Laboratory evaluation of deranged liver chemistries in pregnancy

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Contributions: (I) Conception and design: H Goyal, A Perisetti; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Liver chemistries (LCs) serve as important noninvasive methods of assessing liver function, hepatocellular injury and cholestasis. In pregnant women, alterations in some LCs occur as a result of the normal physiologic changes of pregnancy. Despite this, majority of LCs including platelets, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, gamma-glutamyl transpeptidase (GGT) and lactate dehydrogenase (LDH), remain within normal limits throughout the course of pregnancy. On the contrary, levels of alpha fetoprotein (AFP) and alkaline phosphatase are expected to rise. Similarly, the coagulation system undergoes significant changes, increasing production of clotting factors and reducing native anticoagulants, all which act to induce a prothrombotic state in preparation for the blood loss associated with delivery. It is, therefore, important to distinguish between laboratory changes associated with normal physiological changes and liver diseases in pregnancy. Abnormal LCs occur at an overall rate of 3–5% in pregnant women. Detection of these abnormalities in LC's may indicate an underlying liver disease or disease process affecting the liver, which can have negative health implications for both the mother and unborn fetus. A classic approach to liver disease in pregnancy includes liver diseases that are unique to pregnant women, pre-existing liver diseases, and those emerging coincidentally during pregnancy. A variety of changes in LC's are observed in liver disease in pregnancy, each with a unique pattern of derangements. This review summarizes the differential diagnosis and approach consideration for presentation of deranged LCs in pregnant women, while giving special emphasis to laboratory investigations.

Keywords: Liver chemistries (LCs); liver function tests; pregnancy; liver diseases in pregnancy; abnormal liver function tests in pregnancy

Introduction

The liver plays a pivotal role in normal physiologic function, aiding in metabolism, detoxification, immune function, bile production and secretion, synthesis of albumin and clotting factors, storage of glycogen and minerals and more (1). Given the complex role of the liver, assessing and quantifying its function is an important but an arduous task. Several tests have been assembled to help monitoring liver synthetic function including albumin, prothrombin time (PT)/international normalized ratio (INR), platelet count, and evaluation of hepatocellular injury and cholestasis

Table 1 Changes of the normal liver function tests in pregnancy state

Parameter	Change observed in pregnancy
Alkaline phosphatase	Increase
Alpha-fetoprotein	Increase
Aspartate aminotransferase	Remain within normal limits
Total bilirubin	Remain within normal limits
Alanine aminotransferase	Remain within normal limits
Gamma-glutamyl transpeptidase	Remain within normal limits
Prothrombin time	Remain within normal limits
Activated partial thromboplastin time	Remain within normal limits
Thrombin time	Remain within normal limits
Serum albumin	Decrease
Total protein	Decrease
Serum bile acids	Remain within normal limits

by measurement of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, gamma-glutamyl transpeptidase (GGT) and lactate dehydrogenase (LDH) (2). All of these tests together have been arbitrarily defined as "liver chemistries" (LCs) (3). Abnormal levels of these tests may indicate an intrinsic hepatic or a systemic disease affecting the liver. In special populations such as pregnant women, liver diseases can have significant short- and long-term consequences on mother and fetus. Risks to the fetus are varied depending on the specific type of liver disease present. Short term consequences may include preterm delivery, placental insufficiency, nutritional deficits, fetal growth restriction, distress, bradycardia and meconium stained amniotic fluid, while long term risks include congenital malformations, stillbirth and fatality (4,5). Short term maternal consequences include infection, nutritional deficits, hemorrhage, placental abruption, acute kidney failure and subcapsular hematomas (5,6). Long term, maternal risks may be severe as neuroglial impairment, psychosocial stress, disease recurrence in subsequent pregnancies and mortality (7). Therefore, careful and considerate investigation of abnormal LCs in this patient population is paramount (8).

Anticipated changes in LCs in pregnant women

Despite physiologic changes, the majority of liver tests remain within normal limits throughout the course of pregnancy (*Table 1*). Generally, levels of maternal ALP are expected to increase secondary to excess secretion of ALP by the placenta as well as development of fetal bones. Similarly, levels of alpha fetoprotein (AFP) will also rise as a result of added production by the fetal liver (9).

In anticipation of hemorrhage after delivery, the maternal coagulation system undergoes changes to promote hemostasis. Therefore, there is an increase in clotting factors VII, VIII, IX, X, and fibrinogen (10). On the contrary, there is a decrease in serum albumin, total protein, and biological anticoagulants like protein S and antithrombin (11). However, coagulation related liver tests such as PT, activated partial thromboplastin time (aPTT), and thrombin time (TT), still tend to remain within normal limits in patients who do not have an underlying bleeding disorder. Similarly, AST, ALT, bilirubin, and GGT remain normal throughout pregnancy (11). As such, any abnormal presentation of these labs warrants additional investigation.

Abnormal liver test

While there are expected laboratory changes in pregnant women, some may also present with unanticipated changes in LCs, which may indicate a disease process involving the liver (*Table 2*). Abnormal LCs occur at a rate of 3–5% in pregnant women (12). Detection of abnormal levels of AST, ALT, GGT, and/or bilirubin require further evaluation.

Liver diseases in pregnancy

Liver diseases in pregnancy can be divided into three main categories: (I) liver diseases that are caused by physiologic changes of pregnancy, (II) liver diseases that have developed coincidentally during the course of pregnancy and (III) liver diseases that are chronic or pre-existing prior to pregnancy (*Table 3*, *Figure 1*).

Liver disorders induced by pregnancy

A number of diseases that affect the liver during pregnancy occur as a result of the physiologic changes in pregnancy. When severe, the fetus and mother can experience significant morbidity and mortality (13).

Table 2 Trends in liver chemistries seen in liver disease in pregnancy

	ALT	AST	ALP	Platelets	Albumin	GGT	PT	Bilirubin
Liver disorders induced by pregnancy								
Hyperemesis gravidarum	↑	↔	↔	↔	↔	↔	↔	↔
Pre-eclampsia	↑	↑	↔	↔	↔	↔	↔	↔
Eclampsia	↑	↑	↔	↔	↔	↔	↔	↔
Acute fatty liver of pregnancy	↑	↑	↔	↔	↔	↔	↑	↑
Hemolysis, elevated liver test and low platelets (HELLP)	↑	↑	↔	↓	↔	↔	↔	↑
Liver rupture	↑	↑	↔	↔	↔	↔	↔	↔
Intrahepatic cholestasis of pregnancy	↑	↑	↑	↔	↔	↑	↔	↔
Liver disease emerging coincidentally during pregnancy								
Viral hepatitis	↑	↑	↔	↔	↔	↔	↔	↔
Herpes simplex	↑	↑	↔	↓	↔	↔	↔	↔
Budd-Chiari syndrome	↔	↔	↔	↔	↔	↔	↔	↔
Cholelithiasis	↔	↔	↔	↔	↔	↔	↔	↔
Pregnancy with pre-existing liver disease								
Cirrhosis of liver/portal hypertension	↑	↑	↑	↔	↔	↑	↔	↔
Primary sclerosing cholangitis	↑	↑	↑	↔	↔	↔	↔	↔
Chronic active hepatitis	↑	↔	↔	↔	↔	↔	↔	↔
Primary biliary cholangitis	↔	↔	↑	↔	↔	↑	↔	↔
Autoimmune hepatitis	↑	↑	↔	↔	↔	↔	↔	↔
Wilson's disease	↑	↑	↓	↓	↔	↔	↔	↔

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; PT, prothrombin time. ↑ increase, ↓ decrease, ↔ remains the same.

Table 3 Categories of liver diseases in pregnancy

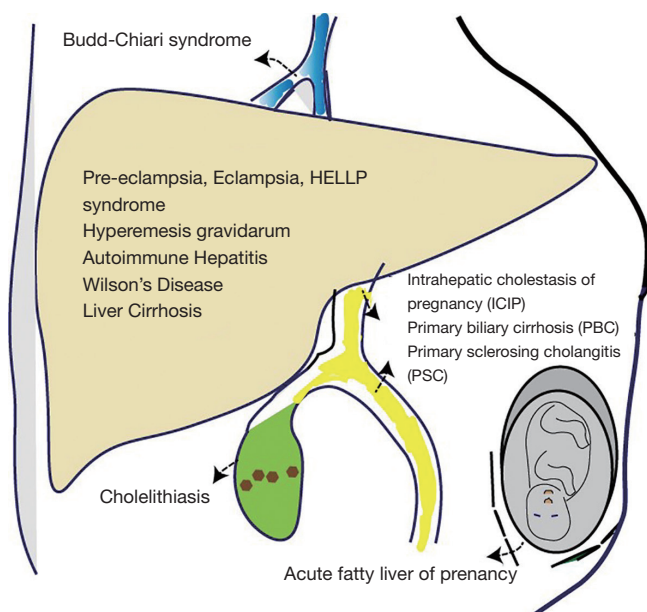| Induced by pregnancy	Preexisting worsened by pregnancy	Emerging coincidental with pregnancy
Hyperemesis gravidarum	Chronic hepatitis B virus	Acute viral hepatitis
Pre-eclampsia	Chronic hepatitis C virus	Cholelithiasis
Eclampsia	Wilson's disease	Budd-Chiari syndrome
HELLP syndrome	Liver cirrhosis/portal hypertension	Drug induced liver injury
Acute fatty liver of pregnancy	Autoimmune hepatitis	Hepatic tumor
Intrahepatic cholestasis of pregnancy	Primary sclerosing cholangitis	
Liver rupture/infarction	Primary biliary cholangitis	

Figure 1 Hepatic disease in pregnancy (schematic).

Hyperemesis gravidarum (HG)

During the first trimester, approximately 0.3–3% of pregnant women can experience HG, characterized by severe, intractable nausea and vomiting, and subsequent dehydration, volume depletion and weight loss. Laboratory values that aid in the diagnosis include serum electrolytes, complete blood count, LCs, amylase, lipase, urinalysis, creatinine, blood urea nitrogen, thyroid function tests and beta-human chorionic gonadotropin (hCG) (14). Commonly, lab abnormalities present in HG include decreases serum electrolytes (primarily potassium, sodium, and chloride). An elevated hematocrit can also be seen due to a fluid volume contraction. Laboratory examination can also demonstrate an increase in the urinary ketones, specific gravity, and blood urea nitrogen. Additionally, hCG and thyroxine, have been shown to increase with the severity of HG, while thyroid stimulating hormone decreases (15,16). Pertaining to LCs, an increase of ALT of up to two to five times the upper limit of normal can occur, while bilirubin levels tend to remain unchanged (17).

Pre-eclampsia, eclampsia, HELLP syndrome

Previously normotensive pregnant patients can develop hypertension (HTN) and experience hypertension-related liver disorders, which include pre-eclampsia, eclampsia, and hemolysis, elevated liver test and low platelets (HELLP) syndrome. Pre-eclampsia, which occurs in nearly 3–5%

of pregnant patients, is a maternal multisystemic organ dysfunction disorder associated with new-onset HTN occurring beyond the 20th gestational week in a patient with no prior history of HTN, and greater than 300 mg of proteinuria within 24 hours (18). Eclampsia presents with the same criteria, with the only additional distinguishing feature of seizures. Associated LC abnormalities in patients with pre-eclampsia include elevated AST and ALT (in about 30% of patients) and mild increase in bilirubin. HELLP syndrome occurs in up to 0.8% of pregnant patients and represents a more severe form of pre-eclampsia. HELLP syndrome constitutes an increase in bilirubin, AST and ALT (200–700 IU/L range), and LDH (>600 IU/L) including thrombocytopenia (<100 K/ L platelets) (19).

Liver rupture and infarction

A rare, but potentially fatal complication on the spectrum of eclampsia includes liver hemorrhage or rupture which is associated with up to 50% mortality. Patients usually present with severe abdominal pain, fever, and other symptoms related to HELLP. LCs are notable for significantly elevated AST and ALT (typically greater than 1,000 U/L), anemia, and leukocytosis (20).

Acute fatty liver of pregnancy (AFLP)

AFLP is development of sudden microvascular steatosis hepatic cells that's leads to liver failure and usually occur in the late stages of pregnancy. AFLP can lead to fatality of both mother and fetus if left untreated (5). Several LC derangements are recognized in AFLP including significantly elevated levels of AST and ALT (up to 1,000 IU) and bilirubin (usually does not exceed 0.0855 mmol/L), in addition to prolonged PT and decreased fibrinogen. Other laboratory abnormalities include elevations in levels of lactic acid, ammonia, and amino acids, which indicates hepatic mitochondrial failure. Patients may also present with thrombocytopenia, leukocytosis, and severe renal dysfunction (13).

Intrahepatic cholestasis of pregnancy (ICP)

ICP is the most common pregnancy-related liver disorder. It is a reversible cholestatic disorder presenting with pruritus on the soles of feet and palms of the hand with spontaneous relief within 6 weeks of delivery (21). Serum bilirubin levels are rarely elevated and measuring serum bile acids is the most effective biochemical test to diagnose ICP. There is a correlation between the level of maternal bile acids and the risk of fetal harm. In ICP, levels of total

serum bile acids are typically elevated by 1.5–15 times. Levels exceeding 40 µmol/L have been associated with unfavorable effects on the fetus (22). Serum AST and ALT can also be elevated (typically increased by 1.5 to 10 times) with variable levels of ALP and GGT (22,23). Similarly, PT typically remains normal, but can be prolonged in cases of vitamin K malabsorption (22).

Liver disease emerging coincidentally during pregnancy

Acute hepatitis

Acute viral hepatitis can be acquired during the course of pregnancy. Acute hepatitis as a result of hepatitis A, B, C, D, and E, cytomegalovirus (CMV), Epstein-Barr virus (EBV) and herpes simplex virus (HSV) are collectively responsible for about 40% of cases of jaundice in pregnant women. Infection with hepatitis A, B, C, or D during pregnancy has little to no risk of fetal or maternal mortality or teratogenicity (24). On the other hand, pregnant women who acquire hepatitis E virus are at increased risks of developing fulminant hepatitis failure. Laboratory analysis most notably reveals an acute increase in ALT, AST, and bilirubin (25).

HSV

HSV is a rare but serious cause of acute hepatitis in pregnant women, with an estimated mortality rate of 40%. The clinical presentation is often vague and nonspecific. LC values that may aid in diagnosis include coagulopathy, thrombocytopenia and increased levels of aminotransferases, while bilirubin tends to remain normal (26).

Budd-Chiari syndrome (BCS)

The physiologic changes in pregnancy increase levels of certain coagulation factors inducing a hypercoagulable state. As a result, thrombophilic vascular diseases can occur at increased frequency. BCS is a rare disorder that results from outflow obstruction of the hepatic venous system secondary to hepatic vein thrombosis. This leads to sinusoidal congestion, ischemic liver injury, and portal hypertension. One out of five cases of BCS occur in women who are pregnant, have a recent history of pregnancy, or have a history of contraceptive use (27). The clinical presentation typically includes right upper quadrant pain, jaundice, hepatomegaly, and ascites. LCs do not typically aid in the diagnosis, as doppler ultrasound is needed to demonstrate venous outflow obstruction (28). However, these patients can have increased levels of clotting factors (I, II, V, VII, X and XII) along with fibrinogen levels and physiologic reduction of anticoagulant protein C concentration.

Cholelithiasis

Pregnant patients are at higher risk of development of gall stones due to deceased gallbladder motility and increased cholesterol secretion due to increase in estrogen and progesterone. Symptomatic gallstone disease during pregnancy has been associated with increased risk of maternal and fetal morbidity, as well as preterm birth (29). Therefore, making a diagnosis is essential. Any elevations in the LCs warrant additional investigation for other causes of acute abdominal pain including choledocholithiasis, acute cholecystitis, gallstone pancreatitis, acute cholangitis, gallstone ileus and more (30).

Drug induced liver injury (DILI)

Obtaining a thorough history of medication use is essential to determining causes of DILI, in addition to review of laboratory values. Patients with hepatocellular injury will have elevated aminotransferases with emphasis on ALT sometimes as high as 25 times the normal limit. Contrarily, patients with cholestatic injury will primarily have a significant rise in ALP that is at least twice the normal limit. Increased levels of bilirubin can be seen in cholestatic and hepatocellular injury and should be considered significant when total bilirubin values are higher than twice the normal limit in conjunction with an increased ALP or ALT (31,32).

Pregnancy with pre-existing liver disease

Pregnancy can also occur in women with pre-existing liver pathology. The most common chronic liver disorder in pregnant women is chronic viral hepatitis which requires diligent monitoring throughout the course of pregnancy and delivery.

Chronic viral hepatitis

Pregnant patients with pre-existing chronic hepatitis B (HBV) or hepatitis C (HCV) infection typically have an uneventful course of pregnancy, with minimal effect on existing liver disease in noncirrhotic patients. The primary concerns in these patients are prevention of vertical transmission and flare of chronic hepatitis, especially in endemic areas. As described earlier, the shift in immunological factors during pregnancy seemingly downregulate the maternal immune system to tolerate the genetically variable tissues between mother and fetus better.

This altered immune status can potentially predispose patients to hepatitis flares by HBV or HCV viremia (33). Laboratory analysis in HBV typically show a rise in ALT that is at least three times the upper limit of normal limits, and hepatitis B surface antigen is present for at least six months duration (34). In chronically infected HCV patients, levels of ALT decrease in the later stages of pregnancy, with a return to baseline following delivery (35).

Autoimmune hepatitis (AIH)

AIH is a chronic inflammatory liver disorder with a predilection towards women. In pregnant patients with AIH, there is an increased risk of premature birth, low birth weight, and fetal demise (36). Because of immunological nature of AIH, the diagnosis is typically based on the clinical, serological, and histological data. Most studies describe elevated levels of ALT and AST, in addition to low complement C4 levels. Additionally, hypergammaglobulinemia (IgG) as well as increase in the autoantibodies aid in diagnosis. Testing for autoantibodies such as serum anti-nuclear, anti-mitochondrial, anti-smooth muscle, and anti-liver/kidney microsomal-1 antibodies is recommended in patients with suggestive clinical features. Lastly, liver biopsy can also aid in confirming the diagnosis although it is not always required (37).

Primary biliary cholangitis (PBC)

PBC is a T-cell immune-mediated disease of the small intralobular bile ducts with a predilection for women. Though post-menopausal women are typically affected, up to 25% of women of childbearing age can also be affected (38). Little data exists regarding changes in disease course and maternal and fetal outcomes in patients with PBC. However, existing studies have reported significantly elevated ALP and GGT values with presence of positive antimitochondrial and antinuclear antibodies. Additionally, liver transaminases may be mildly abnormal, but are typically normal. Lastly, bilirubin levels can increase significantly which are indicative of poor prognosis (39).

Primary sclerosing cholangitis (PSC)

PSC is an idiopathic disorder characterized by chronic inflammation and fibrosis of intrahepatic and extrahepatic bile ducts resulting in alternating ductal strictures and dilation. The clinical presentation typically includes right upper quadrant abdominal tenderness, weight loss, fatigue, and pruritus (40). Up to 70% of diagnosed patients are male. However, women can also be affected and the development of PSC may be influenced by pregnancy. Data is scarce, but there are some reported cases of PSC in pregnancy (41). Laboratory values show an increase in the levels of ALP, AST, ALT, serum IgG as well as magnetic resonance cholangiographic evidence of multifocal biliary tree strictures. Bilirubin levels tend to remain within the normal limits at diagnosis (42,43).

Wilson's disease (WD)

WD disorder is characterized by the accumulation of copper primarily in the liver and brain as a result of defective biliary copper excretion related to mutations in the *ATP7B* gene. The data on pregnancy outcomes in patients with WD is scant, with only a few cases reporting a mix of successful and complicated outcomes (44). Clinical presentation varies, but commonly includes acute or chronic liver failure with or without neuropsychiatric decline. Laboratory abnormalities typically include elevated bilirubin, increased AST and ALT, Coombs-negative hemolytic anemia, and low serum ALP. When severe enough to cause liver failure, laboratory abnormalities in WD reveal an AST/ALT ratio often greater than two. Other labs noted include decreased levels of serum ceruloplasmin and platelets, as well as vitamin k refractory coagulopathy (45).

Cirrhosis of liver/portal hypertension

In women with pre-existing liver cirrhosis, pregnancy is rare due to irregular estrogen metabolism in combination with disturbances in the hypothalamic-pituitary axis that lead to anovulation and infertility (46). When pregnancy does occur, fetal risks include prematurity, spontaneous abortion, and stillbirth. The patient can present with laboratory abnormalities such as increased AST and ALT, with variable elevations in GGT and ALP (47). Bilirubin tends to remain unchanged. As synthetic function declines, the patient can also present with low levels albumin. In advanced fibrosis, laboratory changes include thrombocytopenia, anemia, and leukopenia (48).

Conclusions

In conclusion, liver diseases in pregnancy can be potentially harmful to both mother and fetus. Pregnant patients who present with jaundice or abnormal LCs require laboratory investigations to prevent potential complications. As in any patient, a comprehensive history and physical examination should be performed, in addition to collection of appropriate labs (*Figure 2*). Deranged LCs in pregnant
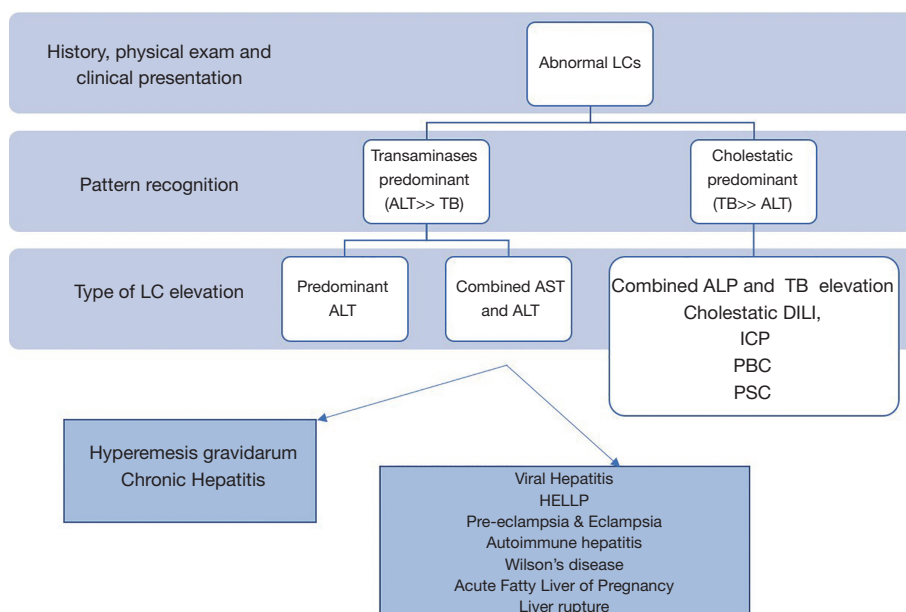
Figure 2 Approach to the abnormal liver chemistries in pregnancy. LC, liver chemistry; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; DILI, drug induced liver injury; ICP, intrahepatic cholestasis of pregnancy; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; TB, total bilirubin; HELLP, hemolysis, elevated liver test and low platelets syndrome.

patients should be interpreted in the appropriate clinical context and further work should be performed for any deviation from laboratory changes that occur as a natural response to the state of pregnancy.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Giuseppe Lippi, Martina Montagnana and Zhi-De Hu) for the series "Laboratory Medicine in Pregnancy" published in *Journal of Laboratory and Precision Medicine*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jlpm.2019.10.05). The series "Laboratory Medicine in Pregnancy" was commissioned by the editorial office without any funding or sponsorship. Hemant Goyal serves as an unpaid editorial board member of *Journal of Laboratory and Precision Medicine* from May 2019 to April 2021. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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