

MISCELLANEA

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THE ROLE AND REGULATION OF SECRETION OF ERYTHROPOIETIN IN PREGNANCY

ROLA I REGULACJA WYDZIELANIA ERYTROPOETYNY W CIĄŻY

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Abstract

Although erythropoietin plays a significant role in human metabolism, relatively little attention has been devoted in scientific literature to its role and mechanisms regulating its secretion in pregnancy. The authors of this article discussed the following issues:

- construction, biological role and regulation of erythropoietin secretion,*
- its extra-hematologic effect,*
- erythropoietin concentration in normal and complicated pregnancy,*
- erythropoietin secretion in placenta, including its effect on placental function,*
- the role of erythropoietin in evaluation of fetal well-being.*

What seems to be a particularly promising trend in further studies is popularizing the measurement of EPO concentration in cord blood or amniotic fluid as fetal hypoxia marker.

Key words: erythropoietin, pregnancy, placenta, fetal hypoxia

Streszczenie

Mimo, że erytropoetyna odgrywa w metabolizmie organizmu człowieka duże znaczenie, zagadnieniu roli i mechanizmom regulującym jej wydzielanie w przebiegu ciąży poświęcono w literaturze naukowej stosunkowo niewiele miejsca. Autorzy w niniejszym artykule omówili następujące zagadnienia:

- budowę, rolę biologiczną i regulację wydzielania erytropoetyny,*
- jej działania pozahematologiczne,*
- stężenie erytropoetyny w ciąży prawidłowej i powikłanej,*
- wydzielanie erytropoetyny w łożysku z uwzględnieniem jej wpływu na funkcję łożyska,*
- rolę erytropoetyny w ocenie dobrostanu płodu.*

Szczególnie obiecującym kierunkiem dalszych badań wydaje się być upowszechnienie oznaczania stężenia EPO we krwi pępowinowej lub w płynie owodniowym jako markera płodowej hipoksji.

Słowa kluczowe: erytropoetyna, ciąża, łożysko, niedotlenienie płodu

DEV. PERIOD MED., 2013, XVII, 3, 270-275

INTRODUCTION

Little attention is devoted in the scientific literature to the role of erythropoietin and the mechanisms regulating its secretion in pregnancy. Most papers deal with the problem of anemia in pregnant women, renal diseases accompanying pregnancy and inducing renal failure. There have been numerous publications, especially

within the last 10 years, on the role of erythropoietin as a predictive factor of intrauterine fetal hypoxia, in particular its duration.

A trend in current studies searching for tangible changes in blood serum erythropoietin concentration in the course of some pregnancy pathologies. The first paper on impaired erythropoietin secretion in pregnant

women with preeclampsia comes from the 1990s. Throughout nearly 20 years several similar papers have been published, however no clear findings have been reported up to now.

CONSTRUCTION, BIOLOGICAL ROLE AND REGULATION OF ERYTHROPOIETIN SECRETION

Erythropoietin (EPO) is a 165 amino acids glycoprotein with a molecular weight of 34 kDa. EPO molecule contains carbohydrate chains and sialic acid residues, indispensable for its production, secretion and fulfilling its biological function (1, 2). EPO activity requires two disulfide bridges between cysteine residues (2).

In adults 80% of EPO is released by type I renal peritubular cells in renal cortical interstitium. 20% of EPO is produced in hepatic stellate cells. However, in fetal life its main source is the liver (1, 3, 4, 5, 6). In acute hypoxia EPO hepatic secretion can exceed 1/3 of total production of this hormone (5). Secretion of small amounts of this hormone as well as EPO receptors were also identified in lungs, Leydig cells in testicles, spleen, endothelium of blood capillaries, as well as brain, uterus, oviducts, milk, B lymphocytes and megakaryocytes (1, 3, 5, 7).

EPO shows circadian secretion rhythm with the lowest values observed in the morning and the highest concentrations at night (2).

Human EPO gene is located on chromosome 7 (locus 7q11-q22), consists of 4 introns and 5 exons and encodes 193 – amino acid polypeptide (5). EPO gene has four key sequences: promoting, encoding, regulatory and the one responsible for tissue specificity (1).

Renal EPO production is stimulated by tissue hypoxia on the level of gene transcription (3, 4, 8, 9). The most frequent reason for hypoxia is anemia, but also insufficient tissue blood flow, impaired gas exchange in the lungs and increased haemoglobin's affinity for oxygen (1). Two transcription factors take part in the process of regulation of EPO production: hypoxia inducible factor-1 (HIF-1) and hepatic nuclear factor-4 (HNF-4) (1, 8, 9). HIF-1 protein consists of two subunits: alpha and beta. HIF-1alpha/HIF-1beta complexes with regulatory sequence in EPO gene, initiating its expression. HNF-4 acts synergistically with HIF-1, and thus the maximum of renal hormone secretion, as well as liver secretion in serious hypoxia, is achieved (1, 4, 10). The mechanism for intrarenal regulation of EPO secretion has not been fully elucidated. The key role seems to lean towards level of sodium reabsorption in the proximal tubule. This process is fully dependent on oxygen partial pressure. Experimental suppression of sodium reabsorption causes reduced EPO production (5).

The key role of the hormone is the regulation of erythropoiesis, i.e. the process of red blood cells production in bone marrow. Through cell membrane receptor EPO affects precursor cells (colony forming unit-erythroid, CFU-e) (3, 4). The EPO receptor (EPO-R) belongs to type I cytokine receptor family. Binding of Epo to its receptor causes homodimerization, followed by activation

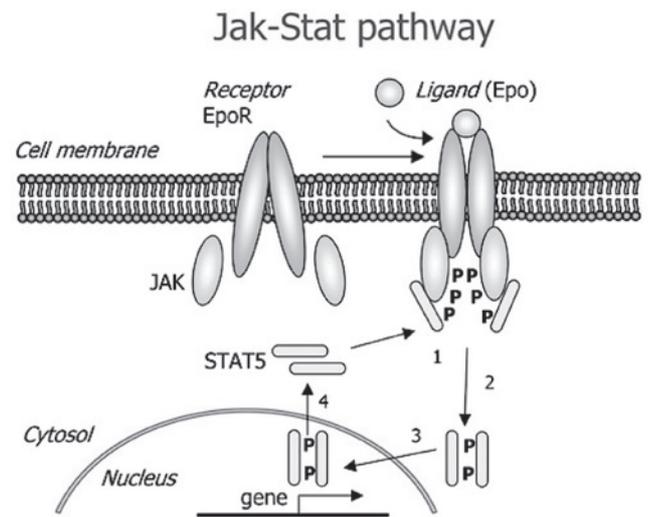


Fig. 1. Signal transmission pathway by receptor for erythropoietin by Klipp et Liebermeister (EPO-R). JAK – Janus kinase, STAT 5 – signal transducer and activator of transcription. 1 – phosphorylation of STAT 5 monomers; 2 – STAT 5 dimerization; 3 – migration to the nucleus; 4 – dephosphorylation and export to the cytoplasm (30).

of tyrosine kinase (Janus like kinase 2; JAK 2). Through signal transducer and activator of transcription 5 (STAT 5) JAK 2 kinases affect the activity of anti-apoptotic genes Bcl-2 and Bcl-XL. The described signal transmission path is presented in Figure 1 (according to Klipp and Liebermeister) (Fig. 1). The consequence of this chain of events is suppression of cells apoptosis in red blood system, as well as its proliferation and differentiation (1, 3, 4, 10).

Normal human serum EPO concentration ranges from 10 to 30 mU/mL when determined with radioimmunological method, which parallels to 2-7 pmol/L (5). Normal range of EPO concentration in pregnant women has not been determined.

EXTRA-HEMATOLOGICAL EFFECTS OF ERYTHROPOIETIN

EPO plays a significant role in acute and subacute response to tissue damage. According to numerous studies, EPO has cytoprotective effect on the cells of brain, heart, kidneys and other tissues. This protection consists of impeded apoptosis and anti-inflammatory activity. This mechanism remains unresolved (3, 6). Proinflammatory cytokines: TNF- α , IL-1 β and IL-6, as well as hypoglycemia and reactive oxygen species are known to increase the expression of EPO and its receptor (2). Except for preventing programmed cell-death and restricting the effects of proinflammatory cytokines, EPO facilitates tissues regeneration and restores its function (2). The above – mentioned signal transmission path JAK 2 \rightarrow STAT 5 \rightarrow Bcl-2 mediates its cytoprotective effect.

Numerous studies prove that EPO prevents apoptosis-induced oxidative stress, one of the key reasons for tissues damage (2, 3, 6). In the early stages of apoptosis destabilization of cell membranes leads to membrane phosphatidylserine

(PS) exposition, which can act as signal initiating cell phagocytosis. In later stage of apoptosis genomic DNA degradation follows. EPO is proved to prevent membrane phosphatidylserine exposition, and to impede genomic DNA degradation (2). Heme oxygenase HO-1 is the main mediator in antioxidative activity of EPO. Apart from HO-1 EPO can act via other antioxidative enzymes: glutathione peroxidase, glutathione catalase, superoxide dismutase (2). Additionally, EPO reduces blood loss following vessel injury and promotes thrombus formation.

It acts synergistically with thrombopoietin accelerating megacaryocyte maturation and production of blood platelets. EPO activates vessel endothelium, increasing the expression of molecules participating in thrombus formation. It stimulates vascular smooth muscles spasm, which reduces local blood flow and blood loss. In the case of long-lasting activity EPO initiates angiogenesis (2, 4).

Antioxidant and antiapoptotic effects of EPO can be used in the therapy of numerous diseases with underlying increased concentration of reactive oxygen species, reduced activity of antioxidative enzymes and advanced apoptosis.

However, biological effect of EPO is not always beneficial. Extra functions of erythropoietin are responsible for adverse effects of long-term EPO use, e.g.: arterial hypertension, retinopathy, prothrombotic effect, coronary vasoconstriction (2, 11). Research on the mechanism of the development of arterial hypertension in the course of treating chronic renal failure – induced anemia with preparations of recombinant human erythropoietin (rHuEPO) have demonstrated that what underlies the disorders is increased intracellular calcium concentration, which results in resistance to vasodilatory effect of nitric oxide. Fischer reports that EPO also causes increased endothelins production, changes in prostaglandin concentrations as well as stimulation of renin and angiotensin production (4).

In the central nervous system EPO-R is present on the neuronal surface, and EPO itself is produced by glial cells (astrocytes). It also occurs in cerebrospinal fluid, although renal EPO does not cross blood brain barrier under normal tissue oxygenation.

Central nervous system is most likely to have its own paracrine EPO system (1). Studies with the use of radioactive iodine have indicated that EPO is present in hippocampus and cortical cortex, i.e. areas most susceptible to hypoxia (1). Numerous in vivo and in vitro studies have found the neuroprotective effect of EPO in brain damages caused by ischemia, hypoxia, subarachnoid haemorrhage (1, 5, 6, 9). EPO is also responsible for proliferation and migration of endothelial cells in capillaries (1). EPO and EPO-R have also been found in glandular epithelium of uterine cavity mucus membrane as well as in basal layer stroma and in endothelial tissue of endometrial blood vessels (1). Uterus is the only organ, where angiogenesis occurs under physiological conditions. This process takes place when endometrium develops throughout the menstrual cycle. With the help of immunohistochemical techniques a gradual increase in EPO and EPO-R concentration was found from the mid – proliferative phase until the end of luteal phase of the menstrual cycle. Temporary EPO concentration increase in uterus is mediated by 17- β -estradiol that acts via estrogen receptor. Therefore,

EPO exerts an angiogenic effect on the endometrium (1). Higher EPO concentration in oviduct is also temporary, estrogen dependent and hypoxia – induced. The role of EPO in oviduct has not been elucidated (1). After the labor, in the period of lactation, EPO concentration increases in colostrum and milk, while it falls in blood serum (1), which implies it is actively secreted to milk. EPO potentially maintains the mother's lactation (1).

EPO and EPO-R have been found in the cells of breast cancer, kidney cancer, primary liver cancer, nephroblastoma, angioblastoma and in erythroleukemia. In the case of neoplastic diseases tissue hypoxia triggers undesirable EPO expression, which stimulates angiogenesis of tumor vessels and protects cancer cells. This may cause the neoplastic disease to develop and progress. However, there is no evidence that exogenous EPO administration influences cancer cells proliferation (1).

ERYTHROPOIETIN CONCENTRATION IN NORMAL AND COMPLICATED PREGNANCY

During pregnancy blood volume increases by around 50%, mainly due to higher blood plasma volume. Red blood cell mass rises by approximately 18-25%. Disproportionate increase of blood volume comparing to erythrocytes results in blood dilution, which is commonly described as 'physiological anemia of pregnancy' (12). Changes in circulatory system during pregnancy affect renal function. Renal blood flow and glomerular filtration increase by 30-50% (13).

EPO concentration has been proved to increase 2-4 – fold in the course of pregnancy (7, 8, 14, 15, 16), and plateau is achieved after 20 weeks of gestation (17). The reason for this phenomenon remains hazy. It is, however, believed that physiological blood dilution in pregnancy, increase of renal oxygen consumption due to intensified glomerular filtration as well as paracrine and autocrine mechanisms are likely to be responsible for increased EPO renal secretion in pregnancy (7).

Pregnancy anemia, most frequently caused by iron deficiency, can have serious consequences for mother and child. Maternal hemoglobin concentration <10,5 g/dL increases the risk of prematurity and low birth weight of the newborn. Iron deficiency is also associated with lower placental mass (14).

Some authors found no correlation between EPO and hemoglobin concentration in women with normal pregnancy in the first or second trimester.

This phenomenon is explained by weakened EPO response to anemia in early pregnancy and its intensification in the final stage (18, 19). Erdem et al. noticed that pregnant women with anemia have significantly lower hemoglobin and ferritin concentration, and higher blood serum erythropoietin level, compared to healthy pregnant patients (18). It was also found that EPO concentration in cord blood of newborn babies born by mothers with anemia is significantly higher than in healthy women's babies (18).

It has finally been acknowledged that anemia in pregnancy causes increased EPO secretion as a response

to low hemoglobin concentration and ferrum deficiency (18, 20). Elevated EPO concentration in cord blood of newborn babies born by mothers with anemia and an evident correlation between maternal and fetal ferritin concentration suggest that fetal erythropoiesis is stimulated by maternal anemia – induced fetal ferrum deficiency (18).

Goldstein et al. have indicated that acute and chronic bleedings in pregnancy as well as multiple pregnancy are associated with patient's elevated blood serum EPO concentration (21).

The link between increased blood serum EPO concentration in pregnant women and the occurrence of preeclampsia is controversial. There are various theories explaining this correlation. One hypothesis assumes that elevated EPO concentration in the blood of patients with preeclampsia is caused by reduced renal perfusion, which results in local relative hypoxia and compensatory increase of renal EPO secretion (16, 21). Another theory links intensified hormone secretion to anemia which is caused by hemolysis, often accompanying preeclampsia (21). According to *Hershkovitz et al.*, increased blood serum EPO concentration in these women results from reduced placental blood flow and its reduced oxygenation, which induces compensatory local EPO secretion by placenta. The described mechanism is supposed to result in increased total EPO pool in blood serum of pregnant patients with preeclampsia (16). In a study by authors of the above – mentioned theory patients with preeclampsia had statistically insignificant increase of EPO concentration compared to healthy pregnant women. In both groups patients did not differ with regard to parameters of laboratory tests for renal functions (urea, creatinine, uric acid). Additionally, no differences were found in compared groups in the level of hemoglobin and hematocrit. Thereupon, it has been acknowledged that placental fraction is responsible for elevated EPO level in patients with preeclampsia (16). In a study by *Goldstein et al.* pregnant women with preeclampsia presented over 2 – fold higher EPO concentration in comparison to normal pregnancies (21). *Koupke et al.* have found that EPO concentration in pregnant patients with preeclampsia was higher than in healthy pregnant women, the difference in results being statistically insignificant however. Moreover, blood serum EPO concentration has been found to negatively correlate with hematocrit value and hemoglobin concentration (22).

In the case of preeclampsia one can also pose a question, if elevated maternal EPO concentration is just a result, or rather one of its drivers. The second option could be advocated by the fact that researchers succeeded in experimentally inducing placental vascular smooth muscles spasm with rHuEPO (16, 23).

PLACENTAL ERYTHROPOIETIN SECRETION AND ITS INFLUENCE ON PLACENTAL FUNCTION

Maternal blood serum EPO pool is increased by placental EPO secretion (7, 16, 23). Using ELISA method

the expression of EPO and its receptor was found in villi and extravillous cytotrophoblast in human placenta at various stages of pregnancy. The presence of EPO-R was noticed in vascular endothelium of fetal – placental circulation (24). It is believed that EPO sustains survival, proliferation and differentiation of trophoblast cells (7). A study by *Clapp et al.* questions the role of placenta as an important, extrarenal source of EPO production (15). No significant association was found between EPO concentration and the development of placenta in the second trimester, its size on the date of labour, as well as infant birth weight (15).

Toth et al. conducted a study, whose aim was to determine the level of EPO and EPO-R expression in trophoblasts in the first trimester of normal pregnancies, miscarriages and hydatid mole (19). Using immunohistochemical methods and real time PCR it was found that EPO-R expression was intensified in trophoblastic villi in the case of pregnancy loss due to miscarriage and hydatid mole. In these cases it was also discovered that EPO expression was higher in extravillous trophoblast. In decidua, in turn, EPO and its receptor's expression was found to be elevated in selected pathologies of early pregnancy (19). In order to decide whether higher EPO and EPO-R expression results from hypoxia in tissues of pregnancies lost due to miscarriage or is a marker of intensified angiogenesis in the case of hydatid mole, further studies are required.

Resch et al. have conducted an experiment on the influence of recombinant human erythropoietin in vitro on human placental blood vessels coming from full-term, uncomplicated pregnancies. The experiment has shown direct, administered dose – dependent, vasoconstrictory effect of rHuEPO on isolated human placental blood vessels. A stronger effect has been observed in relation to veins rather than arteries, which could be explained by differences in the construction of muscle layer in both vessel types (24). This paper also investigated into the influence of losartan (angiotensin II type 1 receptor antagonist, AT1) and of captopril (angiotensin convertase inhibitor) on vasoconstrictory effect of rHuEPO. It has been found that losartan, as opposed to captopril, annuls the described effect. This observation allows to draw a conclusion that vasoconstrictory effect of rHuEPO on human placenta may be mediated by AT1 receptor (24). Similar conclusions result from previous studies by *Barrett et al.* using a rat model (5). Angiotensinogen and EPO display structural similarities (24). In full – term human placenta AT1 receptors dominate, compared to decisively lower expression level of angiotensin II type 2 receptors. A correlation between the development of preeclampsia and AT1 receptor activation has been described (24).

Blood circulation in fetal – placental unit undergoes humoral regulation, whose effect is promptly visible. A₂ thromboxane and endothelin-1 are responsible for vasoconstriction, while nitric oxide and prostacyclin determine vasorelaxation. The effect of genome regulation of vascular walls tension is postponed, as it is based on changes in genes expression and activity of diverse transcriptive factors. A study by *Resch et al.*, using rHuEPO

at concentration of 300 U/mL, has demonstrated its direct vasoconstrictory effect on isolated human placental blood vessels (24). British scientists under Jain have proposed a study model, in which placental vessels were exposed for 24 hours to the influence of EPO at concentration of 3 U/mL. The study was assumed to reflect the maximum, local EPO concentration in vascular system subject to analysis (26). Consequently, findings were opposite to Resch's observation: EPO has suppressed vasoconstrictory effect of A_2 thromboxane and endothelin-1 on placental arterial vessels. The authors have recognized that the hormone used in this study belongs to growth factors modulating the second type of blood flow regulation mechanism, which occurs delayed (26). According to Jain et al. EPO's ability to suppress the effect of the strongest vasoconstrictory substances may be an important defensive mechanism of hypoxic fetus, which reduces vascular resistance and improves its oxygenation (26).

THE ROLE OF ERYTHROPOIETIN IN EVALUATION OF FETAL WELL-BEING

The fact that EPO does not go through the placenta implies that its concentration in cord blood reflects fetal hormone secretion (27, 28). In fetal life EPO is initially produced in the yolk sac, and next in the liver. As pregnancy progresses, its synthesis is taken up by kidneys. The hormone is excreted in urine to amniotic fluid (27). Except for the placenta, EPO secretion can also be found in fetal spleen and bone marrow (24, 26).

Increased fetal EPO concentration is observed in the case of maternal anemia, probably as a result of fetal – placental unit hypoxia (26). Over 10-fold EPO concentration increase in fetal circulation, as an expression of fetal hypoxia, occurs in pregnancies complicated by fetal malnutrition, post term pregnancy and smoking in pregnancy (26, 29). In the literature there are reports of a link between elevated EPO concentration in fetal blood in the case of maternal preeclampsia and diabetes in pregnancy, intrauterine growth restriction, the presence of meconium in amniotic fluid as well as abnormal CTG trace during pregnancy and labour (27, 28). In amniotic fluid higher EPO concentration is observed in pregnancies complicated by hypertension, diabetes and in the case of anti-Rh immunization (28).

Studies on the clinical use of fetal EPO concentration determination for the purpose of evaluation of fetal well – being have been going on for many years. Girsen et al. have described elevated EPO level in umbilical artery of infants with hypotrophy, which was associated with the extent of hemodynamic disorders observed in fetal echocardiography. It was also found that in chronic hypoxia the level of placental EPO exceeded renal hormone secretion (27).

In a study using animal model Kakuya et al. have indicated that EPO concentration in amniotic fluid of pregnant female rats after 9 hours' long hypoxia was comparable to EPO concentration in fetal blood of rats, determined 3 hours after occurrence of hypoxia. It was additionally observed that normalization of EPO level in blood serum lasted for 12 hours, and in amniotic fluid for over 48 hours (29). Based on this data the authors have

drawn the conclusion that elevated EPO concentration in amniotic fluid during labour is an indication of chronic, pre-labour fetal hypoxia (29).

The same authors from Japan have conducted a study in a population of 113 children born in their center in a 4 year period in the early nineties of the twentieth century (1991-1994). It turned out that acute, intrapartum hypoxia was associated with higher EPO concentration in cord blood, without influence on EPO level in amniotic fluid, while chronic fetal hypoxia occurring before the labour resulted in elevated EPO concentration in amniotic fluid (29).

Teramo et al. have observed in their study elevated EPO concentration level in fetal blood serum and in amniotic fluid in pregnancies complicated by chronic arterial hypertension, pregnancy – induced hypertension and preeclampsia. The authors compared the course of pregnancy complicated by hypertension in 75 women with a normal course of pregnancy in 23 women (28) and found i.a. no differences between the groups in fetal blood serum EPO level, pH and remaining blood gasometric parameters in the umbilical artery, as well as in Apgar score in the first minute of life (28). Infants with elevated EPO concentration were admitted to intensive care units 6 times more frequently (29). Elevated EPO concentration was also associated with lower pH in the umbilical artery (<7.26), $pO_2 <12$ mm Hg and Apgar score <8 points in the first minute (28).

The close correlation between EPO level in amniotic fluid and in fetal blood can contribute to practical use of EPO concentration determination as a new marker of intrauterine fetal hypoxia in the case of pregnancy complicated by arterial hypertension.

Similarly, the issue of erythropoietin's significance as another indicator of intensified pathology in pregnancy with impaired fetal – placental circulation still remains relevant and interesting.

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Author's contributions/Wkład Autorów

According to the order of the Authorship/Według kolejności

Conflicts of interest/Konflikt interesu

The Authors declare no conflict of interest.

Autorzy pracy nie zgłaszają konfliktu interesów.

Received/Nadesłano: 26.02.2013 r.

Accepted/Zaakceptowano: 29.04.2013 r.

Published online/Dostępne online

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