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Impact of non-alcoholic fatty liver disease on pregnancy

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Non-alcoholic fatty liver disease (NAFLD) is a major element of the metabolic syndrome, with a prevalence of about 20–30% of all liver diseases [1,2]. This figure depends on certain factors, including obesity, gender and ethnicity, and also on the method of diagnosis. During childbearing age, it has a prevalence around 10%, while some numerous studies have demonstrated the association between NAFLD and polycystic ovary syndrome (PCOS) [3]. In pregnancy, obesity, which is a major risk factor for NAFLD, has been shown to be linked with adverse pregnancy-specific consequences, including, gestational diabetes mellitus (GDM), increased caesarean delivery and preeclampsia, and is increased in women with a previous history of gestational diabetes [4,5]. Moreover, pregnant women with pre-gestational diabetes experience a high risk of poor maternal-foetal and neonatal outcomes [6]. Although clinical associations between NAFLD and certain pregnancy-neonatal outcomes have been reported, much is still unknown or unconfirmed, and there are few well-powered studies where laboratory indices are presented [1–7]. The aim of this study was to investigate links between NAFLD on clinical course and outcomes of pregnancy, and to determine abnormalities in selected routine laboratory tests.

Four hundred women (200 with NAFLD) in their first pregnancy were recruited from Gynaecology and Obstetrics Department, Mansoura University Hospital, Egypt, from March 2015 to June 2017. The women were recruited during the first trimester and evaluated for the presence of NAFLD using abdominal ultrasound scans using accepted criteria, including a bright hepatic echo pattern (compared with the right kidney), a homogeneous or a coarse echo pattern, increased attenuation of the ultrasound beam and loss of intrahepatic architectural details [7]. Data collected included the gestation duration and disorders, including hypertension, GDM (among women with no previous overt diabetes), the nature of the outcome of the pregnancy (spontaneous abortion, stillbirths), body mass index (BMI), preeclampsia, gestational age, and weight and height of the infant. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and written informed consent was obtained from all subjects. Exclusion criteria were multiple pregnancies, type 1-type 2 diabetes and/or fasting plasma glucose ≥6.99 mol/L, potential causes of hepatic steatosis (including chronic hepatitis, HIV infection and drug intake associated with fatty liver (e.g. amiodarone, tamoxifen, ovulatory drugs and corticosteroids, alcohol)), PCOS, smokers and previous history of chronic liver disease.

During the first trimester, the medical history, physical examination and laboratory data on each woman were entered into an electronic medical record. After more than 8 h fasting, the venous blood draws were probed for liver function tests, serum creatinine, triglycerides, total cholesterol and glucose by standard techniques. Serum uric acid levels were assayed by the uricase colorimetric test (MAS ChemTRAK L, Camarillo, CA, USA). Blood pressure value was measured at the time of the first visit (average of three measurements). The diabetes mellitus was diagnosed based on the American Diabetes Association (ADA) criteria as FPG ≥7 mmol/L (126 mg/dL) and/or 2-h plasma glucose ≥11.1 mmol/L (200 mg/dL) after a 75-g oral glucose load. BMI was calculated as weight in kilograms divided by the square of height in metres. The diagnosis of GDM was made according to the ADA criteria of fasting plasma glucose ≥7 mmol/L (126 mg/dL), or random blood glucose ≥11.1 mmol/L (200 mg/dL) that has been confirmed in early pregnancy [8]. The study protocol followed the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from all women. Statistical analysis was performed on SPSS V10. Continuous data are described as mean with standard deviation or median with

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interquartile range, compared by *t*-test and the Mann–Whitney *U* test. Categorical data are presented as *n* (%) and compared by chi-squared testing categorical data. *P*-value <0.05 is taken to be significant.

Table 1 shows there was no significant difference between the groups in age, BMI, preterm delivery (before 37 weeks), foetal growth retardation (infant is at or less than 10th weight percentile at delivery) or emesis gravidarum (severe or protracted nausea and vomiting). However, pregnant women with NAFLD had more GDM, pre-eclampsia (hypertensive gestational disease characterized by high blood pressure and proteinuria) and hypertension (systolic blood pressure /diastolic blood pressure (SBP/DBP) >140/90 mm Hg). Table 2 shows that NAFLD was linked to increased fasting blood glucose, aspartate transaminase (AST), total cholesterol, triglycerides and uric acid. There was no significant difference in alanine transaminase (ALT), bilirubin, albumin, creatinine and haemoglobin.

In the general population, the prevalence of the NAFLD is about 20–30% and around 10% of females of childbearing age (20–40 years) [7]. It remains unclear whether NAFLD associated with pregnancy-specific disorders and neonatal pathology risk, and if the GDM is linked to NAFLD independent of other metabolic risk factors. Although previous studies demonstrated a strong link between both gestational diabetes and NAFLD, our study adds to the literature as follows. Firstly, we included only women with a single pregnancy, while Ajmera et al. showed that GDM is an early risk indicator for the occurrence of NAFLD in multiparous women [8]. Secondly, we excluded women with previous history of diabetes mellitus, whereas Hagström et al., in a large epidemiology study showing that NAFLD is an independent risk factor for GDM, included women with a diagnosis of diabetes mellitus prior to the study. Thirdly, no woman in our study was smoking or had an alcohol intake. Hagström et al. [9] also included women with PCOS with high risk of NAFLD as a control group, while we excluded any women with PCOS. Another study found that GDM is associated with increased incidence of NAFLD, explaining this result by increasing levels of intracellular lipid in hepatocytes, supporting the theory that NAFLD is an independent risk factor for GDM [5]. Pre-eclampsia is a disease with altered vascular reactivity that leads to hypertension and proteinuria in the mother and metabolic alteration of foetus. It is a major public health concern complicating 5–7% of all pregnancies and causing important maternal and perinatal morbidity–mortality [10]. We found a significant increase in pre-eclampsia in women with NAFLD, perhaps linked to the increased frequency of hypertension (but see discussion below). Although previous studies demonstrated that infants of pregnant NAFLD women had a higher incidence of preterm birth with low weight [8], we found no difference as regards infant outcomes between the studied groups.

As regard laboratory findings, perhaps unsurprisingly [11,12], we found abnormal AST, total cholesterol and triglycerides in NAFLD, although several other indices were no different. However, there is a paucity of powered data in this field, and hypertriglycidaemia is unreported in NAFLD pregnancy. Increased glucose almost certainly likely reflects GDM. Bozkurt et al. [13] found that GDM was associated with a higher triglycerides serum level that was linked with the presence of NAFLD in middle-aged women. Although the mean BMI in the NAFLD group is normal, we note that hypertension, hyperglycaemia and hypertension are all part of the metabolic syndrome, so that a proportion of these patients will have this condition. Hyperuricaemia is known to present in 'general' NAFLD [14], so our finding in pregnancy is, although novel, also not surprising. We cannot comment in depth on the aetiology of this finding, but it is unlikely to be the consequence of renal disease, or obesity, as the linked indices (creatinine, BMI respectively) did not differ between the two groups of women. However, Martin and Brown speculated a pathogenic link between uric acid and pre-eclampsia, and our data to some extent support this hypothesis [15]. They point to potential mechanisms, such as increased uric acid production caused by trophoblast breakdown, cytokine release and ischemia, and that uric acid can promote endothelial dysfunction, damage and inflammation, which leads to oxidation. They conclude

Table 1. Clinical characteristics and age of the participants.

	NAFLD *N*: 200	Non-NAFLD *N*: 200	*P*-value
Age (years)	26.3 ± 3.8	25.9 ± 3.8	0.29
BMI (kg/m^2)	24.5 ± 2.0	24.4 ± 1.5	0.43
Gestational diabetes mellitus (*n*, %)	66 (33%)	20 (10%)	0.001
Pre-eclampsia (*n*, %)	50 (25%)	24 (14%)	0.001
Preterm delivery (*n*, %)	22 (11%)	16 (8%)	0.31
Foetal growth retardation (*n*, %)	26 (13%)	20 (10%)	0.35
Hypertension (*n*, %)	15 (7.5%)	5 (2.5%)	0.013
Emesis gravidarum (*n*, %).	16 (8%)	7 (3.5%)	0.086

BMI: body mass index. Data mean (SD) or *n* (%).

Table 2. Laboratory characteristics of the participants.

	NAFLD *N*: 200	Non-NAFLD *N*: 200	*P*-value
Glucose (mmol/dL)	4.9 ± 0.54	4.7 ± 0.42	0.001
ALT (IU/L)	33.2 ± 25.2	29.9 ± 10.1	0.87
AST (IU/L)	34.3 ± 47.7	21.4 ± 12.7	0.002
Albumin (g/L)	39 ± 12	41 ± 10	0.09
Bilirubin (mmol/L)	20 ± 6	24 ± 9	0.73
Total cholesterol (mmol/L)	6.3 ± 2.0	4.8 ± 1.4	0.001
Triglycerides (mmol/L)	2.1(1.6–2.7)	1.8 (1.5–2.5)	0.014
Creatinine (mmol/dL)	50 ± 37	55 ± 30	0.99
Uric acid (mmol/dL)	0.37 ± 0.13	0.28 ± 0.12	0.001
Haemoglobin (g/L)	140 ± 41	134 ± 29	0.107

BMI: body mass index; FBG: fasting blood glucose; ALT: alanine transaminase; AST: aspartate transaminase. Data presented as mean (SD) or median (IQR).

that pre-eclampsia, being characterized by widespread endothelial dysfunction and inflammation, might be propagated by uric acid [15].

We recognize a number of limitations to our study. Although moderately powered overall, we may be underpowered for the presence of emesis gravidarum, the frequency of which is more than doubled in the NAFLD group. Furthermore, our strict inclusion and exclusion criteria mean our data may not be extrapolable to other women, such as the obese and the multigravida. Nevertheless, this work represents an advance in biomedical science because it shows that pregnant women with NAFLD are at increased risk of gestational diabetes, pre-eclampsia, hypertension, and that liver function tests, lipids and uric acid should be carefully monitored during antenatal care.

Disclosure statement

No potential conflict of interest was reported by the authors.

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