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Biochemical and hematological parameters in the 1st trimester of pregnancy

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Abstract

The 1st trimester of pregnancy is accompanied with changes in different biochemical and hematological parameters. Analyses scheduled to be performed in the 1st trimester are complete blood count, blood group, Rh factor and the double test. Many experts also suggest the determination of lipid status parameters as a routine analysis in the early pregnancy. Reliable data about maternal and fetal health can be obtained by the assessment of the above-mentioned parameters. They may be helpful in assessing the risk for pregnancy complication development and/or perinatal adverse outcomes.

Key words: 1st trimester of pregnancy, routine tests, lipid status parameters

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Introduction

Pregnancy is a physiological condition accompanied with changes in different biochemical parameters. The 1st trimester of pregnancy is characterized by organogenesis and is considered crucial for the normal development of the baby (1). Early pregnancy is accompanied with remarkable changes in the vascular system that are necessary for adequate blood flow through the placenta: peripheral vasodilation and increased blood flow, activation of the renin-angiotensin-aldosterone system that leads to vasoconstriction, which is counterbalanced by increased nitric-oxide synthesis that promotes vasodilation. Glomerular filtration rate and thyroid hormones, prolactin, adrenocorticotropic hormone (ACTH), cortisol and aldosterone production are also increased. There are important metabolic changes caused by hormones that allow fetal growth and development (1, 2).

Widely accepted guidelines issued by the American College of Obstetricians and Gynecologists (ACOG) (3, 4) recommend the following tests during pregnancy: glucose, glyco-hemoglobin, complete blood count (CBC), fasting and postprandial insulin, thyroid hormone status, microbiological analyses (rubella, hepatitis B and C, syphilis, chlamydia, gonorrhea, human immunodeficiency virus, tuberculosis), blood type, Rh factor, double, triple, quadruple tests (3, 4). Biochemical and hematological analyses scheduled in the 1st trimester are CBC, blood group, Rh factor and the double test. These tests can help identify potential risks to the mother and fetus and eventually prevent or treat related conditions (3, 4).

According to many published studies (5-8), pregnancy is physiologically followed by changes in lipid status parameters (total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c) and triglycerides (TG)) from the 1st trimester. Recent studies have suggested that deviations from normally expected changes in the lipid profile may be observed in early pregnancy and may be associated with the development of pregnancy complications and adverse perinatal outcome. Therefore, many experts advocate analyzing lipid status parameters in the early pregnancy, especially for those pregnant women who are at higher risk of developing pregnancy complications (5-8).

The purpose of this paper is to present the significance of determining the above-mentioned laboratory parameters in the 1st trimester of pregnancy, in order to assess the risk and prevent pregnancy complications and/or adverse perinatal outcomes.

Complete blood count (CBC)

CBC is widely and routinely used to identify different pathological conditions such as infective diseases, hemoglobinopathies or other forms of hematological diseases (9).

During gestation, plasma volume normally increases, thus causing the effect of hemodilution. Due to hemodilution, the concentration of hemoglobin (Hb), red blood cell (RBC) count and the value of hematocrit (HCT) decrease despite increased erythropoiesis and RBC mass. This condition is referred to as “physiological anemia” of pregnancy, and

deviations of Hb concentrations in both directions are associated with a higher possibility of premature birth, intrauterine growth restriction and fetal death (9, 10). The Hb reference intervals during pregnancy are as follows: 113–147 g/L at 13–20 weeks; 111–143 g/L at 21–28 weeks; 109–145 g/L at 29–34 weeks; 110–147 g/L at 35–42 weeks and 108–156 g/L at delivery, whereas before pregnancy the reference interval is 117–153 g/L (11).

Pathological anemia is estimated to be the most common condition during pregnancy, with a prevalence of 41.3% worldwide. (12). Anemia during pregnancy has been shown to increase the chance of premature birth; for Hb concentration in the 1st trimester at or below 90 g/L [odds ratio (OR): 1.72; 95% confidence interval (CI): 1.30–2.26], Hb concentration ≤ 100 g/L [OR: 1.33; 95% CI: 1.17–1.52] and Hb concentration ≤ 110 g/L [OR: 1.10; 95% CI: 1.02–1.29]. Pregnant women with Hb concentration in the 1st trimester below 90, 100 and 110 g/L had a significantly – 2.14 (95% CI: 1.57–2.91), 1.57 (95% CI: 1.30–1.90) and 1.17 (95% CI: 1.03–1.32) – fold – higher risk of low birth weight delivery compared to pregnant women with Hb levels between 110 and 139 g/L (13).

Iron, folate, vitamin B12 deficiencies or hemoglobinopathies can lead to anemia, the most common blood disorder during pregnancy (14). Anemia caused by iron deficiency is usually characterized by decreased levels of Hb, mean cell volume (MCV), and mean cellular hemoglobin (MCH). If iron deficiency anemia is suspected, serum ferritin should be determined to confirm the diagnosis. (9). If women are already anemic at the beginning of pregnancy, they may develop clinically significant anemia during pregnancy, so the determination of CBC in the 1st trimester will help in planning further interventions.

RBC and HCT decrease in the 1st trimester of physiological pregnancy, being the lowest in the 2nd trimester, and start rising again in the 3rd trimester. MCV and MCH decrease in early pregnancy, while they increase in the 2nd and 3rd trimester. Mean corpuscular hemoglobin concentration (MCHC) has the highest value in the 1st trimester and decreases as pregnancy progresses (9).

White blood cell (WBC) count increases during pregnancy, mostly due to an increased number of neutrophils (9, 15). Mild leukocytosis is considered normal because it is induced by the physiological stress of pregnancy (9) and is not characterized by significant increases in leukocyte bands or other immature forms (15), although there are findings of “left shift” (increased band of immature neutrophils). However, this neutrophilia is usually not associated with infection or inflammation (9).

Single pregnancy-specific reference intervals (RI) have been estimated for each WBC subtype and the data are given in Table I (16). Primarily due to an increase in neutrophils (the upper reference limit, URL was 55% higher), the URL for WBC was elevated by 36%, the URL for lymphocytes was 36% lower and for monocytes it was 38% higher. Monocytosis is proposed to prevent rejection of fetus. Basophils and eosinophils did not differ significantly between pregnant and non-pregnant women. (16).

Table I Reference intervals for WBC in pregnant and non-pregnant women (16)
Tabela I Referentni intervali za bele krvne ćelije (leukocite) kod trudnica i žena koje nisu trudne (16)

Cell type	Non-pregnant 95% reference intervals ($x10^9$/L)	Parametric pregnancy-specific 95% reference intervals*($x10^9$/L)	Non-parametric pregnancy specific 95% reference intervals** ($x10^9$/L)	
			2.5^{th} percentile (90% CI)	97.5^{th} percentile (90% CI)
Total white blood cells	4.0 – 11.0	5.7 – 15.0	5.7 (5.6 – 5.7)	15.0 (14.9 – 15.1)
Neutrophils	2.0 – 7.5	3.7 – 11.6	3.7 (3.6 – 3.7)	11.6 (11.5 – 11.7)
Lymphocytes	1.0 – 4.5	1.0 – 2.9	1.0 (1.0 – 1.0)	2.9 (2.9 – 3.0)
Eosinophils	0.04 – 0.44	0.02 – 0.39	0.02 (0.02 – 0.02)	0.39 (0.39 – 0.40)
Basophils	0.0 – 0.1	0.1 – 0.1	0.0 (0.0 – 0.0)	0.1 (0.1 – 0.1)
Monocytes	0.2 – 0.8	0.3 – 1.1	0.3 (0.3 – 0.3)	1.1 (1.1 – 1.1)

* Parametric RIs were estimated as the mean ± 1.96 multiples of the standard deviation, using logarithmically transformed data between 8 – 40 weeks.

** For reference, conventional non-parametric reference intervals are presented with 90% confidence intervals inaccordance with CLSI/IFCC guidance showing strong concordance between the two methods.

* Parametarski RI je procenjen kao srednja vrednost ± 1,96 umnožaka standardne devijacije, korišćenjem logaritamski transformisanih podataka između 8. – 40. nedelje.

** Konvencionalni neparametarski referentni intervali su predstavljeni sa intervalima poverenja od 90% u skladu sa CLSI/IFCC smernicama koje pokazuju jaku saglasnost između dve metode.

Platelet count is usually low, mainly during the 3rd trimester of pregnancy. This is termed “gestational thrombocytopenia” and is partly due to increased hemodilution and/or platelet activation and rapid clearance (9).

Blood type and Rh factor

Determination of maternal blood type and Rh factor is a mandatory test during pregnancy. In case of hemorrhage during pregnancy or childbirth, it is necessary for blood types and Rh factor to be compatible between the mother and fetus in order to be able to give an appropriate transfusion (17).

Hemolysis in ABO incompatibility occurs almost exclusively in A+ neonates born to women with blood type O. It has been estimated that 15–25% of all mother/fetal pairs are ABO mismatched, although hemolysis occurs in approximately 1%. Hemolytic disease of the newborn (HDN), caused by anti-A and/or anti-B antibodies, usually lead to hyperbilirubinemia with no significant neonatal anemia. This is mainly due to the relatively few antigenic A or B sites on neonatal RBC, leading to RBC coated with

antibodies to a lesser extent, which remain in the circulation longer than in Rh hemolytic disease (18).

Rh incompatibility occurs when a mother has blood with Rh-negative RBC and the newborn has blood with Rh-positive RBC. This may result in a more severe form of HDN than it is caused by ABO incompatibility. As a result of maternal exposure to fetal Rh+ antigens on RBC, the mother's body will initiate an immune response and synthesis of anti-Rh+ antibodies that will attack the fetus blood cells. This immune response rarely causes serious issues in the first pregnancy. However, subsequent pregnancies with Rh incompatibility have a significantly higher risk (18). Moreover, HDN can be developed as a consequence of anti-D antibodies (antibodies against D antigen (Rh factor)) produced in the mother's body sensitized in the 1st pregnancy by a Rh+ fetus. These anti-D antibodies may cause lysis of RBC in subsequent pregnancies, which results in jaundice and brain damage (17, 18). RBC destruction can also lead to significant hemolytic, life-threatening anemia (18). Anti-D antibodies can be formed in many other situations, including amniocentesis, chorionic villus sampling, external cephalic version, bleeding during the pregnancy, major abdominal trauma and late miscarriage (17).

It is interesting to note that ABO hemolytic disease is characterized by a large number of spherocytes with a negligible increase in nucleated RBC, while in Rh hemolytic disease a large number of nucleated RBC and very few spherocytes are observed (18).

Along with blood type determination, it is indicated to analyze antibodies against Rh+ antigens to further prevent adverse outcomes of blood type incompatibility. The analysis includes antibodies against standard RBC antigens (RhD, RhC, RhE). Women with antibody titers >1:4 are considered Rh immunized. Titers tend to correlate more strongly with fetal disease severity in the first sensitized pregnancy than in subsequent pregnancies. The father's Rh factor should also be checked to determine the risk of incompatibility (9).

It should be emphasized that the determination of cell-free fetal DNA (cffDNA) is a future test that would help in the prevention of HDN. CffDNA releases from the placenta into the maternal circulation, where it is mixed with much larger maternal cfDNA (19). Recent meta-analysis showed a sensitivity of 0.993 (95% CI: 0.982– 0.997) and a specificity of 0.984 (95% CI: 0.964–0.993) for cffDNA, which may be useful for the evaluation of RhD genetics of fetus (20).

Furthermore, the data suggested that O blood type may exert some protective effects against preeclampsia when compared with non-O blood type (especially type A and AB) (17). Preeclampsia is the most specific disorder of pregnancy, which manifests as hypertension after 20 weeks of gestation and is accompanied by proteinuria (≥ 300 mg/24 hours) or other organ damage. Preeclampsia is thought to be caused in part by inadequate placentation, altered trophoblast invasion and decreased placental perfusion (21). Several mechanisms have been proposed to play a role in preeclampsia development in pregnant women with non-O blood type. Higher levels of Von-Willebrand's factor and coagulation factor VIII were found in pregnant women with non-O blood type compared to O blood

type, indicating a higher risk for coagulation disorders. Placental protein 13 (PP13), now considered to be an early biomarker of preeclampsia, has important immune functions and binds to A and/or B antigens. This process may reduce protein levels. It is shown that lower levels of PP13 are associated with a higher risk of preeclampsia (17).

In addition, pregnant women with AB blood type had higher fasting glucose levels than those with blood type A. A number of studies also showed a higher prevalence of blood type O in women with gestational diabetes mellitus than in non-diabetic ones (17). Women with blood type AB may be protected against gestational diabetes mellitus (AB vs non-AB blood types: OR: 1.44, 95% CI: 1.13- 1.83) (17).

Double test

To test the possible existence of chromosomal abnormalities, biochemical markers: free-β human chorionic gonadotropin (free β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) along with fetal nuchal translucency (NT) are routinely determined in the form of the "double test" (22, 23). This test is performed in the 1st trimester of pregnancy in screening for trisomies 21, 18 and 13. The screening is carried out at 11-14 weeks of gestation (22).

The test only indicates the risk for the presence of the tested trisomies, so the obtained results represent neither a definitive confirmation nor an exclusion of these conditions (22, 23). However, this test does not provide the assessment of the risk for neural tube defects, such as spina bifida (24).

The results of PAPP-A, free β-hCG and NT are transformed into the multiples of the median (MoM) corresponding to the gestational age (22). It should be noted that MoM levels also depend on maternal weight, ethnicity and smoking status (25). The MoM value is obtained by dividing an individual's marker value by the median level of that marker across the population for the same gestational age. In a healthy pregnancy, the maternal serum PAPP-A levels increase exponentially, while free β-hCG levels decline, after an initial increase, between the 10th and 14th gestational week (22). The MoM values are then transferred into the risk ratio. Results that represent a high risk for trisomies are considered for ratio 1:50 or less. Otherwise, low risk results mean a ratio of 1:1000 or more. Patients with intermediate risk have a ratio between 1:51 and 1:1000 (26). High risk test results indicate additional testing, such as: prenatal cell-free DNA screening, chorionic villus sampling and amniocentesis (4).

The double test identifies about 85% of women who have babies with trisomy 21. A false positive result (FPR) is found in about 5% of women (27). The usefulness of the double test in the 1st trimester of pregnancy has also been confirmed in different studies. In a prospective validation study, the double test was useful in detection of 90%, 97% and 92% of trisomies 21, 18 and 13; more than 95% of monosomy X and triploidies cases; and more than 50% of other chromosomal abnormalities, with FPR of 4% (23). Free β-hCG levels were significantly lower in pregnancies that later developed preeclampsia, which may help predict this condition. No significant difference was found for PAPP-A levels between preeclamptic and non-preeclamptic women (28, 29, 30). A multivariable

model for preeclampsia screening in early pregnancy, consisting of two clinical characteristics – body mass index and mean arterial pressure, and four biochemical markers including PAPP-A, placental growth factor, soluble Feline McDonough Sarcoma (FMS)-like tyrosine kinase-1 and inhibin A, did not reach a performance that would justify its clinical implementation as a screening test (30).

Lipid status parameters

Although not routinely analyzed, lipid status parameters have been recognized as important biomarkers in early pregnancy.

Fat accumulation is an important metabolic process in pregnant women in the 1st trimester which contributes to the normal progress of pregnancy and fetal development (6). TG provide the mother's energy needs, while glucose is preserved for the fetus (6, 31). LDL-c is important for placental steroidogenesis (6). It has been shown that levels of TC and TG are significantly higher in the 1st trimester of pregnancy compared to non-pregnant women, and continue to increase during pregnancy, reaching values that are more than 30% higher for TC, and 3 times higher for TG (31). LDL-c concentrations did not show significant differences between women in the 1st trimester and non-pregnant ones (31), although there are reports of increased LDL-c (6). It is interesting to note that the level of HDL-c increases during pregnancy, with higher concentrations in the 1st trimester compared to non-pregnant women (6). Decreased levels of TC, LDL-c, HDL-c and TG are associated with higher risk for intrauterine growth restriction development (5, 32).

Some authors suggested the establishment of reference intervals (RI) for lipid status parameters which can be specific for each pregnancy trimester. Potential risks for adverse outcomes can be better evaluated if deviations from trimester-specific values are known (6). RI given by Lu et al (6) are presented in Table II.

Table II Reference intervals of serum lipid status parameters (6)
Tabela II Referentni intervali za parametre lipidnog statusa u serumu (6)

	First trimester			Third trimester			
	95% reference interval, mmol/L	Hoffmann method, mmol/L	Absolute difference, %	95% reference interval, mmol/L	Hoffmann method, mmol/L	Absolute difference, %	RCV, %
TC	3.11-6.11	3.07-5.82	1.30-4.98	4.56-9.31	4.50-9.02	1.33-3.22	10.31
TG	0.54-2.33	0.48-2.20	12.50-5.91	1.68-5.67	1.53-5.52	9.80-2.72	20.79
HDL-c	1.06-2.18	1.00-2.18	6.00-0	1.23-2.56	1.19-2.64	3.36-3.03	13.91
LDL-c	1.26-3.80	1.30-3.61	3.08-5.26	1.93-5.90	1.97-5.84	2.03-1.03	13.67

TC: total cholesterol; TG: triglycerides; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol

TC: ukupan holesterol; TG: trigliceridi; HDL-c: holesterol u lipoproteinima visoke gustine; LDL-c: holesterol u lipoproteinima niske gustine

Many studies have found significantly higher TC, LDL-c and TG, and significantly lower HDL-c in the early pregnancy accompanied by conditions such as gestational diabetes mellitus, gestational hypertension, preeclampsia and postpartum hemorrhage, when compared to a healthy pregnancy (6, 33-37). Testing of dyslipidemia in the early pregnancy can be helpful for preeclampsia (35) and gestational diabetes mellitus (38) risk assessment. The positive predictive values for lipid parameters that were between 0.3% and 12.0%, and the negative predictive values between 92.7% and 99.9%, suggested a better performance in ruling out these conditions than in ruling in (6).

It is interesting to note that HDL particles may play important roles in maintaining a healthy pregnancy (39). HDL, via its protective effects such as cholesterol efflux capacity, anti-inflammatory, antioxidant, endothelial and vasodilatory functions, regulation of immune response, antithrombotic and antidiabetic properties, promotes metabolic adaptation and enhanced vascular function (39, 40). Due to excessive inflammation and oxidative stress, HDL may become dysfunctional. HDL particles with altered characteristics have been related to the development of gestational hypertension, preeclampsia, gestational diabetes mellitus, preterm birth (39, 41-43).

Investigating the association of maternal lipid status with different pathological conditions in pregnancy and perinatal outcomes may further help in developing intervention strategies for these conditions.

Conclusion

Most of the above-mentioned parameters are routinely analyzed in the 1st trimester of pregnancy. According to experts' findings, lipid status parameters should also be considered for routine analysis in the early pregnancy. They may provide reliable information about the health of both the mother and fetus, as well as help to predict pregnancy complications and perinatal adverse outcomes.

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Biohemijski i hematološki parametri u prvom trimestru trudnoće

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Kratak sadržaj

Prvi trimestar trudnoće praćen je promenama različitih biohemijskih i hematoloških parametara. Analize koje se rade u 1. trimestru su kompletna krvna slika, krvna grupa, Rh faktor i tzv. „double“ test. Mnogi stručnjaci predlažu određivanje parametara lipidnog statusa kao rutinsku analizu u ranoj trudnoći. Procenom gore navedenih parametara mogu se dobiti pouzdani podaci o zdravlju majke i fetusa, a mogu da posluže i za procenu rizika za razvoj komplikacija u trudnoći i/ili perinatalnih neželjenih ishoda.

Ključne reči: prvi trimestar trudnoće, rutinski testovi, parametri lipidnog statusa