Pathogenesis Specifics of Allergic Reactivity in Hypertensive Conditions of Pregnants

Mukhamedkhanova Sh. T.[1], Yuldasheva D.S.[2], Mirzaev N.B.[3], Ruzieva N.Kh.[4], Aripova F.S.[5]

[1]PhD, Associate Professor, Department of Obstetrics and Gynecology, Pediatric Gynecology, Tashkent Pediatric Medical Institute, 223 Bogishamol Street, Tashkent, Uzbekistan, [2]PhD, Associate Professor, Department of Obstetrics and Gynecology, Pediatric Gynecology, Tashkent Pediatric Medical Institute; 223 Bogishamol Street, Tashkent, Uzbekistan, [3]PhD, Associate Professor, Department of Obstetrics and Gynecology, Pediatric Gynecology, Tashkent Pediatric Medical Institute; 223 Bogishamol Street, Tashkent, Uzbekistan, [4]MD, Associate Professor, Department of Obstetrics and Gynecology, Pediatric Gynecology, Tashkent Pediatric Medical Institute; 223 Bogishamol Street, Tashkent, Uzbekistan, [5]Assistant of the Department of Obstetrics and Gynecology, Pediatric Gynecology, Tashkent Pediatric Medical Institute, 223 Bogishamol Street, Tashkent, Uzbekistan

Abstract

Introduction: Significant allergic reactions and anaphylactic type cytotoxicity are registered in the pathogenesis of cell damage in pregnant women with hypertensive conditions. Determining role of indirect mast cell degranulation and allergic changes in neutrophils during pregnancy that complicated by preeclampsia, allows to identify the allergic status of the body, which is very importance for improving the quality of early diagnosis, treatment and prevention. The purpose of the study was to identify the allergic reactivity of pregnant women suffering from hypertensive disorders and to develop practical recommendations to improve the quality of early diagnosis.

Materials and Method: We observed 6 group of participants: pregnant women with clear allergy clinic, uncomplicated preeclampsia, pregnant women with light stage of preeclampsia, latent sensitization, pregnant women with preeclampsia combined with clear allergy clinic, conditionally healthy pregnant women – 1st control group, practically healthy non-pregnant women – 2nd control group, practically healthy men – 3rd control group. Using non-infection allergens, we called different types of allergic reactions and conducted clinical and allergic examinations, general test of bleed, urine, feces, indirect mast cell degranulation test and neutrophil alteration test.

Results: Within all control groups, the rate of positive reaction against the allergic agents made up less than 10 percent. In all pregnant women with clear clinical picture of allergies complicated or uncomplicated preeclampsia, as well as in pregnant women with preeclampsia with latent sensibilization, mast cell degranulation indexes were 4.5-8.6 times higher than that of control group. Among 90 examined pregnant women, positive reactions of indirect mast cell degranulation were observed in 204 cases.

Conclusion: In cell damage pathogenesis during preeclampsia, anaphylactic and cytotoxic type allergic reactions play important role. The positive reactions of indirect mast cell degranulation in pregnant women with an explicit allergy complicated by preeclampsia is significantly higher than in pregnant women with preeclampsia with hidden sensitization.

Keywords: *Hypertensive conditions in pregnancy, preeclampsia, allergy.*

Introduction

Preeclampsia of pregnant women has been continuing to be one of the urgent problems of modern medicine. This pathology, giving different complications during pregnancy and childbirth, remaining as one of the causes of maternal and perinatal morbidity and

mortality. Preeclampsia is especially lasts severely in pregnant women who permanently live in ecologically unfavorable regions (Sukhikh et al, 2015)[1]. According to world statistics, about half a million women die due to the different complications related to pregnancy and childbirth (Tumanova et al, 2017 and Mukhamedkhanova et al, 2019).[2]

According to results of researches conducted by Stokoz et al (2016)[3] and Chulkov et al (2015), about 1–4% of women aged 18–29 years and about 5–15% of women aged 30–39 years suffered from chronic hypertension between 1999 and 2004 in the United States. Along with this, in 2004, compared to 1998, the number of pregnancy complications caused by preexisting arterial hypertension increased by 50% and reached up to 1.7% of the total number of complications (Wang et al, 2019). Moreover, the number of preterm births and newborns with low weight for gestational age, as well as perinatal mortality rates in such pregnant women were 2-3 times higher compared to normotensive women (Perfilova et al, 2014; Paidas et al, 2016; and Wang et al, 2019)[4],[7]. The incidence of gestational hypertension increased from 10.7 to 30.6 per 1000 births, and 17% of pregnant women with gestational hypertension subsequently developed preeclampsia (Mosimann et al, 2019 and Wang et al, 2019).[5] However, it should also be mentioned that the maternal risks associated with gestational hypertension are usually less than 2 times lower than those of women suffering from chronic hypertension or moderate preeclampsia.

According to the data provided by WHO, the proportion of hypertensive syndrome in the structure of maternal mortality is about 20-30%, every year more than 50 thousand women die during pregnancy owing to complications associated with maternal arterial hypertension. Arterial hypertension increases the risk of detachment of a normally located placenta, massive coagulopathic bleeding. It can also cause eclampsia, impaired cerebral circulation, and retinal detachment as well (Marotti et al, 2017)[6].

The frequency of preeclampsia development is not same in different countries and depends to a large extent on the criteria used for its diagnosis. Although the problem of preeclampsia is studied from different perspectives, many of its aspects remain poorly understood (Stokoz et al, 2016)[4]. Among them, in our opinion, the allergy, more precisely, allergic reactivity of the body, plays very importance in the etiology, pathogenesis, clinic of preeclampsia and its complications. Chulkov et al, 2015; Perfilova et al, 2014; and Paidas et al, 2016)[8].

The prevalence of hypertensive conditions during pregnancy is ranges around 7–30 percent. This pathology worsens the prognosis in mother and in children, and is also causes perinatal mortality. Different complications like placental insufficiency, premature detachment of a normally located placenta, eclampsia, cerebral hemorrhage, acute heart failure, acute renal failure, syndrome of DIC develop with arterial hypertension (Perfilieva et al, 2015)[7].

Introduction of specific, clinical and allergological examinations of pregnant women with preeclampsia: collection of an allergic history, clinical and functional studies, in vitro allergy tests (indirect mast cell degranulation test, neutrophil damage index, determination of the functional activity of neutrophils by tetrazole recovery techniques dye and phagocytosis) into the complex of clinical and laboratory studieswill contribute to the early detection of allergic diseases in pregnant women, which has a great diagnostic, therapeutic and preventive value.

A study of the regional characteristics of the prevalence of pre-eclampsia of pregnant women in different regions of Uzbekistan using the methodology of epidemiological studies under the ISAAC international program allows us to clarify the true disease incidence the population (Mukhamedkhanova et al, 2019)[3].

Purpose of the study is to determine the allergic reactivity of the pregnant women body suffering from hypertensive disorders and to develop practical recommendations that improve the quality of early diagnosis of this serious illness based on the allergological concept. To determine the importance of combining allergies with hypertensive conditions in pregnant women. To determine the role of regional pollen factors in the development of an immediate type allergy in the pathogenesis of cell damage in pregnant women with pre-eclampsia using tests of indirect mast cell degranulation and allergic neutrophil alteration.

Materials and Method

168 individuals were under observation, including pregnant women with a clear clinic of allergy, uncomplicated preeclampsia (n=30), pregnant women with a slight degree of preeclampsia, latent sensitization (n=30), pregnant women with preeclampsia combined

with a clear allergy clinic (n=30), conditionally healthy pregnant women (n=30) - control group No. 1, practically healthy non-pregnant women (n=23) - control group No. 2, practically healthy men (n=25) - control No. 3. The age of pregnant women ranged from 17 to 39 years. The age of non-pregnant women and healthy men was 20-35 years old. We studied pregnant women with gestational age from 19 weeks to 40 weeks of their pregnancy. Among them, the first pregnancy - n=42 (35%); re-pregnants n=44 (36.7%); multiparous women n=34 (28.3%).

Among the allergic diseases in the examined pregnant women there were: allergic rhinitis, sinusitis, conjunctivitis-24 (20%); urticaria, Quincke's edema, neurodermatitis-15 (12.5%); drug allergy 8 (6.7%); food allergy 6 (5%); bronchial asthma 6 (5%); anaphylactic shock 1 (0.8%).

The results of studies in all pregnant women with allergic diseases were approximately the same. The numerical differences between the indicators were unreliable. Therefore, we combined them into one group: pregnant women with hypertension, combined with a clear clinic of allergic diseases.

The following standard non-infectious regional allergens were used: pollen (wormwood, quinoa, chinar, kenaf, aylanthus), household (house dust), epidermal (cat, dog hair, bird feather). Tissue allergens (placenta, kidneys) were prepared in a well-known way. The following method were used: clinical and allergic examination of patients, general blood tests, urine, feces, indirect mast cell degranulation test, neutrophil alteration test.

Allergy in the examined women was manifested in the form of allergic rhino conjunctivitis, allergic dermatoses, and even anaphylactic reactions[8]. In those cases, when pollen allergens were important in the etiology of allergies, a clear seasonality of the disease was observed (mainly in spring and summer seasons)[9]. With sensitization by household and epidermal allergens, the seasonality of the disease was not observed. When sensitizing to food allergens, patients indicated a connection between exacerbation of the symptoms of the disease and the intake of certain foods[10]. When eliminating causally significant foods, a remission of the disease was observed. Specific allergy diagnostics was carried out on the basis of a comprehensive clinical and allergological examination of patients, as well as in vitro allergic tests. The complex principle of specific diagnosis compares favorably with the fact that it allows you to identify specific allergic antibodies, establishes the specificity of the sensitization of an organism to a particular allergen, and conduct differential diagnosis[11]. An allergic history was collected on the basis of a specially compiled questionnaire. An allergic test for indirect mast cell degranulation (MCD) was performed according to generally accepted method. Anti-tissue antibodies were determined by the conventional photometric method. The phagocytic activity of neutrophils in the peripheral blood of patients was determined according to A. Shteltsner. An allergic neutrophil alteration test was performed according to V.A. Fradkin. To determine the functional activity of neutrophils, we used the Nitro Blue-Tetrazolium Test (NBT test)[12].

Results

In all control groups examined (conditionally healthy pregnant women, practically healthy non-pregnant women and practically healthy men), the frequency of positive reactions to tested pollen, domestic and epidermal allergens was below 10 percent and ranged from 4.4 + 0.2 - 3. 6 + 0.23. These indicators are non-specific and indicate the absence of sensitization of the body, since there are no examined specific IgE in the blood serum.

In all pregnant women with a clear clinical picture of allergies complicated or uncomplicated preeclampsia, as well as in pregnant women with preeclampsia with latent sensitization, mast cell degranulation values were significantly higher by 4.5-8.6 times compared to the control, and were within 30.2 + 0.92 - 38.0 + 0.44 ($p < 0.05$).

In general, among 90 examined pregnant women, positive reactions of indirect mast cell degranulation were observed in 204 cases, including pollen allergens in 115 (56.4±3.4%), household (house dust) in 50 (34.5±4.9%), epidermal - in 39 (19.1±2.7%).

The degree of mast cell degranulation in most pregnant women (92.1±3.8 - 94.5±10.1%) with anexplicit allergy clinic, regardless of the presence or absence of preeclampsia, was expressed in ++ and +++, while as in the majority of pregnant women with preeclampsia (91.7±7.9%) with latent sensitization, the degree of mast cell degranulation was weakly expressed (+).

In the vast majority of pregnant women with a clear allergy clinic, cases of combined polysensitization predominated, that is, simultaneous increased sensitivity to several unrelated allergens. For example, pollen+household, pollen+epidermal, etc. Only monosensitization to a particular allergen was observed in pregnant women with latent sensitization. Neutrophil damage in conditionally healthy pregnant women (control group No. 1) and practically healthy non-pregnant women (control group No. 2) were in the range of 0.019±0.001 - 0.002±0.001 (when using placental antigen) and 0.035±0.003 - 0.04±0.002 (when using renal antigen). The difference in the digital data of these two groups of controls is unreliable ($p > 0.05$). This fact indicates that the examined control groups of women have a minimal amount of anti-tissue antibodies in their blood serum. However, these antibodies do not cause serious tissue damage. Pregnant women with overt allergies, uncomplicated preeclampsia, showed an increase in neutrophil damage to 0.04±0.003 - 0.1±0.03, which is 2-2.5 times more than the controls ($p < 0.05$). In pregnant women with preeclampsia, neutrophil damage indicators are also greater than in pregnant women with latent sensitization 3-4 times (0.08±0.004 - 0.13±0.004), and in pregnant women with overt allergies - 4-5 times (0.1±0.002 - 0.19±0.004). These facts indicate the development of autosensitization in pregnant women, complicated by preeclampsia to the tissues of the placenta and kidneys.

First of all, we were interested in the issue of the presence of an immediate allergy. To clarify this issue, we used a methodological technique that allowed us to identify specific allergic antibodies belonging to the IgE class. In all pregnant women with allergies, regardless of the presence or absence of symptoms of hypertension in the blood serum, specific allergic antibodies to the tested allergens were detected. The frequency of positive reactions to the studied allergens in pregnant women with allergies without hypertension and in pregnant women with allergies combined with hypertension was approximately the same, respectively, 15.5-73.0 and 25.6-80.0 percent. The frequency of positive reactions in pregnant women with hidden sensitization combined with hypertension to pollen allergens was 8.6%, domestic - 13.3 percent, epidermal - 6.7 (average 0.6±2.0). The results of studies of this category of patients indicate that in pregnant women with latent (latent) sensitization, the titer of allergic antibodies, in comparison with pregnant women with an explicit allergy clinic, is significantly low ($p < 0 05$).

However, they are all potential allergy sufferers, that is, at any moment the symptoms of allergies can occur. In addition, these data allow us to conclude that the presence of hypertension cannot serve as an obstacle to the synthesis of specific allergic antibodies in patients.

Discussion

In our opinion, in case of hypertensive conditions of pregnant women, there is no inhibition of the functional activity of immunocompetent cells responsible for the synthesis of specific allergic antibodies. This is evidenced by the absence of a difference in the frequency of positive reactions of indirect mast cell degranulation in two groups of pregnant women with an explicit allergy clinic: combined and not combined with hypertension, as well as positive reactions in pregnant women with latent sensitization combined with hypertension[11].

In the process of formation and development of allergic reactivity of the body, the inhibition of the functional activity of neutrophilic leukocytes is noted, which negatively affects the factors of cellular nonspecific protection of the body (i.e., the phagocytic activity of leukocytes decreases, the phagocytic number, phagocytic index, and the strength of phagocytosis).

Allergy in most cases is characterized by the development of polysensitization. In this regard, it was of some interest to analyze our data from these positions. In the literature, polysensitization means the presence of hypersensitivity in the same patient to two or more types of allergens. From our point of view, “the degree of development of an allergy clinic depends on the nature, nature and types of allergens. In this regard, depending on the nature of allergens, the following polysensitization options should be distinguished: 1) true - when one organism is sensitized to two or more related allergens at the same time: only pollen, or only domestic, or only epidermal, etc.; 2) combined - when one organism is sensitized to two or more non-infectious allergens of different nature: pollen and household, pollen and epidermal etc.; 3) mixed - when one organism is simultaneously sensitized to two or more allergens of non-infectious and infectious nature. According to our data, in pregnant women with a clear allergy clinic, cases of true and combined polysensitization predominated regardless of the presence or absence of hypertension: 93.3 and 76.7 percent respectively.A similar pattern was also observed in patients with latent sensitization - 90.0 percent.

At least two types of allergies in pregnant women with hypertensive conditions are noted: a clear clinical manifestation of allergic diseases and latent (latent) sensitization of the body without clinical manifestations of allergic diseases.

The clinical forms of allergy manifestation are diverse: pollinosis, allergic rhinitis and sinusitis, allergic dermatitis, bronchial asthma, anaphylactic shock. Hypertensive conditions associated with allergies are more likely to occur in repeatedly and multiparous women.

With a combination of hypertensive conditions with allergies, cases with a more severe clinical course of the underlying disease predominate, induced, premature and belated deliveries are more common, and surgical interventions are more often used.

In the etiology of allergies in pregnant women with gestosis, exogenous non-infectious allergens are essential. In the pathogenesis of cell damage during gestosis of pregnant women, a complex combination of allergy mechanisms of immediate (chimeric) and delayed (cellular) types is detected.Thus, the conducted studies allow us to come to the following generalizations - preeclampsia often occurs and develops against the background of an allergically altered body reactivity. It can be assumed that the severity of the clinical course of preeclampsia and its complications depends on the presence of a latent or overt allergy. The sensitization of the body in pregnant women is confirmed by a positive reaction of indirect mast cell degranulation, which indicates the presence of specific allergic antibodies (IgE) in the blood serum of the examined. With clinically pronounced forms of allergy, the sensitization of pregnant women, regardless of the presence or absence of preeclampsia in them, is clearly multivalent. The frequency of mixed forms of polysensitization is significantly higher. With latent forms of sensitization of the body of pregnant women, only monosensitization is noted.

The introduction of specific, clinical and allergological examinations of pregnant women with hypertensive disorders into the complex of clinical and laboratory studies: collecting an allergic history, clinical and functional studies, and setting up allergic tests in vitro will contribute to the early detection of allergic diseases in pregnant women, which has a great diagnostic, therapeutic and preventive value.

Conclusion

In the pathogenesis of cell damage during preeclampsia of pregnant women, allergic reactions of anaphylactic and cytotoxic type are of significant importance. The degree of positive and sharply positive reactions of indirect mast cell degranulation in pregnant women with an explicit allergy clinic complicated by preeclampsia is significantly higher than in pregnant women with preeclampsia who have hidden sensitization. Allergies in pregnant women are polyvalent in nature. Furthermore, determination of the parameters of the test for indirect mast cell degranulation and allergic neutrophil alteration in pregnant women complicated by preeclampsia, in combination with other clinical and laboratory studies, makes it possible to identify the allergic state of the body, which is of great importance in improving the quality of specific diagnostics, therapy and prevention.

Study Limitations: Further research is needed to clarify various aspects of the pathogenesis of preeclampsia from the perspective of modern allergology.

Acknowledgements: Many thanks to the staff of Department of Obstetrics and Gynecology, Pediatric Gynecology of Tashkent Pediatric Medical Institute for the cooperation in our research. The patients kindly gave full written permission for this report. We are thankful for that.

Ethical Approval: The ethical approval for the study was granted by the Committee of Ethical Approval for Researches under the Ministry of Health of the Republic of Uzbekistan.

Patient Consent: Written informed consent was obtained from allparticipants of the research for publication of this paper and any accompanying information related to this study. A copy of the written consent is available forreview by the authors.

Conflict of Interest: The authors declare that they have no competing interests.

Funding: No funding sources to declare.

References

1. cSukhikh G. T. ea. “Preeclampsia”. Edited by G. T. Sukhikh, L. E. Murashko - St. Petersburg. GEOTAR-Media. 2015;: p. 576.
2. Tumanova U.N. SAI. “Arterial hypertension in

pregnant women as a risk factor for stillbirth (literature review)". International Journal of Applied and Basic Research. 2017; 8-1: p. 78-82.

3. Mukhamedkhanova Sh. T. YDS, UYM. "Pathogenetic features of allergic reactivity in pregnant women with hypertensive conditions". Journal of theoretical and clinical medicine. 2019; 5: p. 62-64.
4. Stokoz K.Yu. LDS. "The history of the study of preeclampsia and eclampsia in obstetrics". Russian Bulletin of Perinatology and Pediatrics. 2016; 24: p. 223-247.
5. S. CV. "The state of target organs in various forms of arterial hypertension in pregnant women". Scientific Journal "Science Rise". 2015; 6: p. 12-15.
6. Perfilieva M.V. FYI,CAV. "Features of the clinical course and diagnosis of arterial hypertension during pregnancy". Young scientist. 2015; 15: p. 305-308.
7. Perfilova V.N. MLI,TIN. "Consequences of gestosis (preeclampsia)". Russian Bulletin of Perinatology and Pediatrics. 2014; 2: p. 10-17.
8. Paidas MJ KDAY. "Screening and management of inherited thrombophilias in the setting of adverse pregnancy outcome". Clin Perinatol. 2016; 31: p. 783–805.
9. Beatrice Mosimann SKAMDS & LR. "First trimester screening for preeclampsia - a systematic review". Hypertension in Pregnancy. 2019;: p. 11-12.
10. Meng Wang WHMLFLLJJWHWXLKY & JQ. "Maternal asthma and the risk of hypertensive disorders of pregnancy: a systematic review and meta-analysis of cohort studies". Hypertension in Pregnancy. 2019;: p. 12-24.
11. Clivaz Mariotti L. SP,LCR,P–BA. Hypertension in pregnancy. Rev. Med. Suisse. 2007; 3 (124): p. 2015–2016.