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Study the Effects of Liver Steatosis and Body Mass Index on Fetal Growth Pattern Using Ultrasonography

دراسة اثر الكبد الدهني و زيادة كتلة الجسم للأم الحامل على نسق نمو الجنين باستخدام الموجات فوق الصوتية

Research Submitted for Acquiring the Degree of PHD in Medical Diagnostic Ultrasound

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Dedication

To my mother.

Because she didn't stop supporting me at any stage of my life.

I owe her every beautiful thing in my life, and it's not enough.

To my family and friends.

You were behind me when I faced all difficulties.

Acknowledgement

I would like to express my special gratitude to my supervisor **dr. Mohammed Al Fadil Gar Elnabi** for his great support to finish this thesis.

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He gave me the idea and encouraged me to continue this research.

Abstract

The aim of this study was to study the relationship between fetal growth rate and presence of maternal liver steatosis in diabetic and nondiabetic pregnant patients. Assuming there is an effect for maternal liver steatosis, in the presence of high maternal body mass index on the pattern of fetal growth. A sample was taken in police hospital, Omar Sawi medical complex contains 131 pregnant mothers with high body mass index and each was diagnosed with any degree of liver steatosis. Variables used were maternal age, number of gravida, maternal weight and height (to calculate the BMI), presence or non-presence of diabetes, presence of family history of diabetes, in addition to fetal measurements (AC, FL, BPD, FW, AGA), the fetal measurements obtained were compared with chart measurements calculated by LMP, to find any difference between them. The result of this study showed that there is a significance differences between fetal biometry measured by ultrasound and the one estimated by the calculated GA using LMP using paired t-test at $p = 0.05$, where for BPD and FL measured by ultrasound increase by 0.79cm/cm and 0.81cm/cm of the BPD and FL respectively versus that generated by GA-LMP. Regarding EFW versus GA estimated by ultrasound machine and calculated by LMP the result was 134gm/week and 98gm/week respectively. In conclusion liver steatosis affected fetal biometry and hence the estimated gestational age and estimated fetal weight.

ملخص البحث

هدفت هذه الدراسة إلى إيجاد العلاقة بين معدل نمو الجنين ووجود تشحم الكبد لدى الأمهات الحوامل اللاتي تزيد ، كتلة الجسم لديهن عن الحد الطبيعي، في حالة إصابتهن بمرض بداء السكري أو عدمها.

تحتوي العينة، التي تم أخذها من مجمع اللواء عمر ساوي الطبي بمستشفى الشرطة بالخرطوم ، على 131 من النساء الحوامل، اللاتي تم التأكد من تشخيصهن بأي مرحلة من مراحل تشحم الكبد. المتغيرات التي تم استخدامها في الدراسة هي العمر، عدد الولادات السابقة، وزن الأم وطولها، وجود أو عدم وجود داء السكري ، وجود أي تاريخ مرضي في العائلة للإصابة بداء السكري أو عدم وجوده، بالإضافة إلى قياسات الجنين (طول عظمة الفخذ، محيط البطن ، حجم الرأس ، وزن الجنين ومتوسط فترة الحمل). تمت مقارنة القياسات المأخوذة بالقياسات الموجودة مسبقا في الجداول والمستنتجة من تاريخ آخر دورة شهرية للأم الحامل ؛ لإيجاد أية اختلافات بين المجموعتين.

أظهرت نتيجة هذه الدراسة وجود اختلاف بين القياسات المأخوذة بالموجات فوق الصوتية، والقياسات المحسوبة بتاريخ آخر دورة شهرية؛ باستخدا(paired t-test at $p = 0.05$). كان قياس حجم الرأس وطول عظمة الفخذ لدى0.79 0.81على التوالي. ختاما فا وجود تشحم الكبد قد أثر على قياسات الجنين وبالتالي عمر الجنين ووزنه.

List of abbreviations

NAFLD	Non-alcoholic fatty liver disease
NASH	Non- alcoholic steatohepatitis
GA	Gestational age
LMP	Last menstrual period
BPD	Bi parietal distance
FL	Femur length
AC	Abdominal circumference
FW	Fetal weight
BMI	Body mass index
AST	Aspartate transaminase
ALT	Alanine transaminase
DM	Diabetes mellitus
SGS	Small for gestational age
AGA	Average gestational age
MS	Multiple sclerosis
PRAMS	Pregnancy risk assessment monitoring system

List of contents

Chapter one:
Introduction:

Steatosis is an acquired, reversible disorder of metabolism, resulting in an accumulation of triglycerides within the hepatocytes. Most commonly associated with obesity, excessive alcohol intake produces a fatty liver by stimulating lipolysis, as doe's starvation. Other causes of fatty liver include poorly controlled hyperlipidemia, diabetes, excess exogenous or endogenous corticosteroids, pregnancy, total parenteral hyper-alimentation, severe hepatitis, glycogen storage disease, jejnoileal bypass procedures for obesity, cystic fibrosis, congenital generalized lipodstrophy, several chemotherapeutic agents, including methotrexate, and toxins such as carbon tetrachloride and yellow phosphorus. Correction of the primary abnormality will usually reverse the progression for significant chronic disease in a percentage of patients. (www.ncbi.nlm.nih.gov, 2018)

Sonography of fatty infiltration may be varied depending to the amount of fatty infiltration may be varied depending on the amount of fat and whether deposits are diffuse or focal. Diffuse steatosis may be:

Mild (Grade I) – minimal diffuse increase in hepatic echogenicity; normal visualization of diaphragm and intrahepatic vessels Borders.

Moderate (Grade II) – moderate diffuse increase in hepatic echogenicity; slightly impaired visualization of intrahepatic vessels and diaphragm.

Severe (Grade III) – marked increase in echogenicity; poor penetration of the posterior segment of the right lobe of the liver and poor or non-visualization of the hepatic vessels and diaphragm.

Focal fatty infiltration and focal fatty sparing may mimic neoplastic involvement. In focal fatty infiltration, regions of increased echogenicity are present within a background of normal liver parenchyma. Focal fatty sparing may appear as

hypoechoic masses within a dense, fatty infiltrated liver. Sparing also occurs commonly by in segment IV and along the liver margins (Focal sub-capsular fat infiltration may occur in some diabetic patients receiving insulin and in patient on peritoneal dialysis .Geometric margins are present, although focal fat may appear round, nodular, or interdigitated with normal tissue (Carol M, 2011)

Rapid change with time: fatty infiltration may resolve as early as within 6 days. Incidence of steatosis and steatohepatitis correlated with the degree of obesity. Steatohepatitis was found in 18.5% of markedly obese patients and 2.7% of lean patients Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health, leading to reduced life expectancy and/or increased health problems. Maternal obesity may result in negative outcomes for both mother and fetus. The maternal risks during pregnancy include gestational diabetes and preeclampsia. The fetus is at risk for stillbirth and congenital anomalies. Obesity in pregnancy can also affect health later in life for both mother and child. For mother, these risks include heart disease and hypertension. Children have a risk of future obesity and heart disease. Mothers and their off spring are at increased risk for diabetes Fatty liver disease during pregnancy can progress to non-alcoholic fatty liver disease (NAFLD), as the rate of obesity in pregnant women increases, There is increasing concern for the effects of maternal obesity on fetal development, specifically fetal growth. Obesity considered the predisposing factor for many health problems that may affect the mother or fetal development specifically fetal growth. (Meaghan A Leddy, 2008).

Research question:

Is there any relationship between liver steatosis grade and the maternal body mass index and fetal growth patterns? Specifically in second and third trimester in presence or absence of maternal diabetes mellitus?

Literature review:

- Andrew et al. found that Fetuses of mothers with a higher BMI had a smaller mean head circumference at 17 weeks, but caught up to have larger head circumference at birth. Maternal but not paternal BMI, and paternal but not maternal height, were positively associated with placental volume.
- Anna et.al. Found that there are several articles that demonstrated the association between SGA and features of MS. There are three relevant clinical trials demonstrating a strong association between low birth weight and insulin resistance.
- Srinivasan et al. found that an abnormal intrauterine environments in rats resulted in abnormal fetal development. They found that the offspring of obese rats had increased levels of insulin, leptin and the mRNA for neuropeptides in hypothalamus.
- Timothy et al. found that there is no significant relationships between the fetal growth rate and the BMI in the second trimester [R^2 (adj): 0.0% to 1.0% except AC in one subgroup (5.6%)]. Regression analysis did not indicate a significant relationship (adj R^2: 0%–0.2%) between BMI and third-trimester %Dev slopes for any anatomic parameter.

Objectives of the study:

General objectives:

To study the relationship between fetal growth patterns and presence of maternal liver steatosis in diabetic and nondiabetic pregnant patients.

Specific objectives:

To measure FL, BPD, AC, AGA, and FW using ultrasound.

To estimate GA using FL, BPD, AC, and GA using LMP.

To find a significant difference between GA by ultrasound and GA estimated by LMP.

To find the effect of maternal steatosis and high BMI on fetal parameters.

To estimate an equation to the fetal GA and FW for mothers affected by steatosis and high BMI.

Rationale:

Mother's health during pregnancy is important because it influences fetal growth and development during pregnancy. Many studies showed effect of Maternal overweight and obesity are associated with increased risks of infant mortality due to increased risk in term births and an increased prevelvalence of preterm birth. Data

from PRAMS has shown that the prevalence of pre-pregnancy obesity increased by 69% over a 10-year period, from 13% in 1993–1994 to 22% in 2002–2003. Maternal obesity is a risk factor for spontaneous abortion (for both spontaneous conceptions and conceptions achieved through assisted reproductive technology), as well as for unexplained stillbirth (intrauterine fetal demise). A recent meta-analysis of 9 studies revealed that obese pregnant women have an estimated risk of stillbirth that is twice that of normal weight pregnant women. Obesity associated with hepatic steatosis can alter the fetal growth pattern. Effect expected to be more apparent during second and third trimester with there is an increase of fetal growth rate.

Material and method:

The study is case control study, will be performed on female pregnant mothers, Sudanese nationality between 18-45yrs old, with high body mass index and at least stage one of liver steatosis. In police hospital, General Omar Sawi medical complex between 2016 -2018. Multiple gestations, or pregnancy complicated by gestational anomalies will be excluded.

Patient's age, number of previous births, weight and length will be taken from the patient's records. BMI will be calculated using the standard formula described by WHO: the maternal weight in kilograms divided by the squired maternal height.

An abdominal scan will be performed to detect and determine the stage of liver steatosis as described previously.

Fetal measurements will be taken are BPD, FL, AC, GA and fetal weight during routine pregnancy follow up ultrasound Using Mindray machine SD6, made in china, with 5MHz curvilinear transducer.

The data will be collected and analyzed using SPSS, results will be presented in form of tables and graphs.

Chapter two

Anatomy:

The liver is largest gland in the body and has a wide variety of functions. Three of its basic functions are production and secretion of bile, which is passed into the intestinal tract ; involvement in many metabolic activities related to carbohydrate, fat , and protein metabolism and filtration of the blood, removing bacteria and other foreign particles, that have gained entrance of the blood from the lumen of the intestine. The liver synthesize heparin, an anticoagulant substance, and has an important detoxicating function. It produces bile pigments from the hemoglobin of worn – out red blood corpuscles and secrete bile salts; these together are conveyed to the duodenum by the biliary ducts.

The liver is soft and pliable and occupies the upper part of the abdominal cavity just beneath the diaphragm. The greater part of the liver is situated under cover of the right costal margin, and right hemidiaphragm. The convex upper surface of the liver is molded to the under surface of domes of the diaphragm. The posteroinferior, or visceral surface, is molded to adjacent viscera and is therefore irregular in shape; it lies in contact with the abdominal part of the esophagus, the stomach, the duodenum, the right colic flexure, the right kidney and suprarenal gland, and the gall bladder.

The liver may be divided into a large right lobe and small left lobe by the attachment of the peritoneum of the falciform ligament. The right lobe is further divided into quadrate lobe and quadate lobe by the presence of the gall bladder, the fissure for the ligamentum teres, the inferior vena cava, and the fissure for ligamentum venosum. Experiments have shown that, in fact, quadrate and quadate lobes are afunctional part of the left love of the liver. Thus, the right and left branches of the hepatic artery and portal vein and the right and left hepatic ducts, are distributed in the right lobe o the liver, let lobe of the liver, (plus quadrate, plus quadate lobes), respectively. The porta-hepatis, or hilum of the liver, is found in the postero-inferior surface and lies between quadate and

quadrate lobes, the upper part of the free edge of the lesser omentum is attached to its margins. In it lie the right and left hepatic ducts, the right and left branches of the hepatic artery, and portal vein, and sympathetic, and parasympathetic nerve fibers, a few hepatic lymph nodes lie here, they drain the liver and gall bladder, and they send their efferent vessels to the celiac lymph nodes.

The liver is completely surrounded by a fibrous capsule but only partially covered by peritoneum. The liver is made up of liver lobules. The central vein of each lobules are the portal canals, which contain branches, of the hepatic artery, portal vein, and tributary of a bile duct, (portal triad). The arterial and venous blood passes between the liver cells by means of sinusoids and drain to the central vein.

Relations of the liver:

Anteriorly: diaphragm, right and left lower costal margins, right and left pleura and lower margins of both lungs, xiphoid process, and anterior abdominal wall in the subcostal angle.

Posteriorly: diaphragm, right kidney, hepatic flexure of the colon, duodenum, gall bladder, inferior vena cava, and esophagus, and fundus of the stomach. Ligaments of the liver: the falciform ligament, which is two layered fold of the peritoneum, ascends from the umbilicus, to the liver, it has sickle shaped free margin, which contains the ligamentum teres, the remains of the umbilical vein. The falciform ligament, passes on to the anterior and then the superior surface of the liver and then splits into two layers. The right layer form the upper part of the coronary ligament; the left layer forms the upper layer of the triangular ligament. The right extremity of the coronary ligament is known as the right triangular ligament of the liver. The ligamentum teres passes into a fissure on the visceral surface of the liver, and joins the left branch of the portal vein in the porta hepatis. The ligamentum venosum, a fibrous band that is the remains of the ductus venosus, is attached to the left branch of the portal vein and ascends in a fissure on the visceral surface of the liver to be attached above to the inferior vena cava. The

lesser omentum arises from the edge of the porta hepatis and the fissure for ligamentum venosum and passes down to the lesser curvature of the stomach.

Blood Supply:

Arteries

The hepatic artery, a branch of the celiac artery, divides into right and left terminal branch enter the porta hepatis.

Veins: the portal vein divides into right and left terminal braches, they enter the porta hepatis behind the arteries. The hepatic veins (three or more) emerge from the posterior surface of the liver and drain into the inferior vena cava.

Blood circulation through the liver:

The blood vessels conveying blood to the liver are the hepatic artery (30%) and portal vein (70%). The hepatic artery brings oxygenated blood to the liver, and the portal vein brings venous blood rich in the products of digestion, which have been absorbed from the gastrointestinal tract. The arterial and venous blood is conducted to the central vein of each liver lobule by the liver sinusoids. The central veins drain into the right and left hepatic veins, and these leave the posterior surface of the liver and open directly into the inferior vena cava.

Lymph Drainage:

The liver produces a large amount of lymph about one third to one half of all body lymph. The lymph vessels leave the liver and enter several lymph nodes in the porta hepatis. The efferent vessels pass to the celiac nodes. A few vessels pass from the bare area of the liver through the diaphragm to the posterior mediastinal lymph nodes.

Nerve Supply:

Sympathetic and parasympathetic nerves form the celiac plexus. The anterior vagal trunk gives rise to a large hepatic branch, which passes directly to the liver.

Bile Ducts of the Liver:

Bile is secreted by the liver cells at a constant rate of about 40 mL per hour. When digestion is not taking place, the bile is stored and concentrated in the gallbladder;

later, it is delivered to the duodenum. The bile ducts of the liver consist of the right and left hepatic ducts, the common hepatic duct, the bile duct, the gallbladder, and the cystic duct.

The smallest interlobular tributaries of the bile ducts are situated in the portal canals of the liver; they receive the bile canaliculi. The interlobular ducts join one another to form progressively larger ducts and, eventually, at the porta hepatis, form the right and left hepatic ducts. The right hepatic duct drains the right lobe of the liver and the left duct drains the left lobe, caudate lobe, and quadrate lobe.

Hepatic Ducts:

The right and left hepatic ducts emerge from the right and left lobes of the liver in the porta hepatis. After a short course, the hepatic ducts unite to form the common hepatic duct. The common hepatic duct is about 1.5 in. (4 cm) long and descends within the free margin of the lesser omentum. It is joined on the right side by the cystic duct from the gallbladder to form the bile duct.

Bile Duct:

The bile duct (common bile duct) is about 3 in. (8 cm) long. In the first part of its course, it lies in the right free margin of the lesser omentum in front of the opening into the lesser sac. Here, it lies in front of the right margin of the portal vein and on the right of the hepatic artery. In the second part of its course, it is situated behind the first part of the duodenum to the right of the gastroduodenal artery.

In the third part of its course, it lies in a groove on the posterior surface of the head of the pancreas. Here, the bile duct comes into contact with the main pancreatic duct. The bile duct ends below by piercing the medial wall of the second part of the duodenum about halfway down its length. It is usually joined by the main pancreatic duct, and together they open into a small ampulla in the duodenal wall, called the hepato-pancreatic ampulla (ampulla of vater). The ampulla opens into the lumen of the duodenum by means of a small papilla, the major duodenal papilla. The terminal parts of both ducts and the ampulla are

surrounded by circular muscle, known as the sphincter of the hepato-pancreatic ampulla (sphincter of Oddi). Occasionally, the bile and pancreatic ducts open separately into the duodenum.

Gallbladder:

The gallbladder is a pear-shaped sac lying on the undersurface of the liver. It has a capacity of 30 to 50 mL and stores bile, which it concentrates by absorbing water. The gallbladder is divided into the fundus, body, and neck. The fundus is rounded and projects below the inferior margin of the liver, where it comes in contact with the anterior abdominal wall at the level of the tip of the 9^{th} right costal cartilage. The body lies in contact with the visceral surface of the liver and is directed upward, backward, and to the left. The neck becomes continuous with the cystic duct, which turns into the lesser omentum to join the common hepatic duct, to form the bile duct. The peritoneum completely surrounds the fundus of the gallbladder and binds the body and neck to the visceral surface of the liver.

Function of the Gallbladder: When digestion is not taking place, the sphincter of Oddi remains closed and bile accumulates in the gallbladder. The gallbladder concentrates bile; stores bile; selectively absorbs bile salts, keeping the bile acid; excretes cholesterol; and secretes mucus. To aid in these functions, the mucous membrane is thrown into permanent folds that unite with each other, giving the surface a honeycombed appearance. The columnar cells lining the surface have numerous microvilli on their free surface. Bile is delivered to the duodenum as the result of contraction and partial emptying of the gallbladder. This mechanism is initiated by the entrance of fatty foods into the duodenum. The fat causes release of the hormone cholecystokinin from the mucous membrane of the duodenum; the hormone then enters the blood, causing the gallbladder to contract. At the same time, the smooth muscle around the distal end of the bile duct and the ampulla is relaxed, thus allowing the passage of concentrated bile into the duodenum. The bile salts in the bile are important in emulsifying the fat in the intestine and in assisting with its digestion and absorption.

Blood Supply: The cystic artery, a branch of the right hepatic artery, supplies the gallbladder. The cystic vein drains directly into the portal vein. Several very small arteries and veins also run between the liver and gallbladder.

Lymph Drainage: The lymph drains into a cystic lymph node situated near the neck of the gallbladder. From here, the lymph vessels pass to the hepatic nodes along the course of the hepatic artery and then to the celiac nodes

Nerve Supply: Sympathetic and parasympathetic vagal fibers form the celiac plexus. The gallbladder contracts in response to the hormone cholecystokinin, which is produced by the mucous membrane of the duodenum on the arrival of fatty food from the stomach.

Cystic Duct: The cystic duct is about 1.5 in. (3.8 cm) long and connects the neck of the gallbladder to the common hepatic duct to form the bile duct. It usually is somewhat S-shaped and descends for a variable distance in the right free margin of the lesser omentum. The mucous membrane of the cystic duct is raised to form a spiral fold that is continuous with a similar fold in the neck of the gallbladder. The fold is commonly known as the "spiral valve." The function of the spiral valve is to keep the lumen constantly open.

Physiology:

The liver performs important digestive and excretory functions, stores and processes nutrients, synthesizes new molecules, and detoxifies harmful chemicals.

The liver produces and secretes about 600–1000 mL of bile each day, bile contains no digestive enzymes, but it plays a role in digestion because it neutralizes and dilutes stomach acid and emulsifies fats. The pH of 11prior as it leaves the stomach is too low for the normal function of pancreatic enzymes. Bile helps neutralize the acidic 11rior and bring the pH up to a level at which pancreatic enzymes can function. Bile salts emulsify fats. Bile also contains excretory products, such as bile pigments; bilirubin is a bile pigment that results

from the breakdown of hemoglobin. Bile also contains cholesterol, fats, fat soluble hormones, and lecithin.

A porta (gate) is on the inferior surface of the liver, where the various vessels, ducts, and nerves enter and exit the liver.

The hepatic portal vein, the hepatic artery, and a small hepatic nerve plexus enter the liver through the porta. Lymphatic vessels and to hepatic ducts, one each from the right and left lobes, exit the liver at the porta. The hepatic ducts transport bile out of the liver. The right and left hepatic ducts, unit to for a single common hepatic duct. The cystic duct from the gall bladder join the common hepatic duct to form the common bile duct. With join the common pancreatic duct to form the common pancreatic ampulla, an enlargement where the hepatic and pancreatic ducts come together. The hepatopancreatic ampulla empties into the duodenum at the major duodenal papilla (Richard Snell, 2012).

Pathology:

Complications of pregnancy are health problems that occur during pregnancy. They can involve the mother's health, the fetal health, or both.

Complications which may affect the mother include high blood pressure and pre-0eclampsia, also women with gestational diabetes have a likelihood of get it again in the future.

Complications which may affect the fetus include excessive birth weight; due to the extra glucose in the blood stream crosses the placenta.

Diabetes:

Diabetes is high blood sugar, insulin resistance and relative lack of insulin. Symptoms include increased thirst, frequent urination, and unexplained weight loss. Symptoms may also include increased hunger, feeling tired, and sores that do not heal. Gestational diabetes can cause many complication some of them may affect the mother and others may affect the child. Mothers with gestational diabetes are at high risk of preterm delivery because the size of the baby is large they may give birth before the due date. Also those babies born early have risk of

respiratory distress syndrome_ a condition that makes breathing difficult because of the immature lungs.

Hypoglycemia (low blood sugar) shortly after birth; because their production of insulin is high. Also Babies of mothers who have gestational diabetes have a higher risk of developing obesity and type 2 diabetes later in life.

Liver Steatosis

Liver steatosis is a reversible condition, where in large vacuoles of 13rioritizati fat accumulated in liver cells, they are two types, alcoholic and nonalcoholic fatty liver disease.

Alcoholic liver disease happens due to chronic Alcohol consumption, between 90%-100% of heavy drinkers develop fatty liver disease, and 10%-35%vdevelop alcoholic hepatitis, whereas 8%-20% develop cirrhosis.

Nonalcoholic fatty liver disease NAFLD is a common condition in which fatty liver disease develops in individuals who do not drink alcohol. The liver can show any of the three types of changes (steatosis, steatohepatitis, and cirrhosis), though on average inflammation is less prominent than in alcoholic liver disease. NAFLD is consistently associated with insulin resistance and the metabolic syndrome.

Other commonly associated abnormalities are as follows:

• Type 2 diabetes (or family history of the condition)

• Obesity, primarily central obesity (body mass index >30 kg/m2

Clinical features:

NAFLD in most of patients is asymptomatic, that make it the common cause of incidental elevation of serum transaminases, but some patients may have right upper quadrant discomfort, or more severe symptoms of chronic liver disease.

Diagnosis:

Laboratory tests:

No single laboratory test is diagnostic for nonalcoholic fatty liver disease. Liver enzyme levels have low sensitivity and specificity, and do not predict clinical

outcomes. Although elevated liver enzyme levels (i.e., AST and ALT levels) occur more commonly in patients with nonalcoholic steatohepatitis compared with hepatic steatosis, not all patients with nonalcoholic steatohepatitis have elevated AST or ALT levels. Tests to exclude viral hepatitis and hemochromatosis should be performed routinely. Additional laboratory evaluation should be considered in patients with chronically elevated liver enzyme levels or in those with a family history of cirrhosis. These tests include measurement of antinuclear antibody, smooth muscle antibody, α_1-antitrypsin, ceruloplasmin, and thyroid-stimulating hormone levels.

Imaging

Imaging studies assess liver and spleen anatomy, and the presence of hepatic steatosis. They also exclude other diseases. However, they cannot detect inflammation or fibrosis. Ultrasonography is a reliable method for qualitative evaluation and detection of moderate to high amounts of fat in the liver, and should be the first-line imaging technique. Although ultrasonography is noninvasive, inexpensive, and does not expose patients to radiation, it is subject to intra-observer reproducibility and inter-observer variability. The accuracy and reliability also may be reduced by a patient's body habitus. Additionally, the presence of hepatic fibrosis can make ultrasonography unreliable, because the test cannot differentiate between fibrosis and steatosis.

Unenhanced computed tomography is an effective test for evaluation of liver structure, but exposes patients to ionizing radiation. Changes of hepatic attenuation are proportionate to hepatic fat content. Contrast-enhanced computed tomography has lower sensitivity and specificity, and has the additional risks of contrast media exposure. Magnetic resonance imaging is one of the most accurate imaging modalities for the evaluation of nonalcoholic fatty liver disease. Magnetic resonance imaging is technically simple, void of radiation exposure, and allows quantification of hepatic steatosis. However, its use is

limited by high cost and variability of results with different systems (Vinay Kumar, 2013).

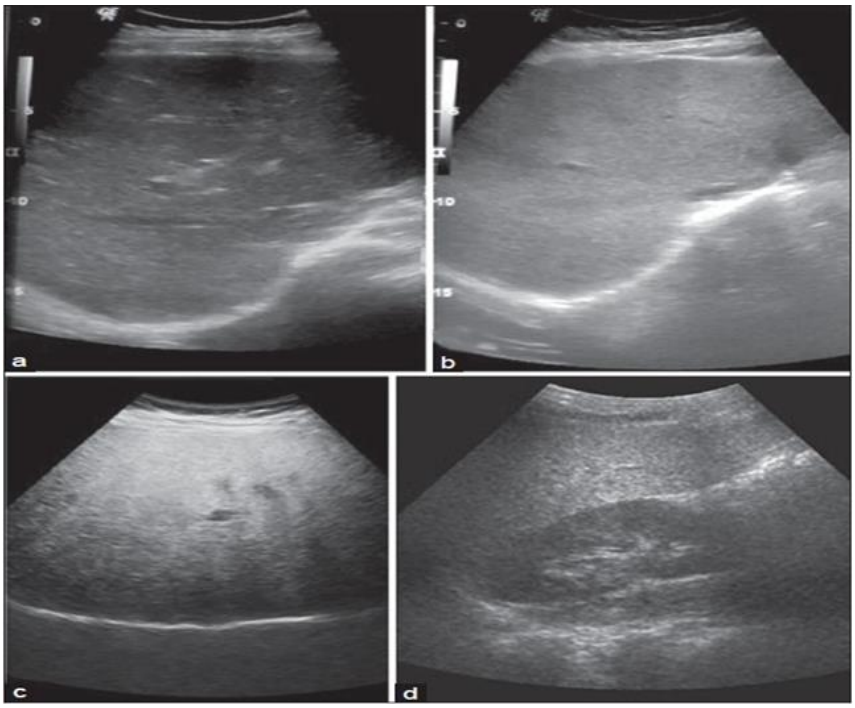

Figure No. 1: (A) Normal liver echogenicity (b) Grade 1 fatty liver with increased liver echogenicity (c) Grade 2 fatty liver with the echogenic liver obscuring the echogenic walls of the portal venous branches (d) Grade 3 fatty liver in which the diaphragmatic outline is obscured. (https://www.researchgate.net/figure/Grades-of-fatty-liver-on-visual-analysis, 2018).

Previous studies:

- **2.4.1. Andrew** et al. examined the differential associations of each parent's height and BMI with fetal growth, to examine the associations of pattern through gestation. Data are from 557 term pregnancies in the Pune Maternal Nutrition Study. Size and conditional growth outcomes from 17 to 29 weeks to birth were derived from ultrasound and birth measures of head circumference, abdominal circumference, femur length and placental volume (at 17 weeks only). Parental height was positively associated with fetal head circumference and femur length. The associations with paternal height were detectible earlier in gestation (17–29 weeks) compared to the associations with maternal height. Fetuses of mothers with a higher BMI had a smaller mean head circumference at 17 weeks, but caught up to have larger head circumference at birth. Maternal but not paternal BMI, and paternal but not maternal height, were positively associated with placental volume. The opposing associations of placenta and fetal head growth with maternal BMI at 17 weeks could indicate prioritization of early placental development, possibly as a strategy to facilitate growth in late gestation. (www.researchgate.net, July, 2016)

2.4.2. Anna et.al. Studied the relationship between the metabolic syndrome and

birth weight. Anna found that there are several articles that demonstrated the association between SGA and features of MS. There are three relevant clinical trials demonstrating a strong association between low birth weight and insulin resistance. In the first study, including 85 SGA subjects and 23 AGA subjects, the authors found a close link between insulin secretion/sensitivity, patterns of rapidity, and length of catch-up-growth process during early postnatal life. In the second study, the authors found that mildly impaired insulin sensitivity in 79 pre-pubertal short children born SGA is associated with growth hormone treatment. (Anna Alaisi, 2016).

- **2.4.3.** Srinivasan M et al. characterized the development of the abnormal intrauterine environment in the 1-HC female rats and the effects on fetal development under such pregnancy conditions for the offspring. 1-HC female rats demonstrated hyperphagia on laboratory chow and increased body weight gain beginning from the immediate post weaning period along with hyperinsulinemia and hyperleptinemia. During pregnancy, 1-

HC female rats showed several metabolic alterations including increased body weight gain and increased plasma levels of insulin, leptin, pro-inflammatory markers, and lipid peroxidation products. Although there were no significant changes in the body weights or litter size of term 2-HC fetuses, the plasma levels of insulin and leptin were significantly higher compared with those of control term fetuses. (www.ncbi.nlm.nih.gov/pmc/articles, 2016).

- **2.4.4.** Timothy p. et al **.**Performed a retrospective review of biometry in the second and third trimesters from 246 normal, term singleton fetuses was performed. four to eight Biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC, and femur diaphysis length (FL) measurements per fetus were available and used to determine second-trimester growth rates. Expected third-trimester size trajectories were generated from these data and percent deviations [%dev = ((observed − expected)/expected) × 100] were calculated. Two-level linear modeling was used to determine %dev slopes and the effect of body mass index (BMI) on these slopes. Relationships between individual second- and third-trimester slopes and BMI were evaluated using linear regression. (https://onlinelibrary.wiley.com/doi/abs/10.1002/jcu.22158, 2015).

Chapter three

2.1. Material and method:

The study is case control study, will be performed on female pregnant mothers, Sudanese nationality between 18-45yrs old, with high body mass index and at least stage one of liver steatosis. In police hospital, General Omar Sawi medical complex between 2016 -2018. Multiple gestations, or pregnancy complicated by gestational anomalies will be excluded. Patient's age, number of previous births, weight and length will be taken from the patient's records. BMI will be calculated using the standard formula described by WHO: the maternal weight in kilograms divided by the squired maternal height. An abdominal scan will be performed to detect and determine the stage of liver steatosis as described previously. Fetal measurements will be taken are BPD, FL, AC, GA and fetal weight during routine pregnancy follow up ultrasound Using Mindray machine SD6, made in china, with 5MHz curvilinear transducer.

2.2. **Scanning technique**: Longitudinal scan from outer margin of the left to the outer margin of the right lobe. Transverse scan with the probe angled cephalic to include the superior margin to the inferior margin of the left and right lobe of the liver. Subcostal scan to examine the whole of the right lobe. Intercostal scan which is a supplementary view for examining the right lobe of the liver especially when the right lobe is well within the rib cage. Stage of liver steatosis was determined as previously mentioned in chapter tow for mild stage 1 to severe in stage 3. Data will be collected and analyzed using SPSS, results will be presented in form of tables and graphs.

4. Chapter four

4.1. Results

The study was done on in 131 pregnant mothers between 18-45 yrs., the maximum maternal weight noted was 130kg, and the maximum height was 176cm. 69% of the total number of patients have mild stage of steatosis, 24% have moderate stage, while 8% have severe stage of steatosis.

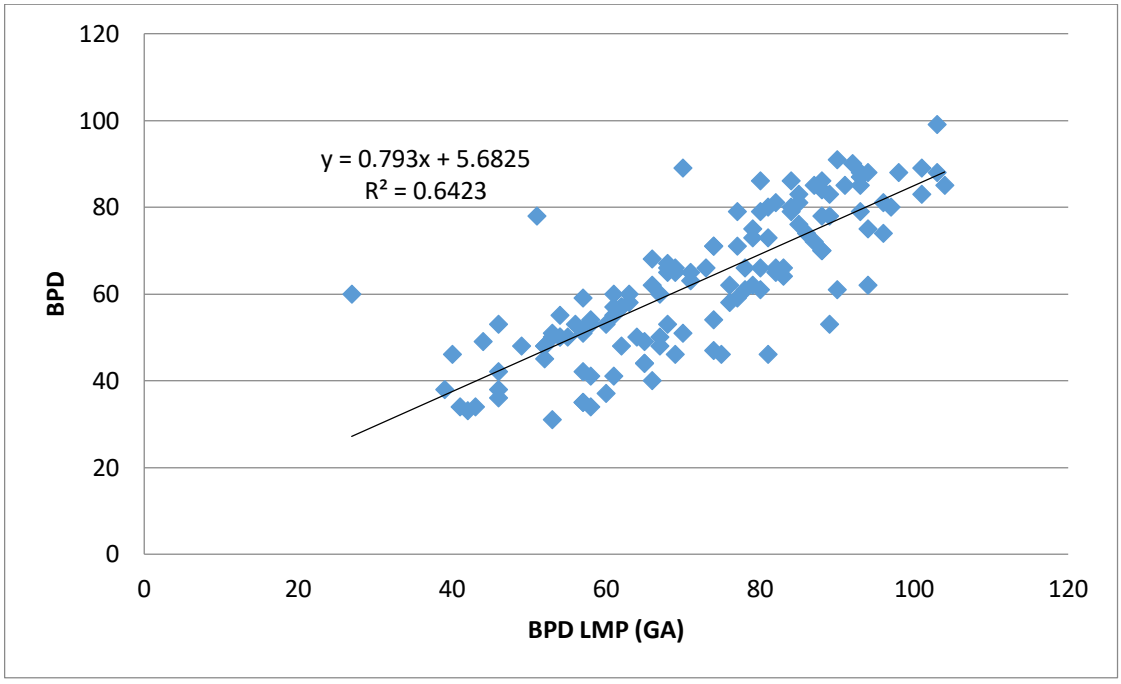

Figure number 4.1. Scattered graph demonstrates the correlation between BPD calculated by LMP, and BPD measured by ultrasound.

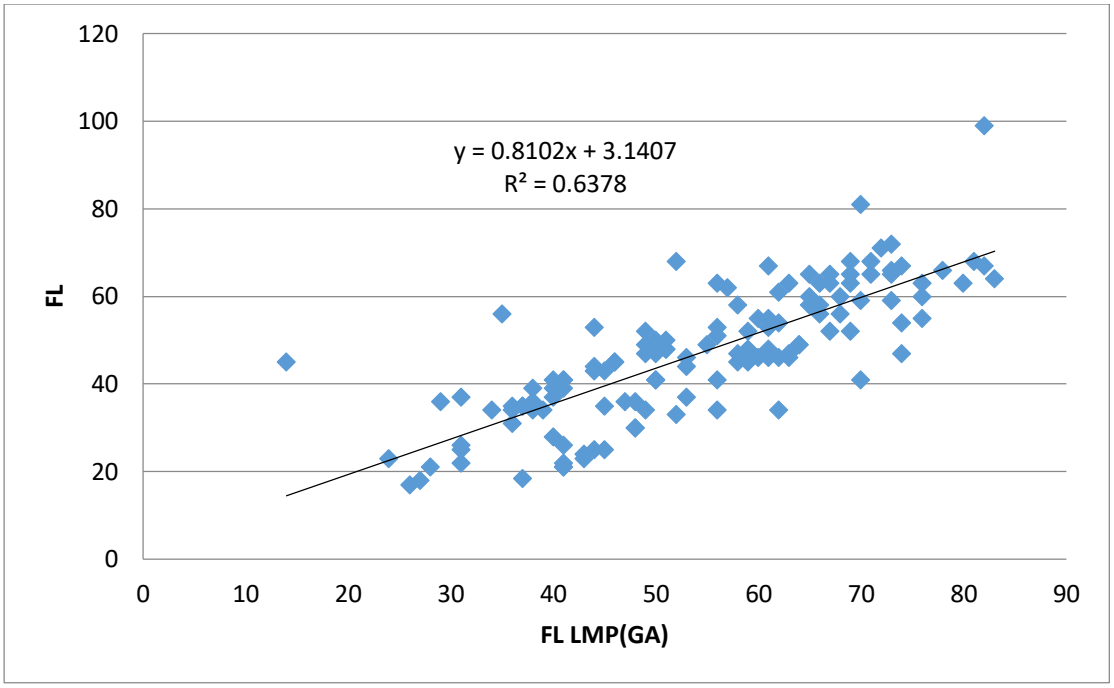

Figure number 4.2. Scattered graph demonstrates the correlation between FL

calculated by LMP, and FL measured by ultrasound.

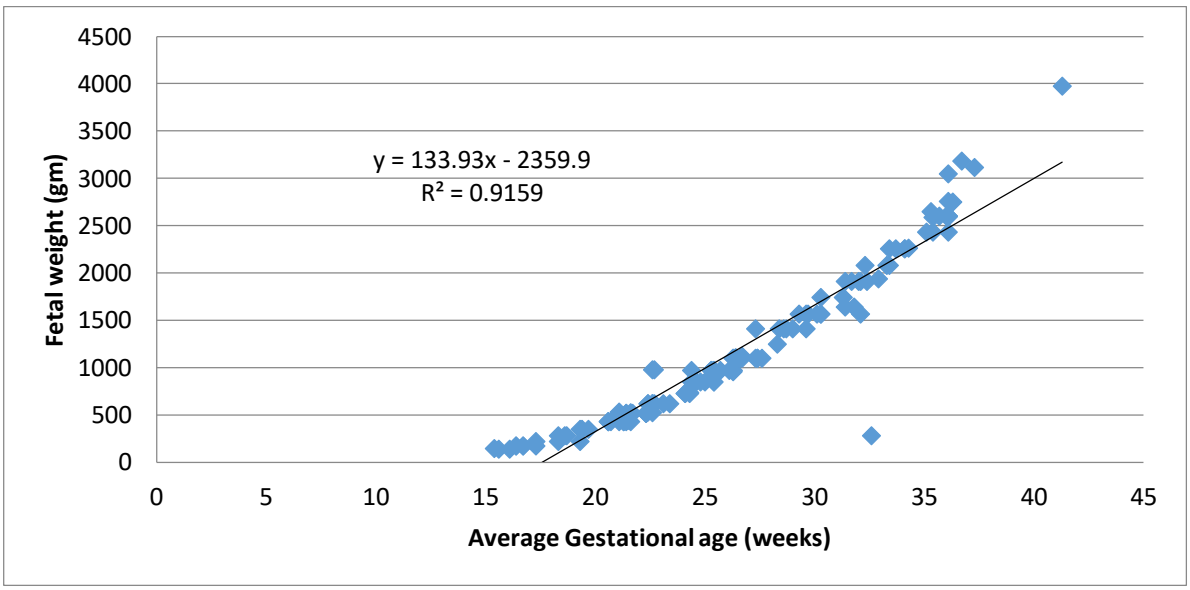

Figure number 4.3. Scattered graph demonstrates the correlation between AGA, and FW measured by ultrasound.

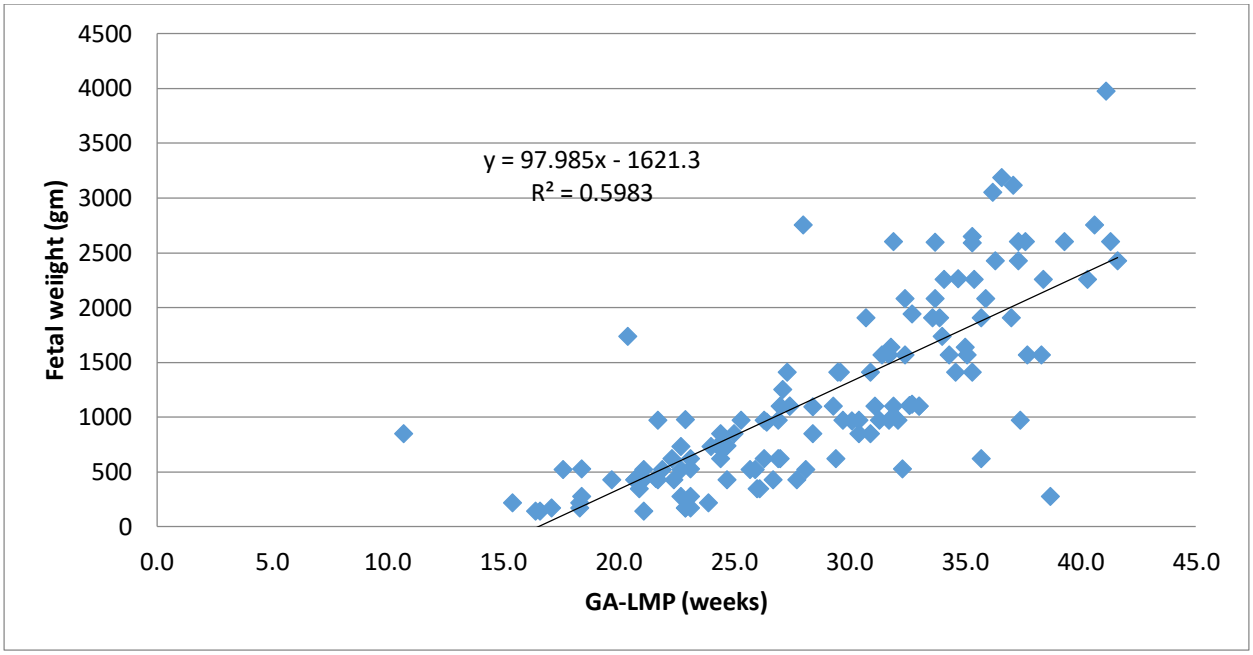

Figure number 4.4. Scattered graph demonstrates the correlation between GA by LMP, and FW measured by ultrasound.

Table 4.1. Demonstrates paired samples statistics of growth patterns of grade1 liver steatosis

Paired Samples Statistics				
Grade 1 liver Steatosis		Mean	N	Std. Deviation
Pair 1	FL	47.680	89	15.8078
	FL_LMP	54.899	89	15.1815
Pair 2	BPD	63.584	89	16.8838
	BPD_LMP	72.831	89	16.8396
Pair 3	Average GA	26.867	89	6.1769
	GA_LMP	29.097	89	6.7492
Pair 4	GAFL	27.117	89	5.9950
	GA_LMP	29.097	89	6.7492
Pair 5	GAAC	27.134	89	6.2295
	GA_LMP	29.097	89	6.7492
Pair 6	GABPD	26.988	89	6.2356
	GA_LMP	29.097	89	6.7492

Table 4.2: demonstrate paired samples correlations of growth patterns of grade 1 liver steatosis

Paired Samples Correlations				
Grade 1 liver Steatosis		N	Correlation	Sig.
Pair 1	FL & FL_LMP	89	.783	.000
Pair 2	BPD & BPD_LMP	89	.781	.000
Pair 3	Average_ GA & GA_LMP	89	.799	.000
Pair 4	GAFL & GA_LMP	89	.796	.000
Pair 5	GAAC & GA_LMP	89	.801	.000
Pair 6	GABPD & GA_LMP	89	.798	.000

Table 4.3 demonstrate paired samples of growth patterns of grade 1 liver steatosis:

Paired Samples Test			
Grade 1 liver Steatosis		t	Sig. (2-tailed)
Pair 1	FL – FL_LMP	-6.654	.000
Pair 2	BPD – BPD_LMP	-7.810	.000
Pair 3	Average GA – GA_LMP	-5.090	.000
Pair 4	GAFL – GA_LMP	-4.522	.000
Pair 5	GAAC – GA_LMP	-4.488	.000
Pair 6	GABPD – GA_LMP	-4.788	.000

Table 4.4: demonstrate paired samples statistics of growth patterns of grade2 liver steatosis

Paired Samples Statistics					
Grade 2 liver Steatosis		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	FL	46.290	31	12.5198	2.2486
	FL_LMP	52.742	31	12.9922	2.3335
Pair 2	BPD	62.161	31	14.7944	2.6571
	BPD_LMP	69.419	31	15.4462	2.7742
Pair 3	Average GA	26.177	31	5.3568	.9621
	GA_LMP	27.935	31	5.8634	1.0531
Pair 4	GAFL	26.455	31	5.2198	.9375
	GA_LMP	27.935	31	5.8634	1.0531
Pair 5	GAAC	26.197	31	5.4284	.9750
	GA_LMP	27.935	31	5.8634	1.0531
Pair 6	GABPD	26.458	31	5.4982	.9875
	GA_LMP	27.935	31	5.8634	1.0531

Table 4.5: demonstrate paired samples correlations of growth patterns of grade2 liver steatosis

Paired Samples Correlations				
Grade 2 liver Steatosis		N	Correlation	Sig.
Pair 1	FL & FL_LMP	31	.840	.000
Pair 2	BPD & BPD_LMP	31	.853	.000
Pair 3	Average GA & GA_LMP	31	.877	.000
Pair 4	GAFL & GA_LMP	31	.881	.000
Pair 5	GAAC & GA_LMP	31	.884	.000
Pair 6	GABPD & GA_LMP	31	.892	.000

Table 4.6: demonstrate paired samples of growth patterns of grade 2 liver steatosis

Paired Samples Test			
Grade 2 liver Steatosis		t	Sig. (2-tailed)
air 1	FL – FL_LMP	-4.975	.000
Pair 2	BPD – BPD_LMP	-4.908	.000
Pair 3	Average GA – GA_LMP	-3.460	.002
Pair 4	GAFL – GA_LMP	-2.974	.006
Pair 5	GAAC – GA_LMP	-3.518	.001
Pair 6	GABPD – GA_LMP	-3.086	.004

Table 4.7: demonstrate paired samples statistics of growth patterns of grade 3 liver steatosis

Paired Samples Statistics			
Grade 3 liver Steatosis		Mean	N
Pair 1	FL	43.636	11
	FL_LMP	52.000	11
Pair 2	BPD	55.818	11
	BPD_LMP	69.818	11
Pair 3	average_=GA	24.782	11
	GA_LMP	27.918	11
Pair 4	GAFL	24.736	11
	GA_LMP	27.918	11
Pair 5	GAAC	24.982	11
	GA_LMP	27.918	11
Pair 6	GABPD	25.382	11
	GA_LMP	27.918	11

Table 4.8: demonstrate paired samples correlations of growth patterns of grade 3 liver steatosis

Paired Samples Correlations			
Grade 3 liver Steatosis		N	Correlation
Pair 1	FL & FL_LMP	11	.856
Pair 2	BPD & BPD_LMP	11	.893
Pair 3	Average GA & GA_LMP	11	.941
Pair 4	GAFL & GA_LMP	11	.953
Pair 5	GAAC & GA_LMP	11	.940
Pair 6	GABPD & GA_LMP	11	.942

Table 4.9: demonstrate paired samples of growth patterns of grade 3 liver steatosis

Paired Samples Test			
Grade 3 liver Steatosis		t	Sig. (2-tailed)
Pair 1	FL – FL_LMP	-3.202	.009
Pair 2	BPD – BPD_LMP	-5.631	.000
Pair 3	Average GA – GA_LMP	-3.824	.003
Pair 4	GAFL – GA_LMP	-4.253	.002
Pair 5	GAAC – GA_LMP	-3.486	.006
Pair 6	GABPD – GA_LMP	-3.138	.011

Table 4.10: demonstrates the number of gravida for each patient

Gravid no	Frequency
1	24
2	28
3	49
4	21
5	7
6	2
Total	131

Figure No. 4.5. : Pie chart: demonstrates the number of gravida for each patient

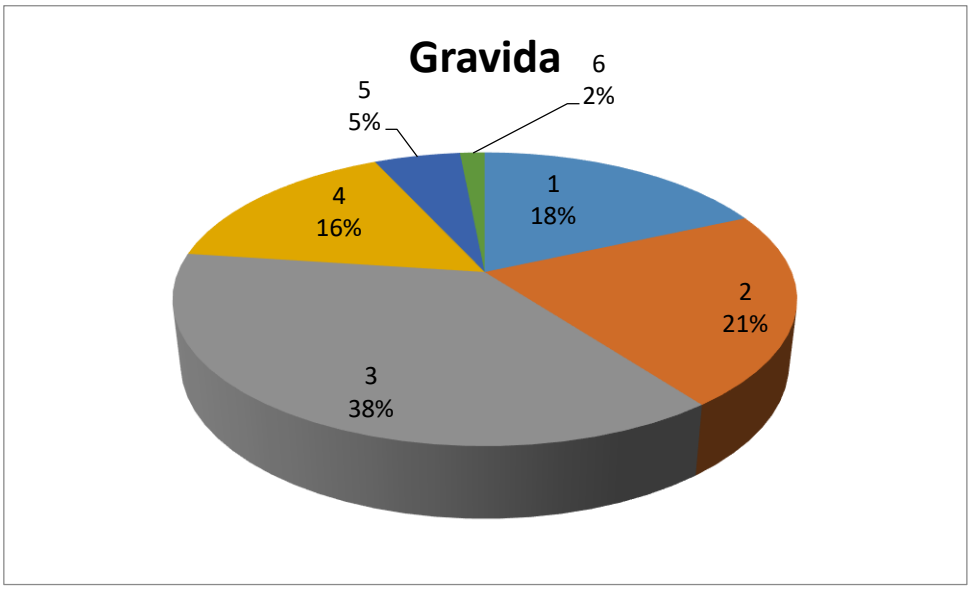

Table 4.11: demonstrate frequency of trimester of pregnancy

Trimester	Frequency
2nd	63
3rd	68
Total	131

Figure No. 4.6. : Pie chart demonstrates demonstrate frequency of trimester of pregnancy

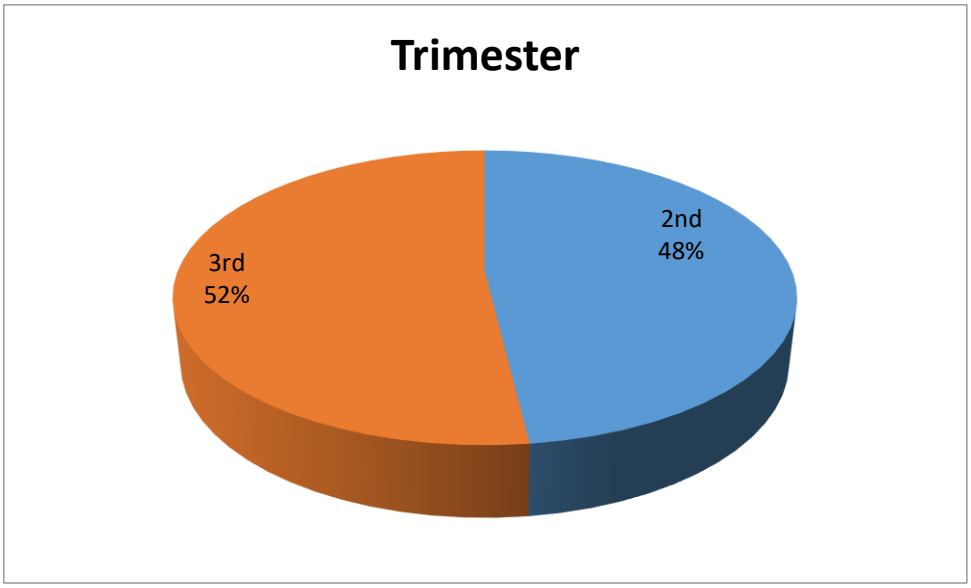

Table 4.12: demonstrate the frequency of the grade of steatosis

Steatosis grade	Frequency
Mild	89
Moderate	31
Sever	11
Total	131

Figure No. 4.7. : Pie chart demonstrates demonstrate the frequency of the grade of steatosis

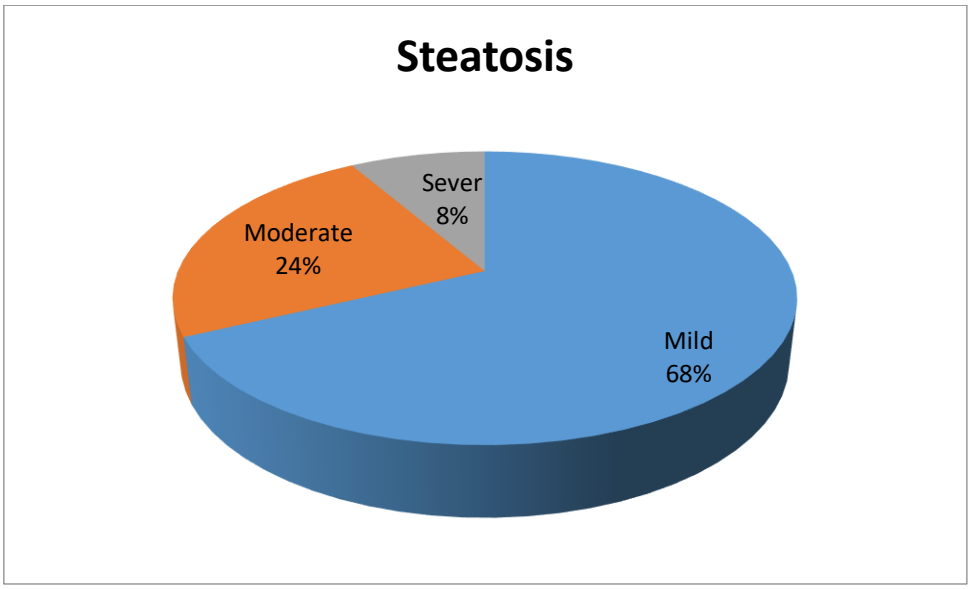

Table 4.13: frequency of diabetic patients

Diabetes	Frequency
Non diabetic	65
diabetic	66
Total	131

Figure No. 4.6. : Pie chart frequency of diabetic patients

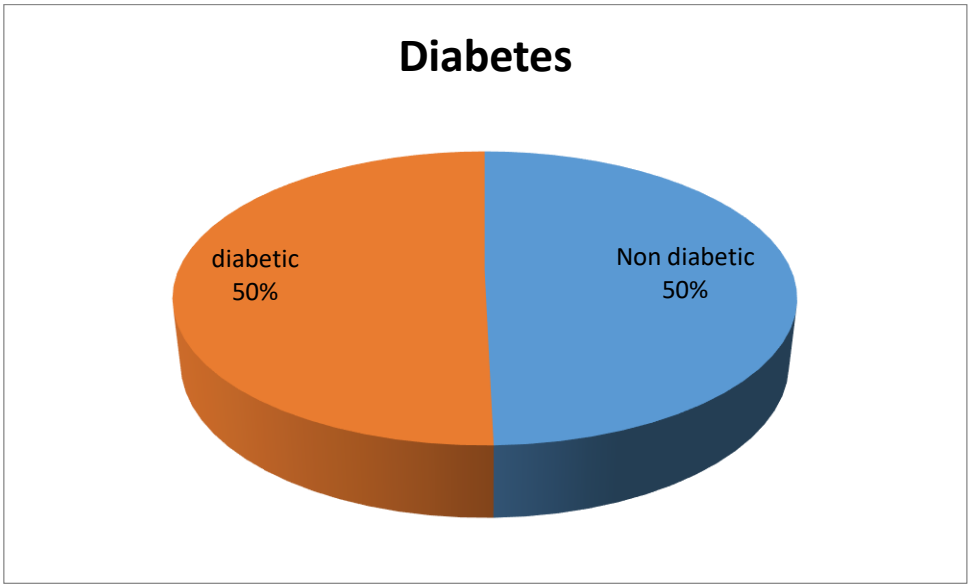

Table 4.14: Frequency of patient's with positive and negative family history of diabetes

Family history	Frequency
Negative	41
Positive	90
Total	131

Figure No. 4.8. : Pie chart demonstrate percentage of patient's with positive and negative family history

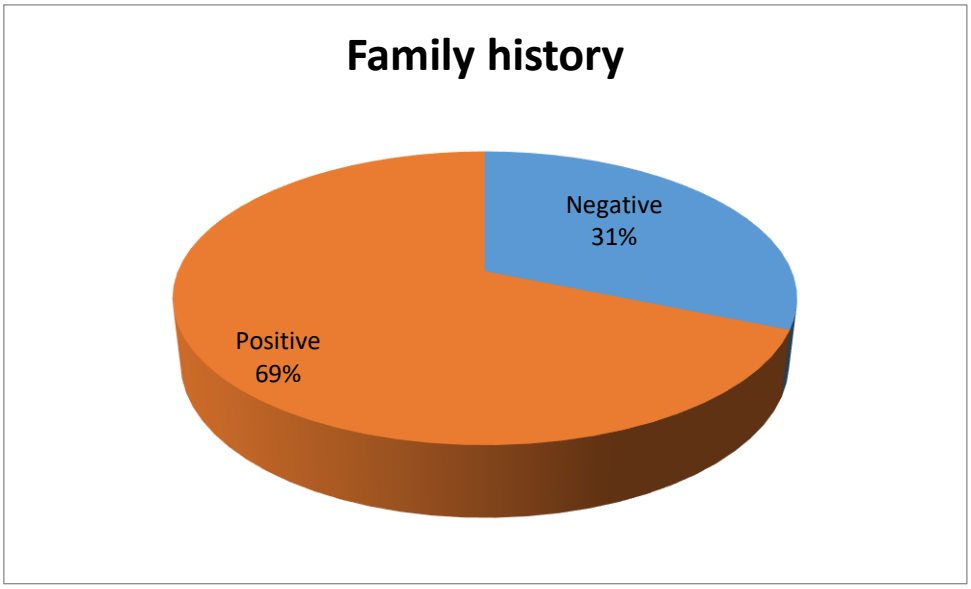

Table 4.16: demonstrate body characteristics

Body characteristics	Mean	STD	MIN	MAX
Age	30.511	7.1483	18.0	45.0
Weight	99.168	12.7498	76.0	130.0
Height	160.519	6.8829	146.0	176.0
BMI	38.375	4.3355	23.9	49.1

Table 4.17: demonstrate frequency of steatosis grades in each stage of pregnancy

		Steatosis grade			
		Mild	Moderate	Sever	Total
Trimester	2nd	40	15	8	63
	3rd	49	16	3	68
Total		89	31	11	131

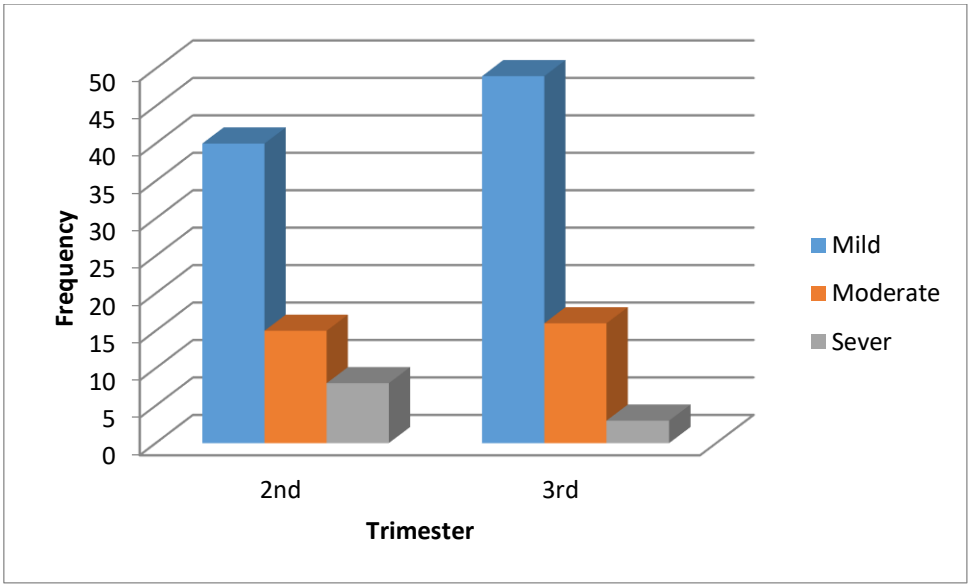

Figure No. 4.9. : BAR graph demonstrate frequency of steatosis grade with trimester

Chapter five

Discussion

The study was done on 131 pregnant mothers, between (18-45yrs old), 48% of them were in second trimester, and 52% were in the third trimester. The maximum height noted was 170cm, the maximum weight was 130kg and maximum BMI 49.1. 50% of them were diabetic and 50% were non diabetic, about 69% of the patients have positive family history of diabetes 68% of them show mild stage of liver steatosis, 24%show moderate stage, while 8% have severe stage of steatosis (Stages of steatosis described before in chapter two).

The total number of patients with mild hepatic steatosis was 89 patients, 40 of them were in the second trimester, and 49 of them were in the third trimester.

31 from the total number of the patients show moderate stage of steatosis, about 15 of them in the second trimester, while 16 of them were in the third trimester.

11patients of the total number have severe stage of steatosis, 8 of them in second trimester, while 3 of them in the third trimester of pregnancy.

The largest percentage of patients were in the first grade of steatosis, this could be attributed to their ages, as most of them in the young reproductive age, and the grade of steatosis is expected to increase with age.

By comparing correlations between the liver steatosis grade and fetal growth patterns in table (4.2, 4.5, and 4.8), there is a reversed proportional correlation between the grade of steatosis and the growth pattern. This phenomena is in line with the previous study number (2.4.2) mentioned in chapter two, which demonstrated a strong association between the presence of metabolic syndrome and presence of fetuses with SGA and MS.

In the same time it's not in line with the study number (2.4.4.) of Timothy p. et al. which didn't discover significant association between significant relationship between BMI and third-trimester fetal growth rate.

This indicates that, growth rate restriction is more associated with presence of metabolic syndrome or impaired liver function which may alter the maternal liver fuction and spontaneously the fetal circulation.

This obviously remarks the biological role of the liver and its metabolic processes in provision of healthy maternal and subsequently fetal circulation.

5.1 Conclusion:

Steatosis is an acquired, reversible disorder of metabolism, resulting in an accumulation of triglycerides within the hepatocytes. Most commonly associated with obesity. Maternal obesity can result in negative outcomes for both women and fetuses. The maternal risks during pregnancy include gestational diabetes and preeclampsia. The fetus is at risk for stillbirth and congenital anomalies. Obesity in pregnancy can also affect health later in life for both mother and child.

The study was done as case control study, on 131 pregnant mothers with high body mass index and liver steatosis, BMI was calculated using the weight and height of each mother from their initial records, and abdominal ultrasound scan was done to determine the grade of liver steatosis. After taking their fetal measurements during the routine pregnancy ultrasound scan, fetal measurements and weight were compared with the corresponding charts measurements calculated by LMP.

The higher frequency of patients noted in the first grade of liver steatosis.

While the lowest frequency was in the third grade, this could be due to difference in pregnancy stage distribution.

The frequency of patients with moderate grade of steatosis was relatively equal for both pregnancy stages included in the study.

The study showed a reversed proportional correlation between the grade of steatosis and the growth pattern, this is mostly attributed to the altered fetal circulation, due to impaired liver function.

Recommendations

Detailed monitoring of fetal growth rate during pregnancy and after birth growth rate and subsequent metabolic and hormonal changes monitoring, with accompanying special life style is recommended.

Mother's health is affecting the children health during and after pregnancy by direct and indirect ways so, more concern of mother health before, during, and after pregnancy and solutions for their health problems is highly recommended.

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