

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Indicators of Preeclampsia in Correlation with Maternal Cytokines in Pregnancy

Ana Daneva Markova, Marija Hadzi-Lega,
Goran Dimitrov, Gligor Tofovski,
Jadranka Georgievska, Elena Dzikova and Ivo Kjaev

Additional information is available at the end of the chapter

Abstract

Aim: the purpose of the actual study was to evaluate, in the third trimester of pregnancy, the relationship between the formation of anti-inflammatory IL-10 cytokine and several indicators of moderate and severe preeclampsia. **Materials and methods:** in the third trimester of gestation, examination of the biochemical markers of preeclampsia (PE) and maternal IL-10 levels was conducted in 100 women with pregnancies complicated by varying degrees of preeclampsia and in 100 normotensive patients, hospitalized at the University Clinic of Gynecology and Obstetrics, Skopje, Republic of Macedonia. Patients with preeclampsia were categorized into moderate and severe preeclampsia groups according to the degree of preeclampsia. Logistic regression of the different parameters for the occurrence of severe preeclampsia analysis was used to determine the predictive value. **Results:** the regression analysis detected systolic blood pressure of 160 mmHg or higher, diastolic blood pressure of 100 mmHg or higher, persistent proteinuria in pregnancy, serum LDH concentration of 450 U/L or higher, and reduced serum concentrations of IL-10 as significant predictors of severe preeclampsia. **Conclusion:** significantly, lower IL-10 concentrations in maternal serum in patients with severe preeclampsia in comparison with respective concentrations in patients with moderate preeclampsia can be considered as major pathognomonic laboratory sign of severe form of preeclampsia.

Keywords: cytokines, indicators, preeclampsia, biochemical markers, prediction

1. Introduction

Preeclampsia (PE), one of the current problems of obstetrics, is a pathological multifactorial syndrome that occurs in the second half of pregnancy and is manifested through a basic

triad of symptoms: swelling, proteinuria, and hypertension and in severe cases, convulsions and coma [1, 2]. Preeclampsia remains one of the most sophisticated problems of modern obstetrics and gynecology. It generally determines the structure of maternal and perinatal morbidity and mortality. The role of immune mechanisms contributing to the development of a normal pregnancy is widely discussed. Their involvement in the pathogenesis of pregnancy complications such as preeclampsia was also noted [3]. The analysis of the scientific literature reveals the conclusion that many aspects of the pathogenesis of preeclampsia are related with systemic inflammatory response syndrome with the development of a destructive inflammatory process, immune disorders, and the imbalance of cytokine regulation of gestation processes [4–6].

The role of vascular endothelial damage with the development of generalized arteriolar spasm as one of the leading mechanisms in the pathogenesis of preeclampsia is supposed to be significant. However, the relationship between the development of endothelial dysfunction and disruption of cytokine regulation in different clinical forms of preeclampsia also requires further research and is currently represented in several scientific works [7].

Proteinuria has been proposed and studied as both an indicator of the severity of the disease and a predictor of the outcome in preeclampsia. Many clinicians still make major management decisions based on the degree of proteinuria in these patients.

Cytokines, such as IL-2, IL-8, and TNF- α , are pro-inflammatory, increased in the blood, in leukocytes during PE. Elevated concentrations of TNF- α have been observed in the blood of women with PE [8]. Further studies support the idea of the involvement of the maternal immune system in the development of preeclampsia which comes from the prim paternity theory [9]. This hypothesis holds that the risk of developing preeclampsia is highest in the first pregnancy [10], and a previous normal pregnancy is associated with a lowered incidence of preeclampsia [11] in the subsequent pregnancy.

In contrast to normal pregnancy, there are indications of increased inflammatory responses [12] and also of an immune deviation toward Th1 in the established preeclampsia pregnancy [13]. Roberts et al. [14] were one of the first to suggest that mediators released in preeclampsia are responsible for the endothelial damage seen in preeclampsia. Subsequent to the damage, the injured endothelium initiates a dysfunctional cascade of coagulation, vasoconstriction, and intravascular fluid redistribution that results in the clinical syndrome of preeclampsia [15].

Numerous studies show that the balance of cytokines has special importance in the regulation of pregnancy. However, the diagnostic and prognostic significance of breaches in the immune balance during preeclampsia has not yet been determined.

2. Aim

The purpose of the actual study was to evaluate the relationship between the formation of anti-inflammatory cytokines and several indicators of moderate and severe preeclampsia in the third trimester of pregnancy.

3. Materials and methods

We conducted a prospective study of 50 women with pregnancies complicated by varying degrees of preeclampsia in the third trimester of gestation with singleton pregnancies between 28 and 40 weeks' gestation (± 1 week), parity (parity 1–4 and parity > 4), and maternal age (< 20 years, 20–35, and > 35 years) and in 50 normotensive patients without threatening signs of hypertension and preeclampsia, hospitalized at the University Clinic of Gynecology and Obstetrics, Skopje, Republic of Macedonia.

The severity of preeclampsia was determined according to the definition of the *WHO Handbook for Guideline Development*, Geneva, 2010. Our inclusion criteria were reproductive age, diagnosed moderate and severe preeclampsia based on the criteria for classification at the time of collection of maternal serum, and the patients' informed consent for inclusion in the survey.

Exclusion criteria were acute and chronic genital and extra genital diseases (essential hypertension, heart failure, diabetes, morbid obesity, immunodeficiency, systemic diseases, chronic infectious diseases, genetic pathology).

Patients with preeclampsia were categorized into moderate (m PE) group A and severe (S PE) preeclampsia group B according to the degree of preeclampsia.

Cytokine levels in the serum were measured by the "sandwich" method of solid-phase enzyme immunoassay using double antibody. As a standard for comparison of each reaction, recombinant cytokines were used, which are part of the test—whale.

Statistical data processing was done using the SPSS 13.0 software for Windows.

4. Results

Regarding patients' distribution by ethnicity, in **Table 1**, Albanians represented more than half of the women with preeclampsia as 44% of participants with symptoms of medium and 68% with symptoms of severe PE. Pregnant Albanians (68%) dominate in the group with normal tension.

The average body mass index (BMI) in the group of pregnant women with preeclampsia was 34.33 ± 4.5 —that was not significantly higher than tile average body mass of the control group (32.88 ± 3.8) ($p = 0.09$). The difference between the average BMI of pregnant women with moderate and severe PE and normotensive patients was significant ($F = 3.8$, $p = 0.026$). Namely, pregnant women with severe PE had significant higher average BMI than normotensive pregnant women (35.57 ± 4.11 vs. 32.88 ± 3.8 , $p = 0.025$).

Statistical analysis is showed, not significant differences in the levels of interleukin 10 in serum between pregnant women with preeclampsia and healthy pregnant women ($p = 0.5$), but the difference between moderate preeclampsia, severe preeclampsia, and control group was highly significant ($p < 0.01$) due to the lower levels of this interleukin in the severe preeclampsia group comparing moderate preeclampsia in relation to the control and due to the significant lower values when comparing control in relation to the moderate preeclampsia

Variable	Groups			
	All PE N = 50	Moderate PE N = 25	Severe PE N = 25	Control (C) N = 50
Age (years) mean \pm SD	32.06 \pm 4.8	29.9 \pm 4.7	34.2 \pm 3.85	31.8 \pm 4.8
All PE/C $t = 0.27$ $p = 0.8$ mPE/sPE/C; $F = 5.5$; $p = 0.005$				
Gestational week, mean \pm SD	34.99 \pm 3.5	35.5 \pm 3.4	34.4 \pm 3.6	34.8 \pm 3.6
All PE/C; $t = 0.2$; $p = 0.8$ mPE/sPE/C $F = 0.6$ $p = 0.5$				
Ethnicity n %				
Macedonian	18 (36%)	10 (40%)	8 (32%)	15 (30%)
Albanian	28 (56%)	11 (44%)	17 (68%)	34 (68%)
Romani	4 (8%)	4 (16%)	0	1 (2%)
BMI mean \pm SD, range	34.33 \pm 4.5 24.2–44	33.1 \pm 4.7 24.2–41	35.57 \pm 4.1 27–44	32.88 \pm 3.8 27–43.9
All PE/C; $t = 1.7$; $p = 0.09$				

Table 1. Age, gestational week, BMI, and IL-10 serum concentration in women with moderate and severe preeclampsia, and women with normal blood pressure (control group).

group. Average concentrations of IL-10 in serum were 23.2 ± 40.7 pg/ml in the total group of preeclampsia patients, 45.5 ± 48.4 pg/ml in the group with moderate preeclampsia, and 0.8 ± 0.4 pg/ml in the group with severe preeclampsia. In patients with normal tension, the average serum concentration of interleukin 10 was 4.2 ± 6.7 pg/ml.

Study data demonstrated that in pregnant women with pregnancy complicated by preeclampsia, the serum concentration of anti-inflammatory interleukin 10 is confirmed as a significant predictor of the occurrence of severe preeclampsia (**Table 2**). Increased serum concentrations of interleukin 10 (in pg/ml) reduced the likelihood of the development of severe preeclampsia by 89.6% (95% CI 0.016–0.678).

Figures 1–3 show that the results of bivariate analysis are of the relationships between serum maternal concentration of IL-10 and serum enzyme LDH, creatinine, platelets, proteinuria, and uric acid.

The obtained values of Pearson's coefficients indicate negative correlations of interleukin 10 with LOH and proteinuria, whereas the correlations of IL-10 with creatinine platelets and uric acid were positive. However significant correlations were confined between interleukin 10 and platelets as well as between IL-10 and proteinuria. The correlation with the platelet count was positive which means that significantly higher concentration of interleukin 10 was confirmed in patients with higher number of platelets in the blood and vice versa. The correlation between interleukin

Variable	B	S.E.	Wald	Sig.	Exp(B)	95.0% CI for Exp(B)	
Age	0.2	0.086	5.350	0.021	1.221	1.031	1.446
Nulliparity (present)	1.816	1.114	2.657	0.103	6.145	0.692	54.534
Systolic blood pressure (≥160 mmHg)	3.711	1.053	12.412	0.000	40.900	5.189	322.371
Diastolic blood pressure (≥100 mmHg)	2.414	0.843	8.192	0.004	11.176	2.140	58.360
Proteinuria (present)	3.081	1.307	5.56	0.018	21.785	1.682	282.123
LDH ≥ 450 (U/L)	2.066	0.915	5.102	0.024	7.896	1.314	47.433
Albumin (serum) (g/L)	-0.239	0.125	3.66	0.056	0.787	0.616	1.006
Creatinine (serum) (umol/L)	-0.067	0.035	3.696	0.055	0.935	0.873	1.001
Platelets (≤150)	-0.006	0.013	0.236	0.627	0.994	0.97	1.019
IL-10 (pg/ml)	-2.324	1.051	4.888	0.027	0.098	0.012	0.768

Dependent variable: severe preeclampsia.

Table 2. Multivariate logistic regression analysis for the factors predictors of severe preeclampsia.

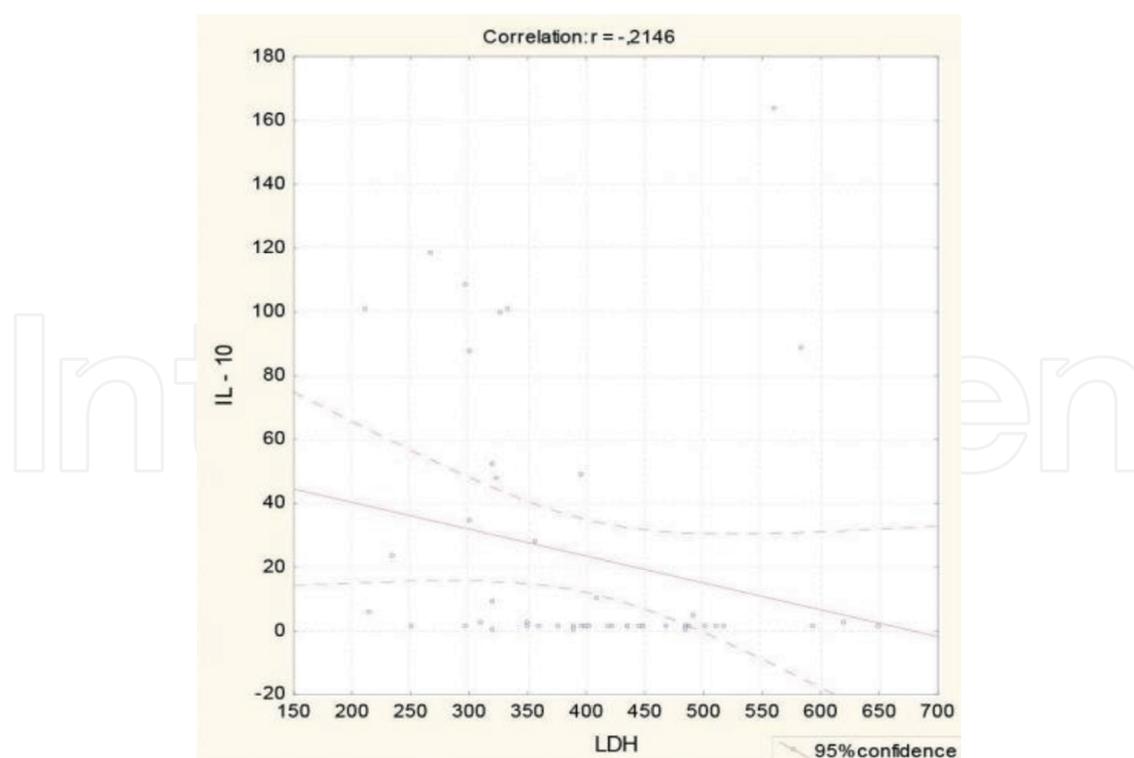


Figure 1. Correlation IL-10/LDH: $r = -0.215$ and $p = 0.134$.

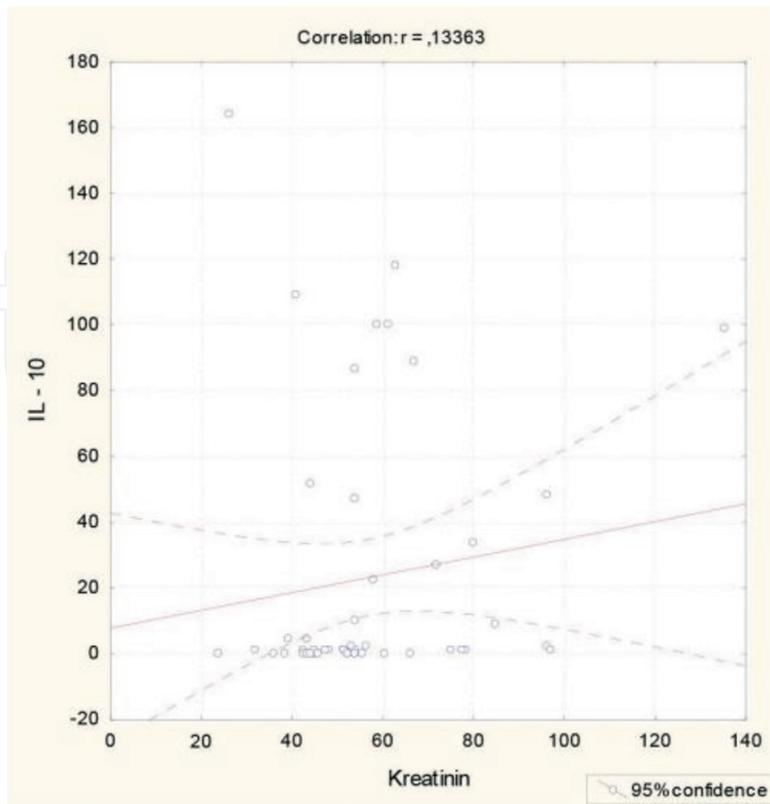


Figure 2. Correlation IL-10/creatinine: $r = 0.134$ and $p = 0.355$.

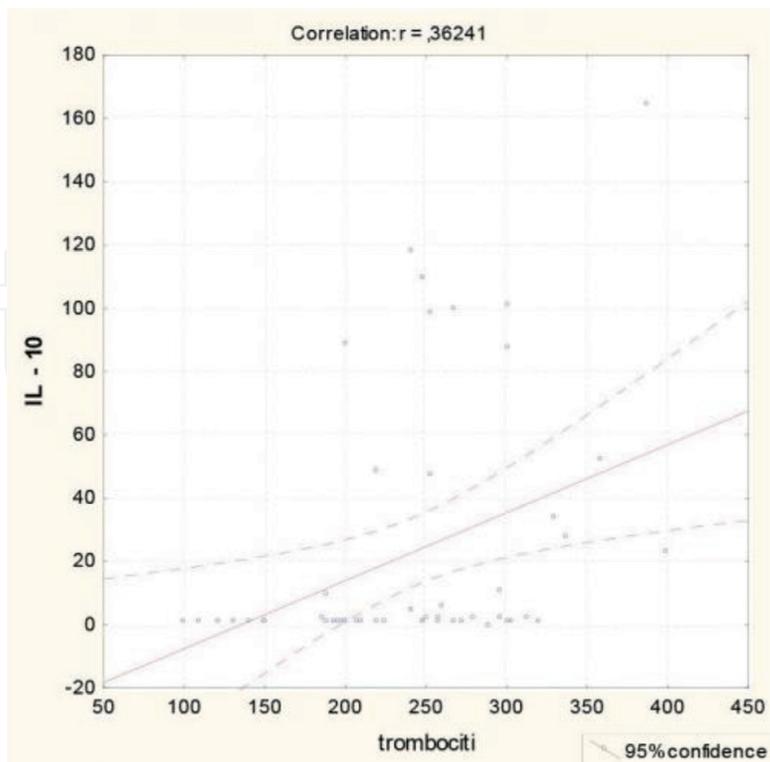


Figure 3. Correlation IL-10/platelets.

10 and proteinuria was negative showing that the serum concentration of interleukin 10 was significantly lower in patients with higher amount of proteins in the urine and vice versa.

5. Discussion

This study demonstrates differences in IL-10 levels in women with preeclampsia compared to the levels in women with a normal pregnancy outcome.

We found that in pregnant women with preeclampsia the increased serum concentrations of IL-10 predicted lower likelihood for the development of severe preeclampsia.

Longitudinal studies in mice demonstrate a sequential change in the cytokine profile in serum including interleukin 10 in peripheral blood and release from spleen elements as pregnancy advances.

In the second half of pregnancy, IL-10 inhibition in mice is related with fetal growth retardation [16]. Progesterone has been shown to increase Th2-type responses in T cells [17]. This study demonstrated that there is a significant alteration in the serum concentration of IL-10 in severe preeclampsia compared with normal pregnancy and in moderate preeclampsia groups of patients.

The regression analysis applied in this study showed diastolic blood pressure of 100 mmHg or higher, systolic blood pressure of 160 mmHg or higher, persistent proteinuria in pregnancy, the serum LDH concentration of 450 U/L or higher, and reduced serum concentrations of IL-10 in maternal serum as significant predictors of severe preeclampsia. While other variables predicted the development of severe preeclampsia, IL-10 decreased such likelihood. IL-10 was also found to be negatively correlated with proteinuria and positively correlated with blood platelets. Significantly higher concentration of IL-10 was confirmed in patients with higher number of platelets in the blood. The serum concentration of IL-10 was significantly lower in patients with higher amount of proteins in the urine.

This study demonstrated platelet count and proteinuria as significant predictors of serum IL-10 concentration—urine proteins predicting lower serum IL-10 while platelets count predicting higher serum concentration of interleukin 10.

Other studies suggest a proportional link between the level of proteinuria and adverse clinical outcomes. In recent study 13,000 pregnant women found significant proteinuria, defined as 21 or more on dipstick analysis, and it was associated with an increase in prematurity rates, intrauterine fetal growth restriction, and increased neonatal morbidity and mortality when associated with hypertension [18]. Other studies suggest that it is the presence of proteinuria rather than the severity, which is associated with poorer outcomes in these complications for mother and stillbirth. There is evidence that even the finding of trace proteinuria in pregnant women with hypertension is associated with an increase in adverse outcomes.

Taking into consideration changes of anti-inflammatory cytokine concentrations in severe preeclampsia, the moderate phase can be analyzed as a critical stage in complicated pregnancy.

6. Conclusion

Cytokines play critical, essential roles in signaling between cells of the immune system, with a prolific range of regulatory activities including the stimulation, recruitment, activation, destroying, and suppression of immune and nonimmune cells.

Analyzing cytokines at the end of pregnancy, last trimester complicated with preeclampsia, is useful. The moderate phase can be considered a critical stage in preeclampsia that comes to the most functional strain homeostatic system.

Abbreviation

BMI	body mass index
PE	preeclampsia
TNF- α	tumor necrosis factor- α

Author details

Ana Daneva Markova^{1,2*}, Marija Hadzi-Lega¹, Goran Dimitrov¹, Gligor Tofovski¹,
Jadranka Georgievska¹, Elena Dzikova¹ and Ivo Kjaev¹

*Address all correspondence to: anadaneva@yahoo.com

1 Medical Faculty, University Clinic of Obstetrics and Gynecology, Ss. Cyril and Methodius University, Skopje, Macedonia

2 Department of Obstetrics and Gynecology, State University Hospital of Skopje, Skopje, Macedonia

References

- [1] Vikhlyaeva M. Preclinical manifestations of systemic disorders. Clinical outcomes and long term effects of preeclampsia. *Obstetrics and Gynecology*. 2009;1:3-6
- [2] Tsatsaris V, Fournier T, Winer N. Pathophysiology of preeclampsia. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2008;1:16-23
- [3] Sukhin GT, Vanko LV. Immune factors in the etiology and pathogenesis of pregnancy complications. *Obstetrics and Gynecology*. 2012;1:128-136

- [4] Lewis DF, Canzoneri BJ, Wang Y. Maternal circulating TNF-alpha levels are highly correlated with IL-10 levels but not IL-6 and IL-8 levels in women with pre-eclampsia. *American Journal of Reproductive Immunology*. 2009;5:269-274
- [5] Kalkunte S, Nevers T, Norris WE, Sharma S. Vascular IL-10: A protective role in pre-eclampsia. *Journal of Reproductive Immunology*; 88:165-169
- [6] Tosun M, Celik H, Avci B, Yavuz E, Alper T, Malatyalioglu E. Maternal and umbilical serum levels of interleukin-6, Interleukin -8, and tumor necrosis factor-alpha in normal pregnancies and in pregnancies complicated by preeclampsia. *Journal of Maternal - Fetal and Neonatal Medicine*. 2010;23:880-886
- [7] Molvarec A, Szarka A, Walentin S, Beko G, Karádi I, Prohászka Z, Rigó J Jr. Serum leptin levels in relation to circulating cytokines, Chemokines, Adhesion molecules and angiogenic factors in normal pregnancy and preeclampsia. *Reproductive Biology and Endocrinology*. 2011;9:124-133
- [8] Bosio PM, PJ MK, Conroy R, O'Herlihy C. Maternal central hemodynamics in hypertensive disorders of pregnancy. *Obstet Gynecology*. 1999;94:978-984
- [9] Lim KH, Friedman SA, Ecker J, Kao L, Kilpatrick SJ. The clinical utility of serum uric acid measurements in hypertensive diseases of pregnancy. *The American Journal of Obstetrics and Gynecology*. 1998;178:1067-1071
- [10] Makarov IO, Shemanaeva TV, Hasanov SR, Popova OP. Preeclampsia as a manifestation of immune endotheliosis. *The Questions of Gynecology, Obstetrics and Perinatology*. 2009;6:17-22
- [11] Sidorova IS, Gurin OI, Milovanov AP. The pathogenesis of preeclampsia as a manifestation of immune-endothelial pathology (acute immune endotheliosis). *Obstetrics and Gynecology*. 2008;6:13-17
- [12] Hashii K, Flljiwara S, Yoshioka N, Kataoka S, Yamada T, Hirano T. Peripheral blood mononuclear cells stimulate progesterone production. By luteal cells derived from pregnant and non pregnant women: Possible involvement of interleukin -4 and interleukin-10 in corpus luteum function and differentiation. *Human Reproduction*. 1998;13:2738
- [13] Chaouat G, Meliani AA, Martal R, et al. IL-10 prevents naturally occurring fetal loss in the CBA 3 DBA/2 mating combination and local defect in IL-10 production in this abortion-prone combination is corrected by in vivo injection of IFN- γ . *The Journal of Immunology*. 1995;154:4261-4268
- [14] Delassus S, Coutinho C, Saucier S, Darehe Kourilsky P. Differential cytokine expression maternal blood and placenta during murine gestation. *The Journal of Immunology*. 1994;152:2411
- [15] Athanassakis I, Iconomidou B. Cytokine production in the serum and spleen of mice from day 6 to 14 of gestation: Cytokine/placenta/spleen/serum. *Developmental Immunology*. 1996;4:247

- [16] Piccinni MP, Giudizi G, Biagotti R, Beloni L, Giannarini L. Progesterone favors the development of human T helper cells producing Th2 type cytokines and promotes both IL-4 production and membrane CD30 expression in established Th1 cell clones. *The Journal of Immunology*. 1995;**155**:128
- [17] Rijhsinghani AG, Thompson K, Tygrette Bhatia SK. Inhibition of interleukin - 10 during pregnancy results in neonatal growth retardation. *American Journal of Reproductive Immunology*. 1997;**37**:232
- [18] Cote AM, Firoz T, Mattman A. The 24-hour urine collection: Gold standard or historical practice. *The American Journal of Obstetrics and Gynecology*. 2008;**199**:625

IntechOpen