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Nonalcoholic Fatty Liver Disease (NAFLD) in Lean, Obese, and Gestational Diabetic Pregnancies: A Descriptive Study

V. Daniel Castracane[1*], Glena Davis[1], Christopher G. Maguire[1], Urvi Shah[1], William A. Meachum[1], Robert P. Kauffman[2]

[1]Department of Obstetrics & Gynecology, School of Medicine, Texas Tech University Health Sciences Center at Permian Basin, Odessa, Texas, USA
[2]Department of Obstetrics & Gynecology, School of Medicine, Texas Tech University Health Sciences Center at Amarillo, Amarillo, Texas, USA
Email: *Daniel.castracane@ttuhsc.edu, Dr. Glena.Davis@gmail.com, Christopher.maguire@ttuhsc.edu, Robert.kauffman@ttuhsc.edu

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of liver disease in the Western world and has a strong relationship to obesity and diabetes. NAFLD has not been well studied in pregnant women. We studied a series of lean, obese, and gestational diabetic pregnant women and determined that liver enzymes would not serve to diagnose the presence of NAFLD in an obstetric population. A total of 59 pregnant women of various gestational ages and maternal weights who denied a history of alcohol intake or preexisting liver disease were recruited from a single-center university general obstetric clinic. Pregnant women underwent a maternal abdominal and obstetrical ultrasound, and blood samples were obtained for assays of liver enzymes, adiponectin and leptin. The presence of hepatic steatosis was established using standardized ultrasound criteria. NAFLD was detected by ultrasound in 48.9% of pregnant women and almost equally distributed between lean and obese women. The incidence of NAFLD in gestational diabetic pregnancies (50%) was comparable to the non-diabetic group with NAFLD in pregnant women. Adiponectin and leptin are similar between gravidas with and without NAFLD. Screening of pregnant women at any stage of pregnancy, early or late, lean or obese, or gestational diabetes after 26 weeks of gestation, would serve as a useful approach to determine NAFLD in pregnant women.

Keywords

Nonalcoholic Fatty Liver Disease, NAFLD, Pregnancy, Obesity, Adipokines, Liver Enzymes, Hepatic Steatosis

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) has become the most prevalent form of liver disease in the Western world and has been related to obesity, insulin resistance, and type 2 diabetes. [1] [2] The prevalence of hepatic steatosis in the normal population can be as high as 20% - 30% and 75% - 92% in the morbidly obese. The "gold standard" generally cited for diagnosis of NAFLD is liver biopsy, but liver biopsy is inappropriate in some populations, especially pregnant women, due to the concern about post-procedural hemorrhage. Accordingly, noninvasive tests are urgently sought to diagnose this condition. The most common noninvasive tests for NAFLD in current practice include abdominal ultrasound and serum liver function test measurement. Unfortunately, NAFLD may be present in the absence of liver enzyme elevation in non-pregnant populations. [2] [3] Younossi *et al*. have reviewed both the clinical and economic burden of NAFLD in the United States and Europe. [4] We suspect that most clinicians do not appreciate the enormity of the clinical and economic burdens of NAFLD, both of which are expected to increase as the incidence of NAFLD continues to increase.

PubMed, the search engine from the National Library of Medicine, lists hundreds of papers on both adiponectin and leptin and their association with NAFLD. We considered these adipokines important enough to include in our study.

A gender difference has been noted, and the prevalence of NAFLD is higher in males than in females. A protective role for estrogen is suggested since postmenopausal women without estrogen treatment have an incidence as high as males, and women treated with postmenopausal estrogen are less likely to have NAFLD. [5] Ethnic differences have also been reported. [6]

Despite the importance and extensive publication of studies related to NAFLD in non-pregnant subjects, comparable studies have not been performed in pregnant women. Indeed, a few years ago, review articles devoted specifically to liver diseases in pregnancy did not even mention NAFLD. [7]-[9] More recently, studies have now included NAFLD as an important observation in pregnant women. [10]-[12] The relationship of NAFLD to obesity, insulin resistance, and diabetes mellitus in non-pregnant women strongly suggests that comparable studies to examine NAFLD in pregnant women would be important in light of the maternal and fetal morbidity associated with obesity and gestational diabetes. In the present study, lean and obese pregnant subjects in the first or third trimester were studied to determine the prevalence of NAFLD in pregnant populations and whether conventional liver enzyme testing could suitably screen for the presence of NAFLD during pregnancy.

2. Methods

Fifty-nine (59) pregnant volunteers were enrolled in either the first or third trimester. First-trimester subjects were either lean (BMI $\leq$ 29.9 kg/m^2) or obese (BMI > 30 kg/m^2), and women in the third trimester were categorized as (1) lean, (2) obese, or (3) confirmed gestational diabetic pregnancies according to the National Diabetes Data Group Criteria. Women admitting any consumption of

alcohol during pregnancy were excluded, as were subjects with other chronic diseases (diabetes mellitus antedating pregnancy, hepatitis, untreated hypothyroidism, etc.). Subjects with obstructive biliary tract disease were also considered ineligible for inclusion in the data analysis.

Each subject provided informed consent for their role in this experimental protocol.

Qualifying subjects submitted a fasting blood sample that was analyzed for hepatitis A, B, and C and for the determination of alanine transaminase (ALT) and aspartate transaminase (AST). Serum levels of adiponectin and leptin were determined using established ELISA assays for these adipokines.

2.1. Normal Description

All subjects underwent abdominal ultrasound in a fasted state and a standard obstetrical ultrasound (unless a recent obstetrical ultrasound was available for analysis). GE Voluson Model 730 scanners were used for all abdominal and obstetrical ultrasound assessments. Obstetrical ultrasounds were performed using a linear array. Height and body weight were recorded for all subjects at the time of the abdominal ultrasound scan, and BMI was calculated in kg/m^2.

Multiple images of the liver, gall bladder, common bile duct, and right kidney were recorded. The presence of fatty infiltration of the liver was established in a qualitative manner when (1) intrahepatic ducts and vessels demonstrated indistinct or "hazy" borders, (2) the ultrasound beam became attenuated due to hepatic hyperechogenicity, and (3) the liver echogenicity was equal to or exceeded that of the adjacent right kidney. [7] [9]-[11] When present, the severity of hepatic fatty infiltration was graded as mild, moderate, or severe according to established protocols (**Figure 1(b)**). All abdominal ultrasound studies were interpreted by one of the authors (RPK) who was blinded to demographic, gestational, and endocrine data.

2.2. Statistics

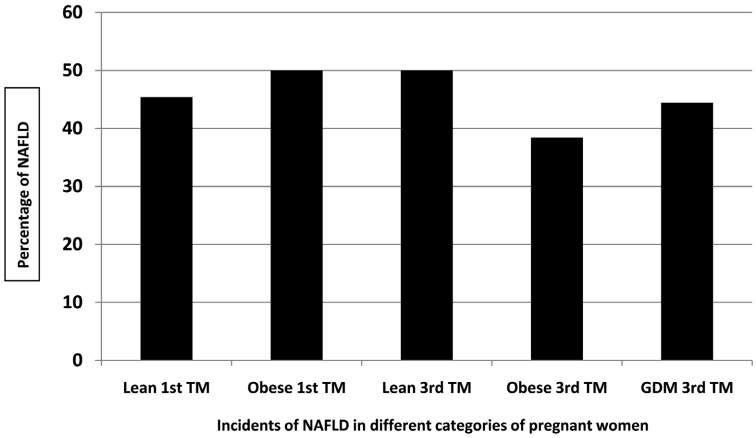
The distribution of continuous data was assessed using the D'Agostino-Pearson test. Continuous data derived from subjects with and without NAFLD were analyzed using Student's t-test for independent samples when variances were equal and Welch's test when variances were unequal. One-way analysis of variance (ANOVA) was used to compare continuous data when 3 independent variables were present. Post-hoc Student-Newman-Keuls test for pairwise comparisons was utilized. Chi-square or Fisher's exact test was used to analyze categorical variables between subjects with and without NAFLD. Statistical significance was assumed when $p < 0.05$.

Med Calc 10.1 (Mariakerke, Belgium) statistical software was used to perform all statistical analyses.

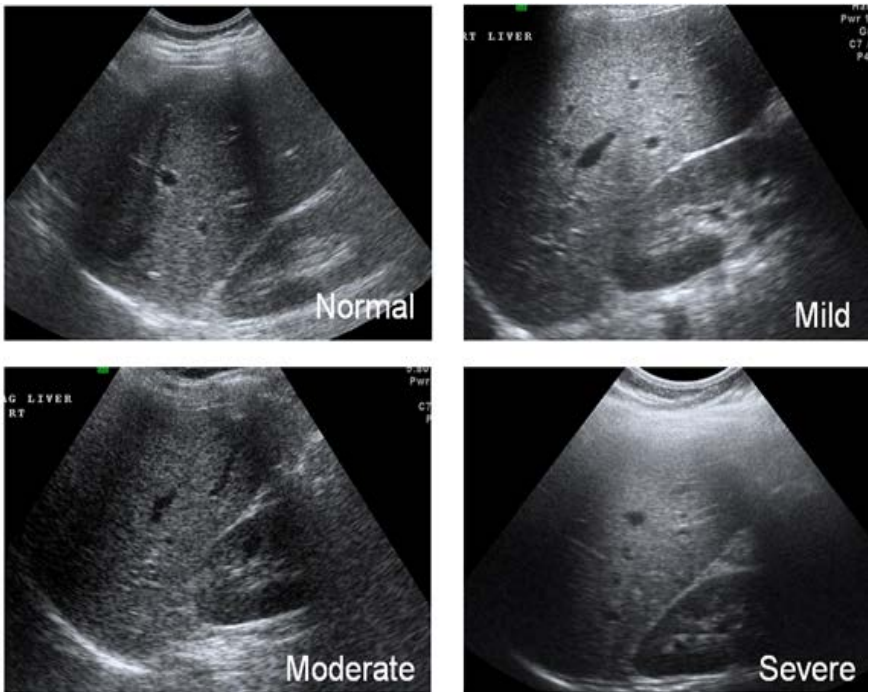
3. Results

No fetal anomalies were detected on ultrasound. Abdominal ultrasound scans of

the liver demonstrated ultrasound evidence of NAFLD in 45.8% of pregnant women enrolled in this study and generally uniformly distributed among the lean, obese, and gestational diabetic groups (Figure 1(a)).



(a)



(b)

Figure 1. (a) Categories of pregnant women with ultrasound evidence of NAFLD (p = NS). (b) Representative ultrasounds with normal liver/renal interface and mild, moderate, and severe fatty infiltration.

None of the ultrasound studies performed demonstrated dilation of the common bile duct or intrahepatic ducts, although five subjects had evidence of cholelithiasis on abdominal ultrasound (all were asymptomatic for biliary tract disease). Among those with stones, 2/22 women had ultrasound evidence of NAFLD and 3/19 demonstrated otherwise normal livers (p = 0.66).

When liver enzymes ALT and AST were compared between the NAFLD group and the non-NAFLD subjects, no significant differences were detected (Table 1 and Figure 2). When serum ALT levels were compared from subjects with mild, moderate, and severe NAFLD, there was a significant stepwise increase corresponding to the severity of NAFLD ($p = 0.002$). However, all values remained in the reported normal range for non-pregnant individuals (Figure 4).

When BMI's were compared between the NAFLD group and those without non-NAFLD, there was no significant difference (Table 1 and Figure 3). A significant age difference was noted between subjects in the NAFLD group and those without ((24.2 ± 0.9) years vs. (28.5 ± 1.1) years, $p = 0.005$). There were no differences in the presence or absence of NAFLD when fasting glucose, fasting insulin, gestational weight gain, and fetal weights at birth were compared. No differences were seen in adiponectin or leptin levels between those with and without NAFLD, but lean women had a significantly higher adiponectin level compared to those with gestational diabetes and obese women (Figure 5).

Table 1. Comparison of gravidas with and without NAFLD. Values are mean (95% CI).

	NAFLD Present	NAFLD Absent	p =
n =	27	32	
Age	24.2 ± 0.9	28.7 ± 0.9	0.001
BMI (kg/m^2)	29.2 ± 1.4	28.2 ± 1.0	0.57
Gravidy	2.3 ± 0.2	3.1 ± 0.3	0.04
Parity	1.2 ± 0.2	1.7 ± 0.2	0.08
Gestational age (lab draw)	26.7 ± 2.2	27.6 ± 1.9	0.78
Fetal weight (g)	3470 ± 130	3462 ± 68	0.96
Maternal weight gain (kg)	14.5 ± 1.1	11.7 ± 1.1	0.09
ALT (U/L)	11.5 ± 0.9	12.2 ± 0.8	0.54
AST (U/l)	13.7 ± 1.1	14.4 ± 0.6	0.59
Glucose (mg/dL)	82.9 ± 2.3	78.7 ± 2.8	0.26
Insulin (μU/mL)	9.7 ± 1.7	9.0 ± 1.7	0.77
HOMA-IR	2.09 ± 0.46	2.00 ± 0.55	0.90
Leptin (ng/mL)	48.3 ± 3.7	43.6 ± 3.5	0.37
Adiponectin (ng/mL)	14.8 ± 1.9	16.1 ± 1.4	0.57
Testosterone (ng/dL)	146.6 ± 14.9	146.9 ± 14.0	0.99
Triglyceride (mg/dL)	220.2 ± 24.0	221.0 ± 14.1	0.75

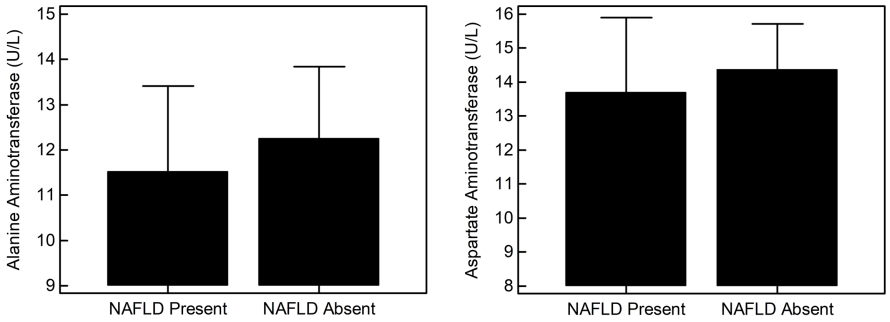


Figure 2. Comparison of ALT and AST in women with and without NAFLD.

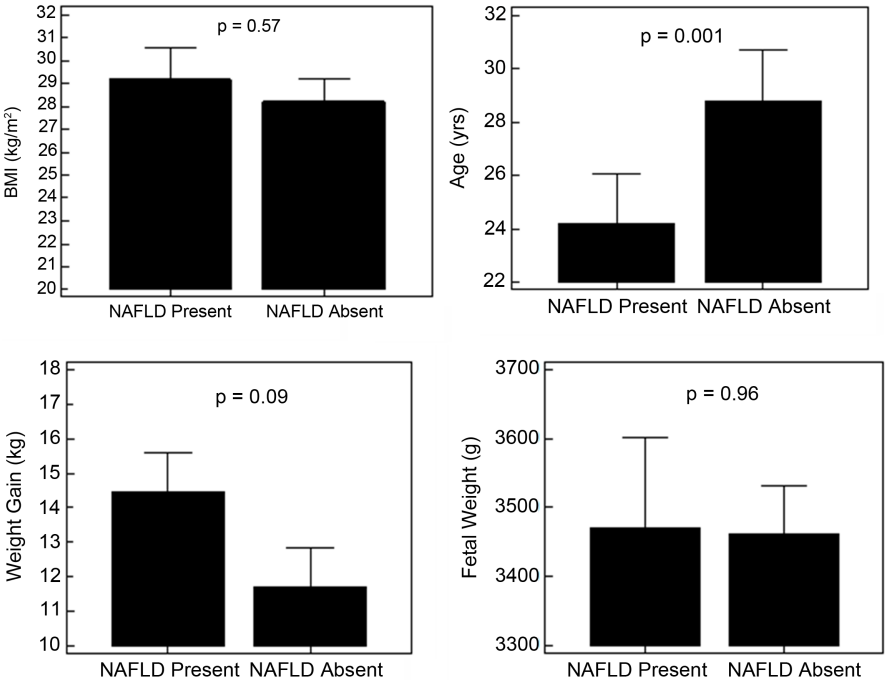


Figure 3. Various morphometric and metabolic parameters in women with and without NAFLD.

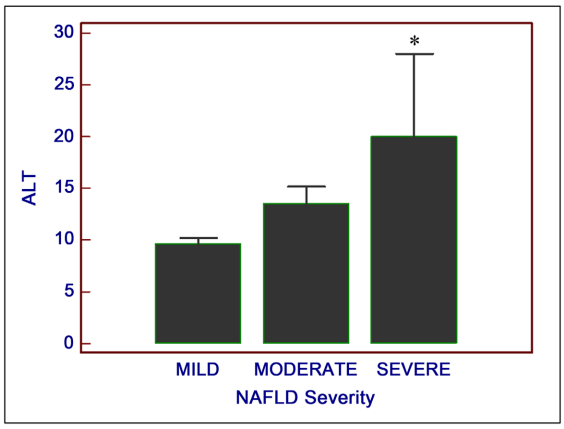


Figure 4. ALT levels by severity of NAFLD (mean ± SEM). One-way ANOVA with post-hoc Student-Newman-Keuls test for pairwise comparison. Asterisk denotes statistical difference from other groups (p = 0.002).

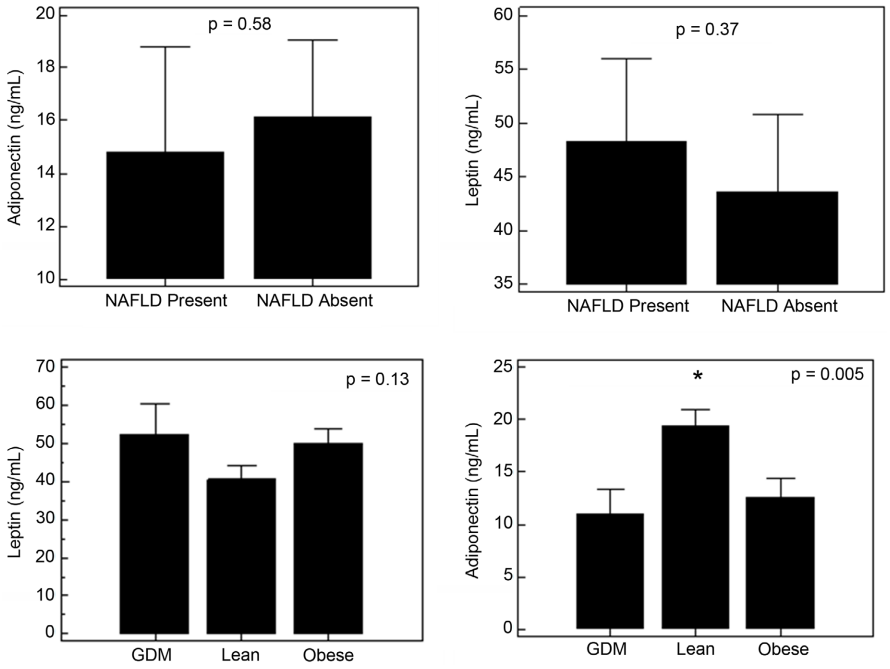


Figure 5. Comparisons of serum adiponectin and leptin levels in women with and without NAFLD, and in women who were lean, obese, and diagnosed with gestational diabetes.

4. Discussion

NAFLD based on ultrasound criteria was frequently encountered in this cross-sectional analysis of pregnant women. NAFLD was detected in lean, obese, and gestational diabetic pregnant women in roughly equal proportions.

4.1. Liver Enzymes

The commonly measured liver enzymes, ALT and AST, were in the normal range for all subjects, whether NAFLD was present or not. Hence, ALT and AST do not appear to be sensitive for screening pregnant women with NAFLD. This finding was unexpected since serum ALT concentrations correlate with liver fat independently of adiposity, and ALT elevation is a commonly utilized screening test for NAFLD in non-pregnant men and women. [13] That notwithstanding, liver enzyme elevations are not universally found in individuals with NAFLD. [2] Liver enzymes in pregnant women tend to measure as much as 20% less than in non-pregnant women. [12] The importance of using a reference range from normal pregnant women is important to understand the results in this specific population. Reference ranges for liver function tests from commercial laboratories are usually based on non-pregnant subjects and rarely on the pregnant population, which would be important for this group of patients. [14] It is logical to presume that this decrease is related to the hemodilution of pregnancy, although changes in liver function related to the hormonal milieu of pregnancy cannot be excluded. A correlation between NAFLD and ALT concentrations during pregnancy is suggested by our data given the fact that in two women in our study with "severe" hepatic steatosis on ultrasound had significantly higher ALT levels compared to

those subjects with lesser degrees of fatty infiltration.

Page and Girling cited increased liver function tests in five pregnant women and two of these women were in the first trimester. [14] [15] This early observation of NAFLD in our study demonstrates an increase in hepatic liver function on ultrasound and supports maternal NAFLD may have been present prior to pregnancy in those two women, cited by Page and Girling, but that pregnancy itself may initiate metabolic changes which contribute to intrahepatic fat accumulation early in pregnancy. [14] [15] In our present study, two pregnant women with the most severe cases of NAFLD, expressed the greatest levels of liver function tests and may represent the ability of liver enzymes to increase during serious hepatic conditions (**Figure 4**).

Surprisingly, pregnant women with NAFLD were younger than those without this condition. This is similar to our findings in women with polycystic ovary syndrome. [3] The reason for this is unclear, but it may denote that the conditions precipitating hepatic fatty infiltration are present at a relatively young age.

Recent studies have indicated a relationship between liver adipose infiltration (hepatic steatosis) and obesity, insulin resistance, and type 2 diabetes mellitus (*i.e.*, metabolic syndrome). More recently, the role of intrahepatic fat has become increasingly associated with the development of type 2 diabetes and maybe a stronger stimulus to the development of type 2 diabetes in non-pregnant individuals than visceral fat accumulation. [16] [17]

4.2. Intrahepatic Fat

The increasing awareness of the role of intrahepatic fat in the development of metabolic syndrome suggests a need for continued study of this condition in pregnancy and for any effects on maternal-fetal outcomes. The presence of intrahepatic fat (NAFLD) in pregnant women may signal a greater risk for the development of gestational diabetes compared to visceral fat accumulation and may even affect the fetal liver. If such a relationship is established, such a finding could contribute to the future development of obesity and diabetes mellitus in children. McCurdy *et al.* found that Japanese macaques fed a high-fat diet during pregnancy led to the fetal development of fatty liver by the third trimester. [17]

4.3. Adipokines

The great interest in adipokines in the NAFLD literature made it a necessary part of these studies. The many studies of adiponectin generally demonstrate that elevated levels have a beneficial effect on NAFLD and conversely, increases in serum leptin have a negative effect. Of course, obesity is associated with increases in serum leptin [18]-[22]. Most of these adipokines studies were done in non-pregnant women or male patients. Similar studies in pregnant females are minimal. It is important to note that adiponectin is decreased in pregnant women in a variety of conditions, generally declining during the course of pregnancy, with insulin resistance and gestational weight gain. [23] On the other hand, leptin levels

generally increase with gestational weight gain. These may represent different conditions that promote the development of NAFLD in gestation, making it difficult to determine the role of these adipokines in NAFLD.

Serum levels of leptin were greater in the NAFLD group, and conversely, serum levels of adiponectin were less in the NAFLD group. These results were not significant, probably related to the small sample size. When we compare leptin levels in GDM, obese, and lean pregnant women, the leptin levels were lower in the lean group than in the GDM and obese pregnant women. The same comparison for adiponectin demonstrated a significantly greater value in the lean group than in GDM and obese pregnant women ($p = 0.01$, **Figure 5**). Further studies of adiponectin and leptin in pregnancy are warranted to determine any comparison with the studies in non-pregnant NAFLD subjects.

4.4. Gestational Diabetes

Gestational diabetes is a risk factor for future development of diabetes in the newborn. This relationship suggests that maternal conditions may influence fetal development. This has not been well studied in the cases of NAFLD, although Soderberg *et al*. suggest that maternal NAFLD may influence the development of this condition in the fetus. [24] They have also provided studies to demonstrate that maternal NAFLD may contribute to this condition in the fetus. [25] Mosca *et al*. reported that forty-five percent of children with NAFLD were born to mothers with ultrasound evidence of steatosis. [26]

Patel *et al*. have recently demonstrated the presence of NAFLD in stillborns. They compared diabetic ($n = 33$) and age-matched non-diabetic control stillborn cases ($n = 48$). [27] Hepatic steatosis was confirmed by histopathology and was more prevalent and severe in the diabetic subjects (78%) than in the lean group (16.6%). While these results confirm the presence of fetal NAFLD during gestation, there is no mention of whether NAFLD in the mother accompanies fetal presentation. There is also no diagnostic measure used in this study to understand the conditions prior to delivery. Further studies of this relationship are required to understand the nature of maternal and fetal NAFLD in human pregnancy.

It has been established that NAFLD occurs during pregnancy and may be associated with risk in both maternal and fetal liver. Since pregnant women are routinely screened with ultrasound, it would be prudent to examine the maternal and fetal liver at whatever stage of gestation standard ultrasound is performed.

Recent reports of the association of metabolic changes in pregnancy, such as obesity and gestational diabetes, have given rise to a new acronym, MAFLD (Metabolic Dysfunction-Associated Steatotic Liver Disease), as a recognition of these metabolic changes in pregnancy, which may influence the development of NAFLD. [28]

Qian *et al*. [29], in a large study from China, were able to show that gestational diabetes is strongly associated with NAFLD. Lavrentaki *et al*. [30] were also able to show the association of gestational diabetes with an increased risk of NAFLD

in a large study from the U K. Lee, S M *et al.* [31] found that NAFLD was associated with the delivery of large babies.

4.5. Strengths and Weaknesses

Strengths of this study include a random selection of lean and obese pregnant women and the performance of abdominal ultrasounds in all study subjects. In addition, the physician reviewing the ultrasound studies was blinded to patient data, therefore eliminating bias that might come with foreknowledge of maternal BMI or gestational diabetic status. Weaknesses of the study included a lack of definitive diagnosis of NAFLD by histological analysis and the absence of validated ultrasound findings for NAFLD in pregnant individuals. As aforementioned, blind liver biopsy during pregnancy in otherwise healthy individuals would carry an unacceptable risk for intra-abdominal hemorrhage and related complications.

4.6. Summary

Ultrasound evidence of NAFLD is commonly encountered in pregnant women, but serum measurements of ALT and AST, probably due to physiologic hemodilution of pregnancy, are not suitable markers to detect pregnant women with this condition. The increasing evidence of NAFLD in pregnancy warrants that pregnant women should be screened for NAFLD when standard ultrasound is performed at almost any stage of pregnancy, early or late, lean or obese, and gestational diabetics after 26 weeks, and would serve as a useful and reliable approach to detect NAFLD in pregnant women. Most women would not object to this request since it would provide a chance for them to visualize their fetus. We look forward to further results as those in the present study to validate this approach for U/S scans as a rapid and convenient method to determine NAFLD in pregnant women.

Key Points

- Liver enzymes are not elevated in pregnant women with NAFLD
- NAFLD is commonly encountered in both obese and thin pregnant and gestational diabetic women.
- Liver enzymes may correlate with the severity of NAFLD in pregnancy, but never approach levels found in non-pregnant women.
- As observed in this study, U/S scans would be most useful in determining NAFLD in different kinds of pregnancy.

Authorship

The proposal was formulated by Robert P. Kauffman and V. Daniel Castracane**,** who both also wrote the manuscript. Christopher G. Maguire supervised the recruitment of subjects in the clinic and supervised daily ultrasound examinations. Robert P. Kauffman was the statistician for these studies. Glena Davis recruited most of the subjects in this study and was involved in ultrasound exams with Christopher G.

Maguire**.** All study sonograms were examined by Robert P. Kauffman, who was blinded to control information in those patients. Urvi Shah and William A. Meachum were involved in sample management and laboratory assay work, and they provided extensive graphic data for preliminary studies at national meetings. They were involved in sample management and laboratory assay work. All authors have read the manuscript and approved the submission.

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Ethical Approval

This study was approved by the Institutional Review Board of Texas Tech University Health Sciences Center School of Medicine, Lubbock, Texas, USA. Case number L08-181, approved 9-24-2008. Written consent was obtained from each participant.

Data Availability Statement

Data and ultrasound studies that support the findings in this study are available on request from Robert P. Kauffman. This manuscript is not under consideration for publication elsewhere; if accepted, it will not be published elsewhere in the same form.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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