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Dyslipidemia as Predictor of Missed Miscarriage

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Abstract

***Background*:** This study aimed at finding the diagnostic and prognostic possibilities of determining apoC-II, as a serological marker for MM in early gestation.

***Methods and Results*:** The study included 182 pregnant women aged between 18 and 45 years at gestational age under 11 weeks. All women were divided into 3 groups. Group 1 included 90 women with MM; Group 2 included 52 women with spontaneous miscarriage; Group 3 included 40 women without pathology (control group). Lipid metabolism disorders were diagnosed according to the Russian national recommendations of the VII revision(the Russian Society of Cardiologists [RSC, 2020]), considering the European recommendations (2019). Proteomic analysis of the blood serum was performed using liquid chromatography-mass spectrometry. Abnormalities in the lipid profile, manifested as isolated hypercholesterolemia, and combined hypercholesterolemia with hypertriglyceridemia, were more common in patients with MM and spontaneous abortions: 62.2% and 59.7% of cases, respectively, which correlates with the identified marker apoC-II in Group 1 and Group 2.

Conclusion: ApoC-II can be considered as the most promising serologic marker for MM in the early gestation period for women with dyslipidemia.(**International Journal of Biomedicine. 2021;11(4):418-421.**)

Key Words: missed miscarriage • dyslipidemia • apolipoprotein C-II • serological markers

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Abbreviations

ApoC-II, apolipoprotein C-II; **ApoC-II**, apolipoprotein C-II; **HDL**, high-density lipoprotein; **LDL**, low-density lipoprotein; **LPL,** lipoprotein lipase; **LC-MS**, liquid chromatography-mass spectrometry; **MM**, missed miscarriage; **TC**, total cholesterol; **TG**, triglycerides; **VLDL**, very low-density lipoprotein.

Introduction

Missed miscarriage (MM) is one of the unsolved problems in the Russian Federation.[1,2] Among the risk factors for MM, the leading place belongs to dyslipidemia and endothelial dysfunction, both in the maternal body, in the fetoplacental complex and in the arteries of the umbilical cord.[1,3]

In a normal pregnancy, lipid parameters including total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and phospholipid gradually increase starting in the 12th week of gestation and continue to do so throughout pregnancy.[4-7]

The accumulation of maternal fat depots and hyperlipidemia are the two principal changes in lipid metabolism during pregnancy.[8] Pregnancy is typified by

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an increase in serum levels of TC and TG pushed by the rise in estrogen, progesterone and lactogen.[9] Both TG and TC are essential for the development of the fetus. However, high levels of maternal TC and/or TG are associated with preterm birth,[10-12] pregnancy-induced hypertension,[13] preeclampsia,[14-16] and large for gestational age.[17-19]

Recently, the ABCD study showed that atherogenic lipid profiles during the first trimester confer an increased risk of adverse pregnancy outcomes including maternal morbidity, mortality, and preterm delivery.[20,21]

The role of dyslipidemia, manifested by abnormally elevated TC, TG, and LDL against the background of low HDL in the pathogenesis of MM in patients with recurrent miscarriage, has been shown in a number of studies.[22,23] Low HDL level can lead to vascular thrombosis and the development of hypoxia in the placenta.[24,25]

Apolipoprotein C-II (apoC-II) is the potent physiological activator of LPL; therefore, it plays a central role in the metabolism of plasma TG. LPL is the main enzyme that hydrolyses plasma TG on triglyceride-rich lipoproteins, such as chylomicrons and VLDL, and on HDL, particularly during fasting.[3] ApoC-II has also been shown to act as an inhibitor of LPL at higher concentrations,[26] although the mechanisms by which this activation and inhibition take place remain poorly understood. Palva et al.[24] showed that the decrease of LPL activity in the heart, along with the inhibitory effects of excess apoC-II, may contribute to the hypertriglyceridemia observed in apoC-II transgenic mice. Fornengo et al.[27] reported a case of drug-resistant hypertriglyceridemia in a patient with increased levels of apoC-II. To date, the mechanisms by which physiological levels of apoC-II activate and excess apoC-II inhibits LPL are not fully understood.

In the modern literature, there are few data on serological markers of MM, a lack which creates the prerequisites for conducting this study aimed at finding the diagnostic and prognostic possibilities of determining apoC-II, as a serological marker for MM in early gestation.

Materials and Methods

In the period from April 2020 to February 2021, 182 pregnant women aged between 18 and 45 years at gestational age under 11 weeks were examined. All women were divided into 3 groups. Group 1 (Gr1) included 90 women with MM; Group 2 (Gr2) included 52 women with spontaneous miscarriage; Group 3 included 40 women without pathology (control group [CG]).

Inclusion criteria were MM, spontaneous miscarriage or physiological pregnancy at gestational age under 11 weeks. Exclusion criteria were autoimmune diseases, infectious diseases, and diseases of the thyroid gland, including thyroid dysfunction.

Examination of patients included clinical methods, questionnaire survey, analysis of case histories, laboratory tests (clinical blood test, blood levels of TG, HDL-C, and LDL-C, urine test, and determination of antibody titer to the TORCH complex), and pelvic ultrasound. All women underwent an assessment of vaginal microcenosis and the quantitative and qualitative composition of the biotope of the cervical discharge.

Lipid metabolism disorders were diagnosed according to the Russian national recommendations of the VII revision(the Russian Society of Cardiologists [RSC, 2020]), considering the European recommendations (2019): TC >5,0 mmol/l; TG >1.7 mmol/l; HDL-C <1.2 mmol/l in females; LDL-C >3.0 mmol/l.

Antibodies to thyroperoxidase (AT-TP) and thyroglobulin (AT-TG) in the blood serum were determined by ELISA using standard test systems from "CHEMA-MEDIKA" (Russia).

Proteomic analysis of the blood serum was performed using LC-MS.

The study was conducted in accordance with ethical principles of the WMA Declaration of Helsinki (1964, ed. 2013) and approved by the RUDN University Ethics Committee. Written informed consent was obtained from all participants.

Statistical analysis was performed using the *Statistica* 8.0 software package (*StatSoft Inc*, USA). Kruskal-Wallis test was used to compare means of 3 groups of variables not normally distributed. A value of $P<0.05$ was considered statistically significant.

Results

For the analysis of potentially significant markers, we studied serological markers found in all 3 groups; in particular, we compared the ratios of protein concentrations in the study groups. If the concentration ratio of the investigated marker in the Gr1/CG pair was close to 1 or equal to 1, then the marker was considered nonspecific; if the concentration ratio of the investigated marker in the Gr1/Gr2 pair was close to 1 or equal to 1, then the marker was also considered nonspecific; however, if the studied ratio was close to 1 or equal to 1 in the Gr1/Gr2 pair and at the same time >1 in the Gr1/CG pair, then the marker was considered potentially specific.

Table 1.

The potentially specific serorlogical marker of MM

Group pair	ApoC-II	ApoC-IV	Complement C5	Complement factor H
Gr1/CG	2.468	0.495	0.494	0.414
Gr1/Gr2	1.658	0.579	0.373	0.399
Gr2/CG	1.489	0.823	1.324	1.035
P-value	0.00016	0.01324	0.00428	0.00119

As can be seen from Table 1, the most specific serorlogical marker of MM may be apoC-II, since the ratio of its concentration was 2.468 in the Gr1/CG pair, 1.658 in the Gr1/Gr2 pair, and 1.489 in the Gr2/CG pair. For all other markers, differences between groups were less pronounced.

Moreover, the potential role of apoC-II was most pronounced in Gr1, which suggests that apoC-II may be the specific marker for MM. When the patients were divided into groups depending on the lipid profile, women with an impaired lipid profile, manifested as isolated hypercholesterolemia, and combined hypercholesterolemia with hypertriglyceridemia, significantly prevailed in gGr1 compared with the CG.

Abnormalities in the lipid profile were more common in patients with MM and spontaneous abortions: 62.2% and 59.7% of cases, respectively, which correlates with the identified marker apoC-II in Gr1 and Gr2 (Table 2, Fig.1). In the control group, abnormalities in the lipid profile were found only in 42.5%.

Table 2.

Abnormalities in the lipid profile in the study groups

Groups		No Dyslipidemia	Dyslipidemia
Group 1 (n = 90)	n	34	56
	(%)	37.7	62.2
Group 2 (n = 52)	n.	21	31
	(%)	40.3	59.7
Group 3 (n = 40)	n	23	17
	(%)	57.5	42.5
P-value $P_{1\text{-}3}$ $P_{2\text{-}3}$		0.1012 0.0365 0.1033	0.1013 0.0365 0.1033

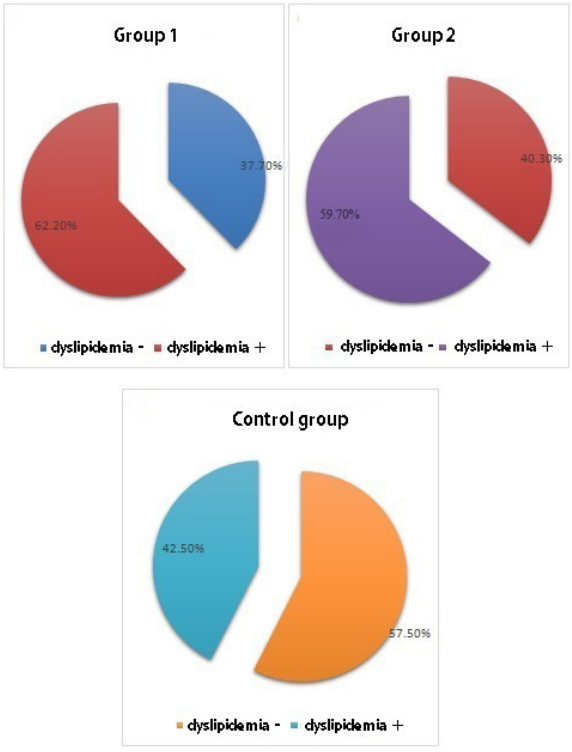

Fig.1 Abnormalities in the lipid profile in the study groups

Conclusion

The results of our study show that apoC-II can be considered as the most promising serologic marker for MM in the early gestation period for women with dyslipidemia. It seems appropriate before planning a pregnancy to conduct an additional examination of women with dyslipidemia who show a high apoC-II value in order to predict the outcome of pregnancy.

Competing Interest

The authors declare that they have no competing interests.

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References

1. Non-developing pregnancy. Chapter 14. In: Radzinsky VE, Orazmuradova AA, editors. Early pregnancy. From pregravid preparation to healthy gestation. Москва : StatusPraesens; 2020:509-537
2. Orazmuradov AA, Akhmatova AN, Haddad Kh, Lopatin AM, Bekbaeva IV, Arakelyan GA, Abitova MZ, Kyrtikov SI, Zokirova NM, Lukaev AA. Predictive Markers of Missed Miscarriage. International Journal of Biomedicine. 2021;11(1):65-67 doi:10.21103/Article11(1)_ShC
3. Wolska A, Dunbar RL, Freeman LA, Ueda M, Amar MJ, Sviridov DO, Remaley AT. Apolipoprotein C-II: New findings related to genetics, biochemistry, and role in triglyceride metabolism. Atherosclerosis. 2017 Dec;267:49-60. doi: 10.1016/j.atherosclerosis.2017.10.025.
4. Chen Q, Chen H, Xi F, Sagnelli M, Zhao B, Chen Y, Yang M, Xu D, Jiang Y, Chen G, Luo Q. Association between maternal blood lipids levels during pregnancy and risk of small-for-gestational-age infants. Sci Rep. 2020 Nov 16;10(1):19865. doi: 10.1038/s41598-020-76845-1.
5. Bartels Ä, Egan N, Broadhurst DI, Khashan AS, Joyce C, Stapleton M, O'Mullane J, O'Donoghue K. Maternal serum cholesterol levels are elevated from the 1st trimester of pregnancy: a cross-sectional study. J Obstet Gynaecol. 2012 Nov;32(8):747-52. doi: 10.3109/01443615.2012.714017.
6. Lippi G, Albiero A, Montagnana M, Salvagno GL, Scevarolli S, Franchi M, Guidi GC. Lipid and lipoprotein profile in physiological pregnancy. Clin Lab. 2007;53(3-4):173-7.
7. Ghio A, Bertolotto A, Resi V, Volpe L, Di Cianni G. Triglyceride metabolism in pregnancy. Adv Clin Chem. 2011;55:133-53. doi: 10.1016/b978-0-12-387042-1.00007-1.
8. Herrera E, Ortega-Senovilla H. Lipid metabolism during pregnancy and its implications for fetal growth. Curr Pharm Biotechnol. 2014;15(1):24-31. doi: 10.2174/1389201015666140330192345.
9. Nasioudis D, Doulaveris G, Kanninen TT. Dyslipidemia in pregnancy and maternal-fetal outcome. Minerva Ginecol. 2019 Apr;71(2):155-162. doi: 10.23736/S0026-4784.18.04330-7.
10. Catov JM, Bodnar LM, Kip KE, Hubel C, Ness RB,

Harger G, Roberts JM. Early pregnancy lipid concentrations and spontaneous preterm birth. Am J Obstet Gynecol. 2007 Dec;197(6):610.e1-7. doi: 10.1016/j.ajog.2007.04.024.
11. Edison RJ, Berg K, Remaley A, Kelley R, Rotimi C, Stevenson RE, Muenke M. Adverse birth outcome among mothers with low serum cholesterol. Pediatrics. 2007 Oct;120(4):723-33. doi: 10.1542/peds.2006-1939.
12. Magnussen EB, Vatten LJ, Myklestad K, Salvesen KÅ, Romundstad PR. Cardiovascular risk factors prior to conception and the length of pregnancy: population-based cohort study. Am J Obstet Gynecol. 2011 Jun;204(6):526.e1-8. doi: 10.1016/j.ajog.2011.02.016.
13. Ziaei S, Bonab KM, Kazemnejad A. Serum lipid levels at 28-32 weeks gestation and hypertensive disorders. Hypertens Pregnancy. 2006;25(1):3-10. doi: 10.1080/10641950500543756
14. Magnussen EB, Vatten LJ, Lund-Nilsen TI, Salvesen KA, Davey Smith G, Romundstad PR. Prepregnancy cardiovascular risk factors as predictors of pre-eclampsia: population based cohort study. BMJ. 2007 Nov 10;335(7627):978. doi: 10.1136/bmj.39366.416817.BE.
15. Clausen T, Djurovic S, Henriksen T. Dyslipidemia in early second trimester is mainly a feature of women with early onset pre-eclampsia. BJOG. 2001 Oct;108(10):1081-7. doi: 10.1111/j.1471-0528.2001.00247.x.
16. Enquobahrie DA, Williams MA, Butler CL, Frederick IO, Miller RS, Luthy DA. Maternal plasma lipid concentrations in early pregnancy and risk of preeclampsia. Am J Hypertens. 2004 Jul;17(7):574-81. doi: 10.1016/j.amjhyper.2004.03.666.
17. Di Cianni G, Miccoli R, Volpe L, Lencioni C, Ghio A, Giovannitti MG, Cuccuru I, Pellegrini G, Chatzianagnostou K, Boldrini A, Del Prato S. Maternal triglyceride levels and newborn weight in pregnant women with normal glucose tolerance. Diabet Med. 2005 Jan;22(1):21-5. doi: 10.1111/j.1464-5491.2004.01336.x.
18. Kitajima M, Oka S, Yasuhi I, Fukuda M, Rii Y, Ishimaru T. Maternal serum triglyceride at 24--32 weeks' gestation and newborn weight in nondiabetic women with positive diabetic screens. Obstet Gynecol. 2001 May;97(5 Pt 1):776-80. doi: 10.1016/s0029-7844(01)01328-x.
19. Kushtagi P, Arvapally S. Maternal mid-pregnancy serum triglyceride levels and neonatal birth weight. Int J Gynaecol Obstet. 2009 Sep;106(3):258-9. doi: 10.1016/j.ijgo.2009.03.004.
20. van Eijsden M, Vrijkotte TG, Gemke RJ, van der Wal MF. Cohort profile: the Amsterdam Born Children and their Development (ABCD) study. Int J Epidemiol. 2011 Oct;40(5):1176-86. doi: 10.1093/ije/dyq128.
21. Vrijkotte TG, Krukziener N, Hutten BA, Vollebregt KC, van Eijsden M, Twickler MB. Maternal lipid profile during early pregnancy and pregnancy complications and outcomes: the ABCD study. J Clin Endocrinol Metab. 2012 Nov;97(11):3917-25. doi: 10.1210/jc.2012-1295.
22. Glotov AS, Vashukova ES, Kanaeva MD, Dvoeglazova MO, Danilova MM, Marochkina EYu, et al. Association study of APOE, LPL and NOS3 polymorphisms with the risk of common cardio pathology in children and pregnant women. ECOLOGICAL GENETICS. 2011;9(4):25-34.
23. Korkmazer E, Ustunyurt E, Tekin B, Cilingir O. Study on potential role of apolipoprotein E in recurrent pregnancy loss. Exp Ther Med. 2013 May;5(5):1408-1410. doi: 10.3892/etm.2013.997.
24. Pulawa LK, Jensen DR, Coates A, Eckel RH. Reduction of plasma triglycerides in apolipoprotein C-II transgenic mice overexpressing lipoprotein lipase in muscle. J Lipid Res. 2007 Jan;48(1):145-51. doi: 10.1194/jlr.M600384-JLR200.
25. Loskutova IV, Bichevskaya RG. Lipid spectrum of blood in pregnant women with recurrent early miscarriage in chronic liver diseases. Sciences of Europe. 2017;20-1(20).
26. Havel RJ, Fielding CJ, Olivecrona T, Shore VG, Fielding PE, Egelrud T. Cofactor activity of protein components of human very low density lipoproteins in the hydrolysis of triglycerides by lipoproteins lipase from different sources. Biochemistry. 1973 Apr 24;12(9):1828-33. doi: 10.1021/bi00733a026.
27. Fornengo P, Bruno A, Gambino R, Cassader M, Pagano G. Resistant hypertriglyceridemia in a patient with high plasma levels of apolipoprotein CII. Arterioscler Thromb Vasc Biol. 2000 Oct;20(10):2329-39. doi: 10.1161/01.atv.20.10.2329.