The Imbalance Angiogenic and Anti-angiogenic Signalings in Placenta Accreta Spectrum

Letizia Alessandrini[a], Rozi Aditya Aryananda[b], Ernawati[b]

*Email: ernawati.spog@gmail.com

[a]Obstetrics and Gynecology Department Resident of Medical Faculty of Universitas Airlangga, dr. Soetomo Academic Hospital, Indonesia

[b]Obstetrics and Gynecology Department Staff of Medical Faculty of Universitas Airlangga, dr. Soetomo Academic Hospital, Indonesia

Abstract

Spectrum placenta accreta was defined as a disruption in the attachment of the trophoblast to the myometrium directly without the presence of a decidua or basement membrane between them. During the early stages of placenta formation, trophoblast invasion is disturbed in the spectrum of placenta accreta. Changes in the structure of the tissue in the uterine scar following surgery or curettage may cause these problems. The invasion of trophoblasts is linked to the processes of vasculogenesis and angiogenesis. This process requires a balance between angiogenic factors and anti-angiogenic factors to produce a good placentation process. In the spectrum of placenta accreta, it is suspected that there is an imbalance between angiogenic factors and anti-angiogenic factors. This has an impact on the ability of trophoblast invasion since the beginning of the formation of the placenta. This study reviews the role of angiogenesis and anti-angiogenesis in the placenta accreta spectrum. A narrative review is done by reviewing some literature that discusses angiogenesis and anti-angiogenesis processes in the placenta accreta spectrum. The search was performed using placenta accreta spectrum, angiogenesis and anti-angiogenesis processes keywords in the PubMed, Google Scholar, and ScienceDirect databases. The collected data is then arranged in a narrative manner.

Keywords: angiogenesis, anti-angiogenesis, placenta accreta spectrum

1. Introduction

The placenta and uterus are the main organs of a pregnancy. The placenta facilitates the transfer of nutrients and gas exchange for the developing fetus. It also plays a role in temperature regulation, produces hormones, and protects against internal infections during pregnancy. The process of pregnancy itself is a change in physiological conditions that are regulated by genetics (eg. genes inherited from the mother), environment (eg. nutrition), and physiological processes (eg. inflammation, hypoxia). In spectrum placenta accreta, there is a change in the uterine scar tissue which could be from a cesarean section or curettage[1]. This causes an increased oxygen tension in the endometrium which contributes to the development of abnormal placentation[2]. Embryos in the early stages of growth require a relatively hypoxic environment, so the placenta tends to implant in acellular and avascular scar tissue sections. Trophoblasts that invade an avascular wound will invade deeper into the endometrium. In one study, it was stated that in cesarean wounds, a single layer suture closure technique could trigger the formation of a relatively hypoxic area and trigger blastocytes to implant in that area in subsequent pregnancies, thereby increasing the

occurrence of placenta accreta. Hypoxic conditions in the placenta could cause excessive capillaries and villous branching[2]. This excessive branching of villous is due to an imbalance between angiogenic and anti-angiogenic factors. Therefore, this exaggerated branching increases the efficiency of the placenta by providing more arterio-venous circuitry so that fetal blood flow to the umbilical cord is balanced with the amount of blood in the intervillous space[3].

The process of changing physiological conditions in early pregnancy also affects the activity of microRNA. The study showed the expression of microRNA was a response to the changes during pregnancy. MicroRNA responds to physiological conditions and facilitates the pregnancy process to run well. MicroRNA has an important role as a regulator at the beginning of the placentation process, including regulating the processes of vasculogenesis and angiogenesis. Dysregulated microRNA causes abnormalities during the pregnancy process, one of which is interference with the process of vasculogenesis or angiogenesis which has an impact on the placentation process in early pregnancy [4].

2. Methods

This study reviews the role of angiogenesis and anti-angiogenesis in the placenta accreta spectrum. A narrative review is done by reviewing some literature that discusses angiogenesis and anti-angiogenesis processes in the placenta accreta spectrum. The search was performed using placenta accreta spectrum, angiogenesis, and anti-angiogenesis processes keywords in the PubMed, Google Scholar, and ScienceDirect databases. The collected data is then arranged in a narrative manner.

3. Results

Placenta Acreta Spectrum

Spectrum placenta accreta was defined as a disruption in the attachment of the trophoblast to the myometrium directly without the presence of a decidua or basement membrane between them. The definition of placenta accreta according to ACOG (American College of Obstetricians and Gynecologists) is an abnormal invasion of trophoblast cells in the myometrial uterine wall [1]. The spectrum of placenta accreta is a pathological condition of the placenta experiencing attachment and is divided into placenta accreta (<50% invasion), placenta increta (>50% invasion), and placenta percreta (invasion to the serous layer and nearby pelvic organs) [5]. Several cases of placenta accreta are characterized by a reduction in the decidual layer, resulting in direct attachment of the villous tissue to the myometrium, excessive invasion, and increased risk of bleeding.

ACOG and the Society for Maternal-Fetal Medicine recommend that patients with spectrum placenta accreta receive subspecialty level III care or higher. This level includes medical staff who have knowledge and experience in dealing with maternal complications that can occur at the time of delivery.

The role of angiogenic and anti-angiogenic factors

The processes of Vasculogenesis and Angiogenesis have an important role in early pregnancy. Adequate vasculogenesis and angiogenesis processes will support uteroplacental flow so that the supply of oxygen and nutrients to the fetus can be fulfilled properly. This can affect in fetal growth [6].

A balance between angiogenic and anti-angiogenic factors is essential for normal placental development. On spectrum placenta accreta, a balance between these factors is not achieved. Although the molecular mechanism of

the placenta accreta spectrum is still not clear, several studies found that there is an imbalance between angiogenic and anti-angiogenic factors in the spectrum of placenta accreta.

Oxygen level during gestation regulates the balance of angiogenic factors in the placenta, including VEGF and PLGF. A study by Schweiki et al. has shown that VEGF expression in tumor cells is increased in hypoxic conditions [7]. In spectrum placenta accreta, multiple fibrosis scar tissue is common with a history of cesarean section. This condition indicates the presence of an ischemic area that causes conditions in the environment to experience hypoxia [8]. This hypoxic condition causes the expression of VEGF and KDR to increase in villious vessels, whereas PLGF and flt-1 increase in villi trophoblasts.

Several studies have shown that the processes of vasculogenesis and angiogenesis are regulated sequentially by growth factors including VEGF, FGF2, and PLGF. Vascular endothelial growth factor (VEGF) is needed in every phase of vascular formation and development. Fibroblast Growth Factor (FGF2) plays a role in the formation of hemangiogenic progenitor cells during early embryogenic development. Placental growth factor (PLGF) has a synergistic role with VEGF in the formation of vascular tissue. The placenta will secrete many growth factors to facilitate the development of the vascular system at the time of entering the third trimester [9].

In normal pregnancy, sFlt-1 levels increase rapidly at 30-32 weeks of gestation, whereas PlGF levels begin to decline after 30 weeks of gestation (Nikuei et al., 2020). PLGF will bind to VEGFR-1 (vascular endothelial growth factor receptor-1) or FLT-1 (fms-related tyrosine kinase-1) and sFLT-1 (soluble fms-like tyrosine kinase-1), but not to VEGFR- 2. When PLGF binds to VEGFR-1, VEGF will experience increased activity because it is competitive in binding to VEGFR-1, this causes VEGF to bind to VEGFR-2 which has strong tyrosine kinase activity [10]

In normal pregnancy, the serum concentration of sFlt-1 is 50-fold higher than in nonpregnant women. In early pregnancy, sFlt-1 concentrations decreased from ± 8 - 20 weeks, then gradually increased at 26-30 weeks. At 35-39 weeks of pregnancy there will be a fairly rapid increase in the concentration of sFlt-1. sFlt-1 levels after delivery will return to normal levels. However, in placenta accreta, sFlt-1 levels begin to decrease towards the end of the second trimester [11]. Research conducted by McMahon et al sought to determine the role of sFlt-1 in the regulation of cytotrophoblast cell invasion and establish a supportive environment in placental separation in patients with placenta accreta spectrum. From this study it was stated that the presence of low sFlt-1 concentrations in patients with placenta accreta spectrum was associated with the depth of invasion of the placenta to the uterine wall [12].

Uyunikoglu et al's study found that from 22 women with cesarean delivery, serum VEGF, PlGF, sFlt-1 were examined before and after surgery. This study found that serum VEGF, PlGF and sFlt-1 in placenta percreta in the preoperative period were lower than in control patients. Postoperative placenta percreta serum PlGF levels were the same as in the control group, but postoperative serum VEGF and sFlt-1 levels were higher than in the control group. Postoperative elevated levels of VEGF and sFlt-1 may be related to the release of mediators from the invasive placental bed into the peripheral blood after delivery. Uyunikoglu et al's study has several limitations, including the study only assessed serum VEGF, PLGF, sFlt-1 without comparing the expression of VEGF, PLGF, sFlt-1 in tissues. Another limitation is the small number of samples due to rare cases of placenta percreta at the time of the study [13].

The results of the study by Uyanikoglu et al. differ from the study by Tseng et al in 2006 which found an increase in VEGF expression in patients with placenta accreta. The weakness of the study conducted by Tseng et al

was that it did not evaluate VEGF levels in the maternal circulation. This study only carried out histopathological evaluation of placental tissue and the study sample included patients who were terminated in the 2nd trimester accompanied by other comorbid diseases [13].

4. Conclusion

Spectrum placenta accreta is one of the pathological conditions in pregnancy caused by the invasion and penetration of the placenta into the myometrium. the development of spectrum placenta accreta has a complex multifactorial process. One of the causative factors is suspected to be an imbalance between angiogenic and anti-angiogenic factors caused by hypoxia/ischemic conditions in the scar tissue from the previous manipulation in the uterus. Further studies are needed to have a deep understanding of the role of angiogenic and anti-angiogenic factors in spectrum placenta accreta.

Conflict of Interest

The author declares that they have no conflict of interest.

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