Review Article

Intriguing Role of Lysophosphatidic Acid (LPA) and its Receptor Mediated Signaling during Implantation: A Review

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\begin{abstract}
Regardless of major advances in medical technologies many Assisted Reproductive Technology (ART) experience recurrent implantation failures (RIF). Lysophosphatidic acid (LPA) signaling cross talks between the mother and the implanted embryo at a very early stage of gestation to enhance endometrium receptivity. LPA is a simple water soluble phospholipid that arbitrates varied biological functions like proliferation, migration and activation of various intracellular signaling pathways in diverse cell types. LPA also has a chief role to play in human and animal reproductive processes including luteolysis, endometrium and ovarian function, estrous cycle regulation, embryo development and implantation, placentation and decasualization with the help of receptor (LPAR1-6) mediated LPA signaling. Further, autotaxin a LPA producing enzyme is found to be upregulated during decasualization of human endometrial stromal cells (HESC). LPA aids in the maintenance of endometrium receptivity by invigorating the expression of prostaglandin endoperoxide synthase 2 (PTGS2). LPA also increases progesterone (P\textsubscript{4}) and prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) secretion and elevation in PGE\textsubscript{2}/PGF\textsubscript{2α} ratio. This review highlights and discusses about the current advancement in receptor mediated LPA signaling in human reproduction, ruminant reproduction pointing to bovine and sheep models, and even in porcine reproduction models and correlating it with human reproductive function.
\end{abstract}

\textbf{Keywords:} Lysophosphatidic acid (LPA), Assisted Reproductive Technology (ART), Recurrent implantation failure (RIF), Autotaxin

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\section*{Introduction}

Despite of all the advancements in reproductive technologies, majority of the implantations are unsuccessful which becomes a very important problem in humans as nowadays women decide to delay motherhood and it ultimately causes problem later. Increasing age decreases the chances of natural fertilization and pregnancy development which ultimately increases the need for new technology like Assisted Reproductive Technology (ART) (Koot \textit{et al}., 2012). Implantation process in human is astonishingly dynamic and controlled by a number of molecular and cellular events.
Though there are many new advanced technologies are emerging, success rates of *in vitro* fertilization (IVF) procedures remain below 30 per cent since many years. Many molecular level studies were conducted to understand the concepts in implantation failure. It is estimated that approximately 10 per cent of women experiences recurrent implantation failure (RIF) after *in vitro* embryo transfers. Numerous factors including oocyte and sperm quality, genetic abnormalities of the embryo, poor endometrium receptivity, immunological disturbances in the implantation site, and some gynecologic pathologies such as endometriosis, uterine fibroids etc. leads to RIF. Embryos implantation failure forms the major rate limiting step.

Unstable maternal immune response towards the embryo causes embryo rejection in some cases ie. before establishing a contact between mother and fetal an abnormal modulation in maternal immune system occurs affecting the fetus resulting in implantation failure. Lysophosphatidic acid (LPA) is a polar phospholipid gaining momentous interest in recent years (Boruszewska *et al.*, 2013). They exert their function with the help of six G protein-coupled receptors (LPAR1-6) acting as an effective signaling molecule with varied functions on many different target tissues. LPA receptors have multiple roles to play in developmental, physiological, and pathological processes (Guo *et al.*, 2013). This review provides a summary of LPA and receptor mediated LPA signaling and current aspects on the successful implantation, pregnancy development and also in the treatment of reproductive disorders.

**Implantation and problems**

Best way to verify the occurrence of implantation events after assisted reproductive technology (ART) is to evaluate the human chorionic gonadotrophin (hCG) levels in serum samples after embryo implantation (Wang *et al.*, 2003 and Koot *et al.*, 2011). Recurrent implantation failure (RIF) is a very challenging phenomenon to be considered for any implantation. Women’s age, oocyte and sperm quality, poor uterine receptivity, parental chromosomal abnormalities, endometriosis are some of the factors that contributes to RIA (Coughlan *et al.*, 2014). Several endometrial factors also cause implantation failures. Many molecular markers including various gene expression (Revel *et al.*, 2011), prostaglandins (Achache *et al.*, 2010), cell adhesion molecules (Revel *et al.*, 2005), mucins (Dentillo *et al.*, 2007), cytokines (Zhang *et al.*, 2011) etc. are used to determine the ideal endometrial receptive period (Quinn *et al.*, 2007, Quinn and Casper, 2008 and Haouzi *et al.*, 2010). Many endometrial studies can be done by using such biomarkers and many new therapies and treatments can be elucidated for treating defective endometrial receptivity (Boomsma *et al.*, 2009).

**Lysophosphatidic mediated signaling**

Lysophosphatidic acid (LPA) is a water-soluble bioactive phospholipid which acts as a signaling molecule. LPA is found to be present in serum (Sano *et al.*, 2002), plasma (Woclawek-Potocka *et al.*, 2009), follicular fluids, ascites (Tokumura *et al.*, 2007), neurons (Fukushima *et al.*, 2000), ovarian cells (Eder *et al.*, 2000) and other cell types. LPA acts as autocoid and exerts its function by activating six high affinity G-protein coupled receptors. So far six receptors have been identified and are called as LPAR1, LPAR2, LPAR3, LPAR4, LPAR5 and LPAR6. LPA performs several developmental, pathological and physiological functions in various cell types with the help of respective receptors. Receptor mediated LPA signaling has evolved
as a new dimension in treating several human
diseases (Lin et al., 2010). LPA also has a
role to play in cell adhesion, differentiation of
various cell types, cell migration and
invasion, cell proliferation, cytoskeletal
rearrangement (Moolenaar, 1995), cellular
interactions (Fukushima et al., 2002), cell
morphogenesis (Van Meeteren and
Moolenaar, 2007) and sometimes even in cell
tumorigenesis (Kim et al., 2006). Many
studies have been conducted to find the
correlation between LPA and female
reproductive physiology (Budnik et al.,
2002) and it was found that LPA signaling pathway
has an influence on embryo implantation
(Zhang et al., 2005).

**LPA signaling in human reproductive tract**

The impact of LPA on the female
reproductive system has been studied for
about 30 years (Liszewska et al., 2009 and
Woclawek-Potocka et al., 2010). Among the
six receptors present, in human it was found
that there was an increase in receptor 3
expression during the early and late secretory
phase and their expression decreases during
mid-secretory phase. LPA and their receptors
had been documented to be present in uterus,
ovary and placenta (Chen et al., 2010 and
Guo et al., 2013). LPA mainly influences the
female reproductive function (Fig. 1) and this
could be clearly understood by the presence
of elevated level of LPA producing autotaxins
in females (Im Kim et al., 2004 and Chen et
al., 2008). Ovarian steroids mainly estrogen
and progesterone controls the human endometrial stromal cells (HESCs) during the
luteal phase of menstrual cycle in human. In
human LPA level increases between weeks 5
and 40 of pregnancy (Tokumura et al., 2002).
During the decidualization process these cells
undergoes proliferation, migration and
differentiation, thus proper decidualization is
important for proper implantation and
successful pregnancy. During decidualization,
LPA receptors 1 and 6 were highly expressed
and autotaxin enzyme level was also found to
be elevated in HESCs. A recent study
suggests that LPA receptor signaling is very
important during human endometrium
decidualization and implantation (Hanoune et
al., 2005). In human follicles, oocytes and
granulose cells contains lysophospholipase D-
Autotaxin which helps in the production of
lysophosphatidic acid from
lysophosphatidylcholine. When compared to
women with natural cycle women receiving
ovarian stimulation tends to have increased
autotaxin activity. LPA signaling plays many
important roles during ovulation by causing
up regulation of IL-8 and IL-6 which
ultimately stimulates the formation of new
vessels in corpus luteum which is very
important for women undergoing invitro
fertilization (Jeong et al., 2016). LPA
signaling is also employed in the maintenance
of human pregnancy.

During pregnancy, level of serum LPA was
found to be increased from both placenta and
fetus. Certain studies also claim that LPA
may be involved in the initiation and
regulation of labour. During the beginning of
labour, endometrium contraction efficiency
may be increased by LPA by the formation of
stress fibres in human myometrial cells. When
implantation occurs in women with
endometriosis LPAR3 expression tend to be
decreased during the mid and late secretory
phase. Thus, by relating the decreased LPAR3
expression along with other endometrium
receptivity biomarkers, P4 resistance
connected to endometriosis can be well
explained. In addition to all the positive
impacts LPA mediated signaling can also
cause adverse effects during human
pregnancy. Abnormal levels of LPA causes
high arterial blood pressure and also
vasoconstriction ultimately affecting the
pregnancy. LPA in human reproductive
tissues maintains ovarian cycle, helps in
pregnancy development as well as takes care of various abnormalities in the female reproductive tract. LPA is also engaged in the direct maintenance of fetus by controlling embryo implantation and vascularization. However, for understanding the role of LPA in human reproduction, many animal models have been developed and studied in order to overcome the ethical restrictions associated with the research on human tissues (Lebovitz and Orvieto, 2014).

LPA signaling in sheep reproductive system

In ovine, endometrium conditions during early pregnancy were well studied and LPA was detected in the endometrium and conceptus of uteri during the early stage of pregnancy in ewes. Any kind of embryo implantation defects can be repaired by prostaglandin administration and cPLA-2, PTGS2, and LPAR3-mediated signaling has a major role to play. In ovine, during d 10 blastocyst which is spherical is transformed into a tubular form on d 11–12, and on d 13-16 it forms a filamentous conceptus this expansion leading to a 15 cm long ovine conceptus. This is mainly due to the rapid expansion of the trophoderm initiating the implantation phases successively leading to transient connection and solid adhesion by d 16-17. In the sheep conceptus, trophoderm cells were known as a source of the autotaxin.

Autotaxin and LPA levels are found to have parallel regulation and were low on d 12-14, their levels elevated on d 15-16. LPA receptors LPAR1 and LPAR3 transcripts levels were at peak on d 14 and the highest level of protein for both receptors was observed at d 17. Unlike LPAR1 which was confined in cellular membranes and nuclear compartments of the trophoderm cells, LPAR3 was present only in membranes (Liszewska et al., 2009). It was observed that ERK(1/2) MAPK was activated after LPAR1-3 activation. In ovine conceptus, LPA-mediated signaling plays a vital role mainly at the time of embryo implantation. LPA increases the release of prostaglandin F₂ and E₂, without any major modifications to cytosolic phospholipase A₂ and prostaglandin synthase-2 expression. Using an ovine trophoderm cell line it was proved that LPA improved the PTGS2 expression and prostaglandin synthesis. Hence it can be concluded that the release of prostaglandin which is mainly induced by LPA mediated signaling is perhaps due to arachidonic acid mobilization. By the combined action of strong expression of PTGS2 enzyme and LPARs there is a massive increase in the synthesis of prostaglandins due to the elevated level of LPA in the uterine lumen.

LPA signaling in bovine reproductive system

Since bovine reproduction characteristics are found to be somewhat similar to that of human ovarian physiology, pregnancy maintenance, embryo implantation and development and any other assisted reproductive techniques (Bettegowda et al., 2008), few studies were conducted to understand the role of LPA in bovine uterus. In addition bovine model has a greater availability of biological material compared to studies in human. In bovine LPA was produced locally and released from its endometrium. LPA was also detected in minute concentrations in the bovine corpus luteum (CL) throughout the estrous cycle and during early pregnancy (Kowalczyk-Zieba et al., 2012). In bovine uteri prostaglandins are very important for estrous cycle regulation and maintenance of early pregnancy. Maintenance of CL, P₄ secretion, maintenance of uterine receptivity is very important for successful implantation which could be made possible by attaining an optimal PGF₂α to PGE2 ratio. LPA works by enhancing the activity of prostaglandin like 2 synthase,
enzyme which converts PGF$_2$α to PGE$_2$.

Total LPA level in the uterine vein blood plasma was found to be significantly higher when compared to that of the jugular vein plasma on days 17-19 of the estrous cycle for 24 h. PLD2 and PLA2G1B gene expression during estrus cycle and early was studied showing that PLD2 expression was stable during estrous cycle and early pregnancy but PLA2G1B expression was higher on days 17-19 of pregnancy claiming that LPA maybe synthesized during all stages of the estrous cycle and pregnancy and preferably higher on d17-19 of pregnancy (Woclawek-Potocka., 2009).

**Table.1** LPA receptors employed in various reproduction functions of different animals

| Sl. No | Animals | Receptors        | Roles                                                                 | Reference               |
|--------|---------|------------------|----------------------------------------------------------------------|-------------------------|
| 1      | Human   | LPAR1 & LPAR3    | Aids in HESC decidualization and maintenance of progesterone level    | Brunner et al., (2014)  |
| 2      | Bovine  | LPAR1           | Modulates prostaglandin (PG) synthesis in the murine endometrium.    | Jeong et al., (2016)    |
| 3      | Sheep   | LPAR1 & LPAR3    | Induces the release of prostaglandin F2a and E2.                     | Liszewka et al., (2009) |
| 4      | Porcine | LPAR3           | Increases uterine endometrial expression of PTGS2.                    | Woclawek-Potocka et al., (2009) |

![Figure.1 LPA signaling in human reproductive tract](image-url)
Autotaxin a major LPA producing enzyme and PLA2 expression were studied in bovine ovary which showed the chance of LPA synthesis in bovine follicles. In bovine endometrium during estrous cycle and early pregnancy correlation between prostaglandin synthesizing enzymes (PGES and PGFS) mRNA and LPA receptor LPAR1 expression were studied showing that PGFS mRNA expression was found to be higher on days 8-10 than on days 17-19 of pregnancy. LPA also induces autocrine and paracrine actions on the bovine endometrium, CL, and the follicle. In the bovine endometrium LPA receptor mediated signaling induce PGES and inhibits PGF2α actions and in CL, LPA stimulates P4 secretion through stimulation of 3βHSD (Sahmi et al., 2004) augments IFN-γ dependent stimulation of ISG15 and OAS1 expression. LPA suppresses TNFα and IFNγ (Abbas et al., 2000 and Sakumoto et al., 2000). LPA stimulates estrogen production and FSH action in bovine ovarian follicle by increasing the genes responsible for the expression of the FSHR and 17β-HSD, which sequentially relates for the involvement of LPA in bovine ovarian follicle development and differentiation.

**LPA signaling in porcine reproductive system**

Many studies were conducted in pigs showing that LPA and its receptor system are present at the maternal conceptus interface. Just like in all other mammals pigs also require proper peri implantation period is very important for successful pregnancy during which a well-synchronized communication between the conceptus and the maternal uterus must be established (Aplin and Kimber, 2004 and Bazer et al., 2012). LPA elevates prostaglandin endoperoxide synthase 2 (PTGS2) in the uterine through LPAR3. Effect of LPA in porcine conceptuses was studied with the help of porcine trophectoderm (pTr) cell line isolated from Day 12 conceptuses and it was found that activation of ERK1/2-P90RSK-RPS6 and P38 pathways are involved(Bettegowda et al., 2008).

For a successful embryo implantation in human endometrium complex collaboration of several factors are important. In *in vitro* studies using many animal models were conducted to reduce RIF and pregnancy failure by effectively rejecting the incompetent embryos. With the advancement of technologies genes and proteins of endometrial receptivity and pregnancy were identified. Many studies show evidences of LPA signaling significance in reproductive function. LPA with its G protein-coupled receptors (LPAR 1–6) exerts diverse cellular effects influencing reproductive function of the female. LPA is proved to be synthesized during reproduction. Thus, it is very important to carefully examine the biological effects of LPA in human reproduction. Due to the ethical limitations in conducting human studies, numerous studies were conducted using various animal models. LPA modulates prostaglandin (PG) synthesis via LPA receptor 3 (LPAR3) and serve as an important factor in the maintenance of early pregnancy in cow. This review focuses on recent studies of LPA signaling that are related to human reproduction function, using cow, sheep, and pig as a relevant model to understand the influence of LPA on the human reproduction function.

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