

## Influence of the Vaginal Opportunistic Microflora on Fetoplacental Complex in Pregnant Women with Preeclampsia

Akylbek Tussupkaliyev, Saule Bermagambetova, Zhanibek Daribay,  
Leila Sarsembaeva and Rashida Bliyeva

West Kazakhstan Marat Ospanov State Medical University  
Aktobe city, Maresyev street 68, 030000, Republic of Kazakhstan.

(Received: 06 April 2014; accepted: 19 August 2014)

**Evaluate the effect of genital infection on fetoplacental system in pregnant women with preeclampsia. Based on this study we can conclude that violation of microbiocenosis of the lower genital tract should be considered as predictor of adverse pregnancy outcomes in women with preeclampsia. Morphological and functional responses of the placenta underlie pathogenetic damages of fetoplacental complex in combination of preeclampsia and genital infection.**

**Key words:** Pregnancy, Preeclampsia, Infection of the genitals, Fetoplacental complex, Health.

Maintaining health and lives of mothers, as well as the reduction of perinatal morbidity and mortality is the main task of the modern obstetrics. Hypertensive states in pregnancy remain to be one of the most important problems of the modern medicine. Its frequency is 16-21% with no tendency to lowering<sup>1-3</sup>. Preeclampsia is one of the main causes of chronic placental insufficiency<sup>4, 5, 3</sup>. Gestosis is often characterized by an incomplete set of clinical symptoms and in 95% of patients it has a combined nature on the background of extragenital pathology (hypertension, diabetes mellitus, cholecystitis, tonsillitis, pyelonephritis, etc.). Pregnant women with chronic foci of infection can be considered as a "risk group" for the development of immunodeficiency states. In utero infection of fetus and the development of preeclampsia are observed more frequently in these states<sup>6</sup>.

Genital infection is one of the most common infectious conditions during pregnancy,

its frequency ranges from 10 to 40%. Under the term "genital infection" we mean a wide range of inflammatory processes of the upper and lower genital tract including sexually transmitted infections<sup>7</sup>. Intrauterine infection (IUI) is the most severe consequence of genital infection for fetal and neonates. Its frequency varies from 6 to 30%<sup>8</sup>.

At the present time intrauterine infection is on the second place (after hypertensive conditions) among the causes of chronic placental insufficiency and fetal malnutrition<sup>9-12; 6</sup>. Scientific researches of T.V. Gabidulin<sup>13</sup> revealed high rates (up to 76.8%) of chronic placental insufficiency in pregnant women with intrauterine infection. Key elements in the formation of hypertensive conditions such as illnesses during the pregnancy are changes in the placenta, as it plays a major role in the implementation of maternal-fetal relationship, being both receptor and executive organ and the main relationship "channel" between mother and fetus.

To date there is a large number of clinical-experimental suggestings that common pathogenetic mechanisms are at the basis of non-specific syndrome of chronic placental insufficiency on the background of hypertensive

\* To whom all correspondence should be addressed.  
Tel.: 87017469069

states and IUI<sup>14-16</sup>. However, in the available literature we have found no data on the characteristics of pregnancy, childbirth and postnatal period, as well as on the state of fetoplacental complex in pregnant women with preeclampsia on the background of intrauterine infection. Question about possible role of opportunistic microflora of the lower genital tract in the initiation of preeclampsia remains to be open.

For this reason we have performed the current study.

**Objective:** To determine the effect of genital infection on the fetoplacental system in pregnant women with preeclampsia.

### **Methodology**

To achieve the goals we have carried out a survey of 220 pregnant and postpartum women hospitalized in the Regional Perinatal Center of Aktobe city, Kazakhstan.

Group I (control) included pregnant women (n = 26) with uncomplicated pregnancies being in dispensary groups of health or virtually healthy women; Group II included pregnant women (n = 107) diagnosed with preeclampsia. Pregnant women in this group were retrospectively divided into three subgroups. Subgroup 1 (n = 36) included pregnant women with preeclampsia who did not have any violations of vaginal and cervical microbiocenosis. The 2<sup>nd</sup> subgroup (n = 40) included pregnant women with no clinical signs of preeclampsia. Women of this group revealed violations of vaginal and cervical microbiocenosis; women of the 3<sup>rd</sup> group (n = 31) included subjects whose pregnancy was accompanied by a combination of preeclampsia and disorders of microbiocenosis of the lower genital tract.

Based on the data of retrospective analysis of adverse pregnancy outcomes, we have performed a prospective analysis of the treatment of 87 pregnant women with clinical signs of preeclampsia in conjunction with disorders of microbiocenosis of the lower genital tract (group III) that were subsequently divided into 2 groups. Group IIIa (n = 23) included pregnant women with preeclampsia and confirmed clinical screening tests. Women of this group also had a positive result of bacteriological studies of vaginal and cervical microbiocenosis disorders. They were treated according to standard procedures depending on the specific pathogen. Subjects in

group IIIb (n = 64) were comparable to the subjects of group IIIa on the severity of the clinical manifestations of preeclampsia and dysbiotic conditions.

In order to perform the work, we have carried out microscopy of the gram stain of the cervical discharge. We also performed vaginal fluid pH assessment, amino test, and looked for atypical squamous cells. From the second trimester of pregnancy we performed microbiological examination of the discharge from posterior vaginal fornix and cervix before and after the treatment. In the culture study we determined species and quantitative composition of all microorganisms of the studied samples. Evaluation of the results was carried out according to the frequency of symbionts identification and by its intensity - decimal logarithm of the average number of microorganisms (Ig CFU). Species identification of isolated pathogens was carried out with the help of the computer program and special identification kits of the company Becton Dickinson BBL Crystal Systems (identification of enteric and non-fermenting microorganisms: gram-positive, anaerobic, *Neisseria/Haemophilus* - about 400 species in all). Determination of the sensitivity of the isolated microorganisms was performed by a disk diffusion method on medium Mueller-Hinton II using NCCLS international standards in the following terms: sensitive, intermediately resistant or resistant. For the light-optical microscopy sections were stained with hematoxylin and eosin. PAS-reaction was carried out using Sigma Diagnostics Periodic Acid-Schiff (PAS) reagent kit. In addition, the connective tissue was detected by staining according to Mason. We also used Sigma Diagnostics Trichrome Stains (Masson) reagent kit.

Doppler registration of the uteroplacental blood flow was carried out using an ultrasound diagnostic tool Toshiba (Eccocoe) SSA-340 A (Japan).

Ultrasound (US) studies were performed on devices "Aloka - SD 500" (Japan) and "Sim - 500U plus" (Italy).

The data was processed using methods of obtaining mean values and mean square error, t-test, and nonparametric statistics (chi-square test) to compare small samples.

## RESULTS

### Analysis of pregnancy

Having analyzed the period of gestation in women of groups 2 and 3 we found a high incidence of threatened abortion. It was clearly correlated with the rate of diagnosed colpitis and bacterial vaginosis. Despite the absence of disorders of vaginal microbiocenosis, the threatened miscarriage occurred in 69.9% subjects of group 1.

Retrospective analysis of pregnancy outcomes showed that gestation period in groups 1 and 2 ended with preterm birth in 97.5%, while in combination of preeclampsia and disorders of the lower genital tract microbiocenosis (group 3) in 100% of cases. These results are consistent with the literature on the high frequency of prenatal rupture of membranes and premature onset of labor at the manifestation of infectious factors.

The highest percentage of births by caesarean section (87.1%) was in the group with a combination of preeclampsia and infection (group 3). Analysis of indications for delivery revealed that the most common cause of cesarean section in the retrospectively studied groups (from 88.9% to 96.3%) was the combination of preeclampsia and unreadiness of the birth canal. Vaginal delivery in all cases was complicated by the development of labor abnormalities.

### Ultrasound examination

On echographic evaluation we noted a discrepancy of placenta with the gestational age in the form of premature maturing in a significantly higher percentage of cases diagnosed in group 3 - 83.9%, while in pregnant women of group 2 (without clinical signs of preeclampsia) this state of placenta occurred only in every second women ( $p < 0.01$ ;  $p < 0.001$ ). The obtained results conform to the literature data to some extent on a high incidence (85%) of premature maturation of the placenta in pregnant women with preeclampsia. At this time the highest thickness of placentas -  $41.5 \pm 2.1$  mm significantly exceed those at term pregnancy, as was noted in the group of pregnant women with combination of preeclampsia and disorders of the lower genital tract microbiocenosis.

In our opinion, the high frequency of threatened abortion and premature births in group

3 along with the identified echographic indicators of the placenta state, as well as the presence of the lower genital tract microbiocenosis disorders, showed a significant role of microbial factors in the development of adverse pregnancy outcomes, not only for the mother, but also for the fetus.

In the modern literature there is an evidence of the significance of detection of endogenous intoxication in preeclampsia generally caused by an excessive intake into the systemic circulation of endotoxin of gram-negative bacteria leading to systemic inflammatory response [17-19; 1]. In pregnant women of the retrospective group in the structure of extragenital diseases there is a high percent of cases with detected abnormality of the urinary system (64.5%), gastrointestinal tract (54.2%) and respiratory tract (44.9%). In group 1 nosological data was observed in considerably higher percentage of cases (75.0%, 66.7%, 66.7%) which probably contributed to the onset of systemic inflammatory response followed by the development of preeclampsia. Probably the presence of extragenital foci of infection along with disturbances of the lower genital tract microbiocenosis and preeclampsia have made a significant contribution to the depletion of the compensatory-adaptive mechanisms in fetoplacental system eventually terminated in fetal death<sup>20-23</sup>. It is possible that the same factors that underlie decompensation of fetoplacental system further lead to the development of irreversible degenerative changes in vital organs and regulatory systems of the mother's body determining lethal outcome in the future.

### Microbiological studies

The data on bacteriological studies have demonstrated a significant incidence of colonization and a high degree of placental tissue colonization by pathogens presented by mixed associations of bacterial flora and viral agents. The results of bacteriological research of the groups did not show any significant differences in the prevalence rate of the microorganisms. When identifying pathogens we have detected the following composition of microbial associates: enterobacteria were the most common causative agents that were diagnosed in 52.3% of the total number of infectious agents; fungi of the genus *Candida* - 36.4%; nonclostridial anaerobes - 50.5%; and *Klebsiella* infections - 14.3%. Bacterial

and viral infection occurred in 30.8% cases. In any case there was no evidence of a single leader in the development of pathological inflammatory changes of the placenta which is consistent with the modern scientific data on the leading role of infectious agents associations of bacterial-bacterial and bacterial-viral etiology in the development of infectious and inflammatory diseases in the mother-placenta-fetus system.

During pathological examination of the afterbirth we detected that the frequency of such comorbid pathologies as chorioamnionitis, choriodecidualitis, intervillitis did not differ considerably and accounted for 70.1% of the total number of studies. In this case, as shown by the results of a retrospective study, antenatal fetal death in these women occurred most likely in the gestational period of  $34.6 \pm 2.6$  weeks of pregnancy. We have found that in cases where dissemination of infection was not limited to pathological changes in the placenta (29.9%) and involved only cord tissues and fetal membranes in the form of arteritis, chorioamnionitis and choriodecidualitis, panplacentitis. In these cases antenatal fetal death developed in considerably early gestation terms and corresponded to  $24.7 \pm 2.2$  weeks of pregnancy. This suggests that the rapid development of decompensation of adaptive reactions of the fetus ending in its antenatal death at the earlier stages of pregnancy indicates failure of the protective properties of the placental barrier against infectious agents and their penetration into the blood flow of fetus.

Thus, according to our research disturbances of the lower genital tract microbiocenosis is one of the pathological endogenous factors that activate the placenta functions and considerably increase the level of its compensatory and adaptive processes in the early term pregnancy, as is evidenced by a high percentage of advancing its degree of maturity typical for gestational term and associated with the phenomena of threatened abortion. On the later stages of gestation, with further prolonged exposure to harmful infectious factors and in case of development of preeclampsia, excessive activation of placental functions and overexertion of the existing compensatory mechanisms are replaced by step breakdown of adaptation with the development of irreversible destructive

processes in the placental tissue. In those cases where umbilical cord vessels besides tissue structures of the placenta are involved in the infectious process on the background of preeclampsia, the placental barrier will be inconsistent to the fetus and on the background of the depletion of all parts of the compensatory-adaptive reactions in a single functional system mother-placenta-fetus. At this time all the necessary conditions for the penetration of infection agents to the fetus develop and this determines the adverse perinatal outcome.

#### **Morphological data**

During the analysis of the morphological studies we have found that involutive-degenerative and circulatory disturbances were at the basis of placental changes in women of group 1. In case of long duration of preeclampsia, and as a result of inadequate therapeutic measures there was dissociated maturation of chorionic villi (22.2% in group 1 and 15.4% in group 2) which manifests itself as poorly vascularized villi. We have not been identified neither intermediate, nor embryonic villi in any case. Typical feature was sclerosis of villi and affection of the vascular bed with severe involutive-degenerative changes.

According to our data, these morphological changes of placentas showed the depletion of its compensatory reactions, formation of its chronic insufficiency. This was manifested by hyperemia of veins, spasm of arteries and ectasia of blood vessels, impaired uterine circulation, infarctions, hemorrhages and fibrinoid deposition in the intervillous space and on the surface of terminal villi. It should be emphasized that women of group 1 despite the absence of clinical manifestations of vaginal and cervical microbiocenosis disorders during pregnancy had morphological features of various infectious diseases in the form of infiltration presented by neutrophilic leukocytes and revealed in the afterbirth. Furthermore, a high content of tumor necrosis factor in leukocytes caused a considerable increase in its concentration in afterbirth. This in turn led to the accumulation of adhesion molecules both in vascular lumen of terminal villi and in cytotrophoblast cells. Taking into account the structure of perinatal losses, we have identified retrospectively that the role of infectious factors on the background of

preeclampsia is quite significant, since the combination of these pathological processes promoted endothelial cell dysfunction, exacerbation of circulatory disorders, developing the effects of ischemia and probably more severe manifestations of preeclampsia.

In the group of pregnant women with diagnosed disorders of the lower genital tract microbiocenosis (group 2) cases of pathological immature of villi were often identified as a delay of chorion maturing at the stage of intermediate immature (34.6%) and fetal villi (26.9%). In our opinion, the presence of intermediate villi indicates violation of the placental maturation caused by the influence of bacterial and viral infection. In group 2 of the retrospective study the reaction of the vascular bed was manifested by a vascular hyperemia of chorionic villi and the umbilical cord, while circulatory disorders were diffuse. There was a marked hyperemia of the intervillous space, formation of diffuse hemorrhage in the basal plate. In 65.4% of cases there were placental infarctions with a predominance of mixed forms (46.3%) and pseudoinfarctions (42.1%). Inflammatory infiltration in the basal lamina was more intense than in group 1 and had diffuse character, in our opinion. Lymphocytes, macrophages, plasma cells, histiocytes, polymorphonuclear leukocytes were found in the infiltrate. Basal focal and diffuse deciduitis was found. In the basal plate we detected multiple foci of necrosis. Along with inflammatory changes in the placenta we detected signs of pathological immaturity and chronic placental insufficiency (atrophy, sclerosis and violations of villi differentiation).

In group 3 macroscopically placenta had the smallest size as compared to groups 1 and 2. There was a higher incidence of focal seals, calcifications and infarctions (33.3%, 65.3% and 77.4%, respectively). Microscopically we detected more pronounced involutive and dystrophic changes: more fibrinoid (44.4%, 65.4%, 74.2%, respectively), more frequent incidence of pseudoinfarctions (11.1%, 46.1% and 76.2%), and the most severe leukocyte infiltration along with minor manifestations of compensatory cell responses.

Analyzing the results of histologic examination of placentas in group 3 of women, we have observed a higher (as compared to the

previous groups) percentage of cases that showed signs of chronic inflammation. Thus, a large part of the villi vessels were thickened, their lumen was narrowed and partly obliterated. There were also large immature villi with no vessels inside. In addition, in the chorionic villi we determined large conglomerates of villi of different sizes. The last were often matted together with fibrin necrobiotic changes. There was a significant percentage of the frequency of extensive zones of infarctions, bleeding, thrombosis of intervillous space, expressed signs of syncytiotrophoblast desquamation and increased proportion of villi exposed to fibrinoid degeneration. In our opinion, the prevalence of the expressed destructive processes with virtually no signs of compensation in the placenta allows to regard changes in fetoplacental complex in this group of women as an absolute placental insufficiency.

It is necessary to emphasize once again that in the group of early pregnancy we diagnosed clinical signs of colpitis, bacterial vaginosis, the highest incidence of pathological conditions complicating the course of the first and second half of pregnancy, significantly higher percentage of combination of classic manifestations of preeclampsia, chronic fetal hypoxia, sub- and decompensated forms of placental insufficiency.

## DISCUSSION

The study data allows to specify routes of afterbirth contamination. So, in group 2 (women diagnosed with disorders of vaginal biotope microbiocenosis) ascending route of infection was the most common. It manifested as primarily chorioamnionitis which is consistent with the current study data [1, 22]. This fact once again emphasizes the role of opportunistic pathogens of vaginal biotope in the onset of infection of placenta, umbilical cord and fetal membranes. Hematogenous route prevailed in group 1 mostly characterized by lesions of chorionic villi - villusitis and intervillusitis. In group 3 consisting of pregnant women with microbiocenosis violations of the lower genital tract complicated by preeclampsia it was the mixed route to be dominated (ascending and hematogenous) in afterbirth infection. In our opinion, this points to the obvious role of elevated concentrations of opportunistic pathogens typical

for violation of microbiocenosis of the lower genital tract. On the other hand we are not able to exclude the role of extragenital pathology in the form of chronic foci of infection (pyelonephritis, tonsillitis, diseases of the gastrointestinal tract) in women of groups 1 and 3.

Thus, summarizing the mentioned findings, it may be noted that long-term and combined effects of pathological factors in group 3 (preeclampsia and violation of lower genital tract microbiocenosis), excessive activation of placenta functions and overexertion of the existing compensatory mechanisms were implemented by the most pronounced pathological changes in the fetoplacental complex. One of the main pathogenetic mechanisms of complicated pregnancy and childbirth in the presence of long-term preeclampsia and violations of lower genital tract microbiocenosis is the infectious damage of the placenta with the development of sub- and decompensated forms of fetoplacental insufficiency. The leading morphological components are the following ones: focal disseminated and diffuse forms of inflammatory reaction caused by persistence of viral and bacterial flora in the placenta; dissemination of inflammatory alterations onto all structures of maternal and fetal part of the placenta; the severity of the common degenerative changes in placental tissue caused by the influence of the infection and pathogenic mechanisms associated with obstetric and extragenital pathology; violation of placental tissue differentiation at the term pregnancy by type of relative immaturity in the form of dissociated maturation; anomaly of compensatory and proliferative responses in the form of relative villus hyperplasia (villi that have retarded differentiation).

### CONCLUSION

Synergizing effect of morphological and compensatory-adaptive reactions in the placentas of women of the studied groups suggests that disorders of the lower genital tract microbiocenosis take the lead over clinical manifestations of preeclampsia and are favorable background for its transition to a more severe forms, determine the severity of fetoplacental complex as well as increase the frequency of gestational and perinatal complications. On the other hand pathogenetic

mechanisms of preeclampsia including autoimmune vascular lesions in the periphery, arising disorders of tissue perfusion and activation of the cytokine cascade, reduce the resistance of tissues to opportunistic lower genital tract microflora and contribute to the manifestation of its pathogenic properties not only at the level of vaginal and cervical biotopes.

Inconsistency of the protective properties of the placental barrier in relation to infectious agents, as well as the development of decompensation of adaptive reactions of the fetus resulting in its antenatal death, develops during the earliest stages of gestation on the background of combination of clinical manifestations of preeclampsia and dysbiotic states of the lower genital tract microbiocenosis. According to our data, the risk of transplacental dissemination of infectious agents involving umbilical cord and fetal membranes in pathological process correlates with the time of development and duration of disorders of the lower genital tract microbiocenosis. It is known that the problem of preeclampsia lies in the field of prevention, early diagnosis, timely and adequate treatment of the underlying condition of the woman's body triggering failure of the adaptive mechanisms and being a non-pathogenetic basis for the development of preeclampsia. According to our data disorders of the lower genital tract microbiocenosis is one of such pathological endogenous factors which activates the function of the placenta in the early pregnancy and considerably improves its compensatory and adaptive processes. In the continued use of harmful infectious factors the risk of preeclampsia development or its transition to a more severe form dramatically increases.

According to our research studies prognosis for the fetus in combination of preeclampsia and disorders of the lower genital tract microbiocenosis depends on the type of infection and its clinical forms, time of manifestation, duration and characteristics of the disease, timing of diagnosis, timely and pathogenetically substantiated therapy, the level of compensatory protective reserves of the mother and fetus. We can assume that the complex of adequate treatment and rehabilitation measures aimed at correcting pathological conditions of pregnancy and occurring on the background of

preeclampsia and disorders of the lower genital tract microbiocenosis will not only prevent the maternal mortality but will also optimize perinatal outcomes. The results obtained during the analysis of the structure of the investigated group of women showed a reasonable need for the prospective analysis of the clinical course of pregnancy, childbirth and neonatal status in pregnant women being at “high” risk of reproductive losses which are based on the controlled reason - disorders of vaginal biotope microecology.

#### ACKNOWLEDGEMENTS

This work was performed within the framework of scientific and technical program “Development of the new technologies of child health and reproductive health protection”, state registration number 007. We express our deep appreciation to the staff of the Department of Obstetrics and Gynecology No. 2 for helping to conduct this study.

#### REFERENCES

1. Serov V.N., N.M. Pasman, Y.I. Borodin and A.M. Buruhina, Gestational toxicosis – adaptation disease. Novosibirsk: RIPEL Plus, 2001; 208.
2. Beznoshchenko G.B., T.I. Dolgikh and G.V. Krivchik, Intrauterine infections (questions of diagnostics and medical tactics). Moscow: Medical book; Nizhny Novgorod: “NGMA”, 2003; 88.
3. Sidorova, I.S., Functional state of fetoplacental system in pregnant women being at high risk for IUI. *Obstetrics and Gynecology*, 2003; 4: 15-24.
4. Efremov, S.N., L.G. Maisuradze and A.S. Pulikov, Placenta characteristics in combination of gestosis and viral placentitis. *Bulletin of Perinatology, Obstetrics and Gynecology*, 2000; 7: 37-41.
5. Arzhanova, O.N., N.G. Kosheleva and G.L. Gromyko, Placental insufficiency: diagnosis and treatment: the essence of method, recommendations. St. Petersburg: 8740B5; LAB2>”, 2001; 31.
6. Makarov, I.O., I.S. Sidorova, N.A. Matvienko and A.B. Edokova, Fetoplacental and immune systems at high risk of intrauterine infection. In the Proceedings of the 2<sup>nd</sup> Russian Forum: Mother and Child, Moscow, 2000; 86.
7. Tussupkaliyev, A.B., The value of intrauterine infection in obstetric and perinatal pathology. Abstract from thesis of Candidate of Medical Sciences, Aktobe State medical academy, Almaty, 2000; 27.
8. Tussupkaliyev, A.B. and G.J. Netalina, Characteristics of gestosis in women with genital infection. In the Proceedings of the International Congress of Obstetricians and Gynecologists: Actual Problems of Reproductology, Almaty, 1999; 89.
9. Kuznetsov, M.I., M.E. Belkovskaya and O.I. Babaeva, Ultrasound picture of “infected” placenta - the most likely signs of placenta. *Ultrasound Diagnostic in Obstetrics and Gynecology*, 2000; 8(4): 284-288.
10. Maltseva, L.I. and E.R. Idiyatullina, Content of lysozyme in the serum of women with threatened abortion having urogenital mycoplasma and mixed infection. In the Proceedings of the 2<sup>nd</sup> Russian Forum: Mother and Child, Moscow, 2000; 93-94.
11. Plaksina, A.K., O.Y. Subbotina and E.N. Kharchenko, Influence of urogenital infection on the course of pregnancy. Materials of the VII Final Scientific Conference IMO Nov.SU. Veliky Novgorod, 2000; 2: 86-88.
12. Kryzhanovskaya, I.O., S.S. Zayac and M.P. Kurochka, Fetoplacental insufficiency. Workbook for obstetricians and gynecologists, residents and interns. Rostov-on-Don,; 2003; 81.
13. Gabidulin, T.V., Course and outcomes of pregnancy on the background of co-chlamydial - viral infection, thesis of Candidate of Medical Sciences. Siberian State Medical University. Tomsk, 2000; 19
14. Abezivanova, M.P., The role of dysbiotic violations of vagina in pregnancy in the development of infectious and inflammatory diseases of the newborn. Abstract from thesis of Candidate of Medical Sciences, Rostov State Medical University. Rostov-on-Don, 2003; 23.
15. Bakhtina, T.P., Pathogenetic substantiation of the methods of intensive care and anesthetic protection during delivery in pregnant women with preeclampsia. Abstract from thesis of Doctor of Medical Sciences, Irkutsk State Institute of Advanced Medical. Irkutsk, 2001; 50.
16. Acker, L.V., B.Y. Warsawsky and S.A. Elchaninova, Indicators of oxidative and antioxidant stress in pregnant women with gestosis. *Obstetrics and Gynecology*, 2000; 4: 17-20.
17. Matvienko, N.A., Mother-placenta-fetus system at high risk of intrauterine infection, *J PURE APPL MICROBIO*, 9(1), MARCH 2015.

- abstract from thesis of Candidate of Medical Sciences, Moscow Medical Academy named after I.M.Sechenov. Moscow, 2000; 24.
18. Evsyukova, I.I., L.I. Koroleva, A.M. Savicheva and B.A. Fomenko, Characteristics of the clinical state and persistence of *Chlamydia trachomatis* in children suffering intrauterine chlamydial infection. *Russian Bulletin of Perinatology and Pediatrics*, 2000; **1**: 14-17.
  19. Datsenko, A.V., I.O. Ulyanova, V.B. Tskhai, E.V. Savapina and S.A. Baykova, The results of ultrasound examination of placental insufficiency in intrauterine infection. *Bulletin of Perinatology, Obstetrics and Gynecology*, 2000; **7**: 8-11.
  20. Korsunsky, A.A., Infant mortality in the Russian Federation: ways to reduce (the presentation of the report at the Board of the Russian Ministry of Health from 09.01.2001). *Pediatrics*, 2001; **2**: 4-8.
  21. Pulikov, A.S., A.A. Danilov, V.B. Tskhai and S.V. Efremov, Morphological and functional features of human placenta in intrauterine infection and late gestosis. *Bulletin of Perinatology, Obstetrics and Gynecology*, 2000; **7**: 135-138.
  22. Maltseva, L.I., L.A. Lobova and T.P. Zefirova, Pathological characteristics of placenta in pregnant women with urogenital infection and antibodies to phospholipids. In the Proceedings of the 2<sup>nd</sup> Russian Forum: Mother and Child, Moscow, 2000; 92-93.
  23. Efremov, S.N., L.G. Maisuradze and A.S. Pulikov, Placenta characteristics in combination of gestosis and viral placentitis. *Bulletin of Perinatology, Obstetrics and Gynecology*, 2000; **7**: 37-41.