

## Controversies on Preeclampsia through the lens of Reproductive Immunology: A Systematic Review

Seyyed Amir Yasin Ahmadi <sup>1</sup>, Farhad Shahsavari <sup>2</sup>, Afshin hasanvand <sup>\*1</sup>.

<sup>\*1</sup> Student Research Committee, Lorestan University of Medical Sciences, Khorramabad, Iran.

<sup>2</sup> Associate Prof of immunology, Lorestan University of Medical Sciences, Khorramabad, Iran.

### ABSTRACT

Preeclampsia which is a kind of pregnancy specific syndrome, is the major cause of maternal and perinatal morbidity and mortality with an incidence of 5-8% of all pregnancies worldwide. Since the exact etiology of preeclampsia is still unknown, there are some controversial issues that we are trying to solve them in present systematic review. Failure of arterial remodeling in endometrium results in inadequate blood supplying of the fetus and preeclampsia and the controversies are mainly about involving immunological mechanisms. The solution of such controversies is to write meta-analysis for future papers and also genetic-polymorphism-wise screening of immunologic molecules in future original research. Further researches is suggested to solve the controversies.

**KEY WORDS:** Preeclampsia, HELLP Syndrome, Reproductive Immunology, Natural Killer Cell.

**Address for correspondence:** Afshin Hasanvand, Student Research Committee, Lorestan University of Medical Sciences, Khorramabad, Iran. **E-Mail:** [afshinhasanvand@yahoo.com](mailto:afshinhasanvand@yahoo.com)

### Online Access and Article Informtaion

Quick Response code



DOI: 10.16965/ijims.2016.104

International Journal of Integrative Medical Sciences

[www.ijmedsciences.com](http://www.ijmedsciences.com)

Received: 07-02-2016

Accepted: 20-02-2016

Reviewed: 07-02-2016

Published: 29-02-2016

Source of Funding: Self

Conflicts of interest: None

### BACKGROUND

Preeclampsia which is a kind of pregnancy specific syndrome is the major cause of maternal and perinatal morbidity and mortality with an incidence of 5-8% of all pregnancies worldwide [1]. The exact etiology of preeclampsia is still unknown. There are several theories about the etiology and pathogenesis of preeclampsia such as endothelial dysfunction, inflammation and angiogenesis. In addition, excess oxidative stress and exaggeration in maternal inflammatory response are related to the pathogenesis of preeclampsia [2,3].

Preeclampsia is appeared from the 20<sup>th</sup> week of pregnancy and is characterized by systolic blood pressure higher than 160 mmHg or diastolic pressure higher than 110 mmHg, low weight infant birth because of not sufficient blood supplying and usually there is proteinuria higher

than 5 gr per 24 hour urine [1]. Hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome is the a severe form of preeclampsia that clinically the kidneys, liver, brain and hemostatic systems are most affected [4]. Preeclampsia is observed in about 0.6% of all pregnancies and the patients with HELLP syndrome are required to be admitted in intensive care unit (ICU) that fortunately mothers' mortality is about 0% nowadays and fetal death is reported 8.9% in Iran [5].

Regarding of being unknown about the physiological and immunological aspects of preeclampsia, there are some controversial issues that we are trying to solve them.

### METHODS

Present paper is a critical systematic review and the data is collected from google scholar search

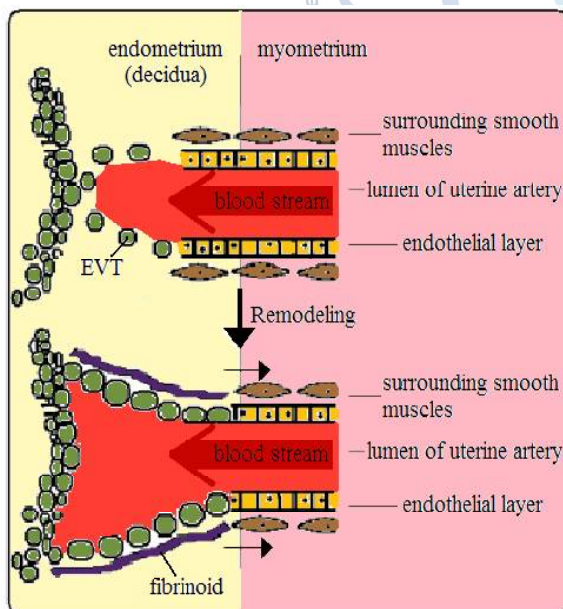
engine and Web of Science official web site through the username and password (IP) of Lorestan University of Medical Sciences.

## RESULTS AND DISCUSSION

Uterine spiral arteries play an important role in supplying nutrients of uterine that in order to reach this aim, these arteries are remodeled; thereby they get physiologic dilating and otherwise leads to preeclampsia [6]. So inadequate placentation results in preeclampsia. Inadequate placentation is also associated with 1<sup>st</sup> trimester pregnancy loss [4].

Vascular remodeling of uterine is one of the controversial issues in embryology and histology that approximately in all related papers it is known as an unknown process. Thus the accepted resultant idea in most of the articles like Ashton et al [7] is that it is necessary for sufficient blood supplying of embryo that uterine arteries go back through the substitution of extra villous trophoblast (EVT) for endothelial cells and the fibrinoid tissue for the smooth muscles surrounding spiral arteries [6-8]. (Figure 1)

**Fig. 1:** Remodeling process of uterine spiral arteries.



A controversial point is how to remodel these arteries. Via our collecting data from previous researches, it can be concluded that in the mentioned going back of spiral arteries, for endothelial layer we have apoptosis [6] while we have cell migration for muscular layer and no apoptosis were observed [8]. The mentioned apoptosis is triggered by the remodeling-

involving leukocytes [like natural killer-cells (NKs), etc] [9].

It has been observed in mice with impaired NKs by Pijnenborg et al (2006) that the muscular layer of spiral arteries still remained intact [6]. Hence it can be concluded this fact that existence of NKs is necessary for migration of these muscular cells. Also in his opinion uterine NKs (uNKs) perform two functions; direct impact on vascular remodeling and the second one is regulatory impact on trophoblast invading. Also, in golden hamster it has been observed [10] that uNKs are involved with vascular remodeling of spiral arteries during implantation period through invading to the arterial wall before invading of the trophoblasts. uNKs gathered in the region of remodeling and result in vascular dilation and angiogenesis by secreting interleukin-8 (IL8) and vascular endothelial growth factor (VEGF) [10]. In contrast, the results of Molvarec et al suggests reduced production of VEGF by circulating immune cells in preeclampsia that might be involved with development of the endothelial dysfunction characteristic of preeclampsia [11]. In addition interferon-gamma (IFN-gamma) secreted by NKs is apoptosis inducer and seems necessary for induction of apoptosis in endothelial layers of spiral arteries [12,13].

It has been observed by Bueno-Sanchez et al (2013) that there is no significant difference in NK subpopulations in two groups of severe preeclampsia and patients with normal pregnancy; but there is significant increasing of pro-inflammatory cytokines such as IFN-gamma and tumor necrosis factor-alpha (TNF-alpha) in patients with severe preeclampsia [1]. But our hypothesis is that this increasing is just a compensatory reaction and not the reason of preeclampsia. Since preeclampsia starts in the second trimester (20<sup>th</sup> week of pregnancy) such cytokines has not been measured in implantation and placentation period (1<sup>st</sup> trimester). So it is necessary to assay the level of these cytokines in the 1<sup>st</sup> trimester in a population and then look forward to arriving the 20<sup>th</sup> week to categorize them in two groups and finally compare the findings. We are of the conviction that shortage of such cytokines in early pregnancy leads to failure of remodeling

and 2<sup>nd</sup> trimester-preeclampsia. Also the author Bueno-Sanchez after a year announced that “compensatory mechanisms of releasing acute response proteins in order to offset the loss of plasma colloid osmotic pressure due to proteinuria has also been proposed” [14].

Although it seems no significant difference between NK subpopulations in the sera of the two groups of severe preeclampsia and patients with normal pregnancy [1], but immune-staining showed a significant decrease in decidua of patients with preeclampsia in CD16<sup>+</sup>CD56<sup>bright</sup> NKs by Lockwood et al (2013) [15] which are immune-regulatory (not cytotoxic) subpopulation of NKs with high IFN-gamma capacity; thereby it is concluded that the mentioned subpopulation seems necessary for prevention of remodeling failure and preeclampsia [16,17]. Then after (2014) Lockwood achieved the fact before [18].

In addition to the factors above, ICOS-B7h signal pathway is considered as an involving item in recent articles (2016). ICOS is of the co-stimulatory molecules of T-regulatory lymphocytes that seems to be synthesized in thymus gland. Blocking of this pathway can result in reduction of fetal survival probability through the reduction of regulatory cytokines such as transforming growth factor- beta (TGF-beta). Also blocking of this pathway is considered as an involving factor for preeclampsia and HELLP syndrome [19,20].

Another controversial issue is how to treat or prevent preeclampsia. Some authors such as Han et al and Beigi et al are of the conviction that anti-inflammatory treatments and anti-coagulation treatments are good to use [21,22]. Whereas the utter conviction the other authors like Groeneveld et al [23] is that such treatments are not effective for pregnancy complications like preeclampsia.

## CONCLUSION

As we mentioned before, it is necessary to assay the level of these cytokines in the 1<sup>st</sup> trimester in a population and then look forward to arriving the 20<sup>th</sup> week of pregnancy to categorize the population in two groups and then compare the findings to predict the hall-markers for preeclampsia and then compare the agents in

1<sup>st</sup> trimester in patients with and without this markers. For example, increased circulating syncytiotrophoblast micro-particles is known as a predicting agent for preeclampsia and is associated with reduction of IFN-gamma in the 1<sup>st</sup> trimester [24] which may leads to arterial remodeling failure. Another way to predict preeclampsia is assaying of the seven involved micro-RNAs proposed by Winger et al (refer to the full text of their article) [25]. For the other controversy which was about using of anti-inflammatory and anti-coagulation treatments, the solution is writing meta-analysis for future paper and also genetic polymorphism screening of immunologic molecules in future original researches which was failed to consider even in high impact journals. Further researches are suggested based on our conclusions to solve the controversies.

## ABBREVIATION

**HELLP** - Hemolysis, Elevated Liver enzymes and Low Platelets

**ICU** - Intensive Care Unit

**EVT** - Extra Villous Trophoblast

**NK** - Natural Killer-cell

**UNKs** - Uterine NKs

**IL** - Interleukin

**VEGF** - Vascular Endothelial Growth Factor

**IFN-gamma** - Interferon-Gamma

**TNF** - Tumor Necrosis Factor

**TGF-beta** - Transforming Growth Factor- beta

## REFERENCES

- [1]. Bueno-Sanchez JC, Agudelo-Jaramillo B, Escobar-Aguilerae LF, Lopera A, Cadavid-Jaramillo AP, Chaouat G, et al. Cytokine production by non-stimulated peripheral blood NK cells and lymphocytes in early-onset severe pre-eclampsia without HELLP. *J Reprod Immunol*. 2013;97(2):223-31.
- [2]. Khosrowbeygi A, Ahmadvand H. Maternal serum levels of adiponectin in preeclampsia. *Journal of Ayub Medical College, Abbottabad : JAMC*. 2009;21(3):79-82.
- [3]. Khosrowbeygi A, Ahmadvand H. Leptin to adiponectin ratio in preeclampsia. *Bangladesh Medical Research Council bulletin*. 2013;39(1):18-21.
- [4]. Eastbrook G, Brown M, Sargent I. The origins and end-organ consequence of pre-eclampsia. *Best Pract Res Clin Ob*. 2011;25(4):435-47.
- [5]. Atashkoei S, Lame MM. Outcome of Patients Admitted to Obstetric Intensive Care Unit With Severe Preeclampsia, Eclampsia or HELLP Syndrome. *Age (y)*. 2015;29:5.3.

- [6]. Pijnenborg R, Vercruyse L, Hanssens M. The uterine spiral arteries in human pregnancy: facts and controversies. *Placenta*. 2006;27(9):939-58.
- [7]. Ashton SV, Whitley GSJ, Dash PR, Wareing M, Crocker IP, Baker PN, et al. Uterine spiral artery remodeling involves endothelial apoptosis induced by extravillous trophoblasts through Fas/FasL interactions. *Arteriosclerosis, thrombosis, and vascular biology*. 2005;25(1):102-8.
- [8]. Bulmer JN, Innes BA, Levey J, Robson SC, Lash GE. The role of vascular smooth muscle cell apoptosis and migration during uterine spiral artery remodeling in normal human pregnancy. *The FASEB Journal*. 2012;26(7):2975-85.
- [9]. Smith SD, Dunk CE, Aplin JD, Harris LK, Jones RL. Evidence for immune cell involvement in decidual spiral arteriole remodeling in early human pregnancy. *The American journal of pathology*. 2009;174(5):1959-71.
- [10]. Pijnenborg R, Robertson W, Brosens I. The arterial migration of trophoblast in the uterus of the golden hamster, *Mesocricetus auratus*. *Journal of reproduction and fertility*. 1974;40(2):269-80.
- [11]. Molvarec A, Ito M, Shima T, Yoneda S, Toldi G, Stenczer B, et al. Decreased proportion of peripheral blood vascular endothelial growth factor-expressing T and natural killer cells in preeclampsia. *Am J Obstet Gynecol*. 2010;203(6).
- [12]. Ahmadi SAY, Tavafi M, Ahmadi PS. A Critical Approach to Administration of Low-Dose Aspirin (LDA) to Improve Implantation Success. *international journal of women's health and reproduction sciences* 2015;3(4):223-4.
- [13]. Chen C-P, Piao L, Chen X, Yu J, Masch R, Schatz F, et al. Expression of interferon  $\alpha$  by decidual cells and natural killer cells at the human implantation site implications for preeclampsia, spontaneous abortion, and intrauterine growth restriction. *Reproductive Sciences*. 2015:1933719115585148.
- [14]. Bueno-Sanchez JC, Pena-Alzate S, Pena RB, Agudelo-Jaramillo B, Cadavid-Jaramillo AP, Chaouat G, et al. Sera from early-onset, severely preeclamptic women directly modulate HLA-E expression in the EA.hy296 endothelial cell line. *J Reprod Immunol*. 2014;104:68-79.
- [15]. Lockwood CJ, Huang SJ, Chen CP, Huang YQ, Xu J, Faramarzi S, et al. Decidual Cell Regulation of Natural Killer Cell-Recruiting Chemokines Implications for the Pathogenesis and Prediction of Preeclampsia. *Am J Pathol*. 2013;183(3):841-56.
- [16]. Mousavi T, Shahsavari F, Farnia P, Tajik N, Soofi M. Study of KIR Expression and HLA Ligands in CD56<sup>sup+</sup> Lymphocytes of Drug Resistant Tuberculosis Patients. *Iranian Journal of Allergy, Asthma and Immunology*. 2011;10(3):189.
- [17]. Shahsavari F, Mousavi T, Entezami K. Association of KIR-HLA interactions with diseases. *Yafteh*. 2011;13(3):82-96.
- [18]. Lockwood CJ, Basar M, Kayisli UA, Guzeloglu-Kayisli O, Murk W, Wang J, et al. Interferon-gamma Protects First-Trimester Decidual Cells against Aberrant Matrix Metalloproteinases 1, 3, and 9 Expression in Preeclampsia. *Am J Pathol*. 2014;184(9):2549-59.
- [19]. Riella LV, Dada S, Chabtni L, Smith B, Huang L, Dakle P, et al. B7h (ICOS-L) maintains tolerance at the fetomaternal interface. *The American journal of pathology*. 2013;182(6):2204-13.
- [20]. Wagner M, Jöst M, Spratte J, Schaier M, Mahnke K, Meuer S, et al. Differentiation of ICOS<sup>+</sup> and ICOS<sup>-</sup> recent thymic emigrant regulatory T cells (RTE Tregs) during normal pregnancy, pre eclampsia and HELLP syndrome. *Clinical & Experimental Immunology*. 2016;183(1):129-42.
- [21]. Boroujeni MB, Boroujeni NB, Gholami MR, Boroujeni MB, Shafiei A, Rasouli M. Low-Dose Aspirin and Uterine Natural Killer Cells in Mice at Day Seven of Pregnancy. *Jentashapir Journal of Health Research*. 2015;6(6).
- [22]. Han AR, Ahn H, Vu P, Park JC, Gilman-Sachs A, Beaman K, et al. Obstetrical Outcome of Anti-Inflammatory and Anticoagulation Therapy in Women with Recurrent Pregnancy Loss or Unexplained Infertility. *Am J Reprod Immunol*. 2012;68(5):418-27.
- [23]. Groeneveld E, Lambers MJ, Lambalk CB, Broeze KA, Haapsamo M, de Sutter P, et al. Preconceptional low-dose aspirin for the prevention of hypertensive pregnancy complications and preterm delivery after IVF: a meta-analysis with individual patient data. *Hum Reprod*. 2013;28(6):1480-8.
- [24]. Germain SJ, Sacks GP, Soorana SR, Sargent IL, Redman CW. Systemic inflammatory priming in normal pregnancy and preeclampsia: The role of circulating syncytiotrophoblast microparticles. *J Immunol*. 2007;178(9):5949-56.
- [25]. Winger EE, Reed JL, Ji XH. First-trimester maternal cell microRNA is a superior pregnancy marker to immunological testing for predicting adverse pregnancy outcome. *J Reprod Immunol*. 2015;110:22-35.

**How to cite this article:** Seyyed Amir Yasin Ahmadi, Farhad Shahsavari, Afshin Hasanvand. Controversies on Preeclampsia through the lens of Reproductive Immunology: A Systematic Review. *Int J Intg Med Sci* 2016;3(2):225-228. DOI: 10.16965/ijims.2016.104