Preimplantation Factor (PIF): a peptide with various functions

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ABSTRACT

Preimplantation Factor (PIF) is a novel fifteen amino acid linear peptide (MVRIKPGSANKPSDD), which has different biological functions in mammalian species e.g. its role in neuron restoration, pregnancy and related disorders, and also in autoimmune diseases. Since all clinical studies have shown that PIF has both local and systemic effects, it can be considered as an integrated therapy for the treatment of inflammation conditions, along with the prevention of advanced disease. The synthetic PIF (sPIF) analog is a good representative of native PIF action, and it regulates peripheral immune cells to achieve endurance without immune suppression - an effective agent in non-pregnant autoimmune models. This study provides information, from evidence-based studies so far about PIF's different functional aspects.

Keywords: preimplantation factor, peptide, pregnancy, immune system

INTRODUCTION

PIF was first introduced by Dr. Eytan Barnea, as a native peptide secreted only by permanent mammalian embryos, as early as the 2-cell stage to the fetus from the beginning to the end stage of viable pregnancy (Roussev et al., 1995). Later, the Barnea Research Group studied the potential therapeutic role of PIF against diseases and immune disorders associated with pregnancy, such as endometriosis, recurrent pregnancy loss (RPL), preclampsia (Barnea et al. 2016a; Goodale et al., 2017; Sbracia et al., 2017). Consequently, PIF as a novel fifteen amino acid linear peptide (MVRIKPGSANKPSDD) has different biological functions in mammalian species, namely its role in neuron restoration, pregnancy and related disorders and also in autoimmune diseases (Barnea et al., 2015; Goodale et al., 2017). PIF showed multi-functional effects in decidua cultures, such as modulating local immunity and systemic maternal immunity without suppression, embryo adhesion enhancement, apoptosis control and trophoblast invasion induction (Duzyj et al., 2010; Paidas et al., 2010; Weiss et al., 2012).

Given the new knowledge about the role of fetal secretions, including PIF in embryo acceptance of the females' immune system throughout viable pregnancy, motherhood like the past is not considered as the only determinant of pregnancy success. In the current review, we attempt to describe the different functional aspects of PIF according to the literature.

FUNCTIONS

Neuron Restoration

PIF plays a major role in the embryo's neural system development and neuroprotection by providing the embryo with proteins engaged in oxidative stress, protein misfolding, and neural development, attacking to protein-di-isomerase/thioredoxin (PDI/TRX) and heat shock proteins (HSPs) (Barnea et al., 2014). Moreover, PIF can target tubulins as well as the neurons' backbone. It can also upregulate decidual proteins involved in neural function, including agrin as a part of the neuromuscular junction; Calpain1 as a cytoskeleton member; NADH dehydrogenase (ubiquinone); iron-sulfur protein 3 (NDUFS3), a modulator of oxidative stress; and protein-tyrosine phosphatase receptor-type F polypeptide-interacting binding protein 1 (PPIF1BP1) as an axon guidance agent (Paidas et al., 2010).

PIF prevents severe brain damage caused by hypoxia and inflammation in the newborn animal model (Weiss et al., 2012). However, PIF facilitates neural repair via local and systemic effects, it suppresses severe paralysis through oxidative stress reduction and protein misfolding in chronic neuroinflammation models. Additionally, the subcutaneous implementation of PIF resulted in declined brain inflammation and increased neural repair in a clinical model of multiple sclerosis (MS) (Weiss et al., 2012). Interestingly, evidence has indicated that PIF targets microglia as the major immune element within the central nervous system. Following the effects of PIF on microglia culture, the reduction in a let-7 microRNA-dependent pathway involving Protein C/A (PKC/PKA) kinases demonstrated its neuro-protective influence on brain injury (Mueller et al., 2014; Mueller et al., 2015). A synthetic preimplantation factor (sPIF), analogous to PIF obtained from the mammalian embryos, can provide neuro-protection in rodent models of experimental autoimmune encephalomyelitis as well as perinatal brain injury (Weiss et al., 2012; Mueller et al., 2015).

Role in pregnancy

PIF is a specific peptide secreted by vital embryos starting at a two-cell stage in mice, four-cell stage in humans, and six-cell stage in bovines. It presents its key role in early fetal as well as maternal signaling (Stamatkin et al., 2010; Mueller et al., 2012a). PIF is acquirable in maternal serum of two days from mouse pregnancy as well as on 2-day post-embryo transfer in human in vitro fertilization (IVF) cycles, (Coulam et al., 1995; Roussev et al., 1995). PIF is detectable during the first trimester of pregnancies that improve to the second trimester (Barnea et al., 1994). Due to the pro-apoptotic effects of PIF, it can create a beneficial pro-inflammatory environment in human decidual cells (Moindjie et al., 2016). However, the absence of PIF declares no pregnancy in bovines, positive detection of PIF at day 20 after artificial insemination auspicates normal calf delivery (Ramu et al., 2013).

PIF is expressed by both the mammalian embryo and its placenta, which shows in maternal circulation with assured autotrophic effect on the embryo until term (Barnea, 2007; Barnea et al., 2012a). Unlike non-viable pregnancy, it is also shown in the maternal circulation throughout a
viable pregnancy (Barnea, 2007; Stamatkin et al., 2011a; Ramu et al., 2013). There are four main supplementary effects of this peptide that are necessary for pregnancy initiation and maintenance, including:

**Embryo development and maintenance as a rescue factor**

The development of in-vitro embryos depends on the autocrine factors they secrete (O’Neill, 1997; Gopichandran & Leese, 2006). Moreover, reactive oxygen species (ROS) are one of the main harmful agents affecting embryos growth that have to be reduced in-vitro (Takahashi, 2012; Latham, 2016). There are persistent concerns about multiple embryos culture for an extended period during IVF that can cause damaging epigenetic effects as well as premature delivery (Nasr-Esfahani et al., 1992). Viable embryos secrete PIF as an internal compound that increases their development and protection against adverse in-vitro conditions (Barnea et al., 1994; Roussev et al., 1995; Duzyj et al., 2010). A study conducted by Goodale et al. (2017) demonstrated that PIF postponed embryo development resulting from RPL attenuating ROS and concluded that the protein disulfide isomerase/thioredoxin (PDI/TRX) was considered as an initial PIF target as well as an important ROS scavenger in the embryo.

Some reports showed that the exogenous administration of sPIF has improved the rate of embryo viability and blastocyst developments in animal models in an autocrine and paracrine manner when compared to the controls (Barnea et al., 2014), while anti-PIF monoclonal antibody had inhibitory effects (Stamatkin et al., 2011a;b).

**Endometrial receptivity induction**

In order to achieve a successful pregnancy, it seems to be necessary the simultaneous adoption of embryonic development and endometrial status during a receptive period known as the implantation window (Miravet-Valenciano et al., 2015).

PIF raises the implantation window and endometrial embryo receptibility, creating a pro-inflammatory situation that promotes embryo adhesion, and regulates apoptosis before the implantation, the responsibility of decidua in the first trimester (Paidas et al., 2010). In this regard, it has been demonstrated the improved embryo receptivity induced by sPIF on decidualized human endometrial stromal cells (HESCs, an implantation model), as well as in decidua in the first trimester (Barnea et al., 2003). The sPIF modulates integrins (crucial pro-implantation biomarkers in non-pregnant endometrial cells) expression, upregulates the expression and discharge of the pro-inflammatory ligands in HESCs. It finally asserts implantation by raising the secretions of amphiregulin, epiregulin and FGFs while diminishing proliferation promoter - betacellulin expression (Barnea et al., 2012a).

**Trophoblast invasion**

Placenta as well as implantation is a key determinant of pregnancy success [30]. The ideal trophoblast invasion of the maternal spiral arteries can supply fetal oxygen and nutrient needs as poor invasion or excessive invasion, leading to obstetrics complications for the mother. PIF can produce a pro-tolerance milieu by enhancing both intracellular expression and surface expression levels of some HLA class-I such as HLA-G, HLA-E, and HLA-C in dose and time-dependent paths in cytotrophoblastic JEG-3 cells (Hakam et al., 2017). Therefore, trophoblast invasion can be used to balance the needs of the fetus that should be provided by the mother and protect the mother from such invasion (McFadyen, 1989; Anin et al., 2004). This process that is regulated by matrix metalloproteinase (MMP) activity, alpha v, and alpha 1 integrin expressions (Moinidjie et al., 2014) can facilitate trophoblast invasion either in vitro or in-vivo by PIF (Duzyj et al., 2010; Stamatkin et al., 2011a;b). Pro invasive or the positive regulatory effects of PIF in extravillous trophoblasts were associated with 1) the increasing of MMP9 activity, and 2) lower expression levels of tissue metalloproteinase-1 (TIMP1) inhibitor. The invasive function of PIF is found to be performed through the mitogen-activated protein kinase (MAPK), phosphoinositide-3-kinase (PI3K), Janus kinase signal transducer and transcription (JAK-STAT) signaling pathways activator (Damsky et al., 1994; Staun-Ram et al., 2004; Knöfler, 2010). Taken together, PIF can be engaged in pathological pregnancies defined as incommensurate or extreme trophoblast invasion.

**Regulation of systemic immunity**

PIF has dual effects in human peripheral blood mononuclear cells (PBMC), minimally affecting innate immunity (Barnea et al., 2012b). In other words, PIF/sPIF can attach to activated PBMCs, resulting in immune tolerance without suppression (Roussev et al., 2013), it also inhibits mixed lymphocyte reaction (MLR) extension in those cells, leading to a T helper 2 (Th2) cytokine bias while maintaining the T helper 1 (Th1) response, causing a remarkable decrease in macrophage penetrations. PIF also reduced the pro-inflammatory expression levels of adhesion molecules, cytokines, and chemokines in the plaque, also reducing circulating Interferon gamma (IFN-γ) (Chen et al., 2016). PIF directly regulates natural killer (NK) cell activity (Barnea et al., 2012b; Roussev et al., 2013; Barnea et al., 2016a). Low-dose PIF is efficient in NK cells toxicity reduction by down-regulating the expression levels of CD 69 (Roussev et al., 2013). The advanced regulatory effects of PIF on the PKC/PI3K phosphorylation pathways was suppressed in the presence of Toll-like receptor 4 (TLR4) siRNA (Hoebe et al., 2003).

PIF operates on macrophages downstream of the lipopolysaccharides cluster definition 14 (LPS-CD14), TLR4, myeloid differentiation protein 2 (MD2) complex communicating with myosin-9, thymosin-α1 and 14-3-3 eta protein objects (Barnea et al., 2016a). Reports on LPS-activated macrophages indicated that PIF has the competence to reduce inducible nitric oxide synthase (iNOS2); in addition, the nitric oxide secretion revealing the protection against graft versus host disease development (Azar et al., 2013; Chen et al., 2016).

**PIF and pregnancy disorders**

RPL is associated with several factors (anatomic, genetic, and hematologic abnormalities). Immune defects represent a major causing factor. Maternal circulating PIF, as well as the administration of sPIF, regulates systemic immunity, protects the embryo development and decreases circulating NK cells cytotoxicity in women with RPL (Christiansen, 2013). Accordingly, PIF deficiency negatively impacts on pregnancy success resulting in RPL; however, sPIF can modulate pregnancy outcome leading to a significantly reduced incidence of recurrent implantation failure and RPL (Kumar & Mahajan, 2013).

sPIF influences ectopic endometrial tissues of women with endometriosis by increasing the FoxP3 mRNA levels in ectopic endothelial cells, resulting in a significant decrease in Tregs of the patient’s peripheral blood when compared to controls. On the contrary, the rate of Treg increased in the peritoneal fluid of those women suffering endometriosis (Olkowska-Truchanowicz et al., 2013). Therefore, the evidence reported by some researchers suggests that PIF expression, as a differential immune modulatory system, might mediate an immune privilege for endometriotic lesions (Olkowska-Truchanowicz et al., 2013; Sbracia et al., 2017).
Preeclampsia is a unique pregnancy disorder, with its pathophysiology beginning early in pregnancy, while its clinical manifestations usually occur in the middle to the late gestational age, and it should be effectively implemented at the beginning of pregnancy (Redman & Sargent, 2005). It is established that the PIF secreted early by viable embryos and then its interaction with its host-mother provided one of the potential mechanisms against preeclampsia (Barnea et al., 2016b).

Furthermore, PIF can prevent developmental disorders by modulating the uterine environment in the first trimester of pregnancy and also it can have a role in reducing the frequency of developing post-natal disorders (Duzy et al., 2014).

**PIF and autoimmune disease (AD)**

Rheumatoid arthritis (RA) and juvenile diabetes mellitus (JDM) are AD diseases positively affected in pregnancy with an improvement of patients symptoms in the first trimester until term (Tandon et al., 2006). In contrast, some AD disorders defined as Lupus, Crohn’s disease and ulcerative colitis are not affected by pregnancy unless they are diagnosed as severe diseases (Tincani et al., 2006; Cornish et al., 2007).

Some evidence points to the potential role of several factors; changing in some reproductive hormones levels, such as estrogen, and hCG increases the number of regulatory T cells (Treg), known to be involved in fighting AD, though these conflicting results suggest that these are not major participants in AD remission either (Langer-Gould et al., 2006; Sargent et al., 2006).

PIF has unique immune-modulatory properties, beyond pregnancy, for the prevention of ADs such as MS, and JDM, as well as preventing the development of graft-versus-host disease (GVHD) following semiallogeneic transplant in preclinical models (Barnea, 2007). We know that PIF therapy could improve hematopoietic recovery and attenuate the production of systemic inflammatory cytokines after sub-lethal radiation exposure (Shainer et al., 2016). The sPIF analog was found to be a good representative with natural PIF action, mediated peripheral immune cells to achieve tolerance without immune suppression as a beneficial agent in autoimmune models in the nonpregnant models (Barnea; 2007; Than et al., 2007; Weiss et al., 2011).

The short-term administration of sPIF can prevent the progression of JDM in the diabetic mouse model through maintaining pancreatic islet function (Weiss et al., 2011). In the case of atherosclerosis, PIF is a strong immunomodulatory drug candidate for immune therapy as well as its prevention without affecting circulating lipids (Chen et al., 2016).

In GVHD, PIF diminished skin ulceration and colon ulceration as well as liver inflammation while preserving positive graft vs. leukemia effects (Azar et al., 2013).

**CONCLUSION**

All clinical studies show that PIF has both local and systemic effects; it can create an integrated development environment for the treatment of various inflammation conditions, along with tackling developed disease.

**CONFLICT OF INTEREST**

All authors declare no financial conflict of interests.

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**REFERENCES**

Azar Y, Shainer R, Almoji-Hazan O, Bringer R, Compton SR, Paids M, Barnea ER, Or R. Preimplantation factor reduces graft-versus-host disease by regulating immune response and lowering oxidative stress (murine model). Biol Blood Marrow Transplant. 2013;19:519-28. PMID: 23266739 DOI: 10.1016/j.bbmt.2012.12.011

Barnea E, Lahijani KI, Roussev R, Barnea JD, Coulam CB. Use of lymphocyte platelet binding assay for detecting a preimplantation factor: a quantitative assay. Am J Reprod Immunol. 1994;32:133-8. PMID: 7880393 DOI: 10.1111/j.1600-0897.1994.tb01103.x

Barnea E, Gonzalez Perez RR, Leavis PC, inventors. New assays for preimplantation factor and preimplantation factor peptides. Patent WO2003004601A2. 2003 Jan 16. Available at: https://patents.google.com/patent/WO2003004601A2/en

Barnea ER. Applying Embryo-Derived Immune Tolerance to the Treatment of Immune Disorders. Ann N Y Acad Sci. 2007;1110:602-18. PMID: 17911476 DOI: 10.1196/annals.1423.064

Barnea ER, Kirk D, Paids M. Preimplantation factor (PIF) promoting role in embryo implantation: increases endometrial integrin-α2β3, amphiregulin and epiregulin while reducing betacellulin expression via MAPK in decidua. Reprod Biol Endocrinol. 2012a;10:50. PMID: 22788113 DOI: 10.1186/1477-7827-10-50

Barnea ER, Kirk D, Ramu S, Rivnay B, Roussev R, Paids MJ. PreImplantation Factor (PIF) orchestrates systemic antiinflammatory response by immune cells: effect on peripheral blood mononuclear cells. Am J Obstet Gynecol. 2012b;207:313.e1-11. PMID: 23021695 DOI: 10.1016/j.ajog.2012.07.017

Barnea ER, Lubman DM, Liu YH, Absalon-Medina V, Hayrabedyan S, Todorova K, Gilbert RO, Guingab J, Barder TJ. Insight into PreImplantation Factor (PIF*) mechanism for embryo protection and development: target oxidative stress and protein misfolding (PDH and HSP) through essential RIPK binding site. PLoS One. 2014;9:e100263. PMID: 24983882 DOI: 10.1371/journal.pone.0100263

Barnea E, Almoji-Hazan O, Or R, Mueller M, Ria F, Weiss L, Paids MJ. Immune regulatory and neuroprotective properties of preimplantation factor: From newborn to adult. Pharmacol Ther. 2015;156:10-25. PMID: 26546485 DOI: 10.1016/j.pharmthera.2015.10.008

Barnea, ER, Vialard F, Moindjie H, Ornaghi S, Dieudonne MN, Paids MJ. PreImplantation Factor (PIF*) endogenously prevents preeclampsia: Promotes trophoblast invasion and reduces oxidative stress. J Reprod Immunol. 2016a;114:58-64. PMID: 26257082 DOI: 10.1016/j.jri.2015.06.002
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Barnea ER, Hayrabadyan S, Todorova K, Almogi-Hazan O, Or R, Guingab J, McElhinney J, Fernandez N, Barder T. PreImplantation factor (PIF*) regulates systemic immunity and targets protective regulatory and cytotoxic interleukin proteins. Immunobiology. 2016;221:778-93. PMID: 26944449 DOI: 10.1016/j.imbio.2016.02.004

Chen YC, Rivera J, Fitzgerald M, Hauzdinger C, Ying YL, Wang X, Todorova K, Hayrabadyan S, Barnea ER, Peter K. PreImplantation factor prevents atherosclerosis via its immunomodulatory effects without affecting serum lipids. Thromb Haemost. 2016;115:1010-24. PMID: 26842698 DOI: 10.1160/TH15-08-0640

Christiansen OB. Reproductive immunology. Mol Immunol. 2013;55:8-15. PMID: 23062611 DOI: 10.1016/j.molimm.2012.08.025

Cornish J, Tan E, Teare J, Teoh TG, Rai R, Clark SK, Tekkis PP. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. Gut. 2007;56:830-7. PMID: 17185356 DOI: 10.1136/gut.2006.108324

Coulam CB, Roussev RG, Thomason EJ, Barnea ER. PreImplantation factor (PIF) predicts subsequent pregnancy loss. Am J Reprod Immunol. 1995;34:88-92. PMID: 8526994 DOI: 10.1111/j.1600-0897.1995.tb00923.x

Damsky CH, Librach C, Lim KH, Fitzgerald ML, McMaster MT, Janatpour M, Zhou Y, Logan SK, Fisher SJ. Integrin switching regulates normal trophoblast invasion. Development. 1994;120:3657-66. PMID: 7529679

Duzyj CM, Barnea ER, Li M, Huang SJ, Krikun G, Paidas MJ. PreImplantation factor promotes first trimester trophoblast invasion. Am J Obstet Gynecol. 2010;203:402.e1-4. PMID: 20708167 DOI: 10.1016/j.ajog.2010.06.000

Duzyj CM, Paidas MJ, Jebrailey L, Huang JS, Barnea ER. PreImplantation factor (PIF*) promotes embryotrophic and neuroprotective decidual genes: effect negated by epidermal growth factor. J Neurodev Disord. 2014;6:36. PMID: 26085845 DOI: 10.1186/1866-1955-6-36

Goodale LF, Hayrabadyan S, Todorova K, Roussev R, Ramu S, Stamatkin C, Coulam CB, Barnea ER, Gilbert RO. PreImplantation factor (PIF) protects cultured embryos against oxidative stress: relevance for recurrent pregnancy loss (RPL) therapy. Oncotarget. 2017;8:32419-32. PMID: 28423690 DOI: 10.18632/oncotarget.16028

Gopichandran N, Leese HJ. The effect of paracrine/autoimmune interactions on the in vitro culture of bovine preimplantation embryos. Reproduction. 2006;131:269-77. PMID: 16452720 DOI: 10.1530/rep.1.00677

Hakam MS, Miranda-Sayago JM, Hayrabadyan S, Todorova K, Spencer PS, Jabeen A, Barnea ER, Fernandez N. PreImplantation Factor (PIF) Promotes HLA-G, -E, -F, -C Expression in JEG-3 Choriocarcinoma Cells and Endogenous Progesterone Activity. Cell Physiol Biochem. 2017;43:2277-96. PMID: 29073617 DOI: 10.1159/000484378

Hoebe K, Du X, George P, Janssen E, Tabeta K, Kim SO, Goode J, Lin P, Mann N, Mudd S, Crozat K, Sovath S, Han J, Beutler B. Positional cloning of LPS2, a key transducer of MyD88-independent TLR signaling. Nature. 2003;424:743-8. PMID: 12872135 DOI: 10.1038/nature01889

Knöfler M. Critical growth factors and signalling pathways controlling human trophoblast invasion. Int J Dev Biol. 2010;54:269-80. PMID: 19876833 DOI: 10.1387/ijdb.082769mk

Kumar P, Mahajan S. Preimplantation and postimplantation therapy for the treatment of reproductive failure. J Hum Reprod Sci. 2013;6:88-92. PMID: 24082648 DOI: 10.4103/0974-1208.117165

Langer-Gould A, Garren H, Slansky A, Ruiz PJ, Steinman L. Late pregnancy suppresses relapses in experimental autoimmune encephalomyelitis: evidence for a suppressive pregnancy-related serum factor. J Immunol. 2002;169:1084-91. PMID: 12097417 DOI: 10.4049/jimmunol.169.2.1084

Latham KE. Stress signaling in mammalian oocytes and embryos: a basis for intervention and improvement of outcomes. Cell Tissue Res. 2016;363:159-67. PMID: 25743689 DOI: 10.1007/s00441-015-2124-9

McFadyen IR. Early fetal loss. In: Rodeck C, ed. Fetal Medicine. Oxford: Blackwell Scientific Publishers; 1989. p. 26-43.

Miravet-Valenciano JA, Rincon-Bertolin A, Villela F, Simon C. Understanding and improving endometrial receptivity. Curr Opin Obstet Gynecol. 2015;27:187-92. PMID: 25827647 DOI: 10.1097/GCO.0000000000000173

Moindjie H, Santos ED, Loeuillet L, Gronier H, de Mazancourt P, Barnea ER, Viallard F, Dieudonne MN. Preimplantation factor (PIF) promotes human trophoblast invasion. Biology Biol Reprod. 2014;91:118. PMID: 25232018 DOI: 10.1095/biolreprod.114.119156

Moindjie H, Santos ED, Gouesse R, Swierkowski-Blanchard N, Serazin V, Barnea ER, Viallard F, Dieudonne MN. Preimplantation factor is an anti-apoptotic effector in human trophoblasts involving p53 signaling pathway. Cell Death Dis. 2016;7:e2504. PMID: 27906186 DOI: 10.1038/cddis.2016.382

Mueller M, Zhou J, Yang L, Gao Y, Wu F, Schoeberlein A, Surbek D, Barnea ER, Paidas M, Huang Y. PreImplantation factor promotes neuroprotection by targeting microRNA let-7. Proc Natl Acad Sci U S A. 2014;111:13882-7. PMID: 25205808 DOI: 10.1073/pnas.1411674111

Mueller M, Schoeberlein A, Zhou J, Joerger-Messleri M, Oppliger B, Reinhart U, Bordey A, Surbek D, Barnea ER, Huang Y, Paidas M. PreImplantation Factor bolsters neuroprotection via modulating Protein Kinase A and Protein Kinase C signaling. Cell Death Differ. 2015;22:2078-86. PMID: 25976303 DOI: 10.1038/cddis.2015.55

Nasr-Esfahani M, Winston NJ, Johnson MH. Effects of glucose, glutamine, ethylenediaminetetraacetic acid and oxygen tension on the concentration of reactive oxygen species and on development of the mouse preimplantation embryo in vitro. J Reprod Fertil. 1992;96:219-31. PMID: 14329593 DOI: 10.1530/jrf.0.0960219

O’Neill C. Evidence for the requirement of autocrine growth factors for development of mouse preimplantation embryos in vitro. Biol Reprod. 1997;56:229-37. PMID: 9002654 DOI: 10.1095/biolreprod56.1.229

J Braz Assist. Reprod. | v.24 | nº2 | Apr-May-Jun/ 2020
Olkowska-Truchanowicz J, Bocian K, Maksym RB, Biłoszewska A, Włodarczyk D, Baranowski W, Żąbek J, Korczak-Kowalska G, Malejczyk J. CD4+ CD25+ FOXP3+ regulatory T cells in peripheral blood and peritoneal fluid of patients with endometriosis. Hum Reprod. 2013;28:119-24. PMID: 23019301 DOI: 10.1093/humrep/des346

Paidas MJ, Krikun G, Huang SJ, Jones R, Romano M, Anunnzio J, Barnea ER. Preimplantation factor (PIF) correlates with early mammalian embryo development-bovine and murine models. Reprod Biol Endocrinol. 2011a;9:63. PMID: 21569635 DOI: 10.1186/1477-7827-9-63

Stamatkin CW, Roussev RG, Stout M, Absalon-Medina V, Ramu S, Goodman C, Coulam CB, Gilbert RG, Godke RA, Barnea ER. Preimplantation Factor (PIF) correlates with early mammalian embryo development-bovine and murine models. Reprod Biol Endocrinol. 2011a;9:63. PMID: 21569635 DOI: 10.1186/1477-7827-9-63

Paidas MJ, Krikun G, Huang SJ, Jones R, Romano M, Anunnzio J, Barnea ER. Preimplantation factor (PIF) correlates with early mammalian embryo development-bovine and murine models. Reprod Biol Endocrinol. 2011a;9:63. PMID: 21569635 DOI: 10.1186/1477-7827-9-63

Stamatkin CW, Roussev RG, Stout M, Coulam CB, Triche E, Godke RA, Barnea ER. Preimplantation factor negates embryo toxicity and promotes embryo development in culture. Reprod Biomed Online. 2011b;23:517-24. PMID: 21900046 DOI: 10.1016/j.rbmo.2011.06.009

Stamatkin CW, Roussev RG, Stout M, Coulam CB, Triche E, Godke RA, Barnea ER. Preimplantation factor negates embryo toxicity and promotes embryo development in culture. Reprod Biomed Online. 2011b;23:517-24. PMID: 21900046 DOI: 10.1016/j.rbmo.2011.06.009

Takahashi M. Oxidative stress and redox regulation on in vitro development of mammalian embryos. J Reprod Dev. 2012;58:1-9. PMID: 22450278 DOI: 10.1262/jrd.11-138N