

Placental eicosanoids as endocrine and paracrine mediators during pregnancy

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Abstract

Eicosanoids, biologically active molecules possessing a wide range of functions, include prostaglandins, thromboxanes and leukotrienes. During pregnancy, eicosanoids are produced by the chorionic membranes and the decidua as well as by the placenta. The eicosanoids play an important role throughout pregnancy. During implantation, they enable the trophoblast to invade and colonize the maternal spiral blood vessels of the myometrium. Through the entire period of fetal growth and development, eicosanoids play a significant role as vasoregulators of fetal - uterine blood

flow and circulation. Prostaglandins also have the ability to affect placental protein synthesis and the modulation of the production of certain other hormones. Finally, eicosanoids promote the initiation and progress of labor. The aim of this study was to review recent literature data on the spectrum of eicosanoids functions during pregnancy while seeking to identify their potential role in pathological conditions.

Key words: eicosanoids; prostaglandins; pregnancy; labor; placenta

Eicosanoids represent a wide category of hormones, among which are prostaglandins, thromboxanes and leukotrienes. Arachidonic acid, a multi - unsaturated fatty acid consisting of 20 carbon atoms, is the initial molecule in the process of their synthesis. Since eicosanoids cannot be stored after their production, their synthesis is dictated by the organism's needs. The primary molecule, arachidonic acid, is an enzyme released by membrane

phospholipids under the action of phospholipase A2. It is of note that the cells of several target tissues may respond to eicosanoids via specific receptors of their cellular membrane.

During pregnancy, eicosanoids are produced by the chorionic membranes and the decidua, while a number of leukotrienes are also produced by the placenta itself. Additionally, the placenta may convert arachidonic acid into thromboxanes, prostacy-

clin, prostaglandins PGE2, PGF2a and PGD2¹.

The role of eicosanoids is important throughout pregnancy. Eicosanoids favor the procedures of implantation as well as the initiation and progress of delivery, while they simultaneously support the maintenance of gestation and normal fetal growth. Oxytocin stimulates the decidual cells thereby increasing the rhythm of PGF2a synthesis². Towards the end of gestation, the concentration of arachidonic acid becomes extremely elevated in the chorionic membranes³. Eicosanoids exert numerous functions all through pregnancy, which can be divided according to the stage of pregnancy.

The aim of this review study was to analyze current literature data concerning the wide range of functions of eicosanoids throughout gestation while concurrently seeking to pinpoint their potential role in pregnancy complications.

Implantation

The crucial role of eicosanoids at the stage of implantation was proven following the observation that indomethacin, a cyclooxygenase inhibitor, inhibits the procedure of implantation as well. In addition, research studies have clearly demonstrated that during implantation, the production of prostaglandins and thromboxanes and, most importantly, the synthesis of prostacyclin enable the trophoblast to invade and colonize the maternal spiral blood vessels of the myometrium. Prostacyclin is a vasodilating molecule which also inhibits platelet aggregation. The final outcome is the creation of an ideal milieu for implantation⁴⁻⁶.

Fetal growth

Eicosanoids participate in the complex procedures of fetal growth and development. Prostaglandins, thromboxanes and prostacyclin play a major role as vasoregulators of the fetal - placental - uterine blood flow and circulation that supplies all the necessary molecules and oxygen to the fetus, thus ensuring normal intrauterine growth⁷.

The PGE2 acts via vasodilation of the uterine ves-

sels and vasoconstriction of umbilical circulation, while PGF2a exerts vasoconstrictive action on both uterine and umbilical circulation. In cases of arterial hypertension in pregnancy or preeclampsia, reduced levels of prostacyclin and an increased production of thromboxanes have been described⁸⁻¹⁰.

However, prostaglandins do not have only a vasoregulatory role. They are also capable of affecting placental protein synthesis and modulating the production of certain other hormones. Although PGF2a is a factor which down - regulates the production of human chorionic gonadotropin (hCG), there are however in parallel controversial data supporting the notion that PGF2a may also stimulate the secretion of hCG. Other in vitro research studies conclude that arachidonic acid - more robustly than its derivatives - is responsible for the down - regulation of hCG. Furthermore, both prostacyclin and PGE2 seem to increase the levels of cAMP.

Labor

The eicosanoids play a major role not only in the initiation but also in the progress of labor. The prostaglandins are involved in the contraction of the uterine smooth muscle cells, while PGF2a enhances the uterine contractions after the administration of oxytocin, which results in the creation of gap ligaments among uterine smooth muscle cells^{2,11}. Estradiol favors this procedure as well. The abovementioned gap ligaments enable the uterine smooth muscle cells to contract in a synchronized manner, one that closely resembles the contractions of the heart ventricles. Finally, prostaglandins act upon the cervix uteri leading to cervical ripening, via softening, and to elimination and dilatation of the cervix early in labor. This ripening resembles to the inflammatory response during which an invasion of polymorphonuclear leukocytes takes place. The above understanding of prostaglandin functions has resulted in recourse to high - dose prostaglandins administration in pregnant women prior to the 24th week of gestation to induce iatrogenic termination of pregnancy (phar-

maceutical abortion) when a major indication for this decision is present.

At specific doses, prostaglandins are ideal for induction of labor. Depending on the mechanism of cervical ripening, prostaglandins are administered in women with a low Bishop score as a method for induction of labor in full - term pregnancies or when the maintenance of gestation increases the risk of perinatal morbidity and mortality (for example, in cases of maternal diabetes mellitus in combination with fetal macrosomia). In addition, their administration is helpful prior to such gynecological procedures as diagnostic or operative hysteroscopy, especially in women without a history of vaginal delivery.

Finally, arachidonic acid has been shown to act similarly when given intraamniotically, this being inverted in cases of prolonged aspirin administration, as aspirin is a cyclooxygenase inhibitor¹²⁻¹⁴.

Factors associated with increased eicosanoids production

The factors which are associated with increased eicosanoids production include corticotropin releasing hormone (CRH), several cytokines and growth factors.

Both CRH and cytokines actively participate in labor, with the increase of eicosanoids representing one of their main potential pathways of action. Additionally, glucocorticosteroids, progesterone and estrogens influence the production of eicosanoids, and especially that of prostaglandins. Furthermore, gonadotropin releasing hormone (GnRH) affects the production of prostaglandins by the placenta. However, the character and the degree of association between chorionic GnRH and placental prostaglandins depends on the age of gestation. Generally, in cases of elevated GnRH levels, the placental production of prostaglandins is higher. Of particular interest is fact that a GnRH antagonist may lead to the down - regulation of prostaglandins production.

Several growth factors, mainly endothelial growth factor (EGF) and platelet activating factor (PAF), fa-

vor prostaglandins production, this leading to increased secretion by the chorionic membranes. PAF plays a major role in regulating prostaglandins secretion during labor, this factor being found in the amniotic fluid during the process of labor but not prior to its initiation¹⁵⁻¹⁷.

Conclusions

It appears clear that eicosanoids crucially contribute to an uncomplicated start of pregnancy through their significant involvement in the process of trophoblast implantation, the maintenance and progress of gestation by means of their participation in the complex procedures of fetal growth and development, and the initiation and progress of labor via multiple actions in the myometrium and the cervix uteri. ■

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