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Case Report

Arterial Stiffness in Pregnant with Non-Alcoholic Fatty Liver Disease During 4th to 31th Gestational Week Follow-Up: A Case Report of Preterm Birth

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Abstract

Introduction: There is a strong correlation between nonalcoholic fatty liver disease (NAFLD) and increased pulse wave velocity (PWV) which is in association with hypertensive complication, postpartum hemorrhage and preterm birth. This is a case report of PWV and NAFLD progressive changes, also laboratory markers in pregnant women during a 4th to 31th gestational week (g.w.) follow-up period with preterm delivery.

Case Presentation: We found by ultrasonography (at 4 g.w.) a mild NAFLD according measured hepatorenal index (HRI) = 1.187 and elevated PWV = 6.37 cm/s in 32-year-old pregnant overweight woman [Body mass index (BMI) = 25.6 kg/m2] with accelerated aminotransferases activity, and impaired glucose and lipid metabolism. The ultrasound examination performed at 31 g.w. found increased BMI by 16%, PWV by 6.4% and HRI by 11.6%. Increased systolic/diastolic blood pressure (10.1%/22.7%) and impaired metabolism of insulin, glucose and lipid were detected, too. The baby boy was born preterm, with normal 5-min and 10-min Apgar score, in 36 g.w.

Conclusion: Increased PWV, NAFLD, impaired metabolism of glucose and lipids, high BMI, insulin resistance and gestational diabetes are risk factors for the premature delivery. Early detection of NAFLD and PWV rise, blood pressure, lipid and glucose metabolism will improve the mother's and newborn's health, and will also contribute to on term deliveries.

Keywords: *Non-Alcoholic Fatty Liver Disease; Pulse Wave Velocity; Hepatorenal Index; Preterm Birth; Arterial Stiffness*

Abbreviations

PWV: Pulse Wave Velocity; NAFLS: Nonalcoholic Fatty Liver Disease; ALT: Alanine Aminotransferase; HRI: Hepatorenal Index

Introduction

Arterial stiffness is an important vascular and flow indicator of vascular endothelial health. It is a measure of the hemodynamic and physical property of arterial walls which reflects the degree of elasticity and flexibility of the artery [1]. Pulse wave velocity (PWV) is a main hemodynamic index of arterial stiffness and it reflect the elasticity of the segmental artery, stiffer part of the artery which results in an increased speed of artery's pulse wave, which results with higher PWV [2]. Nonalcoholic fatty liver disease (NAFLD) includes simple steatosis manifestation of hepatocellular injury, fibrosis, steatohepatitis [3,4]. The public health implications of NAFLD in young adults, including reproductive women, are therefore vast [4]. Pregnancy itself is a state of relative insulin resistance and maternal obesity that increases the risk for NAFLD and gestational diabetes [3,5]. Many studies reported a strong correlation between NAFLD and increased PWV, suggesting a possible link in the pathogenesis of atherosclerosis and NAFLD [6], association with hypertensive complication, postpartum hemorrhage and preterm birth [7]. The prevalence of NAFLD among pregnant women is estimated to be about 10% [7,8]. Thus, the effects of NAFLD on PWV and vascular health are of great interest.

This article is a case report of the arterial stiffness changes and the changes in the degree of NAFLD, also laboratory markers in pregnant women during a 4th to 31th gestational week (g.w.) follow-up period with preterm delivery. We measured the progress of NAFLD through the change of the hepatorenal index (HRI) analyzed by previously explained B-mode echogenicity analyzing software [9] and appropriate laboratory test for lipid and glucose metabolism were undertaken. Aortic stiffness was measured as carotid-femoral PWV assessed by pulsed-Doppler, previously validated [10]. All examinations were performed twice, in the 4th and 31th g.w.

Case Presentation

A 32-year-old pregnant woman, referred by a gynecologist in the 4th g.w., with a body mass index (BMI) of 25.6 kg/m^2 (overweight) comes for abdominal ultrasound examination due to accelerated aminotransferase activity [alanine aminotransferase (ALT) = 75.8 U/L, aspartate aminotransferase (AST) = 59.1 U/L], increased total cholesterol of 6.72 mmol/L and triglycerides of 5.82 mmol/L. The patient was former smoker (4.5 pack-years). She has not consumed alcohol until know.

The pregnancy was verified by 2 positive commercial tests (β HCG = 60 mIU/mL) and ultrasonographically (transvaginal ultrasound): Uterus in AVFL with APD = 35 mm and decidual reaction of the endometrium. The gestational saccus was not detected in this phase yet, but only 3 mm oval hypoechoic area.

The last menstrual period (LMP) refers to 09.06.2021 (conception 23.06.2021, end of the first trimester 31.08.2021, end of the second trimester 14.12.2021) and estimated due date (EDD), the date that spontaneous onset of labor is expected to occur, refers to 16.03.2022. A healthy baby boy was delivered spontaneously on 16.02.2022. The ultrasonogram of the early pregnancy is presented in figure 1.

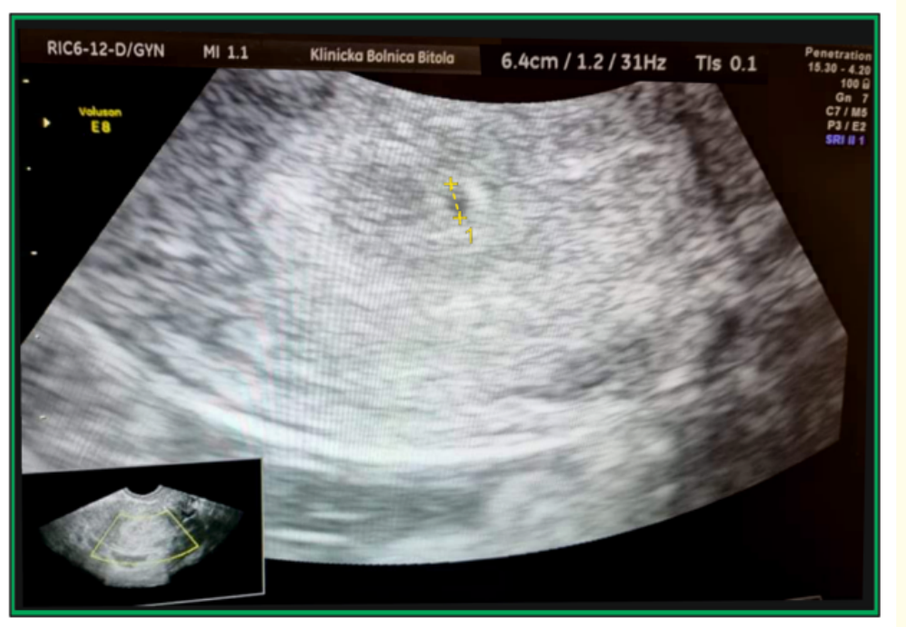

Figure 1: *Transvaginal ultrasound confirmed an early pregnancy (4+g.w.).*

Abdominal B-mode ultrasound examination revealed increased anteroposterior diameter (Dap) of the liver (Dap = 13.6 cm, reference value Dap ref = 12.5 cm), increased liver parenchyma echogenicity and decreased visualization of deep intrahepatic structures such as vessel walls and diaphragm because of ultrasound deep attenuation and vessel blurring. For a better assessment of the degree of liver steatosis a post-processing analysis was used. We retrospectively calculated the HRI, a sonographic index based on the quotient of the liver/kidney parenchyma echogenicity (E), E ; equation 1. We used free online software ImageJ (https://imagej.nih.gov/ij/download.html).

Figure 2: *Toolbar for echogenicity analysis of ROI (region of interest) pixels from imported echosonographic image for post-processing analysis by ImageJ software.*

We found a mild NAFLD according measured HRI = 1.187. NAFLD was classified according to the HRI values as: mild (HRI = 1.05 to 1.24), moderate (HRI = 1.25 to 1.64) and severe (HRI ≥ 1.65) [11].

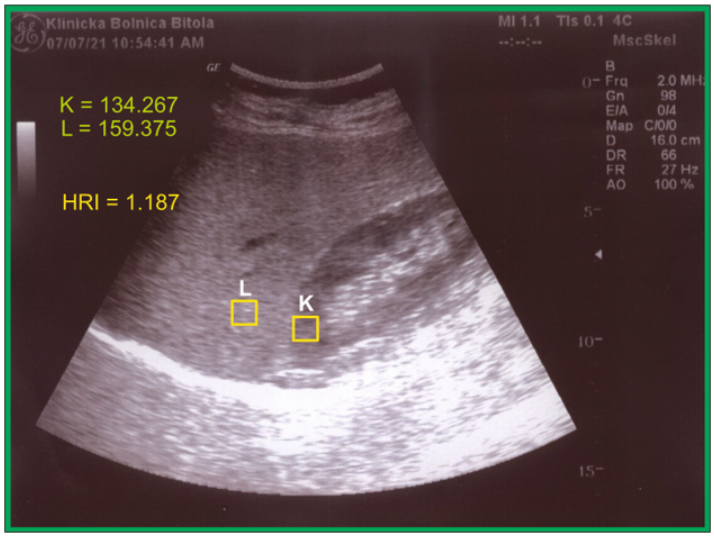

Figure 3: *Basic principle of determining the hepatorenal index (HRI) using pixels brightness analysis by ImageJ software (K: Kidney; L: Liver; HRI: Hepatorenal Index).*

The HRI was calculated by the equation 1: 159.375 is a liver (L) echogenicity divided by 134.267 which is a kidney parenchyma echogenicity (K), that is equal of 1.187. This HRI value determines mild NAFLD.

The measured PWV of 6.37 m/s was slightly increased for the corresponding age and gender normal values of ~6.13 m/s [3,6]. Demographic, laboratory and clinical parameters at baseline are presented in the table 1.

Variable	4th g.w.	31th g.w.	Δ%
BMI (kg/m^2)	25.6	29.7	+16.0
PWV (m/s)	6.37	6.78	+6.4
HRI	1.187	1.325	+11.6
ALT (U/L)	75.8	84.2	+11.1
AST (U/L)	59.1	51.3	-13.2
Total Cholesterol (mmol/L)	6.72	6.94	+3.3
Fasting glucose (mmol/L)	5.31	6.02	+13.4
Triglycerides (mmol/L)	5.82	4.91	-15.6
HbA1c (%)	5.81	6.07	+4.5
Oral GTT after one-hour (mmol/L)	8.27	10.43	Gestational diabetes
Fasting serum insulin (μIU/mL)	6.7	21.37	Gestational diabetes
Blood pressure (mmHg)	118/75	130/92	+10.1/+22.7
g.w.: Gestational Weeks; Δ%: Delta Change Percentage; BMI: Body Mass Index; PWV: Pulse Wave Velocity; HRI: Hepatorenal Index; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; HbA1c: Glycated Hemoglobin; GTT: Glucose Tolerance Test.			

Table 1: *Demographic, laboratory and clinical parameters in two estimated period.*

The control abdominal ultrasound examination of the mother was performed at 31 g.w. and the following results were ascertained: increased BMI by 16.0% (from overweight to obese range, 29.7 kg/m^2), increased PWV to 6.78 m/s or an increase of 6.4%, and increased RI to 1.325 (or an increase of 11.6%) which detected a NAFLD degree change from mild to moderate. A significant increase in the results for ALT, total cholesterol, fasting glucose, glycated hemoglobin (HBA1c), systolic and diastolic arterial blood pressure with an increase of 11.1%, 3.3%, 13.4%, 4.5%, 10.1% and 22.7% was determined, respectively. A significant decrease in the results for AST (-13.2%) and triglycerides (-15.6%) were detected during the control laboratory examination in 31th g.w.

The baby boy was born preterm (as alive baby born before the completion of 37 weeks of pregnancy) classified as moderate to late preterm birth (36 weeks), with length of 47 cm and weight of 2712 g, without induction or Caesarean birth. The 5-minute and 10-minute Apgar score were 8 and 9, respectively.

Discussion

This is a case report of pregnant with normal singleton pregnancy, with mild NAFLD, metabolic syndrome, impaired glucose metabolism and increased PWV, diagnosed according to the medical chart, laboratory and B-mode with color Doppler ultrasound findings at the first examination of the specialist of internal medicine and endocrinologist. Insulin resistance, gestational diabetes mellitus (GDM) and high BMI are crucial factors to the development of NAFLD. GDM measured by increased level of HbA1c is an early marker of insulin resistance (circulus vitiosus) and elevated oral glucose tolerance test, of course and with the increased value of fasting serum insulin (FSU) in the

first trimester [14], as gold standard. More than approximately two - to three - fold increase in the FSU after the 16th-18th g.w. [15] induced by pregnancy is strong sign for gestational diabetes; in our case (21.37/6.7) we detected 3.19 times increase FSU as the pregnancy progressed from 4th to 31th g.w. Köck., *et al*. found a significant difference in the incidence of spontaneous preterm birth in GDM mothers (P = 0.002) [16]. They determined that is an increasing tendency towards spontaneous preterm birth in 187 pregnant women with GDM and prediabetes, compared with 192 normoglycemic pregnant women [16].

GDM is an early and strong marker of insulin resistance, especially when the synergistic effect of the increased BMI is added to it. Insulin resistance is crucial factor to the development of NAFLD, with the combined pathophysiological action of GDM [13]. Forbes., *et al*. in their cross-sectional European study, found that history of GDM is strongly associated with high incidence and prevalence of NAFLD, compared with healthy volunteers [17], which is evidence that the same pathophysiological mechanisms (insulin resistance, metabolic syndrome, NAFLD, impaired glucose metabolism) are responsible among pregnant and non-pregnant women.

The demographic data among the woman from our case showed higher BMI (with a positive tendency to increase during pregnancy) and high gestational diabetes rate among this patient with NAFLD. Women with NAFLD had a 2.78 times higher adjusted relative risk (aRR) of GDM, preeclampsia (aRR = 1.95), low birth weight (aRR = 2.40) and very preterm (< 32 weeks) delivery (aRR = 6.92) [18]. The risk factors from the mentioned reference [18] are consistent with the risk factor for preterm delivery in our case report, as well: progression from mild to moderate NAFLS and progression of BMI from overweight to obese.

PWV significantly decreased at second trimester, and it increased in proportion to the progression of gestation [19], in our case it increased for 6.4%, from 4th to 31th g.w. (Table 1). Katsipi., *et al*. examined the PWV in predicting pre-eclampsia in 118 pregnant women. They estimated GDM, obesity, hypertension and PWV in predicting the outcomes, and found that pre-eclamptic women showed significantly higher PWV compared with non-pre-eclamptic women. The results of univariate analysis from their study found positive association with age, BMI, diabetes and blood pressure [20]. It is evident that the increase of arterial blood pressure of our case (+10.1%/+22.7%), which together with high BMI, GDM, NAFLD and additional risk factors, increase the risk for pre-eclampsia and unwanted birth outcomes. Arterial stiffness is increased in patients with metabolic syndrome, diabetes, hypercholesterinemia, hypertrigliceridemia, high BMI, atherosclerosis, NAFLD and other traditional risk factors [21]. Looking at the results of table 1, we see that the mentioned risk factors are also present in our case of pregnancy. These risk factors and the pregnancy itself are a prerequisite for an increase in PWV and therefore for a risk of premature delivery and/or pre-eclampsia. Murray., *et al*. found that PWV is a main diagnostic tool to assess maternal cardiovascular health in pregnancies complicated by obesity [22].

Women with a preterm delivery are at elevated risk for cardiovascular disease [23]. Reducing the potential risk factors and bringing them under control improves the future health of the mother, normal delivery and the health of the baby.

Conclusion

We conclude that, increased PWV, NAFLD, high blood pressure, hypercholesterolemia and hypertriglyceridemia, high BMI, insulin resistance (GSD) as potential risk factor are the main predisposing factors for the premature delivery of the mother in our case. Early detection of NAFLD through brightens analysis of the echosonographic images and calculation of HRI, detection of elevated PWV, continuous monitoring of arterial blood pressure, lipid status and glucose metabolism will improve the health of the mother, also will contribute to on term and normal deliveries and the health of the newborns.

Including the HRI and PWV measurement into regular practice in pregnancy screening, I am sure, will give remarkable success results.

Conflict of Interest

Nil.

Bibliography

1. Chirinos JA., *et al*. "Large-artery stiffness in health and disease: JACC state-of-the-art review". *Journal of the American College of Cardiology* 74 (2019): 1237-1263.

2. Avramovski P., *et al*. "Bone Strength and Arterial Stiffness Impact on Cardiovascular Mortality in a General Population". *Journal of Osteoporosis* (2016): 7030272.

3. Avramovski P., *et al*. "The predictive value of the hepatorenal index for detection of impaired glucose metabolism in patients with non-alcoholic fatty liver disease". *Indian Journal of Gastroenterology* 39.1 (2020): 50-59.

4. Allen AM., *et al*. "Nonalcoholic fatty liver disease incidence and impact on metabolic burden and death: A 20 year-community study". *Hepatology* 67.5 (2018): 1726-1736.

5. Kim SY., *et al*. "Percentage of gestational diabetes mellitus attributable to overweight and obesity". *American Journal of Public Health* 100.6 (2010): 1047-1052.

6. Cristiane A Villela-Nogueira., *et al*. "NAFLD and Increased Aortic Stiffness: Parallel or Common Physiopathological Mechanisms?" *International Journal of Molecular Sciences* 17.4 (2016): 460.

7. Sarkar M., *et al*. "Non-alcoholic fatty liver disease in pregnancy is associated with adverse maternal and perinatal outcomes". *Journal of Hepatology* 73.3 (2020): 516-522.

8. Vernon G., *et al*. "Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults". *Alimentary Pharmacology and Therapeutics* 34.3 (2011): 274-285.

9. Avramovski P., *et al*. "The predictive value of the hepatorenal index for detection of impaired glucose metabolism in patients with non-alcoholic fatty liver disease". *Indian Journal of Gastroenterology* 39.1 (2020): 50-59.

10. Avramovski P., *et al*. "Accelerated progression of arterial stiffness in dialysis patients compared with the general population". *The Korean Journal of Internal Medicine* 28.4 (2013): 464-474.

11. Webb M., *et al*. "Diagnostic value of computerized hepatorenal index for sonographic quantification of liver steatosis". *The American Journal of Roentgenology* 192 (2009): 909-914.

12. Renz PB., *et al*. "HbA1c Test as a Tool in the Diagnosis of Gestational Diabetes Mellitus". *PLoS One* 10.8 (2015).

13. Ajmera VH., *et al*. "Gestational Diabetes Mellitus Is Strongly Associated With Non-Alcoholic Fatty Liver Disease". *The American Journal of Gastroenterology* 111.5 (2016): 658-664.

14. Sonagra AD., *et al*. "Normal pregnancy- a state of insulin resistance". *Journal of Clinical and Diagnostic Research* 8.11 (2014): CC01-3.

15. T Bitó., *et al*. "Prediction of gestational diabetes mellitus in a high-risk group by insulin measurement in early pregnancy". *Diabetic Medicine* 22.10 (2005): 1434-1439.

16. Köck K., *et al*. "Diabetes mellitus and the risk of preterm birth with regard to the risk of spontaneous preterm birth". *Journal of Maternal-Fetal and Neonatal Medicine* 23.9 (2010): 1004-1008.

17. Forbes S., *et al*. "Increased prevalence of non-alcoholic fatty liver disease in European women with a history of gestational diabetes". *Diabetologia* 54 (2011): 641-617.

18. Hershman M., *et al*. "Implications of Nonalcoholic Fatty Liver Disease on Pregnancy and Maternal and Child Outcomes". *Gastroenterology and Hepatology (N Y)* 15.4 (2019): 221-228.

19. Oyama-Kato M., *et al*. "Change in pulse wave velocity throughout normal pregnancy and its value in predicting pregnancy-induced hypertension: a longitudinal study". *American Journal of Obstetrics and Gynecology* 195.2 (2006): 464-469.

20. Katsipi I., *et al*. "The use of pulse wave velocity in predicting pre-eclampsia in high-risk women". *Hypertension Research* 37 (2014): 733-740.

21. Ghosh A., *et al*. "Impact of Cardiovascular Factors on Pulse Wave Velocity and T otal Vascular Resistance in Different Age Group Patients with Cardiovascular Disorders". *Current Aging Science* 11.4 (2019): 261-268.

22. Murray E., *et al*. "Pulse Wave Velocity as a Tool to Assess Maternal Cardiovascular Health in Pregnancies Complicated by Obesity, Preeclampsia, and Iugr". *Journal of Obstetrics and Gynaecology Canada* 6.40 (2018): 846.

23. Catov JM., *et al*. "Preterm Delivery and Later Maternal Cardiovascular Disease Risk". *Epidemiology* 18.6 (2007): 733-739.

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