Medical Hypotheses 102 (2017) 37–40

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Mild anemia during pregnancy upregulates placental vascularity development

A. Stangret [a,*], M. Skoda [a], A. Wnuk [b], M. Pyzlak [a], D. Szukiewicz [a]

[a] Chair and Department of General and Experimental Pathology with Centre for Preclinical Research and Technology, Medical University of Warsaw, Poland
[b] Chair and Department of Obstetrics, Gynecology, and Oncology, 2nd Faculty of Medical University of Warsaw, Poland

ARTICLE INFO

Article history:
Received 23 September 2016
Accepted 5 March 2017

Keywords:
Pregnancy
Placenta
Angiogenesis
Anemia
Vascular endothelial growth factor (VEGF)
Placental growth factor (PlGF)
Hypoxia

ABSTRACT

The connection between maternal hematological status and pregnancy outcome has been shown by many independent researchers. Attention was initially focused on the adverse effects of moderate and severe anemia. Interestingly, some studies revealed that mild anemia was associated with optimal fetal development and was not affecting pregnancy outcome. The explanation for this phenomenon became a target for scientists. Hemodilution, physiologic anemia and relative decrease in hemoglobin concentration are the changes observed during pregnancy but they do not explain the reasons for the positive influence of mild anemia on a fetomaternal unit. It is hypothesized that hemodilution facilitates placental perfusion because blood viscosity is reduced. Subsequently, it may lead to a decline in hemoglobin concentration.

Anemia from its definition implies decreased oxygen carrying capacity of the blood and can result in hypoxemia and even hypoxia, which is a common factor inducing new blood vessels formation. Therefore, we raised the hypothesis that the lowered hemoglobin concentration during pregnancy may upregulate vascular growth factor receptors expression such as VEGFR-1 (Flt-1) and VEGFR-2 (FLK-1/KDR). Consecutively, increased fetoplacental vasculogenesis and angiogenesis provide further expansion of vascular network development, better placental perfusion and hence neither fetus nor the mother are affected.

Introduction

The association between maternal hematological parameters and pregnancy outcome has been presented by many independent researchers [1–14]. Hemoglobin (Hb) concentration and hematocrit (Ht) values have been analyzed throughout all trimesters of gestation which resulted in determining their recommended values by the Centers for Disease Control (CDC) and World Health Organization (WHO). According to the CDC Hb concentration greater than 11 g/dl in the first and last trimester of pregnancy, greater than 10.5 g/dl in the second trimester, and Ht value greater than 33% in the first and third trimester and greater than 32% in the second trimester are considered optimal [15–17]. However, further investigation of this issue revealed that lowered Hb concentration (9.5–10.5 g/dl) not only does not imply poor pregnancy outcome but indicates optimal fetal development and the lowest risk of pregnancy pathologies [18–22]. Even though the reasons for this phenomenon have been investigated widely the explanation to what extent mild anemia during pregnancy influences intrauterine environment remains unclear. We hypothesize that this may be a result of the angiogenic properties of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) exerted through its tyrosine kinase receptors: VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1/KDR). Furthermore we postulate that increased expression of Flt-1, which binds exclusively to PlGF, influence the growth of the infant birth body weight. We speculate that lowered Hb concentration and Ht values during pregnancy stimulate angiogenic processes within the placenta (through activation of PlGF receptor) providing optimal fetal development.

Evaluation of the idea

Vasculogenesis and angiogenesis within the placenta

Placenta is a unique, highly vascularized organ with the main function to mediate fetal-maternal exchange during pregnancy. Placental vascular network expansion is therefore a dynamic process that involves intravilli vasculogenesis prior to angiogenesis

* Corresponding author at: Pawińskiego 3c Str., Warsaw, Poland.
E-mail address: a.stangret@op.pl (A. Stangret).

http://dx.doi.org/10.1016/j.mehy.2017.03.007
0306-9877/

[23]. Vasculogenesis involves new blood vessels formation from differentiation of pluripotent mesodermal mesenchymal precursor cells into hemangiogenic stem cells and starts during the third week after conception. Angiogenesis, the consecutive process, starts within the fifth week after conception and is defined as the creation of new blood vessels from the pre-existing vasculature. Branching angiogenesis occurs between 32nd day and 24th week post conception. During this period formation of microvessels results in production of multiple short capillary loops which leads to an increase in number of capillary units. This involves two corresponding mechanisms - elongation and ramificaction of preexisting tubes. In the mid and late gestation the prevalence of nonbranching angiogenesis is observed in which microvessels formation involves production of longer but poorly branched capillary loops [24–31]. Fetoplacental vasculogenesis and angiogenesis are regulated by general and pregnancy-specific factors that control formation and maturation of the placental vascular network and hence adequate placental perfusion [32–37]. Disturbances in microvessels growth may result in such pathological conditions as intrauterine growth retardation (IUGR), preeclampsia (PE) or gestational diabetes mellitus (GDM) [38–47].

Concentration of VEGF, PlGF during pregnancy

There is a strong evidence that vasculogenesis and angiogenesis are consecutively regulated by different growth factors [36,48–53] including VEGF which is expressed ubiquitously at sequential steps of angiogenesis. VEGF is a cytokine that has several isoforms (VEGF-A, -B, -C, -D, -E and PlGF). VEGF and PlGF are postulated to be main factors involved in the formation of vascular network during pregnancy. As stated previously their angiogenic properties are exerted through membrane-associated tyrosine kinase receptors VEGFR1 (Flt-1) and VEGFR2 (Flk-1/KDR). According to the research the disruption of genes encoding VEGF receptors leads to an abnormal blood vessels formation causing embryonic lethality [27]. The concentration of VEGF and PlGF varies during gestation and maintaining the proper ratio between those two cytokines provides optimal vascular network development. Expression of VEGF-A (main isoform of VEGF) and VEGFR-2 are increased in early pregnancy. On the contrary, expression of PlGF and VEGFR-1 increase towards term [25].

Regulation of blood vessels formation by local oxygen

Biological variables such as hypoxia or ischemia upregulate the expression of VEGF or PlGF which activate their receptors [54–61]. From the onset of gestation and throughout the entire pregnancy hypoxia is a widely recognized factor which stimulates new blood vessels formation. Therefore, it is postulated to enhance fetoplacental vascularity development causing villi hypercapillarization. However, determination of the adequate values of oxygen tension during early embryo development leads to the conclusion based on the worldwide research that low oxygen conditions encountered during very early gestation are necessary and should not be defined as hypoxic in the pathological sense. Partial oxygen pressure (pO2) prior to 8 weeks of gestation is less than 20 mmHg but reaches a maximum of 60 mmHg at 16 weeks of gestation. After this time it continues to decline gradually until term (45 mmHg). Therefore, while defining "hypoxia" at a given site a particular point in time is important. But there is an unanswered question what oxygen concentration within trophoblast tissues determines hypoxia and what concentration is considered low comparing to the levels found in other tissues [24].

Physiologic anemia during pregnancy

During pregnancy the increase of plasma volume begins at about 6 weeks of gestation. However, plasma volume expansion exceeds the increase in red cell mass which naturally leads to a physiological hemodilution. Therefore, normal adaption changes in pregnancy affect Hb concentration. A consequent reduction in Hb concentration, to the values commonly regarded as indicating anemia, is accounted for "physiologic anemia" which occurs most noticeably during second trimester of gestation [5,6,62]. The excess of blood volume provides better placental perfusion with a concomitant increase in birthweight [1,2,63]. Moreover, hyperviscosity has a detrimental effect on the intervillous space with resultant poor maternal exchange. This can lead to a fetal growth impairment by decreased oxygen and nutrients transport or by fetal corticosteroids that are secreted in response to hypoxia [1,64]. The possible difficulties while diagnosing anemia during pregnancy result from the fact that a reduction in Hb concentration may be either relative or absolute. Hence, determination whether a decreased Hb concentration is a physiological or pathological phenomenon remains debatable [65]. Nevertheless, anemia implies a decrease in the oxygen-carrying capacity of the blood. If so, the insufficient tissue oxygenation may enhance angiogenic processes within the fetomaternal unit. On that account low pregnancy Hb levels might be indicative of hypoxia.

The hypothesis and discussion

Angiogenesis is the process occurring in a healthy human body and in various pathological conditions. Healing wounds or processes occurring in female eutherians during the menstrual or estrous cycle as well as in pregnancy account for physiological angiogenesis [24,27]. Aberrant vascularity development (either excessive or insufficient) can contribute to retinopathies, benign and malignant angiogenic tumors, progression of malignant tumors, arteriosclerosis, myocardial infarction, hypertension or diabetes [25,61].

During the physiological course of pregnancy proper vascularity development is of critical importance. It not only provides *in utero* development and survival of the fetus but also impacts its later life. Most of the pregnancy-related pathologies have been linked to deranged angiogenesis only confirming the crucial role of normal placental vascular formation. Angiogensis is regulated by many general and pregnancy-specific factors among which vascular growth factors concentration and oxygen tension play an important role. Decreased oxygen concentration stimulates formation and development of placental vascularity in the fetoplacental unit. The explanation to what extent maternal hematological status during pregnancy can represent the actual hypoxia within the placental tissues – in the pathologic sense – is still unclear. The ideas mentioned above point to reveal such correlation. However, the molecular explanation for the reasons of the observed changes is still missing.

Morphological changes in the placentas of women with anemia involve the following: increased fetal villous capillarization, greater volume and villous diameter and increased number of capillaries per villus cross section [28,66,67,35]. On the basis of the available data maternal anemia results in branching type of angiogenesis which may lead to a richly enlarged capillary area. Consequently, the placental volume and size are increased, however the functional capacity of the placenta is impaired. [68]. The increased density and the number of capillaries as well as compensatory placental hypertrophy have been reported in anemic women [69,70]. Those are few possible mechanisms that reveal adaptation mechanisms within the placental tissues to lowered Hb concentration