

Estrogen and Preeclampsia: Potential of Estrogens as Therapeutic Agents in Preeclampsia

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Abstract: There is a significant decline in the estrogen levels in preeclampsia, and exogenous administration of estradiol normalizes blood pressure and other associated symptoms of preeclampsia. The decrease in estrogen levels may be due to changes in enzyme activities of hydroxysteroid (17- β) dehydrogenase 1, aromatase, and COMT. There is also a decrease in the novel, estrogenic G-protein-coupled receptor 30 (GPR30) in the placental trophoblast cells in preeclampsia. The activation of GPR30 protects the placenta from hypoxia-reoxygenation injury, decreases apoptosis and increases proliferation through eNOS and PI3K-Akt signaling pathways. Estrogens may also increase Ca²⁺-activated K⁺ channel function, decrease the release of inflammatory cytokines, and oxidative stress to improve placental perfusion. Both preclinical and clinical studies show the decrease in the 2-methoxyestradiol levels in preeclampsia, which may be due to a decrease in estradiol itself along with a decrease in the enzymatic actions of the COMT enzyme. 2-Methoxyestradiol activates HIF1 α and vascular endothelial growth factor receptors (VEGFR-2) to maintain placental perfusion by increasing angiogenesis. The present review discusses the preclinical and clinical studies describing the role of estrogen in preeclampsia along with possible mechanisms.

Keywords: estradiol, oxidative stress, hypertension, inflammation, perfusion

Introduction

Preeclampsia is one of the most common causes of maternal and fetal mortality worldwide.¹ Preeclampsia is characterized by placental hypoxia, reduction in uteroplacental perfusion and progressive rise in blood pressure.² As per the American College of Obstetrics and Gynecology, preeclampsia is defined as the state of pregnancy with systolic blood pressure \geq 140 mmHg systolic or diastolic blood pressure \geq 90 mmHg after 20 weeks of gestation along with significant proteinuria ($>$ 300 mg/24 hours or protein/creatinine ratio $>$ 0.20). In preeclampsia, organ failure very common, and due to persistent hypertension, there may be the malfunction of kidneys, liver, and lungs.³ The development of hypoxia, initiation of inflammation and an increase in oxidative stress may contribute to inducing endothelial dysfunction, which may be important in reducing perfusion of the placenta.⁴

Estrogen is an important female sex hormone, and it produces several important functions in the female genital system. Amongst its different functions, the role of estradiol in maintaining placental perfusion has been identified. Indeed, a very early study in 1932 showed the vascular effects of estrogens and it was shown that crude follicular estrogen results in vasodilatation in the uterine endometrial tissue.⁵

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Subsequent studies supported this finding and showed that estrogens are the potent vasodilators and increase the blood flow to several organs, including the uterus.^{6,7} Owing to its vasodilatory actions, a rise in the estrogen levels during pregnancy may contribute to maintaining the uteroplacental vascular functions. Indeed, it has been found to induce and maintain uterine vasodilation during pregnancy.^{8,9} The mechanisms involved in estrogen-mediated maintenance of uteroplacental vascular function are identified. However, it has been proposed that estrogen may produce vasodilation indirectly through prostacyclin,¹⁰ nitric oxide,¹¹ or endothelium-derived hyperpolarizing factor (EDHR).¹² Estrogen produces its actions through ER α and ER β receptors, which usually initiate transcriptional changes. However, the acute vasodilatory actions of estrogen have been attributed to the non-genomic actions of ER α and ER β .¹³ Interestingly, estrogen has also been found to produce rapid, non-genomic vasodilatory actions via transmembrane G-protein-coupled receptor 30 (GPR30).¹⁴

Since there is a considerable role of estrogen in maintaining the uteroplacental vascular function, it has been postulated that a decrease in estrogen levels may contribute in compromising the placental perfusion during pregnancy. Indeed, several clinical studies have documented a significant decrease in the levels of estradiol during preeclampsia.¹⁵ Accordingly, the exogenous administration of estrogen has been shown to produce beneficial effects in animal models as well as in preeclampsia patients.^{16,17} The precise mechanisms responsible for the decrease in estrogen levels are not clear. It may be possible that the changes in estrogen levels may be due to variations in its metabolism during pregnancy.^{18,19} The present review discusses the pre-clinical and clinical studies describing the role of estrogen in preeclampsia along with possible mechanisms.

Preclinical Studies Showing the Role of Estrogen in Preeclampsia

There have been studies showing the key role of estrogen in the pathobiology of preeclampsia-like features in animals.

Exogenous Estrogen Reduce the Symptoms in Experimental Models

In an endotoxin perfusion-induced experimental model of preeclampsia in 14-day-pregnant rats, injection of 17 β -estradiol (1 mg/kg/d) was shown to significantly reduce the blood pressure and albuminuria. Moreover, it also

attenuated the expression of inflammation-associated adhesion molecule CD(49d) and TNF- α levels in a significant manner. It suggests that 17 β -estradiol has the potential to improve the symptoms of experimental preeclampsia, which may be due to a decrease in the levels of inflammatory mediators.²⁰ Exogenous administration of estradiol has also been shown to produce beneficial effects in L-NAME-induced preeclampsia model in rats by preventing the inflammation and preserving the endothelial functions. In pregnant rats receiving a daily i.p. injection of L-NAME and 100 μ g/kg estradiol, there was a significant decline in the blood pressure and 24-h urine protein in comparison to only L-NAME-receiving pregnant rats. Treatment with L-NAME increased the blood pressure, urinary protein, rate of stillbirths and suppressed fetal weight as compared to normal control animals. Administration of estradiol attenuated L-NAME-induced deleterious effects in a pregnant state. Besides, estradiol increased the levels of nitric oxide and decreased the levels of inflammatory cytokines, including IL-1 β (Figure 1), IL-6, IFN- γ , monocyte chemoattractant protein-1, intracellular adhesion molecule 1 and lymphocyte function-associated antigen-1.²¹

2-Methoxyestradiol is a metabolite of estradiol and is derived by the action of the enzyme catechol-O-methyltransferase (COMT). In COMT-deficient pregnant mice, preeclampsia-like features have been identified in these mice along with a significant decline in 2-methoxyestradiol levels. It is possible that the deficiency of 2-methoxyestradiol indirectly signifies the deficiency of estradiol in preeclampsia; however, this relationship is not very completely proven. Furthermore, exogenous administration of 2-methoxyestradiol was shown to ameliorate all preeclampsia-like features in pregnant mice.²² However, it should be very clear that, unlike humans, animals do not develop preeclampsia and there are important structural differences in the placental anatomy of animals and humans. Therefore, the animal models of preeclampsia do not truly represent the preeclampsia-like state in humans. Nevertheless, these animal models are very useful for the preliminary investigation of drugs with the potential to lower blood pressure during pregnancy.

Mechanisms Involved in Producing Beneficial Effects of Estrogens in Preeclampsia

Ca²⁺-Activated K⁺ Channel Function

The presence of large-conductance K_{Ca} (Ca²⁺-activated K⁺ channel function) on the endothelium is involved in

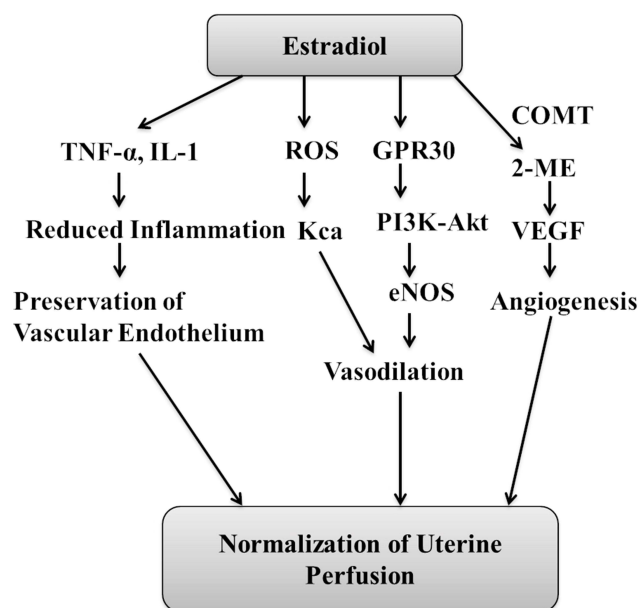


Figure 1 Representative diagram showing the possible mechanisms that may contribute in estradiol-mediated maintenance of uterine perfusion during pregnancy. The decrease in estradiol levels may blunt these protective mechanisms and may lead to the development of preeclampsia.

Abbreviations: 2-ME, 2-methoxyestradiol; COMT, catechol-O-methyltransferase; VEGF, vascular endothelial growth factor; ROS, reactive oxygen species; GPR30, G-protein-coupled receptor 30.

regulating vascular tone by inducing smooth muscle relaxation.²³ There have been studies showing that the upregulation of Ca^{2+} -activated K^{+} channel plays a key role in the normal adaptation of uterine arteries during pregnancy and chronic hypoxia-induced downregulation of these channels may contribute to the development of preeclampsia.²⁴ Through in vitro studies involving uterine arterial smooth muscle cells in pregnant animals, it has been shown that estrogens may increase the large-conductance K_{Ca} (Ca^{2+} -activated K^{+} channel function) in the uterus to decrease preeclampsia and associated complication. Indeed, it has been shown that hypoxia triggers the production of free radicals, which may inhibit large-conductance K_{Ca} . Hypoxia-induced increase in oxidative stress was shown to abolish the estrogen-induced increase in large-conductance K_{Ca} . These negative effects of free radicals were abolished in the presence of antioxidant, N-acetyl cysteine. It suggests the hypoxia-mediated increase in free radicals may negatively regulate the functions of estrogen on the large-conductance K_{Ca} to induce the development of preeclampsia (Figure 1).²⁵

Vascular Endothelial Growth Factor Receptors (VEGFR-2)

Vascular endothelial growth factor (VEGF) is an endogenous angiogenesis promoting factor and the decrease in

VEGF has been related to the development of preeclampsia.²⁶ It is also identified that an excess of placental expressed soluble fms-like tyrosine kinase-1 scavenges VEGF to induce generalized endothelial dysfunction.²⁷ Accordingly, various interventions to restore the angiogenic balance in preeclamptic pregnancies have been found to improve maternal and neonatal outcomes.²⁸ Using the first trimester of human placental villous explants, it has been shown that 2-methoxyestradiol may act by modulating vascular endothelial growth factor receptors (VEGFR-2). It was shown that exposure of placental villous explants to hypoxia produced preeclampsia-like features, including an increase in soluble fms-like tyrosine kinase-1 (antiangiogenic factor). There was also a decrease in the protein and transcript levels of VEGFR-2. However, overnight treatment with 2-methoxyestradiol rescued altered expression levels of VEGFR-2, sFlt-1 and HIF1 α . It possibly suggests that 2-methoxyestradiol may be beneficial in attenuating preeclampsia-like features by modulating VEGFR-2 (Figure 1).²⁹

G-Protein-Coupled Receptor 30, eNOS and Akt

G-protein-coupled receptor 30 (GPR30) is a novel estrogen receptor and these receptors are reported to play a key role in several estrogenic effects. It has been reported that there is a decrease in the expression of GPR30 in the placental extravillous trophoblast cells in the preeclamptic placenta. Moreover, treatment with 17 β -estradiol has been shown to increase the GPR30 expression on the placental HTR8/SVneo cells.³⁰ It has been well reported that the maintenance of appropriate trophoblast cell invasion is very important for a normal pregnancy. On the other hand, the defective trophoblast invasion results in shallow placental implantation and inadequate remodeling of the uterine spiral arteries. It may result in hypoperfusion of the placenta and the development of preeclampsia.³¹ Using immortalized human trophoblast cell-line HTR8/SVneo, the key role of estradiol in inducing trophoblast invasion has been described. Indeed, it has been shown that the selective GPR30 agonist G1 and 17- β -estradiol improve trophoblast cell invasion through PI3K-Akt signaling pathway. However, pretreatment with a selective GPR30 inhibitor G15 was shown to abolish these effects, implying that estradiol may be involved in trophoblast invasion through activation of GPR30.² Another study has shown that selective GPR30 agonist G1 and 17- β -estradiol protect the cultured extravillous trophoblasts (placental tissue removed at the end of pregnancy and cells grown in the

culture media) from the hypoxia-reoxygenation injury. Indeed, these cells were protected from apoptotic cell death and showed higher proliferation in the presence of G1 and 17- β -estradiol. However, the addition of selective GPR30 inhibitor G15 was shown to abolish the protective effects of G1 and 17- β -estradiol, suggesting the key role of GPR30 in regulating cell survival and cell proliferation in the hypoxia-subjected placenta during preeclampsia.³²

Human umbilical vein endothelial cells (HUVECs) are derived from the endothelium of veins of the umbilical cord and have been extensively employed as a laboratory model system to study the function and pathology of endothelial cells including angiogenesis.³³ Using human umbilical vein endothelial cells (HUVECs), it has been shown that 17- β -estradiol promotes angiogenesis through activation of GPR30. It was reported that hypoxia led to a significant decline in the total pipe length of the tube-like structure in endothelial cells, suggesting the inhibitory effects of hypoxia on angiogenesis. However, treatment with 17- β -estradiol significantly attenuated the hypoxia-induced decrease in angiogenesis. Treatment with estradiol also increased the expression levels of GPR30, endothelial nitric oxide synthase (eNOS) and p-Akt levels in the endothelial cells. However, pretreatment with Wortmannin, an inhibitor of PI3K/Akt, significantly attenuated the expression of eNOS and prevented endothelial cell tube formation in estradiol-treated cells. Accordingly, it was proposed that 17- β -estradiol activates GPR30 to stimulate eNOS and Akt signaling in the endothelial cells to promote placental angiogenesis,³⁴ which may contribute to overcoming placental insufficiency during preeclampsia.

Clinical Studies

Decrease in the Estrogen Levels and Its Biosynthetic Enzymes

Decrease in the Estrogen Levels

There have been studies showing a decrease in the plasma levels of estrogen in preeclampsia patients.³⁵ A clinical study identified a significant alteration in the homeostasis of gonadal hormones in preeclampsia patients. It was identified that there was a significant decrease in the levels of estrogen and progesterone, along with a rise in the testosterone content. Furthermore, it was identified that there was a significant decline in the nitric oxide levels in the blood, which possibly signified the presence of endothelial dysfunction. Accordingly, it may be possible that reduction in the levels of estrogen and progesterone may induce

endothelial dysfunction to decrease the levels of vasodilatory molecule, nitric oxide, which may contribute to the development of preeclampsia.³⁶ In preeclamptic pregnancies, the underexpression of estradiol along with upregulation of mRNA and protein levels of estradiol receptors has been reported. The decrease in estradiol levels may be responsible for increasing the expression of estradiol receptors. Accordingly, it is suggested that dysregulation of estradiol and estrogen receptors may contribute to the pathogenesis of preeclampsia.³⁷ More studies have shown a decrease in the plasma levels of estradiol-17 β and estrone in preeclampsia of varying severity, suggesting that the aberrant synthesis and metabolism of estrogens contribute to the pathogenesis of preeclampsia.^{18,19} Due to abnormal metabolism, it has been identified that there is a relative increase in the high plasma levels of 16-keto-estradiol with concomitant low levels of estradiol-17 β and estrone in women with severe preeclampsia. The high levels of this 16-keto-estradiol may be the result of aberrant metabolic changes and may contribute to the development of preeclampsia.¹⁸ However, there is a need for more studies to identify the precise changes in the estrogen metabolic pathways that may contribute to reducing estradiol levels in preeclampsia. A clinical study involving 86 preeclamptic and 97 gestation-matched normotensive pregnancies has shown a significant decrease in the serum levels of estrogen and progesterone, which may contribute to impairing placental function in preeclampsia.³⁸ A very recent clinical study has identified that there is a significant decrease in estradiol levels during preeclampsia along with a decrease in ER α protein, with no significant change in the ER β levels in the nucleus and cytoplasm of syncytiotrophoblasts and stromal cells.³⁹

Alteration in 17 β -Hydroxysteroid Dehydrogenase and Aromatase Enzymes

Hydroxysteroid (17- β) dehydrogenase 1 (HSD17B1) is a steroidogenic enzyme and it catalyzes the conversion of estrone (less active estrogen) to 17 β -estradiol (more active estrogen). It has been shown that there is a decrease in the plasma levels of HSD17B1 in preeclampsia women. Moreover, it has also been shown that HSD17B1 is an independent risk factor for predicting the onset of preeclampsia in pregnant women in the second trimester. Therefore, a decrease in plasma levels of HSD17B1 may contribute to the development of preeclampsia.⁴⁰ Another study revealed the presence of significantly lower estradiol and estrone levels in the plasma of women with

preeclampsia. The decreased circulating levels of estrogens were attributed to significantly lower expression of placental aromatase. Moreover, it was reported that dysregulation of steroidogenesis appeared much earlier than the appearance of symptoms of preeclampsia, which suggests that the abnormalities in steroidogenesis may be employed as important markers to diagnose preeclampsia before the appearance of clinical symptoms.⁴¹

Along with it, there is also a significant change in the enzymatic activities of 17 β -HSD3 (an enzyme involved in testosterone synthesis) and aromatase (an enzyme involved in converting androgens to estrogens) in preeclamptic placentas. Indeed, it has been shown that there is a significant increase in 17 β -HSD3 and a decrease in aromatase in the preeclamptic placentas, which may contribute in reducing the estrogen levels in the plasma during preeclampsia. It was found that testosterone directly repressed the expression of aromatase, while it promoted the miR-22 expression in the preeclamptic placenta. In turn, miR-22 directly inhibited estrogen receptor α expression and indirectly decreased aromatase expression and estradiol production by interfering with estrogen receptor α signaling. It suggests that an increase in testosterone represses estrogen signaling by upregulating miR-22 in the placenta, and this imbalanced steroid hormone production may be critical in the development of preeclampsia.⁴² There is another study showing a significant decrease in placental aromatase activity in preeclampsia patients.⁴¹

Decrease in COMT Activity Leading to Decrease in 2-Methoxyestradiol Levels

2-Methoxyestradiol is a metabolite of estradiol, which is produced by the metabolic actions of COMT. However, apart from just a metabolite of estradiol, it renders important physiological actions in the reproductive system of females.⁴³ It has been documented that the plasma levels of 2-methoxyestradiol are significantly reduced in preeclampsia patients⁴⁴ and this reduction may be possibly due to a decrease in COMT activity⁴⁵ and a decrease in estradiol levels.⁴⁶ In preeclampsia patients with 11 to 14-week pregnancy, a significant decline in the plasma levels of 2-methoxyestradiol has been reported.⁴⁷ There have been more studies showing a decrease in the 2-methoxyestradiol levels in mild to severe preeclampsia in comparison to normotensive full-term pregnancies.⁴⁸ In a study involving 28 severe preeclampsia patients, low levels of 2-methoxyestradiol were reported, which were negatively correlated with

systolic pressure, diastolic pressure and mean arterial pressure. Thus, it provides clinical evidence that 2-methoxyestradiol deficiency is strongly related to the development of hypertension in early-onset severe preeclampsia. The patients fulfilling at least one of the criteria of high systolic blood pressure (160 mm Hg), high diastolic blood pressure (110 mm Hg) or proteinuria (2 g/24 h) were classified in the category of severe preeclampsia.⁴⁹ In preeclampsia women during the third trimester of gestation, a significant decrease in the concentration of 2-methoxyestradiol (1818.41 ± 189.25 pg/mL) was documented in the plasma in comparison to normal control pregnancy (2906.43 ± 200.69 pg/mL). The risk of preeclampsia was decreased as the levels of 2-methoxyestradiol increased in these patients. The 2-methoxyestradiol values were negatively correlated with the systolic peak arterial pressure and proteinuria in preeclampsia. Women with lower 2-methoxyestradiol levels had a more serious clinical condition and required more aggressive therapy.⁵⁰ On the contrary, a rise in the serum levels of 2-methoxyestradiol has been reported in late-onset preeclampsia. A rise in the levels of 2-methoxyestradiol in patients with late-onset preeclampsia may possibly be due to activation of compensatory mechanisms to maintain the serum estrogen levels to normal.⁵¹

Exogenous Administration of Estrogen Exerts Protective Actions

In a clinical study, short-term intramuscular treatment with estradiol has been shown to attenuate blood pressure during preeclampsia state in pregnancy. Moreover, estradiol therapy (17 β -estradiol 10 mg, IM for three days at 9 AM) to preeclamptic women (36–37 gestation weeks) led to a significant decrease in the levels of oxidative parameters including superoxide anion, hydrogen peroxide, peroxynitrite and lipid peroxide in erythrocytes. Moreover, the decrease in blood pressure was positively correlated with the reduction in oxidative stress in erythrocytes during estradiol therapy. It suggests that short-term intramuscular administration of estradiol exhibits antioxidative effects in erythrocytes and reduces blood pressure in preeclampsia.¹⁷ The choice of erythrocytes was made on the basis that it has been shown that the markers of oxidative stress are higher in erythrocytes and are directly associated with the rise in mean arterial pressure in preeclampsia. Moreover, oxidative stress in erythrocytes has also been directly linked to the development of endothelial cell dysfunction in preeclampsia.⁵² There has been another clinical study

documenting that short-term estradiol therapy may contribute to normalizing the blood pressure in preeclampsia patients. Intramuscular injection of 17-beta-estradiol (10 mg) was shown to decrease mean arterial blood pressure in preeclampsia patients. Moreover, it significantly attenuated the markers of oxidative stress including the plasma superoxide anion, hydrogen peroxide, and peroxynitrite. A positive correlation was reported between a decrease in the mean arterial blood pressure and a decrease in the markers of oxidative stress. Accordingly, it may be proposed that the short-term estradiol therapy may normalize mean arterial pressure in preeclampsia patients by decreasing the plasma oxidative stress.¹⁶ There have been several studies showing that the beneficial effects of estradiol may be due to its free radical scavenging actions.^{53,54} The precise mechanisms responsible for the antioxidant actions of estradiol are not precisely clear. It has been suggested that the antioxidant effects of estradiol are independent of the activation of estrogen receptors. On the other hand, the antioxidant actions of estradiol may be due to the presence of a free phenolic hydroxyl group on the A-ring.⁵⁵ The decrease in mean arterial pressure in response to estradiol therapy has also been attributed to its free radical scavenging actions. It has been proposed that due to the free radical scavenging actions of estradiol, not enough free radicals remain to react with nitric oxide and form peroxynitrite. As a consequence, the availability of nitric oxide is increased that may induce vasodilation and participate in decreasing the mean arterial blood pressure in preeclampsia.¹⁶

Summarized Discussion and Conclusion

Clinical studies have shown that there is a significant decline in the estrogen levels in preeclampsia.^{18,35} It is important to mention that preeclampsia has two subtypes, early-onset and late-onset, and these two subtypes have different etiology.⁵⁶ However, there are insufficient studies to describe the relative role of estradiol in these two subtypes of preeclampsia. There has been a study describing that there is no significant difference in the serum levels of estradiol between early-onset and late-onset preeclampsia.³⁸ On the other hand, it has been suggested that 2-methoxyestradiol deficiency is associated with early-onset preeclampsia,⁴⁹ while a rise in the serum levels of 2-methoxyestradiol has been reported in late-onset preeclampsia.⁵¹ Nevertheless, there is a need for more

clinical studies to explore the role and mechanisms of estradiol in two different subtypes of preeclampsia.

The important contribution of the decreased levels of estradiol in the development of preeclampsia is supported by the finding showing that the exogenous administration of estradiol normalizes the blood pressure and other associated symptoms of preeclampsia in animal models^{20,21} and preeclampsia patients.^{16,17} The decrease in estrogen levels may be due to multifold changes in enzyme activities including a decrease in HSD17B1 (responsible for converting estrone to estradiol), aromatase (synthesis of estradiol), COMT (required for the synthesis of 2-methoxyestradiol).^{40,41,45} Furthermore, a significant decrease in novel estrogen receptors, GPR30 has also been identified in the placental trophoblast cells in the preeclamptic placenta.³⁰ It has been identified that the activation of GPR30 protects the placenta from hypoxia-reoxygenation injury, decreases apoptosis and increases proliferation through eNOS and PI3K-Akt signaling pathway.³⁴ Moreover, it is also possible that estrogens increase the function of Ca²⁺-activated K⁺ channel function,²⁵ decrease the release of inflammatory cytokines, oxidative stress to improve placental perfusion.^{20,21} There is also a key role of 2-methoxyestradiol, a metabolite of estradiol, in preeclampsia as both preclinical and clinical studies have shown its reduced levels. The decrease in the levels of 2-methoxyestradiol may be due to a decrease in estradiol itself along with a decrease in the enzymatic actions of the COMT enzyme. One of the most important mechanisms of 2-methoxyestradiol involves the activation of HIF1 α and vascular endothelial growth factor receptors (VEGFR-2) during placental hypoxia that helps to maintain placental perfusion by increasing angiogenesis.²⁹ Based on these, it may be concluded that the lack of endogenous production of estrogen may contribute significantly to the pathogenesis of preeclampsia and thus, exogenous estrogenic administration may be therapeutically exploited in the management of preeclampsia.

Conclusion

There is a decrease in the endogenous production of estrogen in preeclampsia and thus, exogenous estrogenic administration may be therapeutically exploited in the management of preeclampsia. Estrogen-mediated beneficial effects may involve the activation of GPR30, eNOS and PI3K-Akt signaling pathway. It may also increase the function of Ca²⁺-activated K⁺ channel function, decrease the release of inflammatory cytokines and oxidative stress

to improve placental perfusion. 2-methoxyestradiol may activate HIF1 α and vascular endothelial growth factor receptors to maintain placental perfusion.

Funding

This study was supported by fundings from NSFC (Natural Science Foundation of China) 81501279, Finance Department of Jilin Province, China (Grant JLSCZD2019-053), Natural Science Funds in Science and Technology Department of Jilin Province, China (Grant 20160101058JC) (<http://www.jlkjxm.com/>) and Open Project of Key Laboratory of Organ Regeneration and Transplantation, Ministry of Education (Grant Number 15).

Disclosure

The authors report no conflicts of interest in this work.

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