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Original Research

The Role of Fibrinolytic Activity of Blood Plasma in the Development of Obstetric Complications in Overweight Pregnant Women with Metabolic Dysfunction-Associated Steatohepatitis: A Prospective Cohort Study

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Abstract

Background: Obesity and hyperlipidaemia during pregnancy increase the risk of metabolic dysfunction-associated steatotic liver disease. Our aim was to evaluate changes in the fibrinolytic system in overweight pregnant women due to metabolic dysfunction-associated steatohepatitis, compared with a control group and its impact on the development of gestational complications. **Methods**: Prospective cohort study included 69 overweight pregnant women with metabolic dysfunction-associated steatohepatitis and 30 healthy pregnant women (control group). All pregnants with metabolic dysfunction-associated steatohepatitis and obesity were divided into 3 subgroups: IA – 23 overweight pregnant women, IB – 25 pregnants with obesity grade 1, IC – 24 pregnant women with obesity grade 2. To evaluate the fibrinolysis system, we studied total, enzymatic and non-enzymatic fibrinolytic activity of plasma. **Results**: The total fibrinolytic activity of IA, IB and IC groups were, respectively, 15%, 19% and 23% lower than that of controls and the enzymatic fibrinolytic activity in overweight pregnant women with metabolic dysfunction-associated steatohepatitis of IA, IB and IC groups were, respectively 28%, 43% and 54% lower than in controls. Marked suppression of the total fibrinolytic activity and enzymatic fibrinolytic activity of the blood plasma was established in overweight pregnant women with metabolic dysfunction-associated steatohepatitis. These changes can serve as a prerequisite for the occurrence of microthrombosis with the subsequent development of placental dysfunction, fetal growth restriction and fetal distress. **Conclusions**: There are disorders in the system of the coagulation function with a tendency to peripheral microthrombosis, disseminated intravascular coagulation syndrome and macrothrombosis, which can be early prognostic criteria in the development of obstetric and perinatal complications in overweight pregnant women with metabolic dysfunction-associated steatohepatitis. **Clinical Trial Registration**: This work is a fragment of the complex research work of the Department of Obstetrics and Gynecology of I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine "A comprehensive approach to symptom control, recurrent and long-term prognosis in conditions of comorbid pathology in internal medicine clinic and family doctor's practice" (state registration number 0223U000022, 0118U000361 https://nrat.ukrintei.ua/en/searchdoc/).

Keywords: pregnancy; metabolic dysfunction-associated steatohepatitis; obesity; total fibrinolytic activity; plasminogen activation potential; obstetrical complications; fetal growth restriction; placental dysfunction; preeclampsia; postpartum haemorrhage

1. Introduction

An important aspect of antenatal protection of the fetus in the conditions of unfavorable socio-economic and medical influences is the timely diagnostics, prophylaxis and treatment of obstetric and perinatal pathology from the early stages of gestation. Careful dynamic monitoring of pregnancy makes it possible to partially avoid the negative effects of socio-economic factors. However, the rapid increase in the number of pregnant women with low birth weight requires the development of separate, special diagnostic and prognostic programs for their management depending on the characteristics of the course of the somatic disease.

It is known that pregnancy, even under the condition of its physiological course, is accompanied by a significant impact on the work of all types of metabolism, a functional restructuring of the vital activity systems of the body, which allows to ensure functional and hormonal impacts and safely bear and give birth to a child.

Today, the problem of the course of pregnancy, the development of obstetric and perinatal complications in women with steatotic liver disease associated with metabolic dysfunction-associated steatotic liver disease is receiving special attention [1–3]. Metabolic dysfunction-associated steatotic liver disease has become the main cause of chronic liver diseases worldwide [4]. The frequency of metabolic dysfunction-associated steatotic liver disease in women of childbearing age is at least 10%. However, the available literature usually does not provide specific information about the exact diagnosis, i.e., metabolic

dysfunction-associated steatotic liver disease or the presence of liver fibrosis in pregnant women [5,6].

Based on the common scientific view, metabolic dysfunction-associated steatotic liver disease is a clinicopathological complex that includes liver steatosis, steatohepatitis, and fibrosis, which can progress to steatogenic liver cirrhosis [7]. Currently, the main theory of the pathogenesis of metabolic dysfunction-associated steatohepatitis is considered to be the "multiple parallel hits" model, and a significant role in liver damage is assigned to oxidative stress, endothelial dysfunction, activation of low-intensity systemic inflammation, which in turn lead to changes in the platelet load [8–12]. As a result of the interaction of genetic factors and environmental factors, excessive consumption of glucose and fructose, metabolic dysfunction occurs, as well as a change in the transmission of signals between adipose tissue and the liver, which negatively affect the course of pregnancy and childbirth [13–16].

A presence of metabolic syndrome characterized by increased waist circumference (obesity), dyslipidemia, and arterial hypertension is a significant risk factor for metabolic dysfunction-associated steatohepatitis [4,8,15]. Since the main pathogenetic causes of both steatohepatitis and major obstetric complications, especially in the second half of pregnancy, can be endothelial dysfunction, the development of which is often associated with metabolic disorders, including atherogenic dyslipidemia, high concentrations of triglycerides, low-density lipoproteins and a low level of high-density lipoproteins can also contribute to disturbances in the system of fibrinolysis, plasma and platelet homeostasis with the subsequent development of obstetric complications in the form of preeclampsia, placental dysfunction, fetal growth restriction and postpartum bleeding [8,10,17,18].

In recent decades, an increase in the frequency of metabolic liver lesions has been observed in pregnant women [10,13,19,20]. Since the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) at the metabolic dysfunction-associated steatohepatitis stage in obese pregnant women is increasing, the occurrence of obstetric and perinatal complications leads to more frequent operative assisted delivery and birth trauma [7,8,13,21,22]. The purpose of this study was to analyze the fibrinolytic activity of pregnant women with metabolic dysfunction-associated steatohepatitis and to evaluate its impact on the development of gestational complications.

2. Materials and Methods

2.1 Selection of Patients

A prospective cohort study included an examination of 69 overweight pregnant women with metabolic dysfunction-associated fatty liver disease at the metabolic dysfunction-associated steatohepatitis stage, who were treated in the period from 2019 to 2023 in the communal hospital of the Ternopil Regional Council "Ternopil Regional Clinical Perinatal Center "Mother and Child"", Ukraine. The control group included 30 healthy women who were matched for age and gestational weeks. Pregnant women with metabolic dysfunction-associated steatohepatitis (MASH) were divided into three groups, according to their body mass index (BMI): IA group comprised 23 mothers with normal BMI (25–29.9 kg/m^2), IB group comprised 25 mothers with BMI of 30–34.9 kg/m^2 and the IC group, 21 mothers with BMI of 35–39.9 kg/m^2.

The diagnosis of MASH and obesity was established in accordance with the global practical recommendations of the World Gastroenterological Organization Global Guideline Obesity, anamnesis data, clinical, instrumental examination and biochemical markers according to standard methods in accordance with the recommendations of the EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease (2016, 2023) [12,13]. The criteria for inclusion in the study were: the presence of a desired singleton pregnancy without abnormalities of fetal development; absence of clinically significant extragenital pathology in the stage of decompensation; absence of uterine development anomalies; presence of excess body weight or obesity; conscious informed written consent to conduct additional studies, namely the non-alcoholic steatohepatitis test and liver elastography with steatometry; compliance with the recommended treatment regimen.

Exclusion criteria from the study were: viral hepatitis B, C, D; autoimmune hepatitis; toxic liver damage; genetic pathology of the liver; cirrhosis; the presence of extragenital pathology in the stage of decompensation; type 1 and type 2 diabetes mellitus; congenital anomalies of the uterus; multiple pregnancy.

Current prospective cohort study was carried out at the Department of Obstetrics and Gynecology No. 2 of the I. Horbachevsky Ternopil National Medical University, which is located in the clinic of the Ternopil Regional Clinical Perinatal Center "Mother and Child". The study was approved by I. Horbachevsky Ternopil National Medical University on October 29, 2019, meeting protocol No. 14.

This study was further approved by the local ethics committee as State registration number 0223U000022, 0118U000361 and conducted in accordance with the Helsinki Declaration. All participants signed an informed consent before enrollment.

2.2 Evaluation of the Coagulation and Fibrinolytic System

The evaluation of the fibrinolysis system was carried out by studying the total (TFA), enzymatic (EFA) and non-enzymatic (NFA) fibrinolytic activity of plasma, plasminogen activation potential (PAP), the level of fibrinogen in the blood plasma, the activity of antithrombin, which was studied with the help of kits of reagents of the company "Simko Ltd" (Lviv, Ukraine). The laboratory technique is based on the degree of hydrolysis of azofibrin which determines the

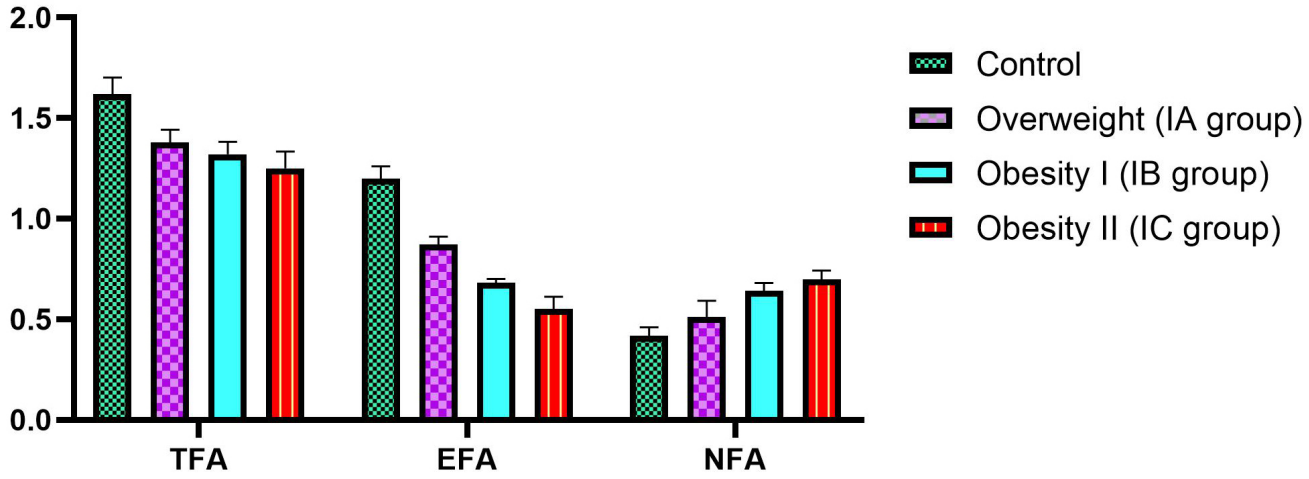

Fig. 1. The state of the fibrinolysis in overweight pregnant women with MASH. MASH, metabolic dysfunction-associated steatohepatitis; TFA, total fibrinolytic activity; EFA, enzymatic fibrinolytic activity; NFA, non-enzymatic fibrinolytic activity.

total fibrinolytic activity in plasma before and after its activation by streptokinase or urokinase. Fibrinolytic activity of blood plasma was evaluated by azofibrin lysis with further determination total (TFA), non-enzymatic (NFA) and enzymatic fibrinolytic activity blood plasma (EFA), which was determined by the formula: EFA = TFA – NFA. The plasmin content is determined by the total fibrinolytic activity before activation, and the plasminogen content is determined by the difference between the enzymatic and non-enzymatic plasma. Interval values for TFA are 1.46–1.65 E_{440}/mL/hour, EFA – 1.15–1.25 E_{440}/mL/hour, NFA – 0.31–0.41 E_{440}/mL/hour, PAP – 17.0–19.0 min, fibrinogen – 2.0–4.0 g/L, antithrombin – 80–120%.

The samples were collected at 37th week of gestation. The research was carried out in the interdepartmental scientific-educational-research laboratory of I. Horbachevsky Ternopil National Medical University (certificate of technical competence No. 132/17 dated November 17, 2017).

2.3 Statistical Analysis

Statistical processing of the research results was performed by using the licensed software package Statistica 10.0 (StatSoft Inc, Tulsa, OK, USA), SPSS-23 (SPSS Inc., Chicago, IL, USA), Microsoft Office Excel 2016 package of statistical functions (Microsoft Corp., Albany, NY, USA). The choice of the statistical analysis method depended on the features of the data to be processed and the assigned tasks. During the description the qualitative characteristics, the total number of observations (n) of the studied characteristic were indicated. We found the arithmetic mean (M) and its error (m). The results were presented as M $\pm$ m. To calculate the value of the standard error and the limits of the 95% confidence interval (CI), a p-value of less than 0.05 was considered statistically significant. We used receiver operating characteristic (ROC) analysis with the calculation of the area limited ROC curve to predict the course of MASH and determine diagnostic significance of TFA.

3. Results

All participants were residents of the Ternopil region and were Caucasian. Biometrics was comparable in all groups of pregnant women. The mean age in groups IA, IB, and IC were, respectively, 24.5 $\pm$ 1.7 years, 27.8 $\pm$ 1.6 years, and 27.8 $\pm$ 1.6 years, a non-significant difference. A total of 31 patients were primiparae (45%) and 38 (55%) were multiparae.

Obese women with MASH had a significant decrease in total fibrinolytic activity due to a decrease in the enzymatic fibrinolytic activity of plasma ($p < 0.0001$) (Fig. 1), which was generally manifested by a decrease of TFA in pregnant women.

The results of coagulation, anticoagulation and fibrinolytic parameters are summarized in Table 1. Total fibrinolytic activity was inversely proportional to BMI: in the IA group, it was 15% lower than in controls, in the IB group, it was 19% lower than in controls, and in the group IC, it was 23% lower than in controls ($p < 0.0001$ for all). At the same time, insufficient compensatory growth of NFA was observed in the IA group – by 1.21 times ($p = 0.049$), in the IB group – by 1.52 times ($p < 0.0001$), in the IC group – by 1.66 times against the group control ($p < 0.0001$), which was manifested in a general imbalance of the coagulation system and a tendency to activate the syndrome of disseminated intravascular blood coagulation.

The constituent components of the third phase of coagulation homeostasis, such as the content of fibrinogen and PAP, which are important markers of not only the coagulation but also the inflammatory process, were increased in all clinical subgroups: accordingly, the level of fibrinogen in group IA was 1.29 times higher ($p < 0.0001$), in the IB

Table 1. The state of the coagulation system and fibrinolysis in overweight pregnant women with MASH.

Parameters	Control group	Overweight	Obesity I	Obesity II	p	p_{1-2} p_{1-3} p_{2-3}
		IA group	IB group	IC group		
	(n = 30)	(n = 23)	(n = 25)	(n = 21)		
TFA, E_{440}/mL/hour	1.62	1.38	1.32	1.25	$p_1, p_2, p_3 < 0.0001$	$p_{1-2} = 0.16$ $p_{1-3} = 0.01$ $p_{2-3} = 0.16$
EFA, E_{440}/mL/hour	1.20	0.87	0.68	0.55	$p_1, p_2, p_3 < 0.0001$	$p_{1-2}, p_{1-3}, p_{2-3} < 0.0001$
NFA, E_{440}/mL/hour	0.42	0.51	0.64	0.70	$p_1 = 0.049$ $p_2, p_3 < 0.0001$	$p_{1-2} = 0.005$ $p_{1-3} = 0.001$ $p_{2-3} = 0.04$
Fibrinogen, g/L	2.87	3.71	4.25	4.63	$p_1, p_2, p_3 < 0.0001$	$p_{1-2} = 0.008$ $p_{1-3} < 0.0001$ $p_{2-3} = 0.20$
PAP, min	17.02	19.21	21.38	24.37	$p_1 = 0.003$ $p_2, p_3 < 0.0001$	$p_{1-2} = 0.01$ $p_{1-3} < 0.0001$ $p_{2-3} = 0.002$
Antithrombin, %	95.46	86.29	80.08	74.33	$p_1 = 0.001$ $p_2, p_3 < 0.0001$	$p_{1-2} = 0.002$ $p_{1-3} < 0.0001$ $p_{2-3} = 0.006$

MASH, metabolic dysfunction-associated steatohepatitis; EFA, enzymatic fibrinolytic activity; NFA, non-enzymatic fibrinolytic activity; PAP, plasminogen activation potential; TFA, total fibrinolytic activity. $p_{1,2,3}$ – differences between women of IA, IB, IC and control group; p_{1-2} – differences between patients with IA and IB subgroups; p_{1-3} – differences between patients with IA and IC subgroups; p_{2-3} – differences between patients with IB and IC subgroups. *t*-test was used for other variables in the table.

group – 1.48 times ($p < 0.0001$), in the IC group – 1.61 times ($p < 0.0001$) with a statistically significant intergroup difference, and PAP in 1.12 times ($p = 0.003$); 1.25 times ($p < 0.0001$) and 1.43 times ($p < 0.0001$), higher respectively, compared to the parameter in the control group. A negative marker of blood disaggregation was a decrease in the activity of antithrombin, which also correlated with an increase in BMI: in the group of pregnant women with MASH and excess body weight by 9.7% ($p = 0.001$), with obesity grade 1 – by 16.2% ($p < 0.0001$), obesity grade 2 – by 22.2% ($p < 0.0001$) compared to the control, with a statistically significant intergroup difference ($p < 0.0001$).

Therefore, we used ROC analysis to determine the diagnostic significance of TFA in the development of gestational complications associated with MASH, which was confirmed by the increase of the NASH test. ROC curve for the NASH test was 0.86 (95% CI 0.74–0.98; $p < 0.0001$). The threshold value for the NASH test, at the increase of which MASH was diagnosed, was calculated at the level of >1.1, and the sensitivity and specificity, respectively, were 66.6%; 71.1% (Fig. 2).

The main obstetric complications in overweight pregnant women with MASH that developed during pregnancy are presented in Fig. 3. We observed an increased prevalence of miscarriage, which was diagnosed 7.9 times more among patients with MASH as a whole than in the control group (odds ratio (OR) = 10.23, 95% CI 1.29–80.68, $p = 0.02$). Placental dysfunction was diagnosed 6.3 times more often in women of the main group than in the control group (OR = 10.15; 95% CI 2.23–46.04, $p = 0.002$); fetal growth restriction below the 10th percentile was observed in 21.7% of pregnant women with MASH versus 3.3% of the control group (OR = 8.05; 95% CI 1.01–64.09, $p = 0.04$); postpartum haemorrhage occurred in 13.0% of cases, then as it was not the case in the control (OR = 9.57; 95% CI 0.53–170.12, $p = 0.12$), and on the background of obesity grade 2, bleeding occurred more often than in other subgroups (OR = 20.33, 95% CI 1.05–390.99, $p = 0.04$).

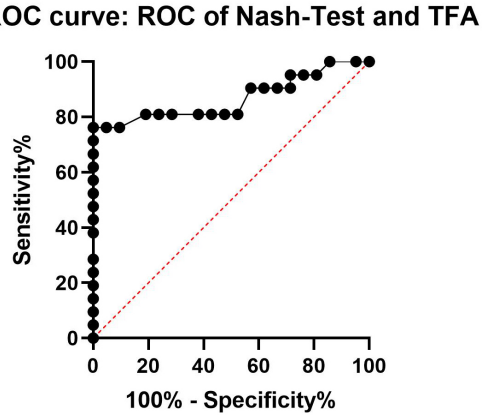

Fig. 2. Diagnostic significance of TFA for determining the progression of MASH, as confirmed by NASH-test. ROC, receiver operating characteristic curve.

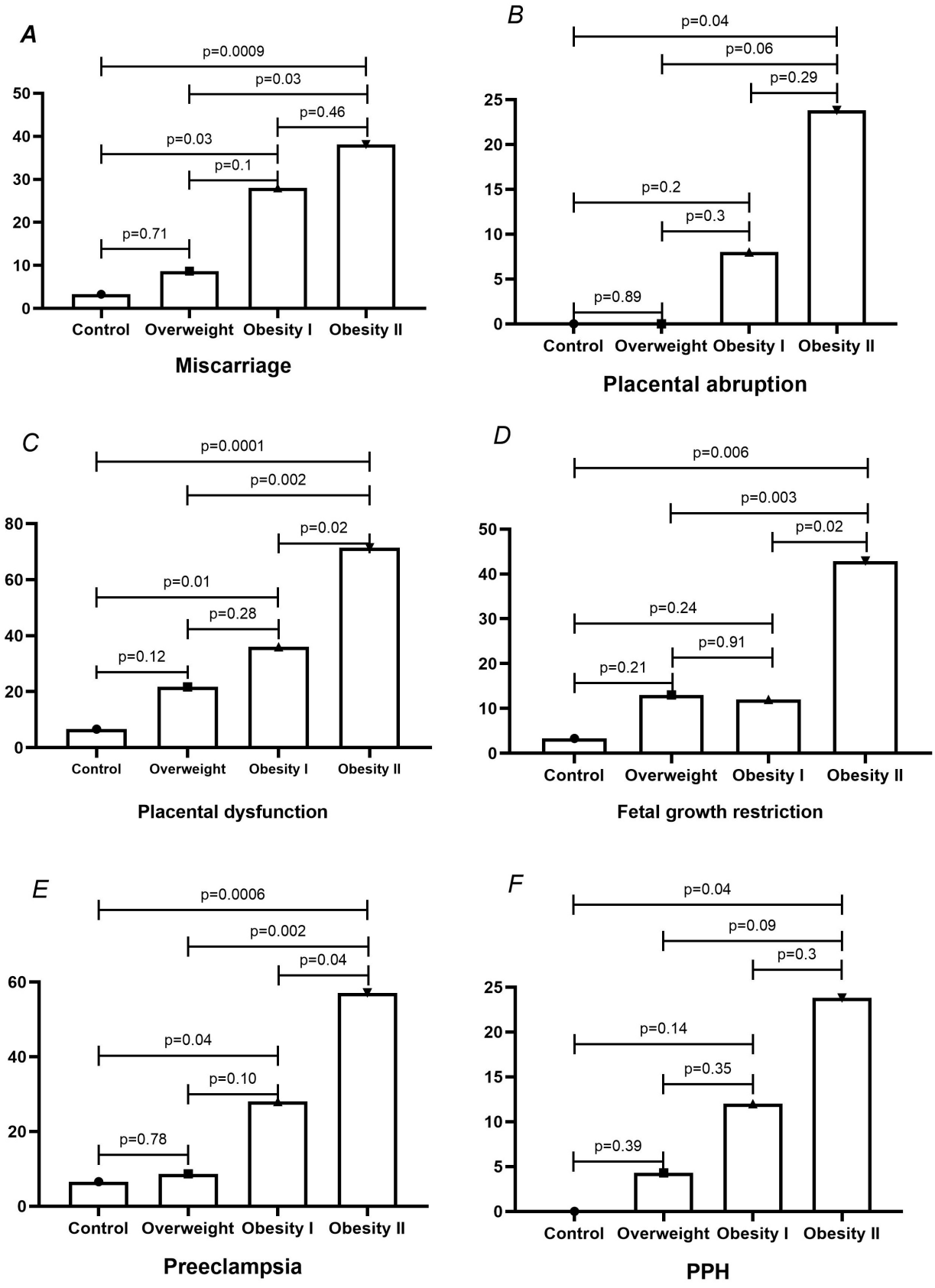

Fig. 3. Frequency of development of obstetric complications in overweight women with MASH. (A) Miscarriage. (B) Placental abruption. (C) Placental abruption. (D) Fetal growth restriction. (E) Preeclampsia. (F) Postpartum haemorrhage (PPH).

There is a significant increase in such obstetric complications as miscarriage by 7.9 times more, placental dysfunction by 6.3 times more, fetal growth restriction (FGR) in each 1 out of 5 pregnant women, preeclampsia in each 1 out of 4 women, and obstetric haemorrhage in each 1 out of 10 women among overweight pregnant women with MASH, that requires timely treatment of comorbid pathology (MASH on the background of obesity) from the early stages of pregnancy with timely prevention of obstetric risks.

4. Discussion

The physiological course of pregnancy is accompanied by hypercoagulation due to an increase in blood coagulation factors against the background of reduced fibrinolytic activity. Excess body weight is a trigger for the development of steatohepatitis and the activation of a low-intensity inflammatory syndrome. In overweight pregnant women with MASH, a likely pathological decrease in TFA was detected, that occurred due to a decrease in enzymatic fibrinolytic activity and was accompanied by an increase in non-enzymatic fibrinolytic activity, which indicates the role of chronic inflammation in the progression of MASH against the background of obesity.

The obtained results can be characterized as a hypercoagulable state due to the significant inhibition of anticoagulant factors and fibrinolytic systems and the activation of plasma factors of coagulation - fibrinogen due to low-intensity systemic inflammation. The next pathogenetic step is the activation of a significant number of intercellular adhesion molecules, polymorphic cell infiltration and microcirculation disorders. At the same time, proinflammatory cytokines activate tissue factors and cause secondary coagulopathy. The process is switched to coagulation factors of the external pathway. The regulatory synthesis and release of plasminogen activator inhibitor is disrupted. These processes in turn slow down fibrinolysis and create conditions for microthrombosis.

The connection between obesity in pregnant women and the deficiency of coagulation hemostatic system factors and fibrinolysis indicate the role of the accumulation of atherogenic lipids in the liver in the progression of steatohepatitis with the subsequent development of endothelial dysfunction, that leads to the formation of placental dysfunction, preeclampsia and FGR. However, we would like to note that the local processes of fibrinolysis and fibrin formation during implantation are desynchronized and lead to FGR in the conditions of hypofibrinolysis during MASH.

Due to the findings of our prospective cohort study, we established a pronounced suppression of the total and enzymatic fibrinolytic activity of the blood plasma against the background of probable insufficient growth of the non-enzymatic fibrinolytic activity of the blood in overweight pregnant women in MASH. The enhancement of non-enzymatic fibrinolysis can be explained by the body's compensatory response to the pronounced inhibition of the enzymatic fibrinolysis link. These changes can serve as a prerequisite for the occurrence of micro- and macrothrombosis with the subsequent development of placental dysfunction, FGR, fetal distress, miscarriage, occurrence of bleeding during pregnancy and childbirth.

Significant changes in hemocoagulation and fibrinolysis indicators were found in all clinical groups of examined overweight pregnant women with MASH, which indicates the presence of blood hypercoagulation, which is confirmed by a shortening of the prothrombin time and a significant decrease in the activity of antithrombin against the background of an increase in the level of fibrinogen. The results obtained by us on the increase of fibrinogen may indicate the threat of blood clot formation in the vessels of the uterus and placenta, which will also contribute to the increase of a significant number of obstetric and perinatal complications (placental dysfunction, the threat of preterm delivery, preeclampsia, FGR, fetal distress, etc.).

Therefore, in the first trimester of pregnancy against the background of impaired functional state of the liver and excess body weight or obesity, there is an increased risk of spontaneous abortion [8,20–22]. In the second and third trimesters, complications in pregnant women with MASH are dominated by miscarriage (24.6%) and FGR (21.7%), placental dysfunction and preeclampsia (42.0% and 30.4%, respectively), postpartum haemorrhage (13.0%), demonstrating the impact on their development, metabolic disorders in pregnant women with MASH and confirmed by the results of our study [23–26]. In the postpartum period, MASH is associated with the occurrence of microthrombosis and deep venous thrombosis in 36%, postpartum haemorrhage in 13%, and placenta abruption in 10.1% [8,20].

It can be assumed that such changes in the coagulation regulation that we have found arise in connection with a malfunction of vascular mechanisms against the background of atherogenic dyslipidemia in MASH. According to our data, we observed a violation of the "platelet-plasma homeostasis-fibrinolysis system-obstetric complications" system, which is confirmed by a decrease in the potential activity of plasminogen against the background of an increase in the level of fibrinogen and contributes to an increase in the risk of thrombosis and, as a result, the development of placental dysfunction, preeclampsia, FGR, obstetric haemorrhage.

5. Conclusions

In overweight pregnant women with metabolic dysfunction-associated steatohepatitis, there are disorders in the system of the coagulation function with a tendency to peripheral microthrombosis, disseminated intravascular coagulation syndrome and macrothrombosis, which can be early prognostic criteria in the development of obstetric and perinatal complications.

It was established that the identified hemocoagulative disorders depend on the degree of metabolic dysfunction and obesity caused by liver failure in steatotic disease, the diagnostic significance of which is confirmed by ROC analysis.

6. Prospects

The results of the study confirm that overweight pregnant women with MASH have a high risk of obstetric complications, which requires additional examination of the state of the liver, metabolic disorders and the development of individual programs for managing such pregnancies.

Abbreviations

EFA, enzymatic fibrinolytic activity; FGR, fetal growth restriction; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NFA, non-enzymatic fibrinolytic activity; PAP, plasminogen activation potential; PPH, postpartum haemorrhage; TFA, total fibrinolytic activity.

Availability of Data and Materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

LB and SH designed the article. LB and VK collected the data. NB contributed to the analysis of the publications and supervision. LB wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by I. Horbachevsky Ternopil National Medical University on October 29, 2019, meeting protocol No. 14. All participants signed an informed consent before enrollment.

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Conflict of Interest

The authors declare no conflict of interest.

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