

## **Monocyte/HDL-cholesterol ratio as an early prognostic marker of pregnancy complications development**

**Jovana Vulić<sup>1</sup>, Jelena Radojković<sup>1</sup>, Jelena Vekić<sup>1</sup>,  
Aleksandra Stefanović<sup>1</sup>, Daniela Ardalić<sup>2</sup>, Željko Miković<sup>2,3</sup>,  
Tamara Gojković<sup>1</sup>, Jelena Munjas<sup>1</sup>, Aleksandra Zeljković<sup>1\*</sup>**

<sup>1</sup>Department of Medical Biochemistry, University of Belgrade – Faculty of Pharmacy, Belgrade, Serbia

<sup>2</sup>Gynecology and Obstetrics Clinic Narodni Front, Belgrade, Serbia

<sup>3</sup>Department of Gynecology and Obstetrics, Faculty of Medicine, University of Belgrade, Serbia

\*Corresponding author: Aleksandra Zeljković, e-mail: [aleksandra.zeljkovic@pharmacy.bg.ac.rs](mailto:aleksandra.zeljkovic@pharmacy.bg.ac.rs)

Received: 9 November 2024; Revised in revised forme: 16 January 2025; Accepted: 20 January 2025

---

### **Abstract**

Pregnancy complications increase the long-term cardiovascular risk for both the mother and the child. Inflammation is a common mechanism underlying the development of pregnancy complications and atherosclerosis. This study aims to investigate whether the monocyte/HDL cholesterol ratio can serve as a predictive marker for the risk of pregnancy complications. A total of 84 pregnant women participated in this study, 41 of whom had a normal pregnancy course, while 43 experienced complications. Lipid status parameters were measured using enzymatic methods and total blood count was measured using a hematology analyzer. In the first trimester of pregnancies with complications we observed significantly higher levels of total cholesterol ( $P < 0.01$ ), low-density lipoprotein cholesterol (LDL-C) ( $P < 0.01$ ) and triglycerides ( $P < 0.001$ ) compared to pregnancies without complications, whereas no differences were observed in high-density lipoprotein cholesterol (HDL-C). Pregnant women with complications had a significantly higher proportion of monocytes throughout the entire pregnancy, and lower concentrations of HDL-C in the second trimester ( $P < 0.05$ ). The risk of developing complications in pregnancy was 11 times higher if the monocyte/HDL-C ratio was elevated in the first trimester (OR: 11.42; 95% CI: 4.05–32.19;  $P < 0.001$ ). Our results indicate that monocyte/HDL-C ratio could be used as a simple and cost-effective early prognostic biomarker of pregnancy complications.

**Key words:** pregnancy, complications, monocyte/HDL-C ratio

---

<https://doi.org/10.5937/arhfarm75-54675>

## Introduction

Pregnancy requires significant cardiometabolic adaptation of the maternal body to ensure optimal fetal growth and development. The physiological course of pregnancy involves a series of metabolic changes, leading to the development of insulin resistance and dyslipidemia in the second half of gestation. The characteristics of dyslipidemia in physiological pregnancy are reflected in elevated serum concentrations of all lipid parameters (1, 2). Due to the simultaneous increase in cholesterol concentrations in both low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particles, dyslipidemia occurring during physiological pregnancy is not considered to be a proatherogenic disorder.

Research indicates that approximately 80% of women will experience at least one pregnancy during their lifetime, with complications occurring in about 30% of these cases (1). These complications can adversely affect pregnancy outcomes, posing risks to the health and life of both the mother and the child (3). The most common complications are hypertensive disorders of pregnancy, preeclampsia, gestational diabetes (GDM), and intrauterine growth restriction (IUGR). In pregnancies complicated by these conditions, the lipid profile shows proatherogenic features, characterized by hypertriglyceridemia and decreased HDL-cholesterol (HDL-C) levels (4). Increasing evidence indicates that pregnancy complications increase the long-term risk of cardiovascular diseases for both the mother and the child (1).

Inflammation is a key underlying mechanism contributing to the development of most pregnancy complications. Inflammatory processes are well-recognized as playing a role in regulating reproduction, from the menstrual cycle and early pregnancy to childbirth (5). It has been shown that the expression of inflammatory mediators IL-6 and IL-8 changes throughout the menstrual cycle, indicating their roles in implantation and neovascularization of the growing endometrium, respectively (6). During pregnancy, the primary purpose of this process is the regulation of immune mechanisms to maintain tolerance to fetal antigens (5). However, an intensified inflammatory response, arising from factors such as incomplete spiral artery remodeling or obesity-induced hyperglycemia, can escalate into pathological inflammation, subsequently triggering a systemic reaction that results in vascular endothelial damage (5, 7). In addition to its role in pregnancy complications, endothelial dysfunction is an early event that precedes the development of atherosclerosis (8). This suggests that inflammation and endothelial dysfunction are potential mechanisms by which pregnancy complications contribute to increased future risk of cardiovascular diseases.

Monocytes play a significant role in the initiation and progression of atherosclerosis. Within the subendothelial space, monocytes absorb oxidatively modified LDL particles, forming foam cells (9). Additionally, monocytes produce proinflammatory mediators and reactive oxygen species, thereby contributing to the development of oxidative stress. HDL is an antiatherogenic lipoprotein particle that exerts anti-inflammatory and antioxidant effects. It has been established that HDL can inhibit the

migration and activation of monocytes, as well as the proliferation and differentiation of monocytic progenitor cells. Moreover, HDL prevents the oxidative modification of LDL particles (9). Considering that previous studies have shown an increase in monocyte counts and a decrease in HDL-C levels during complicated pregnancies, this study aimed to investigate whether the monocyte/HDL-C ratio can predict the risk of pregnancy complications.

## **Patients and Methods**

The study included 84 pregnant women, 41 of whom had a normal course of pregnancy, while 43 developed pregnancy complications. All pregnant women were monitored at the Gynecology and Obstetrics Clinic “Narodni Front” in Belgrade. In the group that developed complications, 13 women had hypertension, with 3 of them concomitantly having GDM or IUGR. A total of 20 women developed preeclampsia, with 6 also having GDM and 4 having IUGR. Among them, 4 women had either GDM or IUGR alone, while 2 experienced both complications at the same time. As part of regular check-ups in the first (T1: 11–14 weeks of gestation), second (T2: 22–25 weeks of gestation), third trimester (T3: 28–32 weeks of gestation) and before delivery (T4), systolic and diastolic blood pressure and body mass index (BMI) were assessed in all pregnant women. BMI was defined as weight (kg)/height<sup>2</sup> (m<sup>2</sup>). At each visit, blood samples were obtained for both biochemical and hematological analyses.

All participants were informed about the study's aims and design and signed an informed consent prior to enrolment. The study was designed according to the ethical guidelines defined by the Helsinki Declaration and gained the approval of local ethical authorities.

Concentrations of glucose, total proteins, urea, creatinine, uric acid lipid status parameters (total cholesterol, triglycerides, LDL-C and HDL-C) were determined using a Beckman AU480 analyzer employing commercial kits (Beckman, USA). Hematological analyses were performed on the Sysmex XN hematology analyzer (Sysmex Corporation, Japan). For this study, we analyzed the total leukocyte count and the proportions of granulocytes, monocytes, and lymphocytes. Monocyte/HDL-C ratio was calculated by dividing the proportion of monocytes to HDL-C concentration. Continuous quality control, which ensures the reliability of the results, was carried out for both biochemical and hematological analyses.

Data distribution was tested using the Kolmogorov-Smirnov test. Normally distributed data are presented as arithmetic mean  $\pm$  standard deviation and analyzed using the Student's t-test. The monocyte/HDL-C ratio did not follow a normal distribution; therefore, the results were compared using the nonparametric Mann-Whitney U test and presented as medians and interquartile ranges. The association between elevated monocyte/HDL-C ratio and the development of pregnancy complications was analyzed using multiple logistic regression analysis. In all statistical analyses, a P-value of less than 0.05 was considered significant. Statistical analyses were performed by using the statistic package PASW Statistics 18 (IBM, Armonk, New York, United States).

## Results

Table I shows the demographic characteristics and first-trimester biochemical parameters of pregnant women with and without complications. In addition to a statistically significantly higher BMI, pregnant women with complications also demonstrated significantly higher systolic and diastolic blood pressure, as well as elevated serum levels of glucose, total cholesterol, triglycerides, LDL-C, and uric acid. On the other hand, a statistically significant decrease in the concentration of creatinine and urea was observed in pregnant women with complications. Although the differences in HDL-C concentrations were not statistically significant, a trend of lower levels was observed in the group with complications.

**Table I** Demographic and biochemical parameters at first trimester in the studied pregnant women

**Tabela I** Demografske karakteristike i biohemijski parametri u prvom trimestru trudnoće u ispitivanim grupama

Parameter	Pregnancy with complications	Pregnancy without complications	P-value
N	43	41	
Age (years)	31 ± 5.9	30 ± 4.2	0.229
BMI (kg/m <sup>2</sup> )	25.5 ± 5.2	21.5 ± 2.9	< 0.001
Systolic pressure (mm/Hg)	119.7 ± 14.4	111.8 ± 12.1	< 0.01
Diastolic pressure (mm/Hg)	78.9 ± 10.3	71.3 ± 8.9	< 0.01
Glucose (mmol/L)	4.83 ± 0.7	4.25 ± 0.4	< 0.001
Total proteins (g/L)	67.2 ± 3.7	68.7 ± 10.4	0.370
Total cholesterol (mmol/L)	5.52 ± 1	4.93 ± 0.8	< 0.01
Triglycerides (mmol/L)	1.61 ± 0.7	1.08 ± 0.3	< 0.001
LDL-C (mmol/L)	2.98 ± 0.8	2.51 ± 0.7	< 0.01
HDL-C (mmol/L)	1.81 ± 0.5	1.93 ± 0.4	0.220
Urea (mmol/L)	2.8 ± 0.6	3.1 ± 0.6	< 0.05
Creatinine (μmol/L)	56.7 ± 7.4	63.6 ± 6.4	< 0.001
Uric acid (μmol/L)	203 ± 46.7	172.5 ± 33.7	< 0.01

The results were compared using the Student's t-test and presented as mean values ± standard deviation.

Table II shows the total leukocyte count and leukocyte differential count across all trimesters in pregnant women with and without complications. It has been shown that, during the first two trimesters, pregnant women with complications had a significantly higher leukocyte count compared to those without complications. Moreover, we observed that women with pregnancy complications had a significantly higher proportion of monocytes throughout pregnancy.

**Table II** Leukocytes total count and the proportion of leukocyte subpopulations in pregnant women with and without complications

**Tabela II** Broj leukocita i leukocitarna formula kod ispitanica sa i bez komplikacija u trudnoći

Trimester	Parameter	Pregnancy with complications	Pregnancy without complications	P-value
T1	Leukocytes (x10 <sup>9</sup> /L)	9.0 ± 1.8	8.0 ± 1.9	< 0.05
	Lymphocytes (%)	23.9 ± 6.6	25.3 ± 5.4	0.312
	Monocytes (%)	5.1 ± 1.2	3.2 ± 0.9	< 0.001
	Granulocytes (%)	70.9 ± 7.2	71.4 ± 5.5	0.706
T2	Leukocytes (x10 <sup>9</sup> /L)	10.3 ± 2.0	9.2 ± 2.0	< 0.05
	Lymphocytes (%)	20.7 ± 4.7	22.5 ± 3.6	0.052
	Monocytes (%)	5.4 ± 1.6	4.7 ± 0.9	< 0.05
	Granulocytes (%)	73.9 ± 5.5	72.8 ± 4.0	0.283
T3	Leukocytes (x10 <sup>9</sup> /L)	10.3 ± 2.1	9.7 ± 2.2	0.176
	Lymphocytes (%)	21.2 ± 4.8	23.7 ± 4.3	< 0.05
	Monocytes (%)	5.4 ± 1.5	4.3 ± 1.0	< 0.001
	Granulocytes (%)	73.5 ± 5.5	72.0 ± 4.6	0.195
T4	Leukocytes (x10 <sup>9</sup> /L)	9.7 ± 2.4	10.2 ± 5.5	0.628
	Lymphocytes (%)	22.9 ± 5.9	25.2 ± 3.9	0.039
	Monocytes (%)	5.7 ± 1.0	4.1 ± 1.0	< 0.001
	Granulocytes (%)	71.4 ± 6.3	70.6 ± 4.1	0.498

The results were compared using Student's t-test and are presented as mean values ± standard deviation.

Table III presents a comparative overview of HDL-C concentration changes across all trimesters in both groups of pregnant women. Women without complications showed a greater increase in HDL-C levels during the second trimester compared to those with complications. Additionally, the results indicate significantly lower HDL-C concentrations in pregnant women with complications during this period.

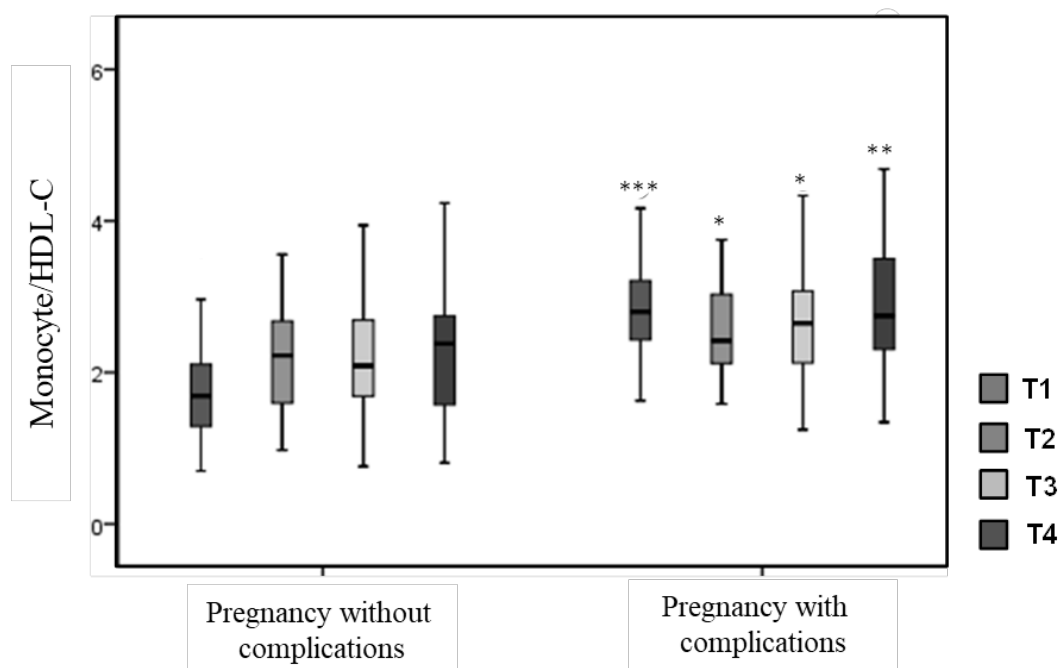
**Table III** HDL-C concentrations across trimesters in pregnant women with and without complications development

**Tabela III** Koncentracije HDL-h po trimestrima kod ispitanica sa i bez razvoja komplikacija u trudnoći

Trimester	Pregnancy with complications	Pregnancy without complications	P-value
HDL-C (mmol/L), T1	1.8 ± 0.5	1.9 ± 0.4	0.220
HDL-C (mmol/L), T2	2.0 ± 0.4	2.3 ± 0.5	< 0.05
HDL-C (mmol/L), T3	2.1 ± 0.6	2.0 ± 0.5	0.944
HDL-C (mmol/L), T4	2.0 ± 0.5	1.9 ± 0.5	0.357

The results were compared using Student's t-test and are presented as mean values ± standard deviation.

Figure 1 shows the monocyte/HDL-C ratio values throughout pregnancy in both groups of participants. In all trimesters of complicated pregnancies, this ratio was significantly higher compared to pregnancies without complications. Specifically, in the first trimester, the median monocyte/HDL-C ratio in the group without complications was 1.69 (interquartile range: 1.28–2.16), whereas in the group with complications it was 2.80 (interquartile range: 2.40–3.25;  $P < 0.001$ ). In the second trimester, this ratio was 2.22 (interquartile range: 1.59–2.69) in the group without complications, in comparison with 2.42 (interquartile range: 2.12–3.05;  $P < 0.05$ ) in the group with pregnancy complications. In the third trimester, the monocyte/HDL-C ratio was 2.09 (interquartile range: 1.68–2.75) in the healthy pregnancy group vs. 2.65 (interquartile range: 2.10–3.23;  $P < 0.05$ ) in the group with complications development. Finally, the median immediately before delivery for the group without complications was 2.38 (interquartile range: 1.56–2.89), and 2.75 for the group with complications (interquartile range: 2.27–3.53;  $P < 0.01$ ).



Results were compared using the Mann-Whitney U test and are presented as medians with interquartile ranges. \*\*\*  $P < 0.001$ ; \*\*  $P < 0.01$ ; \*  $P < 0.05$  compared to pregnancies without complications.

**Figure 1. Monocyte/HDL-C ratio by trimesters in participants with and without pregnancy complications**

**Slika 1. Odnos monociti/HDL-h po trimestrima kod ispitanica sa i bez komplikacija u trudnoći**

Table IV presents the results of multiple logistic regression analysis, which was conducted to determine whether the monocyte/HDL-C ratio in the first trimester could indicate the risk for pregnancy complications. The analysis revealed that the likelihood of developing complications is approximately 11 times higher if the monocyte/HDL-C ratio is elevated in the first trimester. In the multivariate analysis, a model that was created included traditional risk factors for pregnancy complications (maternal age, pre-pregnancy BMI and systolic and diastolic blood pressure values). It was found that even after adjusting for these demographic factors, pregnant women with an elevated monocyte/HDL-C ratio in the first trimester still had a significantly higher likelihood of developing complications ( $P < 0.001$ ).

**Table IV** Monocyte/HDL-C ratio in the first trimester and risk for pregnancy complications

**Tabela IV** Odnos monociti/HDL-h u prvom trimestru kao indikator rizika za nastanak komplikacija u trudnoći

Dependent variable	OR (95% CI)	P-value
Monocyte/HDL-C ratio	11.42 (4.05–32.19)	< 0.001
<b>Adjusted for:</b>		
Maternal age	13.23 (3.86–45.41)	< 0.001
Pre-pregnancy BMI		
Systolic blood pressure		
Diastolic blood pressure		

All variables are continuous. OR – odds ratio; 95% CI – confidence interval.

## Discussion

Healthy physiological pregnancy is associated with complex and intense modifications of the lipid profile, which greatly resemble to proatherogenic lipid changes. Generally, the lipid profile in physiological pregnancy involves an increase in the serum concentration of all lipid parameters. Since fatty acids are an important source of energy and cholesterol is a precursor for the synthesis of steroid hormones and cell membranes, such specific changes in the maternal lipid profile are expected and aimed to meet the needs of the fetus. However, in pregnancy with complications, there is a significant increase in serum triglyceride concentrations (10), resulting from increased synthesis of very-low-density lipoproteins (VLDL) induced by estradiol and their slower removal from circulation due to reduced activity of hepatic lipase (HL) and lipoprotein lipase (LPL). Additionally, the activity of cholesteryl ester transfer protein (CETP), which increases during pregnancy, facilitates the transfer of triglycerides to LDL and HDL particles in exchange for cholesterol esters. These processes ultimately result in the accumulation of triglycerides in LDL and HDL particles, making them smaller and

denser, and increasing their proatherogenic potential. Small dense LDL particles are more susceptible to oxidative modification, and they bind with higher affinity to vascular wall proteoglycans and with lower affinity to LDL receptors (11). Some studies have shown that changes in the structure of LDL and HDL particles are associated with the development of pregnancy complications, such as preeclampsia, IUGR and GDM (10). Recently published studies have suggested that a mother's predisposition to developing complications during pregnancy could be explained, at least in part, by elevated lipid profile parameters during early pregnancy (12).

In this study, we compared clinical, biochemical and hematological parameters in the first trimester of pregnancies with and without complications. It is important to note that pregnant women with complications had significantly higher triglycerides, total cholesterol and LDL-C concentrations (Table I), confirming the previously stated hypothesis that the lipid profile in early pregnancy may indicate a risk for the development of complications (12). Our results are consistent with the findings of a study that concluded that elevated triglyceride concentrations during early pregnancy could be associated with unfavourable outcomes (13). However, in this study, the differences in HDL-C concentrations in the first trimester between pregnancies with and without complications were not significant, which could be attributed to the fact that HDL-C reaches its peak only in the second trimester of pregnancy (11).

An increasing number of studies indicate that inflammation during early pregnancy is associated with the occurrence of complications, primarily preeclampsia (8), due to an excessive inflammatory response accompanied by a significant increase in the secretion of pro-inflammatory cytokines. This pronounced response triggers the production of reactive oxygen species (ROS), which contributes to oxidative stress and disrupts the delicate balance between pro- and antioxidant factors in the vasculature (14). In turn, the excess ROS in the placenta inhibits nitric oxide (NO) activity, leading to endothelial dysfunction, vasoconstriction, and reduced trophoblast invasion. Ultimately, insufficient trophoblast invasion leads to placental ischemia, a central factor in the pathogenesis of preeclampsia (8). Additionally, several studies have shown that inadequate or insufficient resolution of inflammation plays an important role in the development of complications and that suppression of the inflammatory response may have a favorable impact on pregnancy outcomes (5, 6, 8). Although there is a plethora of biochemical markers of inflammation (15), complete blood count is regularly monitored during pregnancy and leukocytes are the most accessible markers. It has been shown that the total number of leukocytes increases throughout pregnancy, including labor and the postpartum period (16). This increase has been considered a physiological response to the stress induced by the pregnant state (17). Hormonal changes, such as elevated levels of estrogen and cortisol, play a prominent role by stimulating the bone marrow to produce more white blood cells (WBCs) and prolonging the survival of neutrophils through the inhibition of their apoptosis, resulting in a higher number of circulating neutrophils. Additionally, stress hormones like cortisol and catecholamines further enhance leukocyte production and release from the bone marrow. The mild systemic inflammatory response associated



with pregnancy also stimulates the production of cytokines, which contributes to the increase in leukocyte numbers. Following childbirth, this rise in WBCs remains elevated as part of the body's response to the stress of labor, helping to protect the mother from infections and supporting the healing process (18). An absolute monocytosis is also observed, particularly in the first trimester, which gradually decreases as the pregnancy progresses, with monocytes playing a role in preventing fetal allograft rejection by infiltrating the decidual tissue (17). Our analysis showed that pregnant women with complications had significantly higher leukocyte counts in the first two trimesters, compared to pregnant women without complications. Additionally, we found significantly higher proportions of monocytes throughout pregnancy in women with complications (Table II). However, it should be mentioned that our results are not consistent with the findings published by Canzoneri et al., who did not find significant differences in monocyte counts between women with preeclampsia and healthy pregnant women, although the authors did observe a slight increase in monocyte numbers in preeclampsia cases (19). The relatively small number of subjects included might be the cause for such a discrepancy between the results, so our preliminary findings should be tested by future large-scale studies. The most similar research to ours was conducted by Melekoglu et al., who examined the hematological and lipid parameters in the serum of pregnant women with late preeclampsia. The authors did not find statistically significant differences in monocytes count between the group with preeclampsia and the control group. However, when only women with severe preeclampsia were analysed, the results showed a significantly higher number of monocytes compared to the control group (20), which is consistent with the results of our study. Additionally, a study conducted by Wang et al. showed a statistically significant increase in monocytes in pregnant women with hyperglycemia and GDM (21). It is important to note that the mentioned studies focused on a single pregnancy disorder, while our examinees developed various complications, including hypertensive disorders, preeclampsia, GDM and IUGR. Considering that some of our participants developed multiple complications, it can be assumed that a more intense inflammatory response occurred, which resulted in a statistically significant difference in the proportion of monocytes compared to pregnancies without complications. Indeed, it has been shown that IUGR is associated with a shift of maternal monocyte subpopulations towards pro-inflammatory intermediate subset (22). In addition, the same study has demonstrated increased M2 polarization in IUGR cases, when compared to healthy pregnancies. Impaired monocyte distribution was also reported in women with GDM, with a higher prevalence of CD14+ cells (23). Moreover, in vitro research has revealed that hyperglycemia can induce pro-inflammatory activity in human monocytes (24), thus implying the role of these cells in the progression of diabetic complications.

Monocytes play an important role in the progression of atherosclerosis (15), the fundamental pathophysiological mechanism of which is inflammation. Namely, when the vascular endothelium is damaged, the expression of adhesion molecules on its surface increases (25). This allows monocytes to bind to the endothelium and subsequently

migrate into the subendothelial space, where they differentiate into macrophages. It has been established that patients with cardiovascular diseases have elevated monocyte counts (26). Based on the aforementioned information, it can be concluded that the significant increase in monocytes during complicated pregnancies indicates active inflammation, but it may also be associated with the risk of developing cardiovascular diseases later in life, which should be confirmed in future prospective studies.

HDL particles are extremely heterogeneous and are present in circulation in multiple subfractions of varying size and composition (27). Compared to other lipoproteins, HDL stands out for its rich and diverse protein content (28), which enables multiple atheroprotective functions of this lipoprotein (29–31). HDL is also believed to play a role in regulating processes essential for maintaining a normal pregnancy, while its dysfunction is thought to promote the development of complications associated with excessive inflammation, including preterm birth and preeclampsia (27). Indeed, the increase in HDL-C distinguishes hyperlipidemia during physiological pregnancy from pathological dyslipidemia which precedes the development of atherosclerosis. By analyzing HDL-C concentrations across trimesters in pregnancies with and without complications, we found that women with complications had significantly lower concentrations during the second trimester, which is a timeframe when complications typically manifest (Table III). Our findings are consistent with those reported in other studies, which have also shown significantly lower HDL-C levels in the second trimester in women with preeclampsia (20, 32) and GDM (33, 34) compared to healthy pregnant women. Overall, these results suggest that dyslipidemia during pregnancy may play a role in the development of complications.

Recently, the monocyte/HDL-C ratio has been recognized as a novel marker and prognostic indicator of mortality and morbidity in various chronic diseases, including cardiovascular diseases, chronic kidney disease, hypertension and metabolic syndrome (20). This has created opportunities for further exploration of its potential role in diagnosing disorders rooted in chronic low-grade inflammation. Usta et al. demonstrated that a high monocyte/HDL-C ratio is associated with polycystic ovary syndrome and obesity (35). To date, only one study has examined the significance of this parameter in preeclampsia. The authors found that the monocyte/HDL-C ratio was significantly elevated in women with preeclampsia and suggested its potential prognostic value (20). However, a limitation of that study was that it was conducted in the third trimester, focusing solely on late-onset preeclampsia cases. Our findings show significantly higher monocyte/HDL-C values throughout all trimesters in pregnancies with complications compared to uncomplicated pregnancies (Figure 1). Considering that pregnancy complications can adversely affect pregnancy outcomes and pose risks to both maternal and fetal health (1), identification of biomarkers capable of predicting their development as early as the first trimester would be of great importance. Our results indicate that the likelihood of developing complications is approximately 11 times higher if the monocyte/HDL-C ratio is elevated in the first trimester, and such association remains significant even after adjusting for traditional risk factors for pregnancy

complications (Table IV). To the best of our knowledge, no research has examined the relationship between the monocyte/HDL-C ratio in the first trimester of pregnancy and the risk of developing complications. Furthermore, our study encompassed a wider range of complications, suggesting that this parameter could potentially be applied not only for assessing the risk of hypertensive disorders in pregnancy, but also for GDM and IUGR. Given that this study did not find any differences in HDL-C concentrations during the first trimester, and that most previous studies did not observe differences in monocyte counts between pregnant women with and without complications, our results point out that the combination of these two parameters may be valuable for early risk assessment of pregnancy complications.

According to our knowledge so far, this study is the first in the territory of Serbia that examines the importance of the monocyte/HDL-C ratio as a predictor of pregnancy complications. However, several limitations should be mentioned. Considering the relatively small sample size, our preliminary findings need to be validated in a larger study. Furthermore, given that our research included a variety of pregnancy complications, future studies should investigate the significance of the monocyte/HDL-C ratio for each complication individually. Although this study focused on the total number and relative proportion of leukocyte subpopulations, as they are widely available and routinely monitored during pregnancy, the lack of other inflammation markers could be considered a limitation. Additionally, other components of HDL particles were not determined, nor were their functional properties examined, which should be addressed in future research.

## **Conclusion**

This study demonstrated that elevated monocyte/HDL-C ratios during the first trimester are associated with a higher risk of developing pregnancy complications. Our findings suggest that the monocyte/HDL-C ratio might serve as a simple and cost-effective early prognostic biomarker. Since the monocyte count is routinely determined as part of a complete blood count and HDL-C concentration is also a standard test, combining these two parameters could facilitate and improve the prevention of pregnancy complications.

## **Acknowledgements**

This work was supported by the Science Fund of the Republic of Serbia [Grant no. 7741659, High-density lipoprotein MetabolOMe research to improve pregnancy outcome—HI-MOM]. The authors appreciate the support from the Ministry of Science, Technological Development and Innovation, Republic of Serbia (Grant Agreement with the University of Belgrade – Faculty of Pharmacy No: 451-03-65/2024-03/ 200161 and No: 451-03-66/2024-03/ 200161).

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Author Contributions

Conceptualization: J. Vekić, A. Zeljković; Data curation: D. Ardalić, T. Gojković, J. Munjas; Formal analysis: J. Vulić, J. Radojković, J. Vekić, A. Zeljković; Funding acquisition: A. Stefanović; Investigation: J. Vulić, J. Radojković, T. Gojković, J. Munjas; Methodology: D. Ardalić, J. Vulić, J. Radojković, T. Gojković, J. Munjas; Project administration: A. Stefanović; Resources: A. Stefanović, Ž. Miković; Software: J. Vulić, J. Radojković, J. Vekić, A. Zeljković; Supervision: J. Vekić, A. Stefanović, A. Zeljković; Validation: J. Vekić, A. Stefanović, A. Zeljković; Visualisation: J. Vulić, J. Radojković, J. Vekić, A. Zeljković; Roles/Writing – original draft: J. Vulić, J. Radojković; Writing – review & editing: J. Vekić, A. Zeljković. All authors have read and agreed to the published version of the manuscript.

## References

1. Hauspurg A, Ying W, Hubel CA, Michos ED, Ouyang P. Adverse pregnancy outcomes and future maternal cardiovascular disease. *Clin Cardiol.* 2018;41(2):239–46.
2. Waage CW, Mdala I, Stigum H, Jenum AK, Birkeland KI, Shakeel N, et al. Lipid and lipoprotein concentrations during pregnancy and associations with ethnicity. *BMC Pregnancy Childbirth.* 2022;22(1):246.
3. Coco L, Giannone TT, Zarbo G. Management of high-risk pregnancy. *Minerva Ginecol.* 2014;66(4):383–9.
4. Jin WY, Lin SL, Hou RL, Chen XY, Han T, Jin Y, et al. Associations between maternal lipid profile and pregnancy complications and perinatal outcomes: a population-based study from China. *BMC Pregnancy Childbirth.* 2016;16:60.
5. Nadeau-Vallée M, Obari D, Palacios J, Brien MÈ, Duval C, Chemtob S, et al. Sterile inflammation and pregnancy complications: a review. *Reproduction.* 2016;152(6):R277–R292.
6. Vilotić A, Nacka-Aleksić M, Pirković A, Bojić-Trbojević Ž, Dekanski D, Jovanović Krivokuća M. IL-6 and IL-8: An overview of their roles in healthy and pathological pregnancies. *Int J Mol Sci.* 2022;23(23):14574.
7. Yang Y, Wu N. Gestational diabetes mellitus and preeclampsia: Correlation and influencing factors. *Front Cardiovasc Med.* 2022;9:831297.
8. Wang Y, Li B, Zhao Y. Inflammation in Preeclampsia: Genetic Biomarkers, Mechanisms, and Therapeutic Strategies. *Front Immunol.* 2022;13:883404.

9. Ganjali S, Gotto AM Jr, Ruscica M, Atkin SL, Butler AE, Banach M, Sahebkar A. Monocyte-to-HDL-cholesterol ratio as a prognostic marker in cardiovascular diseases. *J Cell Physiol.* 2018;233(12):9237–46.
10. Zeljković A, Ardalić D, Vekić J, Antonić T, Vladimirov S, Rizzo M, et al. Effects of Gestational Diabetes Mellitus on Cholesterol Metabolism in Women with High-Risk Pregnancies: Possible Implications for Neonatal Outcome. *Metabolites.* 2022;12(10):959.
11. Ardalić D, Stefanović A, Spasić S, Zeljković A, Vekić J, Spasojević-Kalimanovska V, et al. Lipidni status fiziološke nekomplikovane trudnoće. *Arh farm.* 2016;66:191–206.
12. Ardalić D, Stefanović A, Banjac G, Cabunac P, Miljković M, Mandić-Marković V, et al. Lipid profile and lipid oxidative modification parameters in the first trimester of high- risk pregnancies - possibilities for preeclampsia prediction. *Clin Biochem.* 2020;81:34–40.
13. Vrijkotte TG, Krukziener N, Hutten BA, Vollebregt KC, van Eijnden M, Twickler MB. Maternal lipid profile during early pregnancy and pregnancy complications and outcomes: the ABCD study. *J Clin Endocrinol Metab.* 2012;97(11):3917–25.
14. Harmon AC, Cornelius DC, Amaral LM, Faulkner JL, Cunningham MW Jr, Wallace K, LaMarca B. The role of inflammation in the pathology of preeclampsia. *Clin Sci (Lond).* 2016;130(6):409–19.
15. Herkiloglu D, Gokce S. Correlation of monocyte/HDL ratio (MHR) with inflammatory parameters in obese patients diagnosed with polycystic ovary syndrome. *Ginekolo Pol.* 2021;92(8):537–43.
16. Dockree S, Shine B, Pavord S, Impey L, Vatish M. White blood cells in pregnancy: reference intervals for before and after delivery. *EBioMedicine.* 2021;74:103715.
17. Chandra S, Tripathi AK, Mishra S, Amzarul M, Vaish AK. Physiological changes in hematological parameters during pregnancy. *Indian J Hematol Blood Transfus.* 2012;28(3):144–6.
18. Zhu J, Li Z, Deng Y, Lan L, Yang J. Comprehensive reference intervals for white blood cell counts during pregnancy. *BMC Pregnancy Childbirth.* 2024;24(1):35.
19. Canzoneri BJ, Lewis DF, Groome L, Wang Y. Increased neutrophil numbers account for leukocytosis in women with preeclampsia. *Am J Perinatol.* 2009;26(10):729–32.
20. Melekoğlu R, Yaşar Ş, Zeyveli Çelik N, Özdemir H. Evaluation of dyslipidemia in preeclamptic pregnant women and determination of the predictive value of the hemato-lipid profile: A prospective, cross-sectional, case-control study. *Turk J Obstet Gynecol.* 2022;19(1):7–20.
21. Wang J, Zhu QW, Cheng XY, Sha CX, Cui YB. Clinical significance of neutrophil-lymphocyte ratio and monocyte-lymphocyte ratio in women with hyperglycemia. *Postgrad Med.* 2020;132(8):702–8.
22. Alahakoon TI, Medbury H, Williams H, Fewings N, Wang XM, Lee VW. Distribution of monocyte subsets and polarization in preeclampsia and intrauterine fetal growth restriction. *J Obstet Gynaecol Res.* 2018;44:2135–48.
23. Angelo AGS, Neves CTC, Lobo TF, Godoy RVC, Ono É, Mattar R, Daher S. Monocyte profile in peripheral blood of gestational diabetes mellitus patients. *Cytokine.* 2018;107:79–84.
24. Thiem K, Keating ST, Netea MG, Riksen NP, Tack CJ, van Diepen J, Stienstra R. Hyperglycemic Memory of Innate Immune Cells Promotes In Vitro Proinflammatory Responses of Human Monocytes and Murine Macrophages. *J Immunol.* 2021;206:807–13.
25. Liu Z, Fan Q, Wu S, Lei Y. Associations of Monocytes and the Monocyte/High-Density Lipoprotein Ratio With Extracranial and Intracranial Atherosclerotic Stenosis. *Front Neurol.* 2021;12:756496.

26. Williams H, Mack CD, Li SCH, Fletcher JP, Medbury HJ. Nature versus Number: Monocytes in Cardiovascular Disease. *Int J Mol Sci.* 2021;22(17):9119.
27. Woollett LA, Catov JM, Jones HN. Roles of maternal HDL during pregnancy. *Biochim Biophys Acta Mol Cell Biol Lipids.* 2022;1867(3):159106.
28. Tanaka S, Couret D, Tran-Dinh A, Duranteau J, Montravers P, Schwendeman A, et al. High-density lipoproteins during sepsis: from bench to bedside. *Crit Care.* 2020;24(1):134.
29. Deng S, Xu Y, Zheng L. HDL Structure. *Adv Exp Med Biol.* 2022;1377:1–11.
30. Giammanco A, Noto D, Barbagallo CM, Nardi E, Caldarella R, Ciaccio M, et al. Hyperalphalipoproteinemia and Beyond: The Role of HDL in Cardiovascular Diseases. *Life (Basel).* 2021;11(6):581.
31. Efrat M, Aviram M. Paraoxonase 1 interactions with HDL, antioxidants and macrophages regulate atherogenesis - a protective role for HDL phospholipids. *Adv Exp Med Biol.* 2010;660:153–166.
32. Li J, Lu J, Wang M, Hu W, Jin N, Li X, et al. Predictive Value of Second-Trimester Maternal Lipid Profiling in Early-Onset Pre-eclampsia: A Prospective Cohort Study and Nomogram. *Front Med (Lausanne).* 2021;8:688312.
33. Rahnemaei FA, Pakzad R, Amirian A, Pakzad I, Abdi F. Effect of gestational diabetes mellitus on lipid profile: A systematic review and meta-analysis. *Open Med (Wars).* 2021;17(1):70–86.
34. Ryckman KK, Spracklen CN, Smith CJ, Robinson JG, Saftlas AF. Maternal lipid levels during pregnancy and gestational diabetes: a systematic review and meta-analysis. *BJOG.* 2015;122(5):643–51.
35. Usta A, Avci E, Bulbul CB, Kadi H, Adali E. The monocyte counts to HDL cholesterol ratio in obese and lean patients with polycystic ovary syndrome. *Reprod Biol Endocrinol.* 2018;16(1):34.

# **Odnos monociti/HDL-holesterol kao rani prognostički marker razvoja komplikacija u trudnoći**

**Jovana Vulić<sup>1</sup>, Jelena Radojković<sup>1</sup>, Jelena Vekić<sup>1</sup>,  
Aleksandra Stefanović<sup>1</sup>, Daniela Ardalić<sup>2</sup>, Željko Miković<sup>2,3</sup>,  
Tamara Gojković<sup>1</sup>, Jelena Munjas<sup>1</sup>, Aleksandra Zeljković<sup>1\*</sup>**

<sup>1</sup>Katedra za medicinsku biohemiju, Univerzitet u Beogradu – Farmaceutski fakultet, Beograd, Srbija

<sup>2</sup>Ginekološko-akušerska klinika Narodni Front, Beograd, Srbija

<sup>3</sup>Katedra za ginekologiju i akušerstvo, Medicinski fakultet, Univerzitet u Beogradu, Srbija

\*Autor za korespondenciju: Aleksandra Zeljković, e-mail: aleksandra.zeljkovic@pharmacy.bg.ac.rs

---

## **Kratak sadržaj**

Komplikacije u trudnoći povećavaju rizik za razvoj kardiovaskularnih oboljenja u kasnijem životu majke i deteta. Inflamacija je zajednički mehanizam koji se nalazi u osnovi razvoja komplikacija u trudnoći i ateroskleroze. Cilj rada je bio da se ispita da li se na osnovu odnosa monociti/HDL-holesterol može predvideti rizik za razvoj komplikacija u trudnoći. U istraživanju su učestvovala 84 trudnice, od kojih je 41 imala urednu trudnoću, a 43 trudnoću sa komplikacijama. Parametri lipidnog statusa su određeni enzimskim metodama, a broj i udeo leukocita na hematološkom analizatoru. Tokom prvog trimestra trudnoće sa komplikacijama bile su uočene značajno više koncentracije ukupnog holesterola ( $P < 0,01$ ), holesterola u česticama lipoproteina niske gustine (LDL-h) ( $P < 0,01$ ) i triglicerida ( $P < 0,001$ ) nego u trudnoći bez komplikacija, dok razlike u koncentraciji holesterola u česticama lipoproteina visoke gustine (HDL-h) nisu bile značajne. Trudnice sa komplikacijama su imale značajno viši udeo monocita tokom cele trudnoće, a niže koncentracije HDL-h u drugom trimestru ( $P < 0,05$ ). Utvrdili smo da je verovatnoća za razvoj komplikacija u trudnoći oko 11 puta veća ukoliko je u prvom trimestru odnos monociti/HDL-h povišen (OR: 11,42; 95%CI: 4,05–32,19;  $P < 0,001$ ). Naši rezultati ukazuju da bi se odnos monociti/HDL-h mogao koristiti kao jednostavan i ekonomičan rani prognostički biomarker razvoja komplikacija u trudnoći.

**Ključne reči:** trudnoća, komplikacije, odnos monociti/HDL-h

---