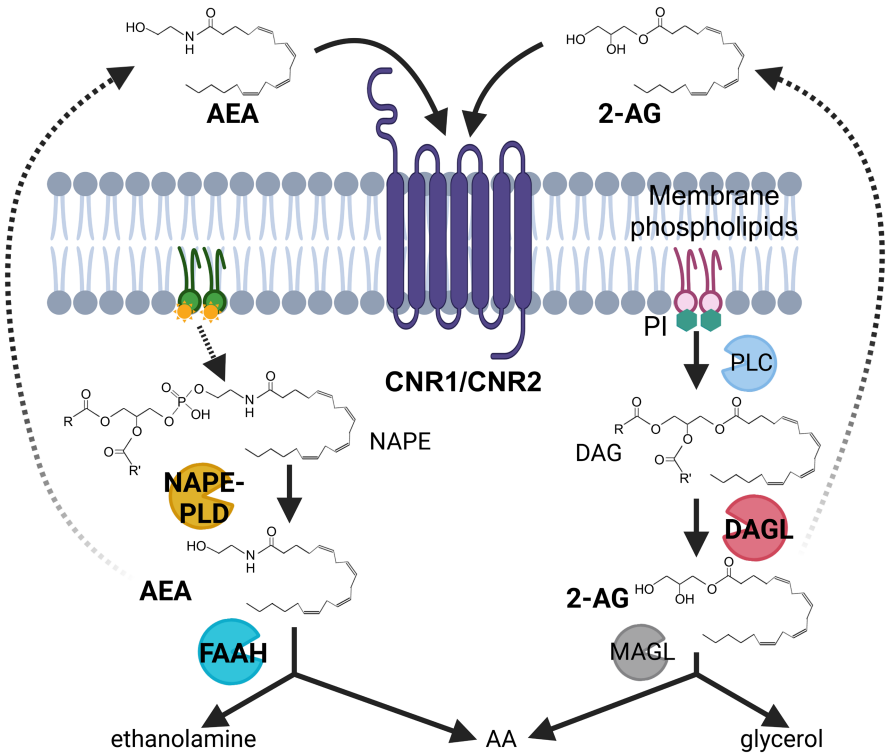

FIGURE 5 Endocannabinoid pathway. Among endocannabinoids, anandamide (arachidonoylethanolamide: AEA) is produced by N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD) and degraded by fatty acid amide hydrolase (FAAH). On the other hand, 2-arachidonoyl glycerol (2-AG) is produced by diacylglycerol lipase (DAGL) and degraded by monoacylglycerol lipase (MAGL). Both cannabis activate cannabinoid receptors CNR1 and CNR2. NAPE, N-acyl phosphatidylethanolamine; PI, Phosphatidyl inositol; PLC, Phospholipase C. The hexagon and sun icons represent inositol and choline, respectively. The image was prepared by Biorender.com.

DKO.[83] Moreover, embryo invasion is compromised in the mutant uteri, which facilitates abortion. Trophoblastic cells are crucial for embryonic invasion and subsequent placentation.[97] Trophoblastic stem cells derived from *Cnr1* KO exhibit decreased invasive activity compared to the WT control group.[82,96,97] In addition, the trophoblast-specific deletion of *Cnr1* leads to defects in placentation and reduced birth rates; however, these anomalies are less severe than those found in the systemic deletion of *Cnr1*.[82]

Marijuana, which contains the cannabinoid Δ^9-tetrahydrocannabinol (Δ^9-THC), is clinically used to alleviate morning sickness. However, in Western countries, it is commonly abused by pregnant women.[99] Moreover, circulating AEA levels are correlated with increased abortion rates in pregnant women.[100] The roles uncovered in mouse studies may hold promise for the future treatment of these human pathologies.

4 | CONCLUSIONS

In conclusion, appropriate communication between the embryo and endometria is crucial for successful pregnancy and childbirth, which is evidently governed by lipid mediators (Figure 6, Table 1). This review summarizes accumulating evidence demonstrating the significance of lipid mediators in establishing and maintaining early pregnancy. As lipid synthases and receptors are highly conserved across species,[33,50,73,79] the lipids, exhibiting significant impact in mouse models, are considered to play pivotal roles in other mammals, including humans. The possible involvement of bioactive lipids in the maintenance of pregnancy in humans was reported.[66,100] LPA synthesis was detected in follicular fluids collected from IVF patients.[66] Another study found that patients with higher levels of circulating anandamide tend to experience failed pregnancies after IVF-ET.[100] However, as these human studies have been occurred on IVF patients, the role of bioactive lipids in pregnancy in healthy subjects remains unclear. One reason for the limitation in human research is the ethical difficulty of collecting pregnant human uterine tissues. In addition, it is difficult to accurately estimate pregnancy stages in humans, especially during the peri-implantation period, without dissecting specimens of pregnant uteri.[101] However, recently, in vitro models of human implantation and embryogenesis have been actively tested,[102–105] which may contribute to future lipid research in human feto-maternal interfaces.

Despite the progress in lipid research focusing on uterine functions, several questions remain unanswered. In previous studies, researchers have primarily utilized systemic KO mice for each lipid-related gene. This makes it difficult to determine whether the phenotypes result solely from uterine dysfunctions or if other organs are also involved. Uterine-specific gene deletion using Cre-loxP systems such as *Pgr*-Cre[106] or *Ltf*-iCre[107] could be used to clarify the distinct roles of lipid mediators in the uterus. While the roles of SPHK1/2 and cannabinoids have been studied in-depth, it remains unclear how LPA and PGs influence uterine functions. Establishment of uterine-specific KO for each LPA/PGs receptor will clarify their uterine roles. As they have common downstream G-proteins, it is possible that LPA/PGs receptors share certain functions.[108] Therefore, multiple KO of LPA/PGs receptors might be required in future studies.

While the crucial roles of lipids have been identified, the spatiotemporally regulated functional mechanism of each lipid molecule remains unclear due to technical limitations. These include ethical barriers to investigating human pregnancy and difficulties in

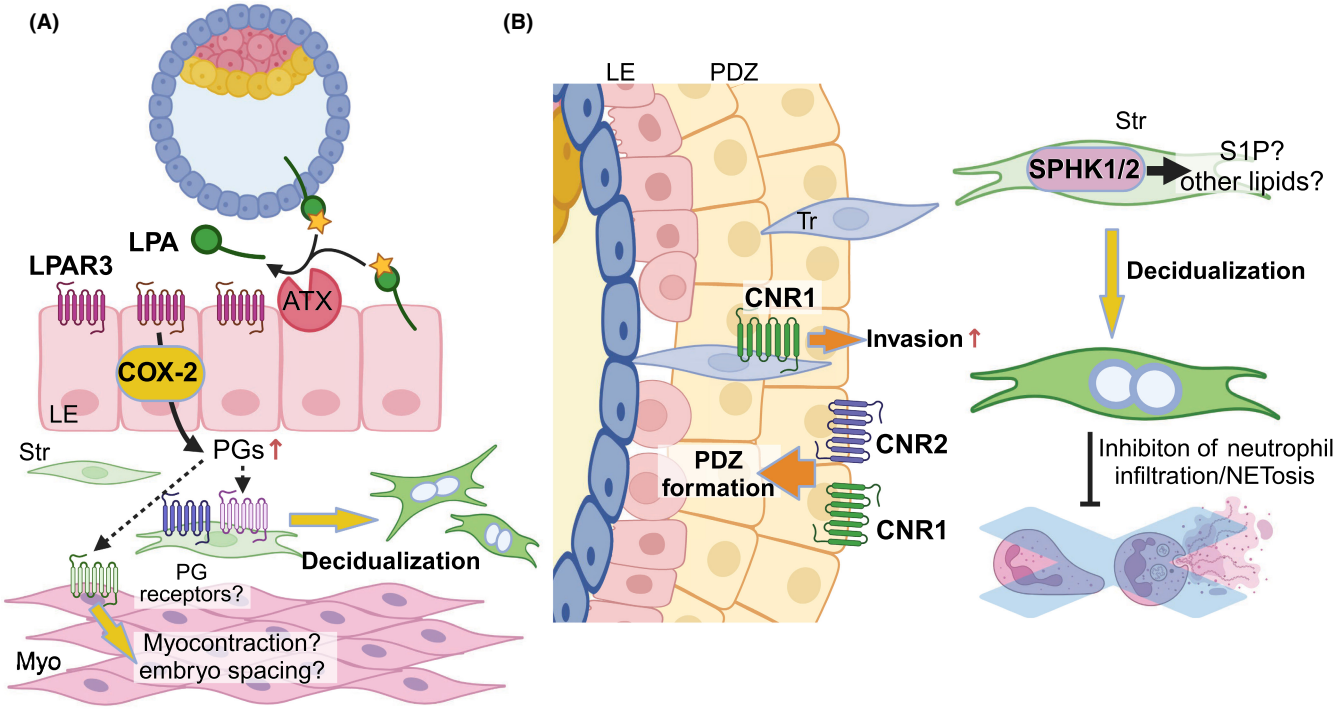

FIGURE 6 Summary of bioactive lipids in the feto-maternal interface. (A) LPAR3 on luminal epithelia (LE) is activated at the site of blastocyst–endometrial interaction, evoking COX-2 – PGs pathways. LPAR3 – PGs seem involved in decidualization. They may also contribute to myocontraction, which leads to embryo spacing. (B) Endocannabinoids facilitate embryo invasion by inducing primary decidual zone (PDZ) formation as well as trophoblast (Tr) migration. Sphingosine kinases (SPHK1/2) contribute to decidualization, inhibiting neutrophil migration and NETosis. Myo, Myometria; Str, Stroma. The image was prepared by Biorender.com.

TABLE 1 Summary of the functions of lipid mediators in uteri during early pregnancy.

	Enzymes involved in lipid synthesis and their expression sites in uteri during pregnancy	Functional downstream receptors in uteri during pregnancy and their expression sites	Function in uteri during early pregnancy	References
PGs	COX-1/luminal epithelia before the attachment COX-2/luminal epithelia and stroma in the vicinity of the attached embryos	Unknown PPARδ?/decidua	Embryo spacing Timed embryo implantation Decidualization	27,34,36–49
LPA	ATX/luminal epithelia	LPAR3/luminal epithelia during the receptive phase	Embryo spacing Timed embryo implantation Decidualization	50,51,55–59,65–68,70,71
Sphingolipids	SPHK1 and SPHK2 /decidua	S1PR2 and S1PR3?/decidua	Decidualization	58,74–78
Cannabinoids	NAPE-PLD for AEA and DAGLα for 2-AG/luminal epithelia	CNB1/trophectoderm and PDZ CNB2/ICM and endothelia	Decidualization Embryo invasion	80–85,90–100

detecting lipid mediators in situ. Recently, spatial transcriptomes and lipidomes have been rapidly developed, and novel roles of lipids have been unveiled. Further studies on lipids can contribute to developing new methods for diagnosing and treating infertility in humans.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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