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REVIEW ARTICLE

Placental growth factor (PlGF) as an angiogenic/inflammatory switcher: lesson from early pregnancy losses

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Abstract

Placental growth factor (PlGF) is an angiogenic factor which belongs to vascular endothelial growth factor (VEGF) family. In addition to the angiogenic function of PlGF, in some conditions such as preeclampsia and early pregnancy losses, it can induce inflammatory reactions which could be accompanied with reduced angiogenesis. Hence, it is crucial to investigate inflammatory and angiogenic switching states and understand underlying mechanisms. PlGF is expressed in endometrium, placenta and trophoblast cells and is involved in maturation of uterine NK cells. Up-regulation of PlGF directs VEGF to VEGFR-2 and reinforces angiogenesis. However, when VEGF/VEGFR-2 signaling pathway is impaired, PlGF may shift to severe inflammation and cause tissue damages which could lead to early pregnancy losses. Downregulation of PlGF has also been reported in pregnancy complications. In this review, we discussed the role of PlGF in embryo implantation failure and early pregnancy loss and also possible mechanisms regarding the role of PlGF in angiogenic/inflammatory switching in early pregnancy losses. Furthermore, we summarized the effects of various compounds on PlGF expression and briefly talked about its therapeutic potential that may be an opportunity for prevention of pregnancy loss.

Keywords

Early pregnancy loss, embryo implantation failure, placental growth factor, vascular endothelial growth factor

History

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Introduction

Most of the pregnancy losses occur during the early period of gestation when the placenta is established [1,2] and possibly these losses are due to angiogenesis imbalance in different parts of the female reproductive system such as the placenta [3]. Thus, the study of angiogenic factors and its behavior within this period of time seems important and may shed light on mechanisms of pregnancy complications.

Placental growth factor (PlGF) exerts its functions via fms-like tyrosine kinase 1 (Flt-1) receptor [4] and collaborates with vascular endothelial growth factor (VEGF) to reinforce angiogenesis [5]. It has various roles such as induction of vessel growth, proliferation, migration and survival of endothelial cells in different tissues [5–9] and well known as a vital factor for maintaining pregnancy. Moreover, its reduction has been reported in pregnancy-related disorders such as preeclampsia [10]. However, little is known about its exact mode of actions in embryo implantation, early pregnancy and the related failures.

Expression of PlGF has been reported in the endometrium, decidua, placenta, uterine NK cells (uNK cells) and trophoblasts [3,11–18] and it's both angiogenic and inflammatory manners have been considered as crucial factors for successful conception [19]. But in some cases controlled angiogenesis shifts to severe inflammation which may have adverse effects on pregnancy and therefore leads to pregnancy losses [17,20]. In the current study, we reviewed studies regarding the association between PlGF with embryo implantation failure and early pregnancy loss with a focus on gestational period until the end of the first trimester.

Embryo implantation

The early stage of pregnancy known as embryo implantation refers to adherence of blastocyst to the wall of the uterus [21]. In human, 6–10 d after the peak of luteinizing hormone window of implantation coincides with changes in endometrium cells which take the blastocyst closer to the endometrium [22]. Within this period of time, the endometrium becomes vascularized and produces decidual cells which originate from the stromal cells [21].The deciduas can be divided into two parts, decidua basalis (DB) which is located at the basal site of the embryo and is associated with trophoblast and decidua parietalis that is not attached to embryo [23]. After implantation and during the first trimester, decidual tissues are replaced by the placenta [24]. Attachment of blastocyst to the endometrium initiates implantation process. The blastocyst and endometrium have loose and strong connections to each other which known as apposition and adhesion, respectively [24]. First, zona pellucida is removed from the blastocyst by lytic factors during a process called ''hatching'' [24]. Then, trophoblast cells start to penetrate endometrium and differentiate into the new type of cells, syncytiotrophoblasts and cytotrophoblasts [21]. The syncytiotrophoblasts continue penetrating to invading into the uterine stroma. About 2 d after embryo

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implantation, called ''lacunar stage'', syncytiotrophoblasts derived secretions create lacunae in deciduas and associate with the maternal vessels [21]. Following it, villous stage accompanies the establishment of villi [21] and it is the initiation of forming the placenta known as placentation which parallels the increasing in uterine blood flow and angiogenesis [3]. These alterations are needed for regulation of placental vessel construction and adaptation of the maternal vascular system in pregnancy [25,26]. Impaired vascular development may be linked to the reduction of uterine and umbilical blood flow which effects maintaining the pregnancy and may lead to pregnancy complications such as the preeclampsia and abortion [3]. PlGF is one of the important angiogenic factors which involve in early pregnancy angiogenesis as its decline is related to pregnancy complications [27].

Placental growth factor

PlGF is a member of VEGF family and is located on chromosome 14q24 [28–30]. It has four isoforms in which PlGF 2 and 4 have heparin binding domains while PlGF 1 and 3 do not have such domain [30]. PlGF shares the receptor (Flt-1) with VEGF [31], although VEGF and PlGF activate distinct tyrosine residues of Flt-1 [32]. PlGF is involved in vessel growth and promotes the proliferation, migration and survival of endothelial cells [5–9]. PlGF leads to releasing angiogenic factors from macrophages [33] and also it interferes with the activity of dendritic cells and their antigen recognition ability [34,35].

The mode of action of PlGF in stimulation of endothelial cell growth is displacement of VEGF from the Flt-1 by occupying this receptor and thus directing VEGF toward activation of VEGFR-2 [36]. Moreover, PlGF activates Flt-1 and reinforces VEGF/VEGFR-2 signaling via cross-talk with this pathway [32].

Knockout of PlGF gene inhibits vessel growth in adipose tissue, tumors and inflamed tissues [31]. PlGF has been considered as a pathologic factor rather than physiologic as its expression is low in normal tissues while increases in pathological conditions such as inflammation and cancers [31].

PlGF, an angiogenic/inflammatory switching factor

The roles of PlGF in development or restriction of various diseases have been reported. Despite the inert function of PlGF in healthy conditions, its roles in pathological conditions by angiogenic and inflammatory switching mechanism have thoroughly been discussed [31]. Considering the PlGF involvement, the diseases could be divided into two groups: First, included ischemic tissues in which induced expression of PlGF promotes angiogenesis and mononuclear cells mobilization to the ischemic region and thus up-regulation of PlGF is useful for reducing ischemia-induced complications. Some examples of these types of diseases are ischemic cardiovascular disease, skin wound healing and preeclampsia. [5,37–44]. Another group of disorders are known as inflammatory diseases such as atherosclerosis, liver cirrhosis, arthritis and cancers in which the role of PlGF is infiltration of macrophages and T-cells and initiation of severe inflammation [45]. In spite of the first group in which angiogenesis was accompanied by the inflammatory process, in the second group severity of inflammation is excessively increased and induces tissue damage. Hence, down-regulation of PlGF could ameliorate symptoms of these disorders [31].

PlGF in embryo implantation and early pregnancy

The expression of PlGF has been detected in endometrial epithelium and syncytiotrophoblasts in lacunar stage and also in cytotrophoblasts and stroma cells in the villous stage [12]. Coinciding with the vascularization in implantation sites, PlGF expression is increased by the invasion of extravillous trophoblast (EVT) into DB [15]. Endometrial/desidual PlGF is produced mainly by uNK cells and is involved in maturation of these cells [46]. Circulation NK cells penetrate into the endometrium by chemokines and convert to uNK cells (CD16-) that are involved in implantation receptivity [47]. If implantation takes place, endometrium NK cells switch to uNK cells by the mediation of IL-15, and this alteration leads to the production of angiogenic factors such as PlGF by them [48,49]. Also, a spiral arterial modification that is necessary for maternal–fetal nutrient and waste exchanges is related to mononucleate uNK cells and reduced population of these cells has been reported in PlGF null mice [46]. Moreover, abnormal elevation of NK cells may lead to oxidative stress which is associated with recurrent spontaneous abortion (RSA) [50]. Santi et al. [16] have reported that the expression of PlGF in good endometrium with subsequent pregnancy was significantly higher than bad endometrium without success to pregnancy. However, we recently evaluated follicular fluid levels of PlGF among pregnant and non-pregnant women and did not observe any significant differences [51].

When we reviewed studies regarding the roles of PlGF in embryo implantation, we found out that angiogenic and also inflammatory switch are mentioned in these reports. PlGF expression increases after embryo implantation and also with gestational age and fortifies angiogenesis which leads to a good outcome. However, up-regulation of PlGF also occurs when the pathological condition causes switching the controlled angiogenesis to severe inflammation and may lead to damage tissues and pregnancy losses. We summarized these studies in Table 1.

Table 1. Up/down-regulation of PlGF in embryo implantation and early pregnancy.

PlGF	Comments	References
Up-regulation		
Good outcome	Endometrial PlGF expression significantly increases during early pregnancy.	[3]
	Endometrial PlGF expression is significantly higher in good endometrium and leads to pregnancy compared to bad endometrium which not leads to pregnancy.	[16]
Bad outcome	Expression of PlGF is increased in arrested implantation sites compared to healthy sites.	[17]
	Desidual NK cells have a higher PlGF expression in high-risk pregnancies.	[18]
	Women with high progesterone levels have higher endometrial PlGF expression.	[11]
	PlGF overexpression in fetal T cells leads to angiogenesis failure and gestational loss.	[20]
Down-regulation		
	Expression of PlGF in serum and trophoblast is decreased during 5–12 weeks of pregnancy in cases of ectopic pregnancy, missed abortion, miscarriage, preeclampsia and early pregnancy loss.	[14,64–68]

Up-regulation of PlGF and embryo implantation

The expression of PlGF is higher in the lymphocytes of arrested implantation sites than normal sites [17] and it has been

demonstrated that desidual NK cells have a higher PlGF expression in high-risk pregnancies compared to low-risk pregnancies according to the uterine artery resistance [18]. It has been reported that high progesterone levels before oocyte retrieval is associated with low implantation rate [52–54]. For clarification possible mechanisms, Chen et al. [11] have assessed endometrial expression of PlGF in women with high and low serum progesterone levels on the day of hCG injection and they have observed higher PlGF expression in the endometrial glandular and stromal cells in those with high progesterone levels. They suggested that progesterone elevation may decline implantation rate through an imbalance in angiogenic factors notably, PlGF. Progesterone exerts its action via its receptors on the endometrium cells or indirectly through glucocorticoid receptors in uNK cells and possibly elevation of PlGF is a target for progesterone [11].

Kang et al. [20] have shown that overexpression of PlGF in fetal T cells could cause growth retardation, insufficient angiogenesis and decrease of regulatory T cells that may lead to gestational loss and also activates pathways such as Braf, ERK and HIF-1α signaling in the placenta. This is another important study regarding the uncontrolled switching of the angiogenesis to inflammation via PlGF that causes pregnancy loss and angiogenic failure in embryo development [20].

The possible explanation for these adverse outcomes of elevated PlGF in pregnancy is that arrested implantation sites switch their states from controlled angiogenesis to inflammation. In implantation sites, if increased PlGF levels coincide with the VEGF elevation, we could infer that elevated levels of PlGF increases production of VEGF and causes displacement of VEGF from the Flt-1 by occupying this receptor and directing it toward activation of VEGFR-2 which finally reinforces angiogenesis [5,17]. However, in studies which have reported adverse effects of high PlGF on pregnancy [11,17,18,20], probably elevation of PlGF did not accompany with the increased levels of VEGF as decreased levels of VEGF expression has been reported in the cases with abortion [55,56]. Therefore, loss of VEGF function in arrested implantation sites, instead of cross talk between VEGF/VEGFR-2 and PlGF/Flt-1 pathways leads to switching angiogenesis to the inflammatory pathway (Figure 1a). However, exact mechanisms are remained to be clarified.

On the other hand, correlation of NOS3 and PlGF has been reported in the endometrium of normal pregnant women [3,57]. It is well known that NOS3 is downstream of VEGF/VEGFR-2 signaling pathway [58] and it is obvious that such correlation has been observed when this pathway is active. Therefore, it could hypothesize that in the arrested implantation sites and pregnancy loss cases, the correlation between PlGF and NOS3 are impaired which leads to insufficient angiogenesis.

Adrenomedullin2 (ADM2) is expressed in uterus and placenta [59,60] and its plasma levels increase during pregnancy [61]. ADM2 has vasodilatory effects and its blocking causes fetoplacental growth restriction [62]. Also, administration of ADM2 antagonist into implantation sites in the rat decreases PlGF, NOS3 and VEGF expressions in placenta and also serum levels of estradiol and progesterone [63]. Therefore, ADM2 possibly up-regulates PlGF, VEGF and NOS3 in the implantation sites and reinforces angiogenesis in early pregnancy (Figure 1b). However, effects of ADM2 on PlGF, NOS3 and VEGF in inflammatory conditions especially resulted pregnancy loss have not been investigated yet.

Downregulation of PlGF

Decreased serum and trophoblast PlGF levels in the early stage of pregnancy has been seen in some pregnancy-related complications such as ectopic pregnancy, missed abortion, miscarriage and preeclampsia (5–12 weeks) [14,64–68]. But in the early stage of normal pregnancies, PlGF levels increase significantly [3]. Furthermore, decreased PlGF expression has been reported in the endometrium and endothelial cells of arrested implantation sites in which VEGF expression also was declined in the early pregnancy [17]. On the other hand, oxidative stress which refers to an imbalance between oxidant and antioxidant capacity is associated with miscarriage and early pregnancy losses [69]. It is believed that hypoxia downregulates PlGF and up-regulates sFlt-1 in the early stage of pregnancy [70,71] also it has been reported that expressions of superoxide dismutase 1 (SOD-1) and heme oxygenase 1 (HO-1) increase in parallel with PlGF by increasing the gestational age [14]. Besides the reduction of these antioxidant enzymes as well as PlGF has been demonstrated in women with preeclampsia [72]. Thus, it can be concluded that hypoxic conditions in early pregnancy may induce reduction of PlGF (Figure 1c) and consequently the antioxidant enzymes. Such reductions in angiogenic and antioxidant factors may lead to pregnancy complications such as miscarriage and preeclampsia. In consistence with the association of PlGF and antioxidant enzymes it has been demonstrated that antioxidant supplementation increases PlGF, HO-1 and SOD-1 levels in pregnant women with low antioxidant status [72,73].

Regulation of PlGF expression by different effectors

Effects of various factors on PlGF expression are listed in Table 2. It has been indicated that higher IFN-gamma levels in trophoblasts, endometrium and lymphocytes of arrested implantation sites in the early pregnancy, may be responsible for increased and decreased levels of PlGF in lymphocytes and endometrium, respectively [17]. It has been reported that there is a positive correlation between TNF-alpha and PlGF expressions in endothelial cells [17]. Kato et al. [74] have recently reported that up-regulation of PlGF in the trophoblast cells of healthy pregnant women who had an artificial abortion was under the influence of IFN-gamma and TNF-alpha.

It has been shown that keratin regulates vascular remodeling in the decidua and placenta. Its deficiency may cause severe hypoxia and decrease the PlGF signaling in the EVT [75]. Also, keratin deficiency causes elevation of uNK cells that are one of the important sources for PlGF [75]. Furthermore, abnormal elevation of uNK cells has been previously reported in PlGF null mice [46] and another study has emphasized that abnormal elevation of these cells could cause oxidative stress and finally RSA [50]. Therefore, keratin deficiency affects amounts of uNK cells and PlGF signaling and consequently causes complicated pregnancies [75].

Anti-b2-glycoprotein I (anti-b2-GPI) antibody has been observed in the serum of recurrent abortion cases and has also the suppressive effect on trophoblast cells [76]. Ichikawa et al. [77] have conducted a study to clarify possible mechanism regarding these observations and they have suggested that anti-b2-GPI antibody binds to trophoblast cell-surface phosphatidylserine and thereby suppresses PlGF production from these cells which may consequently cause pregnancy losses. There are some other factors such as folate [78], TLR4 ligands [74] and cadmium [79] which possibly are involved in regulation of PlGF expression; however, further investigations are required to clarify exact PlGF expression regulators and their mechanism.

Antioxidant supplementation increases PlGF expression in the plasma at 8–12 weeks of pregnancy [72] and reduces the incidence of preeclampsia among them [72].

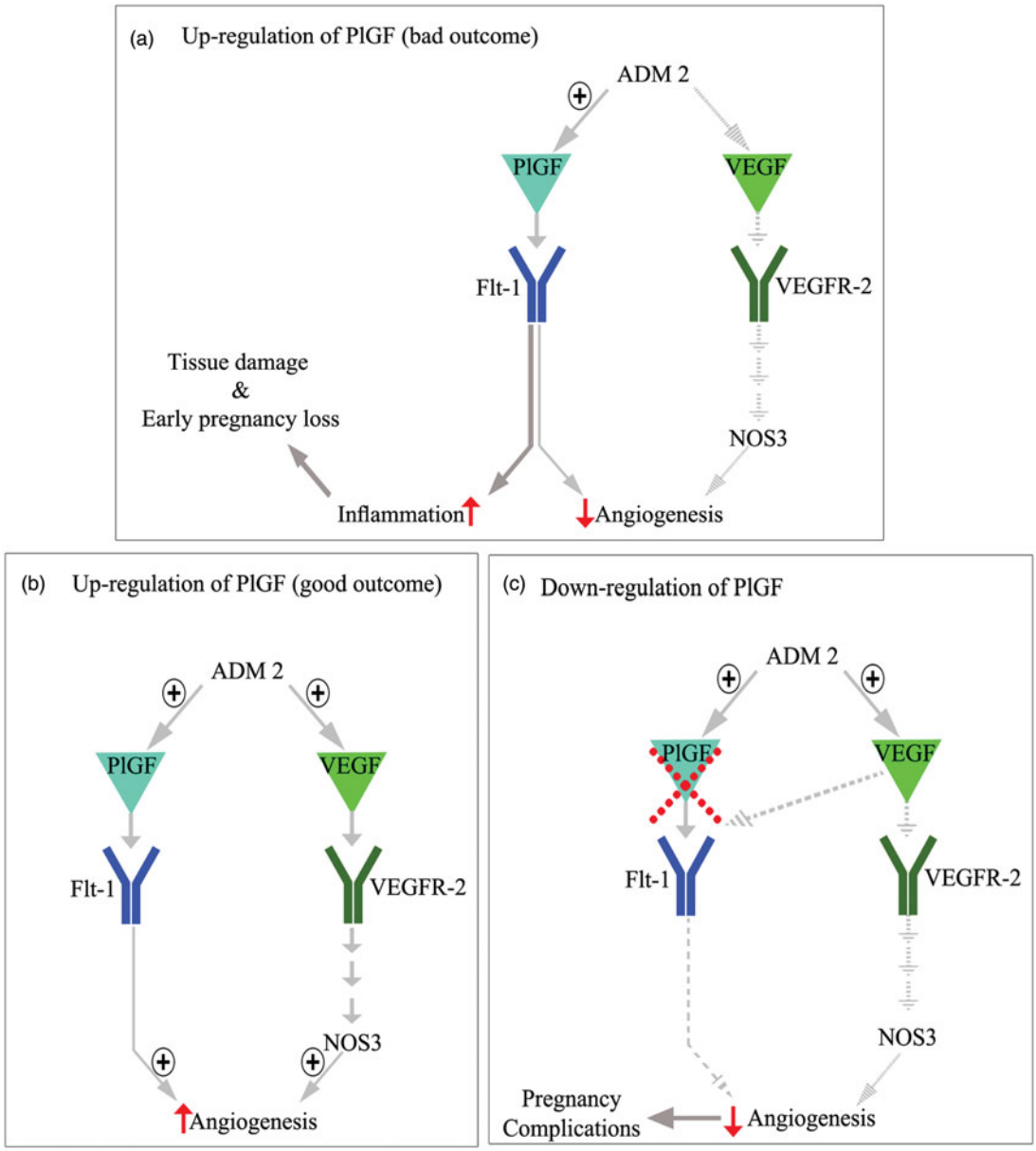

Figure 1. Proposed mechanisms for regulation of PlGF in early pregnancy and related losses. (a) Impairment of VEGF/VEGFR-2 pathway shifts PlGF/Flt-1 pathway to severe inflammation that may cause tissue damages and early pregnancy losses. (b) ADM2 up-regulates both VEGF and PlGF expressions and consequently causes initiation of both distinct pathways (PlGF/Flt-1 and VEGF/VEGFR2) which reinforces angiogenesis. (c) Downregulation of PlGF/Flt-1 pathway leads to impair directing the VEGF to VEGFR2 and consequently reduces angiogenesis that can cause pregnancy complications. PlGF: placental growth factor; VEGF: vascular endothelial growth factor; Flt-1: fms-like tyrosine kinase 1; ADM2: adrenomedullin2, VEGFR-2: vascular endothelial growth factor receptor-2.

PlGF as a possible therapeutic target

PlGF blockade in order to the reduction of angiogenesis and inflammation in cancer treatment has been carried out by gene inactivation, anti-PlGF antibodies and PlGF/Flt-1 peptide antagonists [80].

Clinical deployment of anti-PlGF antibodies for the treatment of cancer has not shown any side effects and also dose-limiting toxicities [81]. On the other hand, PlGF gene delivery and overexpression had ameliorative effects in nervous and vascular systems, skeletal muscle and skin [82–86]. Thus, gain or loss of PlGF function depends on the diseases and type of involved tissues could possibly be effective. We discussed up and downregulation of PlGF in different conditions (listed in Table 1) and until now no study has been conducted regarding the therapeutic functions of PlGF in embryo implantation and early pregnancy except study of Spradley et al. [87] which have recently designed to unravel effects of PlGF therapy on reduction of sFlt-1 levels and ischemia-driven hypertension. It is believed that placental ischemia causes an angiogenic imbalance that may be associated with hypertension and reduced uterine perfusion pressure [13,88]. In addition, sFlt-1 elevation is another consequence of hypertension response in women with preeclampsia that antagonizes PlGF angiogenic actions [89]. So, they have concluded that PlGF therapy inhibits progression of hypertension and be able to declines sFlt-1 levels. They have suggested that PlGF therapy may have lesser side effects than VEGF administration, because VEGF in addition to the Flt-1, binds to VEGFR-2 and could lead to higher vascular permeability and edema. However, in contrast to VEGF, PlGF only binds to Flt-1 and its administration is safer and has less off-target effects [87].

Table 2. Regulation of PlGF expression by various factors.

PlGF	Factors	Tissues/Cells	References
Up-regulation			
	Estradiol	Endometrium	[57]
	Progesterone	Endometrium	[11]
	Keratin	Placenta	[77]
	Folate	Desidual	[78]
	Adrenomedullin 2	Placenta	[63]
	Cadmium	HEEC + endometrial stromal cells	[79]
	TNF-α	Trophoblasts	[74]
	IFN-x03B3	Trophoblasts	[74]
	Epherin B2	Trophoblasts	[90]
	Antioxidant supplementation	Plasma	[72]
Down-regulation			
	Anti-β2-glycoprotein I (anti-β2-GPI) antibody	Trophoblasts	[77]
	Cadmium	HEEC	[79]
	TLR4 ligands	Trophoblasts	[74]

HEEC, human endometrial endothelial cells; TNF-α, tumor necrosis factor alpha; IFN-x03B3, interferon-gamma; TLR4, toll-like receptor 4.

Taken together, it seems that PlGF therapy is a novel opportunity to reduce ischemia-induced early pregnancy failures and it would be applicable for clinical uses. However, more investigations are needed to clarify its clinical values.

Conclusion and perspectives

In spite of inert roles of PlGF in physiological conditions, it is involved in embryo implantation and early pregnancy as its functions could be categorized into two angiogenic and inflammatory switch mechanisms. Its collaboration with VEGF reinforces angiogenesis, while impairment of VEGF/VEGFR-2 signaling pathways shifts PlGF to inflammatory pathways that possibly leads to arrest implantation sites and thereby pregnancy losses. However, little is known about these mechanisms and further research is needed to understand how and when PlGF shifts to the severe inflammatory states along its angiogenic functions. For future works, it is better to consider collaboration of PlGF with VEGF and NOS3 in the samples of women who have had an early pregnancy loss. Furthermore, ADM2 that regulates expression of these factors could open up new roads for a better understanding of underlying mechanisms in early pregnancy losses. If we can unravel PlGF inflammatory and angiogenic switch mechanisms, we would be able to implement PlGF therapy on different conditions and test its clinical values in the prevention of gestational losses.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. The authors are not directly employed by the Government of Iran. Mohammad Nouri is an academic member of Tabriz University of Medical Sciences. Other authors are students in Clinical Biochemistry.

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