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

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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 [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 20th 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 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.

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

METHODS

Present paper is a critical systematic review and the data is collected from google scholar search.
RESULTS AND DISCUSSION

Uterine spiral arteries play an important role in supplying nutrients of uterus 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 1st trimester pregnancy loss [4].

Vascular remodeling of uterus 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 Pijenborg 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 deference 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 (20th week of pregnancy) such cytokines has not been measured in implantation and placentation period (1st trimester). So it is necessary to assay the level of these cytokines in the 1st trimester in a population and then look forward to arriving the 20th 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 2nd 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 deference 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^CD56^{bright} 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 synthetized 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 1st 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 1st 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.

REFERENCES

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