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REVIEW

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The role of mediating factors involved in angiogenesis during implantation

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Abstract

Angiogenesis is a critical component of normal implantation and placentation and underlines the importance of vascularization in early pregnancy. Differentiated expression of angiogenesis factors in different decision tissues during different stages of implantation, indicates their involvement in the regulation of vascular remodeling and angiogenesis. Disorders in vascular development may play a role in the pathogenesis of recurrent abortions. The success of implantation, placentation and subsequent pregnancy evolution requires coordination of vascular development and adaptations at both sides of the maternal–fetal interface. The human implantation process is a continuous process, which begins with the apposition and attachment of the blastocyst to the apical surface of the luminal endometrial epithelium and continues throughout the first trimester of pregnancy until the extravillous trophoblast invades and remodels maternal vascularization. Numerous regulatory molecules play functional roles in many processes, including preparation of the endometrial stroma (decidualization), epithelium for implantation, control of trophoblastic adhesion and invasion. These regulatory molecules include cytokines, chemokines, and proteases, many of which are expressed by different cell types, having slightly different functions as the implant progresses.

Keywords: angiogenesis, pregnancy loss, vascular endothelial growth factor, placental growth factor, tumor growth factor-beta.

Introduction

The blastocyst implantation process represents a series of reciprocal interactions between the blastocyst and maternal tissues. The purpose of this process is to not only provide the necessary nutrition for the development of the embryo by connecting the vascular system of the embryo to the maternal circulation, therefore ensuring a physiologically and endocrinologically appropriate environment until the formation of the placenta; but to likewise protect the embryo from any attack by the maternal immune system [1].

The implantation process has often been referred to as nesting, the term coming from the Latin word "nidus", signifying a nest or breeding site, with the blastocyst implanting at the antimesometrial pole. Synchronization between the development of the embryo and the preparation of the uterus is essential, as it would otherwise lead to the failure of the implantation process, it being a necessary condition for the embryo's subsequent development.

An in-depth understanding of embryonic development during both the pre-implantation and implantation process will help ensure the identification of aberrant mechanisms leading to pregnancy loss, as well as offer new strategies for improving fertility rates along with preventing further complications related to pregnancy. The mechanisms that coordinate blastocyst development and maternal uterine receptivity are not yet fully known.

Angiogenesis is a key component of normal implantation and placentation, with the vascular component playing an important role in the early stages of pregnancy. This hypothesis was confirmed by studies done on mice. Thus, a single dose of an antiangiogenic compound was sufficient to inhibit the process of angiogenesis, either before or shortly following implantation, which ultimately resulted in the disruption of the placenta and resorption of all embryos [2].

Studies conducted in the last two decades have pointed to the involvement of numerous proteases, metabolites, ions, growth factors, cytokines, matrix proteins which can modulate the angiogenesis/vasculogenesis processes either positively or negatively.

The mediating factors of angiogenesis can be grouped into:

▪ Cells: trophoblasts, uterine natural killer (uNK) cells, B- and T-lymphocytes, macrophages;

▪ Soluble products: vascular endothelial growth factor (VEGF), placental growth factor (PlGF), fibroblast growth factors (FGFs), transforming growth factor-beta (TGF-β), human chorionic gonadotropin (hCG), insulin-like growth factor-II (IGF-II), angiopoietin (Ang) and its receptors.

Trophoblast

The trophoblast constitutes the interface between fetal and maternal tissues, hence playing a key role in promoting angiogenesis during implantation. The trophoblast is a source of angiogenic growth factors. Zooming in on the placenta at approximately 21 days, the cytotrophoblast and syncytiotrophoblast at the level of chorionic villi produce numerous angiogenic factors, as well as their corresponding receptors [3, 4].

During the implantation process, the cytotrophoblast migrates to the maternal decidua, where it differentiates into the extravillous trophoblast which, in turn, will express various angiogenic factors along with their receptors [5]. Several studies have shown that giant trophoblastic cells acquire unique features during differentiation and can synthesize a variety of angiogenic, vasoactive and hormonal factors [6–8].

uNK cells

uNK cells are phenotypically and functionally different from those found in circulating blood (pNK). They play a crucial role in the production of integrins, which allow for their migration, decidualization, and endometrial invasion. In the decidua and under the action of progesterone, maturation of pre-uNK cells into granular uNK cells containing many leukocytes from the implantation site takes place. These cells serve as an important source of angiogenic and angiomodulatory factors, of cytokines (Ang-1, Ang-2), growth factors (PlGF, VEGF-C), interleukin (IL)-18, interferon-gamma (IFN-γ), which are essential for the successful implantation and development of the placenta [9].

B- and T-lymphocytes

The human decidua incorporates T-lymphocytes and, to a lesser extent, B-lymphocytes, which are heavily involved in the immunological acceptance of the embryo [10]. Information regarding the roles of T-cells and/or B-cells in the process of angiogenesis, during implantation, is limited. It is, however, known that B-cells express *c-Myc* proto-oncogenes, which stimulate the production of VEGF and therefore influence the process of angiogenesis [11].

In contrast to B-cells, T-cells have been studied for their involvement in successful implantation and subsequent pregnancy. This has been observed mainly from an immunological point of view, and less relating to their contribution to the angiogenic process. T-helper cells are involved in angiogenesis by way of producing cytokines that control endothelial cell proliferation, apoptosis, and migration, modulating the process of angiogenesis either positively or negatively [11].

After implantation, the embryo is surrounded by lymphocytes and macrophages, which will be activated to induce the synthesis of cytokines, such as tumor necrosis factor-alpha (TNF-α), a pro-inflammatory T-helper 1 (Th1) cytokine which plays a significant role in controlling angiogenesis by way of stimulating the production of angiogenic factors at the decidual level [12]. The function of TNF-α has been extensively studied, highlighting its influence on the inhibition of embryo and fetal development [13], regulation of VEGF production in the first trimester of pregnancy, and indirect modulation of vascular permeability of the placenta and the angiogenic process [14].

Other pro-inflammatory Th1 cytokines that have been studied *in vitro* and marked as being involved in regulating angiogenesis, but in the negative sense, are IFN-γ and IL-12. IFN-γ, specifically when synthesized by lymphocytes, inhibits epithelial cell growth and capillary formation. IL-12 exhibits anti-angiogenic properties, thereby inhibiting the production of VEGF [11]. Both IFN-γ and IL-12 are vital mediators of uNK cells, activating and stimulating their modulatory function, involved in the formation of the maternal spiral artery during pregnancy [15].

Anti-inflammatory T-helper 2 (Th2) cytokines, such as IL-4, IL-5, IL-6, IL-10, IL-13, are associated with the release of human placental lactogen (hPL) and hCG from the trophoblast [16]. Of these cytokines, IL-6 has pro-angiogenic effects, whereas IL-4 can influence endothelial cell function in both a positive and a negative sense [17].

Macrophages

Macrophages are commonly present in the endometrium of non-pregnant women, their number increased in response to insemination [18]. The maternal decidua contains 20–30% macrophages. In addition to these macrophages, the placenta accommodates a distinct variety of macrophages, known as Hofbauer cells. These cells express angiogenic growth factors, such as VEGF and IL-17 [19]. It was also found that Hofbauer cells exhibit immunoreactivity towards the VEGF receptor-1 (VEGFR-1) (also referred to as FLT-1/flt-1, Fms-like tyrosine kinase receptor-1), thus highlighting their involvement in the angiogenesis occurring at the fetal–placental border [20, 21]. Macrophages from the decidua secrete various compounds, such as endothelial growth factor (EGF), TGF-β, platelet-derived growth factor (PDGF), IGFs, FGF [22], which feature pro-angiogenic effects. Furthermore, macrophages have been shown to inhibit angiogenesis through the release of anti-angiogenic mediators, such as the soluble variant of the VEGFR-1 (sVEGFR-1, sFLT-1, sflt-1), a mediator with a key role in pregnancy loss [23].

PlGF

PlGF is a pro-angiogenic growth factor, belonging to the VEGF family [24] and is produced mainly by the trophoblast in four isoforms [25]. PlGF acts on three receptors: neuropilin-1 (NRP-1), neuropilin-2 (NRP-2) and VEGFR-1 [26]. Under hypoxic conditions, PlGF expression decreases in the trophoblast and sVEGFR-1 expression is induced [27]. Studies have demonstrated that PlGF is associated with an increase in placental perfusion at the maternal–fetal interface [28] and PlGF also induces the relaxation of placental vessels *ex vivo*

[15]. PlGF is involved in mediating the molecular and morphological pathways of vasculogenesis and angiogenesis at the level of the placental villi, either directly or indirectly by synergizing with VEGF [29].

FGFs

FGFs are a family of 22 polypeptides with a high affinity for heparin sulfate proteoglycans. They bind to the heparin located on the surface of these structures, thereby being an essential mechanism for intracellular signal transduction. FGFs bind to one or more of the four known receptors (FGFR 1–4) [30]. The significance of these growth factors in mediating angiogenesis during implantation has been insufficiently studied in humans. Only a few isoforms, FGF2, FGF4, FGF7, FGF9, have been investigated during implantation, with evidence of involvement in implantation and during the beginning of pregnancy being highlighted for FGF2/FGFb (also known as basal FGF). FGF2/FGFb was first isolated from human placental tissue and is known as a mitogenic and angiogenic growth factor *in vivo* [31]. *In vitro*, the trophoblast has been shown to produce and release FGF2 in the appropriate culture media [32].

TGF-β

TGF-β is part of a large family of proteins, which perform numerous functions. TGF-β1 protein has been extensively studied, showing involvement in spermatogenesis, ovulation, implantation, trophoblast differentiation, angiogenesis, and immunoregulation at the maternal–fetal interface [33]. *In vitro* studies have shown that TGF-β1 can induce angiogenesis, either directly at the chorioallantoic membrane [34] or indirectly by increasing VEGF expression in the trophoblast [14, 35].

Ogasawara *et al.* have shown that an excessive increase of TGF-β1 may be associated with a higher incidence of spontaneous abortions, explained by the inhibitory action of TGF-β1 on trophoblastic invasion [36]. Studies in mice have demonstrated that null mutations of TGF-β1 contribute to an increase in mortality due to defects in the vasculogenesis of the yolk sac, high levels of disorganized vessels and, in some cases, absence of vessels and impaired endothelial differentiation [37].

hCG

Beyond its classical effects (within the female reproductive tract), hCG also exhibits significant neovascular activity. The mechanism by which hCG induces angiogenesis would be an increase in the release of VEGF in the endometrial epithelial cells [38] and/or the trophoblast [34]. Studies have determined that high levels of hCG, released from the trophoblast level at the beginning of embryogenesis, suggest that hCG could be making a decisive contribution to endometrial angiogenesis during implantation [39].

IGF-II

IGF-II is considered to be a major modulator of placental and fetal growth and is likewise involved in placental transport [40]. Studies have illustrated that IGF-II is expressed by the trophoblast during early implantation, and IGF-II receptors' involvement has been highlighted in developing vessels near implantation sites, thus suggesting that IGF-II may influence the angiogenesis of the decidua [41]. The biological activity of IGF-II is regulated by the presence or absence of specific binding factors/proteins (IGFBP), with studies having determined that the increased presence of the IGFBP-1 factor in the uterine lumen causes inhibition of embryonic vascularization and even inadequate implantation [42].

Ang and Tie receptors

Ang has two tyrosine kinase receptors, which are specific for endothelial cells, *tunica interna* endothelial cell kinase-1, -2 (Tie-1 and Tie-2) [43]. The Tie-2 receptor is the functional one and it can bind to Ang-1 and Ang-2, both being growth factors from the Ang family. The two factors act antagonistically by competing for the binding of Tie-2. Thus, Ang-1 after binding to Tie-2 induces vascular remodeling, maturation, and stabilization by stimulating per endothelial cell recruitment, whereas the binding of Ang-2 is followed by destabilization of blood vessels and initiation of neovascularization processes [44]. Alteration of the normal ratio of these proteins, Ang-1/Ang-2, has been found to produce an altered angiogenic response [45].

Vuorela *et al.* have shown reduced expression in the endometrial vascular endothelium of Tie-1 and Tie-2 receptors in recurrent abortions when compared with tissue samples of a normal pregnancy and of the same age [46]. Low expression of Tie-1 in the trophoblast has been noted, as well [47].

Matsumoto *et al.* have shown that VEGF together with angiopoietins and their Tie-2 receptor are involved in modulating angiogenesis during the decidualization process, following implantation [48].

Regulation of placental vasculogenesis and angiogenesis

Angiogenesis is an extensive process, mediated by complex interactions between inhibitors and activators, vital for the growth and development of all tissues, including the placenta, during which new capillaries are formed from pre-existing blood vessels.

The placenta is an extremely fast-growing tissue with high metabolic needs and serves as an exchange organ between maternal and fetal systems. At the level of the placenta, a dynamic angiogenic process is initiated from the beginning until the end of pregnancy to provide support for both its regular growth and functioning [49–51].

The angiogenic process consists of three sequential stages: (*i*) degradation of the vascular substrate membrane and interstitial matrix by endothelial cells, (*ii*) migration and proliferation of endothelial cells, and (*iii*) tubulogenesis and capillary vessel formation.

The initial trigger for these stages is the initiation of a "switch on" signal in preexisting vessels in response to angiogenic factors. Endothelial cells can adhere to and assemble into new vascular structures, thus playing an important role in regulating vasculogenesis and angiogenesis. Vasculogenesis and angiogenesis are two essential processes required in establishing the circulation between the uterus and the placenta.

Studies conducted so far have highlighted the importance of vasculogenesis and angiogenesis during early pregnancy, while data regarding the time of placental angiogenesis initiation, changes in vascular development and expression of angiogenic factors during this period, is scarce [52–54].

Grazul-Bilska *et al.* have shown that the proliferation of vascular cells, vascular growth, along with the expression of certain angiogenic factors and their receptors, as well as of the factors involved in the regulation of angiogenesis, all take place starting from early pregnancy. They have similarly highlighted the fact that the expression of certain angiogenic factors increases from day 16 of gestation, with all previously mentioned processes being closely correlated [55–57].

Under normal physiological conditions, angiogenesis occurs mainly in the uterus and ovaries of adult women during the cycle of reproduction and pregnancy [58].

VEGF

Increased vascular permeability and angiogenesis are crucial for successful implantation, decidualization, and placentation. Several studies have primarily tracked the changes throughout the uterus, specifically the expression of several genetic determinants known to regulate vascular permeability and angiogenesis, including VEGF and its receptors, without further investigating the angiogenic status of the uterus [58–61].

VEGF, along with its receptors, is known as an essential growth factor, integral to the modulation of vascular permeability and angiogenesis. Initial studies indicated the involvement of VEGF as a vascular permeability factor, only subsequently having its role stated as a potent mitogen for endothelial cells and a key regulator of vasculogenesis and uterine angiogenesis during implantation [61, 62].

The VEGF family consists of several members: VEGF-A, PlGF, VEGF-B, VEGF-C, VEGF-D, and their specific receptors. VEGF has several isoforms seen in both humans and mice: $VEGF_{121}$ and $VEGF_{165}$ being predominant isoforms in humans, while $VEGF_{120}$ and $VEGF_{164}$ are isoforms found in mice [60, 63]. VEGF's effects are mediated by two tyrosine kinase receptors, VEGFR-1 and VEGFR-2 (KDR/flk, KDR, kinase insert domain receptor – human receptor designation and flk, fetal liver kinase – the receptor name used in mice) [64].

VEGFR-1/FLT-1 is composed of seven extracellular immunoglobulin domains, a single transmembrane region, and an intracellular tyrosine-kinase sequence [65]. The gene encoding FLT-1 is located on chromosome 13q12-q13 [66]. This receptor has a high affinity for VEGF-A, VEGF-B, and PlGF. Studies have shown that it is expressed in the trophoblast and its expression is regulated by hypoxia [67].

Two soluble isoforms of FLT-1 have been revealed: (*i*) sFLT-1, secreted by endothelial cells, monocytes and by the placenta [68], is considered to be a potent anti-angiogenic factor due to its inhibition of VEGF-A and PlGF binding [69], but also through the formation of heterodimers together with KDR [70]; (*ii*) sFLT-14, secreted by non-epithelial cells, specifically vascular smooth muscle cells [71], is also regarded as a potent inhibitor of VEGF-A activity.

VEGFR-2/KDR/flk1 has a structure similar to that of VEGFR-1 [66]. The gene encoding KDR is located on chromosome 4q11-q12. KDR has an affinity and binds to VEGF-A, VEGF-C, and VEGF-D, proteins that are implicated in regulating KDR expression. Studies have pointed to this receptor as being the main messenger of the VEGF signaling pathways in endothelial cells, inducing chemotaxis, actin reorganization, and endothelial proliferation [72–76].

Klagsbrun *et al.* have in their studies highlighted two other multifunctional co-receptors, belonging to the VEGF family, NRP-1 and NRP-2 [77]. NRP-1 functions as a receptor for various ligands, such as VEGF-A and VEGF-B. However, in human endothelial cells, it is expressed as a receptor specific for $VEGF_{165}$ [78]. NRP-1 has a pivotal role in stabilizing VEGF/VEGFR complexes, thereby stimulating the transmission of VEGF signals. It has been observed that the interaction of VEGF-A with NRP-1 is essential for VEGF-A to bind to KDR, activate it, and regulate it signaling, as well as its biological actions [79–82]. Moreover, in the case of NRP-2, the interaction of VEGF-A or VEGF-C with this receptor is an essential step in KDR activation, which promotes endothelial cell survival and motility [83].

Experimental studies performed on laboratory animals have demonstrated that VEGF isoforms, along with their receptors FLT-1, KDR, and NRP-1, are differentially expressed in utero during implantation. Thus, it has been observed that the $VEGF_{164}$ isoform predominant in mice, mainly interacts with flk1 and NRP1 receptors [58, 60].

Other studies have highlighted the influence of steroid hormones on VEGF expression and its receptors in the uterus during pregnancy [62, 84]. Namely, Hyder & Stancel have hypothesized that estrogen directly regulates the transcriptional expression of VEGF, with the *VEGF* gene containing elements that respond to this hormone. Estrogen rapidly stimulates uterine vascular permeability, quite noteworthy because vascular permeability is a prerequisite for angiogenesis [83].

The earliest commencement of vasculogenesis in the human placenta is at 21 days after conception, through the formation of hemangioblastic cords and is observed early in the tertiary chorionic villi area [85]. The initial period of vasculogenesis is followed by a branching phase (from day 32 to 25 weeks after conception), during which hemangioblastic cords develop in a richly branched capillary bed [19]. In this specific phase of angiogenesis, it has been shown that placental expression of VEGF-A, FLT-1, and KDR is exceptional and noteworthy, while PlGF expression is moderate [86].

Demir *et al.* have illustrated that, in the process of organizing the very first blood vessels, angiogenic factors are paramount to the initiation of angiogenesis, which is provided by cytotrophoblastic cells. Furthermore, it has been observed that an additional source of VEGF-A is the stromal cells, including the Hofbauer cells (placental macrophages) [21, 29].

In another study, about an *in vitro* experiment on the chorioallantoic membrane of chickens, Wilting *et al.* have shown that the binding of VEGF-A to FLT-1 and KDR is followed by stimulation of the branching phase of angiogenesis [87].

Beginning with gestation week 25, during angiogenesis, the transition from the branching phase to the non-branching phase is taken up, during which the expression of VEGF-A and KDR decreases and the expression of PlGF, FLT-1 and sFLT-1 increases [46, 88–90].

Conclusions

The implantation is a process by which embryonic blood vessels are brought into functional communication with the maternal circulation, leading to the formation of a functional placenta and pregnancy, a process that functions as a two-way interaction between the blastocyst and the maternal endometrium. Understanding the phenomena that occur during the pre-implantation period and the mechanisms of implantation was an attempt for biologists and obstetricians, depending on the correct assessment of the causes of infertility and the embryonic quality, the main factor in obtaining descendants of good biological quality. Also, information can be useful in developing some contraceptive methods to limit the growth of the global population.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Anda Lorena Dijmărescu, Cristian Adrian Siloşi and Lidia Boldeanu equally contributed to the manuscript.

References

[1] Zhang Y, Zhao A, Wang X, Shi G, Jin H, Lin Q. Expressions of natural cytotoxicity receptors and NKG2D on decidual natural killer cells in patients having spontaneous abortions. Fertil Steril, 2008, 90(5):1931–1937. https://doi.org/10.1016/j.fertnstert.2007.08.009 PMID: 18023431

[2] Klauber N, Rohan RM, Flynn E, D'Amato RJ. Critical components of the female reproductive pathway are suppressed by the angiogenesis inhibitor AGM-1470. Nat Med, 1997, 3(4):443–446. https://doi.org/10.1038/nm0497-443 PMID: 9095179

[3] Cross JC, Hemberger M, Lu Y, Nozaki T, Whiteley K, Masutani M, Adamson SL. Trophoblast functions, angiogenesis, and remodeling of the maternal vasculature in the placenta. Mol Cell Endocrinol, 2002, 187(1–2):207–212. https://doi.org/10.1016/s0303-7207(01)00703-1 PMID: 11988329

[4] Geva E, Ginzinger DG, Zaloudek CJ, Moore DH, Byrne A, Jaffe RB. Human placental vascular development: vasculogenic and angiogenic (branching and nonbranching) transformation is regulated by vascular endothelial growth factor-A, angiopoietin-1, and angiopoietin-2. J Clin Endocrinol Metab, 2002, 87(9):4213–4224. https://doi.org/10.1210/jc.2002-020195 PMID: 12213874

[5] Wulff C, Weigand M, Kreienberg R, Fraser HM. Angiogenesis during primate placentation in health and disease. Reproduction, 2003, 126(5):569–577. https://doi.org/10.1530/rep.0.1260569 PMID: 14611629

[6] Adamson SL, Lu Y, Whiteley KJ, Holmyard D, Hemberger M, Pfarrer C, Cross JC. Interactions between trophoblast cells and the maternal and fetal circulation in the mouse placenta. Dev Biol, 2002, 250(2):358–373. https://doi.org/10.1016/s0012-1606(02)90773-6 PMID: 12376109

[7] Cross JC. Genetic insights into trophoblast differentiation and placental morphogenesis. Semin Cell Dev Biol, 2000, 11(2):105–113. https://doi.org/10.1006/scdb.2000.0156 PMID: 10873707

[8] Hemberger M, Nozaki T, Masutani M, Cross JC. Differential expression of angiogenic and vasodilatory factors by invasive trophoblast giant cells depending on depth of invasion. Dev Dyn, 2003, 227(2):185–191. https://doi.org/10.1002/dvdy.10291 PMID: 12761846

[9] Leonard S, Murrant C, Tayade C, van den Heuvel M, Watering R, Croy BA. Mechanisms regulating immune cell contributions to spiral artery modification – facts and hypotheses – a review. Placenta, 2006, 27(Suppl A):S40–S46. https://doi.org/10.1016/j.placenta.2005.11.007 PMID: 16413937

[10] Aagaard-Tillery KM, Silver R, Dalton J. Immunology of normal pregnancy. Semin Fetal Neonatal Med, 2006, 11(5):279–295. https://doi.org/10.1016/j.siny.2006.04.003 PMID: 16784908

[11] Naldini A, Carraro F. Role of inflammatory mediators in angiogenesis. Curr Drug Targets Inflamm Allergy, 2005, 4(1):3–8. https://doi.org/10.2174/1568010053622830 PMID: 15720228

[12] Hayashi T, Matsuoka K, Saitoh M, Takeda S, Kimura M. Influence of alpha-tumor necrosis factor and beta-interleukin-1 on production of angiogenetic factors and thymidine phosphorylase activity in immortalized human decidual fibroblasts *in vitro*. J Obstet Gynaecol Res, 2006, 32(1):15–22. https://doi.org/10.1111/j.1447-0756.2006.00347.x PMID: 16445521

[13] van Nieuwenhoven ALV, Heineman MJ, Faas MM. The immunology of successful pregnancy. Hum Reprod Update, 2003, 9(4):347–357. https://doi.org/10.1093/humupd/dmg026 PMID: 12926528

[14] Chung IB, Yelian FD, Zaher FM, Gonik B, Evans MI, Diamond MP, Svinarich DM. Expression and regulation of vascular endothelial growth factor in a first trimester trophoblast cell line. Placenta, 2000, 21(4):320–324. https://doi.org/10.1053/plac.1999.0481 PMID: 10833366

[15] Szukiewicz D, Szewczyk G, Watroba M, Kurowska E, Maslinski S. Isolated placental vessel response to vascular endothelial growth factor and placenta growth factor in normal and growth-restricted pregnancy. Gynecol Obstet Invest, 2005, 59(2):102–107. https://doi.org/10.1159/000082622 PMID: 15591804

[16] Druckmann R, Druckmann MA. Progesterone and the immunology of pregnancy. J Steroid Biochem Mol Biol, 2005, 97(5):389–396. https://doi.org/10.1016/j.jsbmb.2005.08.010 PMID: 16198558

[17] Naldini A, Pucci A, Bernini C, Carraro F. Regulation of angiogenesis by Th1- and Th2-type cytokines. Curr Pharm Des, 2003, 9(7):511–519. https://doi.org/10.2174/138161203339 1423 PMID: 12570799

[18] Robertson SA. Seminal plasma and male factor signaling in the female reproductive tract. Cell Tissue Res, 2005, 322(1):43–52. https://doi.org/10.1007/s00441-005-1127-3 PMID: 15909166

[19] Pongcharoen S, Somran J, Sritippayawan S, Niumsup P, Chanchan P, Butkhamchot P, Tatiwat P, Kunngurn S, Searle RF. Interleukin-17 expression in the human placenta. Placenta, 2007, 28(1):59–63. https://doi.org/10.1016/j.placenta.2006.01.016 PMID: 16549200

[20] Cooper JC, Sharkey AM, McLaren J, Charnock-Jones DS, Smith SK. Localization of vascular endothelial growth factor and its receptor, flt, in human placenta and decidua by immunohistochemistry. J Reprod Fertil, 1995, 105(2):205–213. https://doi.org/10.1530/jrf.0.1050205 PMID: 8568762

[21] Demir R, Kayisli UA, Seval Y, Celik-Ozenci C, Korgun ET, Demir-Weusten AY, Huppertz B. Sequential expression of VEGF and its receptors in human placental villi during very early pregnancy: differences between placental vasculogenesis and angiogenesis. Placenta, 2004, 25(6):560–572. https://doi.org/10.1016/j.placenta.2003.11.011 PMID: 15135240

[22] Guilbert L, Robertson SA, Wegmann TG. The trophoblast as an integral component of a macrophage–cytokine network. Immunol Cell Biol, 1993, 71(Pt 1):49–57. https://doi.org/10.1038/icb.1993.5 PMID: 8436411

[23] Girardi G, Yarilin D, Thurman JM, Holers VM, Salmon JE. Complement activation induces dysregulation of angiogenic factors and causes fetal rejection and growth restriction. J Exp Med, 2006, 203(9):2165–2175. https://doi.org/10.1084/jem.20061022 PMID: 16923853 PMCID: PMC2118387

[24] Torry DS, Mukherjea D, Arroyo J, Torry RJ. Expression and function of placenta growth factor: implications for abnormal placentation. J Soc Gynecol Investig, 2003, 10(4):178–188. https://doi.org/10.1016/s1071-5576(03)00048-0 PMID: 12759145

[25] Torry DS, Hinrichs M, Torry RJ. Determinants of placental vascularity. Am J Reprod Immunol, 2004, 51(4):257–268. https://doi.org/10.1111/j.1600-0897.2004.00154.x PMID: 15212678

[26] Autiero M, Luttun A, Tjwa M, Carmeliet P. Placental growth factor and its receptor, vascular endothelial growth factor receptor-1: novel targets for stimulation of ischemic tissue revascularization and inhibition of angiogenic and inflammatory disorders. J Thromb Haemost, 2003, 1(7):1356–1370. https://doi.org/10.1046/j.1538-7836.2003.00263.x PMID: 12871269

[27] Ahmed A, Dunk C, Ahmad S, Khaliq A. Regulation of placental vascular endothelial growth factor (VEGF) and placenta growth factor (PlGF) and soluble Flt-1 by oxygen – a review. Placenta, 2000, 21(Suppl A):S16–S24. https://doi.org/10.1053/plac.1999.0524 PMID: 10831117

[28] Welch PC, Amankwah KS, Miller P, McAsey ME, Torry DS. Correlations of placental perfusion and PlGF protein expression in early human pregnancy. Am J Obstet Gynecol, 2006, 194(6):1625–1629; discussion 1629–1631. https://doi.org/10.1016/j.ajog.2006.01.012 PMID: 16635470

[29] Demir R, Kayisli UA, Cayli S, Huppertz B. Sequential steps during vasculogenesis and angiogenesis in the very early human placenta. Placenta, 2006, 27(6–7):535–539. https://doi.org/10.1016/j.placenta.2005.05.011 PMID: 16029887

[30] Ornitz DM, Itoh N. Fibroblast growth factors. Genome Biol, 2001, 2(3):reviews3005.1–reviews3005.12. https://doi.org/10.1186/gb-2001-2-3-reviews3005 PMID: 11276432 PMCID: PMC138918

[31] Moscatelli D, Joseph-Silverstein J, Presta M, Rifkin DB. Multiple forms of an angiogenesis factor: basic fibroblast growth factor. Biochimie, 1988, 70(1):83–87. https://doi.org/10.1016/0300-9084(88)90162-9 PMID: 2840975

[32] Hamai Y, Fujii T, Yamashita T, Kozuma S, Okai T, Taketani Y. Evidence for basic fibroblast growth factor as a crucial angiogenic growth factor, released from human trophoblasts during early gestation. Placenta, 1998, 19(2–3):149–155. https://doi.org/10.1016/s0143-4004(98)90003-0 PMID: 9548181

[33] Li W, Newell-Price J, Jones GL, Ledger WL, Li TC. Relationship between psychological stress and recurrent miscarriage. Reprod Biomed Online, 2012, 25(2):180–189. https://doi.org/10.1016/j.rbmo.2012.03.012 PMID: 22687324

[34] Islami D, Bischof P, Chardonnens D. Modulation of placental vascular endothelial growth factor by leptin and hCG. Mol Hum Reprod, 2003, 9(7):395–398. https://doi.org/10.1093/molehr/gag053 PMID: 12802046

[35] Qian D, Lin HY, Wang HM, Zhang X, Liu DL, Li QL, Zhu C. Involvement of ERK1/2 pathway in TGF-beta1-induced VEGF secretion in normal human cytotrophoblast cells. Mol Reprod Dev, 2004, 68(2):198–204. https://doi.org/10.1002/mrd.20061 PMID: 15095341

[36] Ogasawara MS, Aoki K, Aoyama T, Katano K, Iinuma Y, Ozaki Y, Suzumori K. Elevation of transforming growth factor-beta1 is associated with recurrent miscarriage. J Clin Immunol, 2000, 20(6):453–457. https://doi.org/10.1023/a:1026459800016 PMID: 11202235

[37] Dickson MC, Martin JS, Cousins FM, Kulkarni AB, Karlsson S, Akhurst RJ. Defective hematopoiesis and vasculogenesis in transforming growth factor-beta 1 knock out mice. Development, 1995, 121(6):1845–1854. PMID: 7600998

[38] Berndt S, Perrier d'Hauterive S, Blacher S, Péqueux C, Lorquet S, Munaut C, Applanat M, Hervé MA, Lamandé N, Corvol P, van den Brûle F, Frankenne F, Poutanen M, Huhtaniemi I, Geenen V, Noël A, Foidart JM. Angiogenic activity of human chorionic gonadotropin through LH receptor activation on endothelial and epithelial cells of the endometrium. FASEB J, 2006, 20(14):2630–2632. https://doi.org/10.1096/fj.06-5885fje PMID: 17065221

[39] Zygmunt M, Herr F, Keller-Schoenwetter S, Kunzi-Rapp K, Münstedt K, Rao CV, Lang U, Preissner KT. Characterization of human chorionic gonadotropin as a novel angiogenic factor. J Clin Endocrinol Metab, 2002, 87(11):5290–5296. https://doi.org/10.1210/jc.2002-020642 PMID: 12414904

[40] Constância M, Hemberger M, Hughes J, Dean W, Ferguson-Smith A, Fundele R, Stewart F, Kelsey G, Fowden A, Sibley C, Reik W. Placental-specific IGF-II is a major modulator of placental and fetal growth. Nature, 2002, 417(6892):945–948. https://doi.org/10.1038/nature00819 PMID: 12087403

[41] Pringle KG, Roberts CT. New light on early post-implantation pregnancy in the mouse: roles for insulin-like growth factor-II (IGF-II)? Placenta, 2007, 28(4):286–297. https://doi.org/10.1016/j.placenta.2006.04.006 PMID: 16824595

[42] Licht P, Russu V, Lehmeyer S, Möll J, Siebzehnrübl E, Wildt L. Intrauterine microdialysis reveals cycle-dependent regulation of endometrial insulin-like growth factor binding protein-1 secretion by human chorionic gonadotropin. Fertil Steril, 2002, 78(2):252–258. https://doi.org/10.1016/s0015-0282(02)03226-0 PMID: 12137859

[43] Eklund L, Olsen BR. Tie receptors and their angiopoietin ligands are context-dependent regulators of vascular remodeling. Exp Cell Res, 2006, 312(5):630–641. https://doi.org/10.1016/j.yexcr.2005.09.002 PMID: 16225862

[44] Wakui S, Yokoo K, Muto T, Suzuki Y, Takahashi H, Furusato M, Hano H, Endou H, Kanai Y. Localization of Ang-1, -2, Tie-2, and VEGF expression at endothelial–pericyte interdigitation in rat angiogenesis. Lab Invest, 2006, 86(11):1172–1184. https://doi.org/10.1038/labinvest.3700476 PMID: 16969369

[45] Sato TN, Tozawa Y, Deutsch U, Wolburg-Buchholz K, Fujiwara Y, Gendron-Maguire M, Gridley T, Wolburg H, Risau W, Qin Y. Distinct roles of the receptor tyrosine kinases Tie-1 and Tie-2 in blood vessel formation. Nature, 1995, 376(6535):70–74. https://doi.org/10.1038/376070a0 PMID: 7596437

[46] Vuorela P, Carpén O, Tulppala M, Halmesmäki E. VEGF, its receptors and the Tie receptors in recurrent miscarriage. Mol Hum Reprod, 2000, 6(3):276–282. https://doi.org/10.1093/molehr/6.3.276 PMID: 10694277

[47] Pietrowski D, Tempfer C, Bettendorf H, Bürkle B, Nagele F, Unfried G, Keck C. Angiopoietin-2 polymorphism in women with idiopathic recurrent miscarriage. Fertil Steril, 2003, 80(4):1026–1029. https://doi.org/10.1016/s0015-0282(03)01011-2 PMID: 14556828

[48] Matsumoto H, Ma WG, Daikoku T, Zhao X, Paria BC, Das SK, Trzaskos JM, Dey SK. Cyclooxygenase-2 differentially directs uterine angiogenesis during implantation in mice. J Biol Chem, 2002, 277(32):29260–29267. https://doi.org/10.1074/jbc.M203996200 PMID: 12034746

[49] Reynolds LP, Borowicz PP, Caton JS, Vonnahme KA, Luther JS, Buchanan DS, Hafez SA, Grazul-Bilska AT, Redmer DA. Utero-placental vascular development and placental function: an update. Int J Dev Biol, 2010, 54(2–3):355–366. https://doi.org/10.1387/ijdb.082799lr PMID: 19924632

[50] Manolea MM, Dijmărescu AL, Popescu FC, Novac MB, Diţescu D. Evaluation of the implantation site morphology in spontaneous abortion. Rom J Morphol Embryol, 2015, 56(1):125–131. PMID: 25826496

[51] Dijmarescu AL, Vrabie S, Manolea MM, Novac M, Iliescu D, Tudorache S, Camen I. Preoperative risk assessment of malignancy in ovarian tumors and correlation with histopathological outcome. Conference Proceedings of 6th Congress of the Ultrasound Society in Obstetrics and Gynecology/ 34th Fetus as a Patient International Congress, May 16–19, 2018, Bucharest, Romania, 167–171.

[52] Demir R, Seval Y, Huppertz B. Vasculogenesis and angiogenesis in the early human placenta. Acta Histochem, 2007, 109(4):257–265. https://doi.org/10.1016/j.acthis.2007.02.008 PMID: 17574656

[53] Novac L, Tudorache S, Manolea MM, Dijmarescu AL, Novac V, Miescu M, Moldoveanu A, Vrabie S, Camen I, Iliescu D. The use of Doppler ultrasound as early parameter for detection of fetal compromise in restricted fetuses. Conference Proceedings of 5th Romanian Congress of the Romanian Society of Ultrasound in Obstetrics and Gynecology, April 20–22, 2017, Târgu Mureş, Romania, 445–449.

[54] Manolea MM, Dijmarescu AL, Neamtu S, Iliescu D, Tudorache S, Sandulescu S, Novac M. Yolk sac and embryonic heart rate as predictors for early pregnancy loss. Conference Proceedings of 5th Romanian Congress of the Romanian Society of Ultrasound in Obstetrics and Gynecology, April 20–22, 2017, Târgu Mureş, Romania, 318–323.

[55] Grazul-Bilska AT, Borowicz PP, Johnson ML, Minten MA, Bilski JJ, Wroblewski R, Redmer DA, Reynolds LP. Placental development during early pregnancy in sheep: vascular growth and expression of angiogenic factors in the maternal placenta. Reproduction, 2010, 140(2):165–174. https://doi.org/10.1530/REP-09-0548 PMID: 20400519

[56] Novac L, Niculescu M, Iliescu D, Manolea M, Dijmarescu L, Comanescu A, Tudorache S, Cernea N, Căpitănescu R, Novac M. Chorial villositary vasculogenesis correlated with ultrasound morpho-functional markers of the trophoblast. In: ***. Advance in perinatal medicine. Conference Proceedings of 22nd European Congress of Perinatal Medicine, May 26–29, 2010, Granada, Spain, Monduzzi Editore, 2010, 143–148.
[57] Novac MV, Niculescu M, Manolea MM, Dijmărescu AL, Iliescu DG, Novac MB, Rotaru LT, Stoenescu MF, Tabacu MC, Tudorache Ş, Busuioc CJ, Gheonea IA. Placental findings in pregnancies complicated with IUGR – histopathological and immunohistochemical analysis. Rom J Morphol Embryol, 2018, 59(3):715–720. PMID: 30534809
[58] Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other diseases. Nat Med, 1995, 1(1):27–31. https://doi.org/10.1038/nm0195-27 PMID: 7584949
[59] Chakraborty I, Das SK, Dey SK. Differential expression of vascular endothelial growth factor and its receptor mRNAs in the mouse uterus around the time of implantation. J Endocrinol, 1995, 147(2):339–352. https://doi.org/10.1677/joe.0.1470339 PMID: 7490564
[60] Halder JB, Zhao X, Soker S, Paria BC, Klagsbrun M, Das SK, Dey SK. Differential expression of VEGF isoforms and $VEGF_{164}$-specific receptor neuropilin-1 in the mouse uterus suggests a role for $VEGF_{164}$ in vascular permeability and angiogenesis during implantation. Genesis, 2000, 26(3):213–224. https://doi.org/10.1002/(SICI)1526-968X(200003)26:3<213::AID-GENE7>3.0.CO;2-M PMID: 10705382
[61] Hyder SM, Nawaz Z, Chiappetta C, Stancel GM. Identification of functional estrogen response elements in the gene coding for the potent angiogenic factor vascular endothelial growth factor. Cancer Res, 2000, 60(12):3183–3190. PMID: 10866309
[62] Ferrara N, Davis-Smyth T. The biology of vascular endothelial growth factor. Endocr Rev, 1997, 18(1):4–25. https://doi.org/10.1210/edrv.18.1.0287 PMID: 9034784
[63] Tischer E, Mitchell R, Hartman T, Silva M, Gospodarowicz D, Fiddes JC, Abraham JA. The human gene for vascular endothelial growth factor. Multiple protein forms are encoded through alternative exon splicing. J Biol Chem, 1991, 266(18):11947–11954. PMID: 1711045
[64] Andraweera PH, Dekker GA, Roberts CT. The vascular endothelial growth factor family in adverse pregnancy outcomes. Hum Reprod Update, 2012, 18(4):436–457. https://doi.org/10.1093/humupd/dms011 PMID: 22495259
[65] Shibuya M, Yamaguchi S, Yamane A, Ikeda T, Tojo A, Matsushime H, Sato M. Nucleotide sequence and expression of a novel human receptor-type tyrosine kinase gene (*flt*) closely related to the *fms* family. Oncogene, 1990, 5(4):519–524. PMID: 2158038
[66] Tammela T, Enholm B, Alitalo K, Paavonen K. The biology of vascular endothelial growth factors. Cardiovasc Res, 2005, 65(3):550–563. https://doi.org/10.1016/j.cardiores.2004.12.002 PMID: 15664381
[67] Gerber HP, Condorelli F, Park J, Ferrara N. Differential transcriptional regulation of the two vascular endothelial growth factor receptor genes. *Flt-1*, but not *Flk-1/KDR*, is up-regulated by hypoxia. J Biol Chem, 1997, 272(38):23659–23667. https://doi.org/10.1074/jbc.272.38.23659 PMID: 9295307
[68] Shibuya M. Vascular endothelial growth factor receptor-1 (VEGFR-1/Flt-1): a dual regulator for angiogenesis. Angiogenesis, 2006, 9(4):225–230; discussion 231. https://doi.org/10.1007/s10456-006-9055-8 PMID: 17109193
[69] Kendall RL, Thomas KA. Inhibition of vascular endothelial cell growth factor activity by an endogenously encoded soluble receptor. Proc Natl Acad Sci U S A, 1993, 90(22):10705–10709. https://doi.org/10.1073/pnas.90.22.10705 PMID: 8248162 PMCID: PMC47846
[70] Kendall RL, Wang G, Thomas KA. Identification of a natural soluble form of the vascular endothelial growth factor receptor, FLT-1, and its heterodimerization with KDR. Biochem Biophys Res Commun, 1996, 226(2):324–328. https://doi.org/10.1006/bbrc.1996.1355 PMID: 8806634
[71] Sela S, Itin A, Natanson-Yaron S, Greenfield C, Goldman-Wohl D, Yagel S, Keshet E. A novel human-specific soluble vascular endothelial growth factor receptor 1: cell-type-specific splicing and implications to vascular endothelial growth factor homeostasis and preeclampsia. Circ Res, 2008, 102(12):1566–1574. https://doi.org/10.1161/CIRCRESAHA.108.171504 PMID: 18515749
[72] Millauer B, Wizigmann-Voos S, Schnürch H, Martinez R, Møller NP, Risau W, Ullrich A. High affinity VEGF binding and developmental expression suggest Flk-1 as a major regulator of vasculogenesis and angiogenesis. Cell, 1993, 72(6):835–846. https://doi.org/10.1016/0092-8674(93)90573-9 PMID: 7681362
[73] Peters KG, De Vries C, Williams LT. Vascular endothelial growth factor receptor expression during embryogenesis and tissue repair suggests a role in endothelial differentiation and blood vessel growth. Proc Natl Acad Sci U S A, 1993, 90(19):8915–8919. https://doi.org/10.1073/pnas.90.19.8915 PMID: 7692439 PMCID: PMC47471
[74] Quinn TP, Peters KG, De Vries C, Ferrara N, Williams LT. Fetal liver kinase 1 is a receptor for vascular endothelial growth factor and is selectively expressed in vascular endothelium. Proc Natl Acad Sci U S A, 1993, 90(16):7533–7537. https://doi.org/10.1073/pnas.90.16.7533 PMID: 8356051 PMCID: PMC47176
[75] Waltenberger J, Claesson-Welsh L, Siegbahn A, Shibuya M, Heldin CH. Different signal transduction properties of KDR and Flt1, two receptors for vascular endothelial growth factor. J Biol Chem, 1994, 269(43):26988–26995. PMID: 7929439
[76] Yoshida A, Anand-Apte B, Zetter BR. Differential endothelial migration and proliferation to basic fibroblast growth factor and vascular endothelial growth factor. Growth Factor, 1996, 13(1–2):57–64. https://doi.org/10.3109/08977199609034566 PMID: 8962720
[77] Klagsbrun M, Takashima S, Mamluk R. The role of neuropilin in vascular and tumor biology. Adv Exp Med Biol, 2002, 515:33–48. https://doi.org/10.1007/978-1-4615-0119-0_3 PMID: 12613541
[78] Mamluk R, Gechtman Z, Kutcher ME, Gasiunas N, Gallagher J, Klagsbrun M. Neuropilin-1 binds vascular endothelial growth factor 165, placenta growth factor-2, and heparin *via* its b1b2 domain. J Biol Chem, 2002, 277(27):24818–24825. https://doi.org/10.1074/jbc.M200730200 PMID: 11986311
[79] Sulpice E, Plouët J, Bergé M, Allanic D, Tobelem G, Merkulova-Rainon T. Neuropilin-1 and neuropilin-2 act as coreceptors, potentiating proangiogenic activity. Blood, 2008, 111(4):2036–2045. https://doi.org/10.1182/blood-2007-04-084269 PMID: 18065694
[80] Pădureanu V, Boldeanu MV, Streaţă I, Cucu MG, Siloşi I, Boldeanu L, Bogdan M, Enescu AŞ, Forţofoiu M, Enescu A, Dumitrescu EM, Alexandru D, Şurlin VM, Forţofoiu MC, Petrescu IO, Petrescu F, Ioana M, Ciurea ME, Săftoiu A. Determination of *VEGFR-2* (*KDR*) *604A>G* polymorphism in pancreatic disorders. Int J Mol Sci, 2017, 18(2):439. https://doi.org/10.3390/ijms18020439 PMID: 28218664 PMCID: PMC5343973
[81] Boldeanu L, Siloşi CA, Pădureanu V, Dijmărescu AL, Manolea MM, Tabacu MC, Boldeanu MV, Popescu-Drigă MV, Poenariu IS, Pădureanu R, Novac LV, Novac MB. Determination of *VEGFR-2* (*KDR*) *-604A>G* polymorphism in recurrent pregnancy loss. Rom J Morphol Embryol, 2018, 59(4):1053–1059. PMID: 30845284
[82] Pădureanu V, Enescu AŞ, Siloşi I, Forţofoiu M, Enescu A, Bogdan M, Forţofoiu MC, Genunche Dumitrescu A, Tudoraşcu DR, Mita A, Streata I, Ioana M, Petrescu F, Săftoiu A. The association between chronic pancreatitis and the *iNOS-2087A>G* polymorphism. Rom J Intern Med, 2017, 55(2):89–95. https://doi.org/10.1515/rjim-2017-0009 PMID: 28125406
[83] Hyder SM, Stancel GM. Regulation of angiogenic growth factors in the female reproductive tract by estrogens and progestins. Mol Endocrinol, 1999, 13(6):806–811. https://doi.org/10.1210/mend.13.6.0308 PMID: 10379879
[84] Siminel MA, Gheonea C, Stănescu MR, Comănescu AC, Dijmărescu AL, Neamţu SD, Cotoi BV, Nedelcuţă RM, Niculescu EC. Velamentous insertion of the umbilical cord vessels with *vasa praevia* – a case report. Rom J Morphol Embryol, 2015, 56(1):301–308. PMID: 25826521
[85] Demir R, Kaufmann P, Castellucci M, Erbengi T, Kotowski A. Fetal vasculogenesis and angiogenesis in human placental villi. Acta Anat (Basel), 1989, 136(3):190–203. https://doi.org/10.1159/000146886 PMID: 2481376

[86] Kaufmann P, Mayhew TM, Charnock-Jones DS. Aspects of human fetoplacental vasculogenesis and angiogenesis. II. Changes during normal pregnancy. Placenta, 2004, 25(2–3): 114–126. https://doi.org/10.1016/j.placenta.2003.10.009 PMID: 14972444

[87] Wilting J, Birkenhäger R, Eichmann A, Kurz H, Martiny-Baron G, Marmé D, McCarthy JE, Christ B, Weich HA. $VEGF_{121}$ induces the proliferation of vascular endothelial cells and expression of *flk-1* without affecting lymphatic vessels of chorioallantoic membrane. Dev Biol, 1996, 176(1):76–85. https://doi.org/10.1006/dbio.1996.9993 PMID: 8654896

[88] Reynolds LP, Caton JS, Redmer DA, Grazul-Bilska AT, Vonnahme KA, Borowicz PP, Luther JS, Wallace JM, Wu G, Spencer TE. Evidence for altered placental blood flow and vascularity in compromised pregnancies. J Physiol, 2006, 572(Pt 1):51–58. https://doi.org/10.1113/jphysiol.2005.104430 PMID: 16469783 PMCID: PMC1779650

[89] Torry DS, Leavenworth J, Chang M, Maheshwari V, Groesch K, Ball ER, Torry RJ. Angiogenesis in implantation. J Assist Reprod Genet, 2007, 24(7):303–315. https://doi.org/10.1007/s10815-007-9152-7 PMID: 17616801 PMCID: PMC3455012

[90] Stoenescu VE, Niculescu M, Novac L, Manolea MM, Tomescu PI, Dijmărescu AL, Novac MB, Tudorache Ş, Iliescu DG. Immunohistochemical reaction of the glandular epithelium in endometrial hyperplasia compared to endometrial carcinoma. Rom J Morphol Embryol, 2017, 58(3):791–800. PMID: 29250656

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