# JAUNDICE IN PREGNANCY

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# Introduction

Liver disease is a rare complication of pregnancy, but when it occurs it may do so in a dramatic and tragic fashion for both mother and infant. Diseases such as acute fatty liver of pregnancy (AFLP) may begin innocuously with mild symptoms and liver enzyme abnormalities but, if left untreated, can progress to jaundice, liver failure, and death.

(Bacq & Riely , 2004)

- Some of the normal physiologic changes of pregnancy can mimic abnormalities associated with liver disease.
- Telangiectasia, particularly on the chest, back, and face, and palmer erythema occur in up to 60 percent of normal pregnant women but disappear after delivery.

(Riely, 2001)

Extreme vigilance is needed to detect early signs and symptoms of liver dysfunction and to distinguish these from the anticipated benign hepatic changes of pregnancy. Prompt management can save the life of the mother and the baby. Management of liver disease in pregnancy requires a concerted effort between the primary care physician, liver specialist, obstetrician, and, on rare occasions, a liver transplant team.

(Moskovitz et al., 2004)

# Anatomical, Physiological, and Biochemical changes during pregnancy.

# Anatomic Changes:

- Liver weight increases during pregnancy has not been documented. Liver size is difficult to estimate in pregnancy, but records fail to show any substantial increase in liver weight in comparison with nonpregnant controls.

- Therefore, detection of hepatomegaly is strong evidence for the presence of liver disease.

(Fagan, 1986)

# Physiology

- Hepatic blood flow is maintained at a constant rate in pregnancy despite marked changes in the cardiovascular system.
- Blood flow increases to the kidneys and other organs, but hepatic blood flow is unaltered, which results in a decline of approximately 35% in the proportion of cardiac output delivered to the liver.

(Fagan, 1986)

# Biochemical changes during pregnancy

- The total serum protein concentration declines approximately 20% in midpregnancy, primarily a result of the substantial decline in serum albumin which may be attributed to simple dilution caused by the increase in total blood volume, although most other serum proteins either remain unchanged or increase in concentration.

(Maher et al., 1993)

- A significant rise in serum fibrinogen regularly accompanies pregnancy. As a consequence of increase fibrinogen synthesis.
- Other coagulation proteins, including factors VII, VIII, IX, and X, may be increased during pregnancy or after estrogen treatment.

(Steingrub, 2005)

- Most studies have failed to document significant bilirubin Elevation in the absence of specific cause during normal pregnancy. Therefore, an increased serum bilirubin level in pregnancy should be considered presumptive evidence for the presence of liver or hematologic disease.

(Steingrub, 2004)

- Alkaline phosphatase activity is increased during the third trimester both because of leakage of placental alkaline phosphatase into the maternal circulation and because of increased maternal bone turnover.

(Riely, 1999)

Serum bile acid level is quite helpful in any form of cholestasis. The serum level is normal in normal pregnancy.

Levels of serum aminotransferase-aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are normal in normal pregnancy. Therefore, these two serum enzyme determinations remain sensitive indicators of liver damage during pregnancy. The ALT is especially useful, because significant elevation of this enzyme does not occur with injury to tissues other than liver.

(Bacq et al., 2004)

# Summary of physiological changes in the liver during pregnancy

- **Increased:**
- Blood volume and cardiac ouput rise by 35%–50%
- Alkaline phosphatase levels rise threefold or fourfold due to
- placental production
- Clotting factor changes create a hypercoagulable state
- **Decreased:**
- Gallbladder contractility
- Hemoglobin
- Uric acid levels
- Albumin, total protein, and antithrombin III concentrations
- **No change:**
- Liver aminotransferase levels (aspartate aminotransferase,
- alanine aminotransferase, gamma-glutamyl transferase)
- Bilirubin level
- Prothrombin time

# Spectrum of liver diseases in pregnancy

(Fleming & Zein, 2005)

- **Preexistent liver diseases**
  - Portal hypertension, cirrhosis, primary biliary cirrhosis
  - Autoimmune hepatitis
  - Wilson disease
  - Chronic infection with hepatitis B or hepatitis C virus
  - Alcoholic liver disease

- **Liver diseases coincidental with but not induced by pregnancy**
  - Acute viral hepatitis and other viral infections
  - Alcohol-related diseases
  - Gallstone disease
  - Budd-Chiari syndrome

- **Liver diseases induced by pregnancy**
  - First trimester
    - Hyperemesis gravidarum
  - Second and third trimesters
    - Intrahepatic cholestasis of pregnancy
    - Preeclampsia, eclampsia, and the HELLP syndrome
    - (hemolysis, elevated liver enzymes, low platelet counts)
    - Acute fatty liver of pregnancy

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# Hyperemesis Gravidarum

- Hyperemesis gravidarum can be defined as excessive nausea and vomiting in pregnancy that result in dehy-dration and ketosis, severe enough to necessitate hospitalization. Although this is not primarily a liver disorder, it affects the liver in up to 50% of patients.

(Jeffrey et al., 2003)

- The origin of the liver disease associated with hyperemesis gravidarum is unclear. Not all affected patients have liver disease; therefore, the vomiting does not appear to be secondary to the liver involvement. Starvation alone does not seem to be an adequate explanation for the liver dysfunction, particularly in as much as biopsy in affected patients fails to show the fatty infiltration typical of starvation.

(Mazzotta & Magee, 2000)

- Factors thought to favor an increased risk for hyperemesis gravidarum include obesity, nulliparity, and twin gestation.

(Goodwin, 1998)

- Affected patients present in the first trimester, usually by weeks 10 to 12. They have persistent nausea and vomiting and experience weight loss, often of significant amounts. They also have ptyalism (excessive spitting).

(Lammert et al., 2000)

- Laboratory testing demonstrates abnormal liver values in up to 50% of affected patients; the most sensitive test is the ALT, which may rise as high as 1000 U.
- Severely affected patients also have elevations in bilirubin.

(Jeffrey et al., 2003)

Improvement in the nausea and vomiting and resolution of the liver test abnormalities occur when most affected patients are given intravenous fluids and put to gut rest. Antiemetic therapy is helpful. Corticosteroid therapy has been reported with success. Patients affected with hyperemesis gravidarum have no increased rate of prematurity, infants with low birth weight, or infants with birth defects. (Tsang et al., 1996)

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# Intrahepatic Cholestasis of Pregnancy

- The syndrome has been variously called recurrent jaundice of pregnancy, cholestatic jaundice of pregnancy, jaundice of late pregnancy, and hepatosis of pregnancy. ICP, however, is the preferred term, because jaundice is inconstant in any type of cholestatic disorder.

(Gonzalez-Peralva et al., 1996)

- The frequency of ICP is clearly higher among certain ethnic groups, including Scandinavians and Chileans. In the latter group, ICP may appear in 2.4% or more of pregnan-cies, the highest reported incidence in the world. The incidence is quite high (20.9%) in twin pregnancies.
- Several studies have demonstrated a familial and genetic predisposition to the syndrome in Sweden, Chile, and the United States.

(Lammert, et al., 2000)

## Clinical Description

Pruritus is the dominant and initial symptom and appears in the third trimester in more than 70% of cases. Most of the remaining patients date their onset of symptoms to the second trimester.

The symptom may become very severe and usually involves the trunk and the extremities, including the palms and the soles of the feet. As a result of the pru-ritus, insomnia, fatigue, and even mental disturbances have been reported

(Milkiewicz et al., 2002)

Many patients report the appearance of dark urine without frank jaundice shortly after the onset of pruritus. Only a minority of patients develop obvious jaundice, and this is usually mild.

It is notable that abdominal pain, biliary colic, fever, anorexia, nausea, vomiting, and arthralgias are absent.

(Milkiewicz et al., 2002)

- The improvement in both pruritus and jaundice begins to occur quite promptly after delivery, most often within 24 hours. However, jaundice may continue for several days after delivery, and some of the abnormal chemistry profiles persist for as long as several months.
- Subsequent pregnancies are frequently accompanied by recurrences of the syndrome.

(Mazella et al., 2001)

# Biochemical Changes

| CLINICAL FEATURES | BIOCHEMICAL CHANGES | |
|---|---|---|
| Pruritus | Serum bile acid | 10-to 100 fold |
| Jaundice* | Alkaline Phosphatase | 7- to 10 fold ↑ |
| No Anorexia or malasie | 5' Nucleotidase | Two Folds↑ |
| 2nd or 3rd trimester onset* | GGTP | Normal to slight ↑ |
| Recurrent* | Bilirubin (total) | Normal to 5 mg/dL |
| Familial* | AST/ALT | ↑↑ |
| | Prothrombin time | Normal to twofolds↑ |
| | Cholesterol | Two to Fourfolds ↑ |
| | Triglyceride | Normal to twofolds ↑ |

*These clinical features are not invariably present. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGTP, γ-glutamyl-transpeptidase. ↑, increase.

# Effects on the Mother

- Although earlier reports suggested that the only effect of ICP on the mother was related to the discomfort of pruritus, more recent studies have suggested more serious compli-cations. These include an increased risk of postpartum hemorrhage, especially in those given cholestyramine, and an increased risk for the development of gallstones after pregnancy.

(Glantz, et al., 2005)

# Effects on the Fetus

- The implications of ICP for the fetus are considerably more ominous. An increased incidence of prematurity and fetal death has been reported in several studies. Fetal distress is reported in one third of patients, leading to cesarean section in 30% to 60% of cases and prematurity in over 50% in some series. Stillbirths are recorded in more than 9%. These outcomes are more likely if the disorder begins earlier in pregnancy. Thus, ICP very clearly increases the risks to the fetus.

(Glantz, et al., 2004)

# Treatment

- Therapy is directed at alleviating pruritus in the mother. Ursodeoxycholic acid has been used successfully in the treatment of cholestasis in other settings, most prominently primary biliary cirrhosis. Improvement in both liver function test results and the symptom of pruritus has been documented in women with ICP treated with a standard 15-mg/kg/day dosage. A larger dosage, 20 to 25 mg/kg/day has been shown to be effective with no adverse affects on either mother or baby.

(Mazella et al., 2001)

- Phenobarbital in a dosage of 100 mg/day has been reported to be effective in approximately 50% of patients. Cholestyramine may be somewhat effective and is usually given in a dosage of 4 g four or five times per day.
- Cholestyramine may worsen the malabsorption of fats and fat-soluble vitamins. Therefore, the prothrombin time must be monitored in patients treated with this regimen, and parenteral vitamin K should be given before delivery.

(Eloranta et al., 2002)

- Intravenous or oral S'-adenosyl-1.-methionine has been reported to lead to a significant improvement in pruritus and in serum transaminase and bilirubin levels, perhaps by reducing the negative effects of estrogens on bile secretion.

(Frezza et al., 1999)

- Some investigators recommend elective induction at 38 weeks or as early as 36 weeks in the presence of jaundice or if the fetus's lungs have matured.

(Rioseco et al., 1994)

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# Preeclampsia and eclampsia

- Preeclampsia affects up to 5% to 10% of pregnancies, usually occurring in the late second and third trimesters and less frequently occurring before 20 weeks' gestation. Preeclampsia commonly occurs in nulliparous women or multiparous women who are nonwhite; are older than 34; or have new partners, past or current history of hypertension, or previous postpartum hemorrhage.

(Benedetto et al., 2002)

- The disease is characterized by a triad of hypertension, proteinuria, and peripheral edema, and hypertension and proteinuria characteristically regress after delivery. Eclampsia is characterized by seizures, coma, and other signs of preeclampsia, including hypereflexia, funduscopic changes in severe cases, cerebral edema, hepatic infarction, acute renal failure, congestive heart failure, and acute respiratory distress syndrome.

(von Dadelszen et al., 2000)

# Pathophysiology

- A uteroplacental mismatch, whereby the demands of the fetal placenta exceeds the maternal circulatory supply leads to placenta hypoperfusion, local hypoxia, endothelial cell dysfunction, abnormal expression of inflammatory mediators, alteration of vasomotor tone, and activation of the coagulation cascade.

(Sawhney et al., 2000)

# Clinical manifestations

- The clinical course of preeclampsia includes nausea, vomiting, and epigastric pain and is associated with elevated levels of LDH, alkaline phosphatase, AST, ALT, and uric acid. The level of uric acid is an excellent marker for assessing disease severity and progression. Liver function tests are abnormal in 20% to 30% of patients with preeclampsia and may be attributed to vasoconstriction of the hepatic vascular bed.

(Maki et al., 2000)

- The maternal mortality rate is less than 1% at institutions with special skills in treating preeclampsia. Approximately 80% of maternal deaths are attributed to central nervous system complications, usually cerebral edema. Hepatic complications, including sub-capsular hematoma and rupture, infarction, and hepatic failure, account for the remaining causes of mortality.

(Rolfes & Ishak, 1986)

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# HELLP Syndrome

- The HELLP syndrome is a multi-system disease variant of severe preeclampsia that is characterized by microangiopathic hemolytic anemia (MAH), hepatic dysfunction (hepatic necrosis), thrombocytopenia (platelet count, <100,000/ mm3), and, in the syndrome's most severe form, DIC.

- HELLP syndrome is more common among older multiparous women.
- HELLP syndrome affects up to 20% of pregnancies involving severe preeclampsia.
- Although up to 11% of the cases occur before 27 weeks of gestation, most cases (70%) occur between 27 and 36 weeks of gestation and about a third occur after delivery. Exacerbations may occur after delivery, followed by recovery within 72 hours.

(Martin et al., 1999)

# Clinical manifestations

- Several conditions mirror HELLP syndrome, and timing of illness and findings may assist in differentiating HELLP syndrome from other diseases.

(Winbery & Blaho., 2001)

# differential diagnosis of HELLP syndrome

| Thrombotic coagulopathies | Consumptive disorders | Miscellaneous |
|---|---|---|
| Hemolytic uremic syndrome<br>Thrombotic thrombocytopenia purpura<br>Drug-induced hemolytic anemia<br>Sepsis<br>DIC | AFLP<br>Sepsis<br>DIC<br>Abruptio placentae<br>Amniotic fluid embolism | Systemic lupus<br>Antiphospholipid syndrome<br>Cholecystitis<br>Appendicitis |

- Frequent presenting symptoms include nausea, malaise, epigastric or right upper quadrant abdominal pain (65%–90% of cases), and edema. In a large series, HELLP syndrome was observed with DIC (21% of patients), abruption placenta (16%), acute renal failure (8%), and pulmonary edema (6%). The maternal mortality rate is approximately 1% to 4%, and the perinatal mortality rate ranges from 10% to 20%, depending on gestational age and severity of the condition at the time of delivery.

(Sibai et al., 1993)

Maternal morbidity in HELLP syndrome can be classified into the following four categories (in decreasing order of frequency)

- Coagulation disorders associated with hemorrhagic complications,
- Cardiopulmonary dysfunction,
- Central nervous system disorder and
- Hepatic or gastrointestinal dysfunction.

(Isler et al., 1999)

- Women with HELLP syndrome should be considered to be at increased risk for obstetrical complications in subsequent pregnancies (preterm deliveries, IUGR, abruption-placenta), and the risk for recurrence ranges from 4% to 25% . Infants born to mothers with HELLP syndrome are at risk for thrombocytopenia.

(Sibai et al., 1995)

# Laboratory investigation

Risk factors for HELLP syndrome include the following:

- LDH level, > 1400 IU/L
- AST level, > 150 IU/L
- ALT level, > 100 IU/L
- Platelet count, < 50,000/mm3
- Uric acid level, > 7.8 mg/dL
- Creatinine level, > 1.0
- Creatine phosphokinase level, > 200 IU/L

# Liver function

- Patients usually are not jaundiced. Total bilirubin concentration rarely exceeds 1 to 2 mg.
- HELLP syndrome rarely leads to subcapsular hemorrhage; hepatic rupture often leads to death of the mother and fetus. Typically, these patients present with shock and hemoperitoneum. The condition also may manifest hepatic infarcts with associated fevers, high levels of aminotranferase (N5000 IU/L), and anemia.

(Krueger et al., 1995)

# Therapy and outcome

- The maternal morbidity rate has been reported to be as high as 24%, but it ranges between 1% to 4% in optimal medical environments. In patients who died, the mean gestational age was 31 weeks, and death was attributed to sepsis, hemorrhagic shock, intracerebral insults, and cardiac pulmonary failure. Investigators found 16% maternal death rate attributed to hepatic complications.

(Martin et al., 1999)

- The neonatal mortality rate associated with HELLP syndrome (10%–20%) has been attributed to placenta ischemia leading to abruption, extreme prematurity, and intrauterine asphyxia. Factors associated with perinatal survival in preterm pregnancies with HELLP syndrome include achievement of a birth weight of at least 600g, elapsed time of 48 hours after medical therapy with steroids for perinatal lung maturity, and caesarian delivery.

(Barton & Sibai, 1992)

- Termination of pregnancy and the removal of the chorionic villi is the only therapy that minimizes maternal and fetal compromise. Timing of delivery depends on the severity of the maternal condition (DIC, MOSD, abruption), fetal condition, placenta reserve, and gestational age. With few exceptions, patients with pregnancies of at least 34 weeks' gestation and class I pregnant patients with HELLP syndrome require prompt delivery.

- ***HELLP syndrome - antepartum management***
  - assess and stabilize the maternal condition
  - correct coagulopathy if DIC is present
  - give intravenous magnesium sulfate to prevent seizures
  - provide treatment for severe hypertension to prevent stroke
  - transfer to tertiary center if appropriate
  - if subcapsular hematoma of liver, computed tomography or ultrasound of the abdomen

- ***HELLP syndrome - antepartum management***
  - evaluate fetal well-being
    - non stress test
    - biophysical profile
  - timing of delivery
    - if > 34 weeks gestation, deliver
    - if < 34 weeks gestation, administer corticosteroids, then deliver in 48 hours

- ***HELLP syndrome - management for cesarean birth***
  - use general anesthesia if platelet count is < 75,000 / $mm^3$
  - transfuse 5 to 10 units of platelets before surgery if platelet count is < 50,000 / $mm^3$
  - leave vesicouterine peritoneum open
  - install subfascial drain

- ***HELLP syndrome - management for cesarean birth***
  - schedule secondary closure of skin incision or subcutaneous drain
  - administer postoperative transfusions as needed
  - perform intensive monitoring for at least 48 hours postpartum
  - consider dexamethasone (10 mg IV every 12 hours) until postpartum resolution of disease occurs

- ***HELLP syndrome - management of women with a subcapsular liver hematoma***
  - general considerations - blood bank aware for potential need of many units of blood
  - general or vascular surgeon consultation
  - avoid direct and indirect manipulation of liver
  - closely monitor hemodynamic status
  - management of hematoma depends on whether it is ruptured or not

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# Acute Fatty Liver of Pregnancy

- Sheehan, first recognized this disorder as a distinct syndrome in 1940.
- He named it Acute yellow atrophy but it is now more commonly known as acute fatty liver of pregnancy.

(Sheehan, 1940)

- (AFLP) is rare, encountered in a tertiary maternity hospital approx-imately once a year, with a reported incidence of 1 in 13,000 to 1 in 16,000 deliveries.
- Preeclampsia is present in 50% or more of cases of AFLP and may play a role in its origin.

(Vigil-De, 2001)

- Reports of occasional recurrent cases and an asso-ciation with a deficiency of long-chain 3-hydroxyacyl-cocnzyme A (Co A) dehydrogenase, raise the interesting notion that, at least in some instances, this disease results from an inborn error of metabolism.

(Ibdah et al., 1999)

# Clinical Characteristics

- AFLP occurs in the latter half of pregnancy, usually close to term. As with HELLP syndrome, affected patients may present after delivery. It is reported to occur more commonly in a first pregnancy and in the presence of multiple pregnancy, also prevalent in preeclampsia. There are reports of an association between AFLP and gestation of a male fetus.

(Castro et al., 1999)

- Affected women have nonspecific symptoms, including, promi-nently, nausea and vomiting, malaise and fatigue, jaun - dice, thirst, headache, and altered mental status. These can be signs and symptoms of acute hepatic failure.

- In severe cases that go untreated, there is progression over hours or days to fulminant hepatic failure, with hepatic coma, hypo-glycemia, severe coagulopathy with hemorrhage from the gastrointestinal tract or the uterus and death.

- Most affected women have signs of coexistent preeclampsia, including modest elevations in blood pressure, hyperuricemia, and proteinuria.

# Polydipsia

With or without polyuria, frequently is an early symptom in AFLP.

The patient may drink 2 or 3 liters of liquids overnight. it often exceeds the magnitude of vomiting. It has been interpreted as a transient diabetes insipidus.

(Cammu et al., 1987)

# Laboratory tests

| Clinical features | Biochemical changes | |
|---|---|---|
| Nausea, Vomiting | Bilirubin (total) | Slight ↑, normal |
| Malaise, Fatigue | AST/ALT | ↑normal to 1000 U |
| Jaundice | GGTP | Slight↑ |
| Abd. Pain | Prothrombin time | ↑↑ |
| Preeclampsia | Fibrinogen | ↓↓ |
| Coma | Uric acid | ↑ |
| Bleeding | Ammonia | ↑ |
| Onset in second half of gestation; postpartum onset possible | Glucose | ↓ |
| | Leukocytes | ↑ |
| | platelets | ↔, ↑ |

- Imaging may be useful; fat in the liver has been demonstrated in AFLP with ultrasonography and CT scanning.
- Liver biopsy is not indicated for diagnosis

(Barton et al., 1998)

# Characteristics of HEELP syndrome and AFLP

| HELLP | AFLP |
|---|---|
| **Early**<br>Platelet count, 50,000-150,000/$mm^3$<br>LDH level, 600-1400 IU/L<br>Bilirubin/PT levels, Normal | **Early**<br>Platelet count, >100,000/$mm^3$<br>Uric acid – abnormal<br>LDH level, normal<br>PT- Abnormal<br>Bilirubin/PT levels, abnormal |
| **Late**<br>Platelet count, <50,000/$mm^3$<br>LDH level, >1400 IU/L<br>Bilirubin/PT levels, abnormal | **late**<br>Platelet count, <100,000/$mm^3$<br>LDH level, < 600 IU/L<br>Hypoglycemia<br>PT- Abnormal |

# *Complications*

- cerebral edema,
- renal failure (60%),
- hypoglycemia (53%),
- infections (45%)
- gastrointestinal hemorrhage (33%),
- coagulopathy (30%),
- fetal death
- severe postpartum hemorrhage

# Course and Management

- Patients with undiagnosed AFLP are at risk for progres-sion, with an unpredictable but often short time course, to fulminant hepatic failure and death for both mother and fetus.
- Now it is rare for a patient to die, with appropriate diagnosis and aggressive management.
- Similarly, the outlook for the fetus of the affected pregnancy has also improved, although it remains worse than that of the mother.

(Usta et al., 1994)

All patients should be hospitalized as soon as the diagnosis of AFLP is suspected

Moderate or severely affected patients (encephalopathic, deeply jaundiced, with a prothrombin time less than 40% of the control), or with any extrahepatic complications, should be attended in intensive care units.

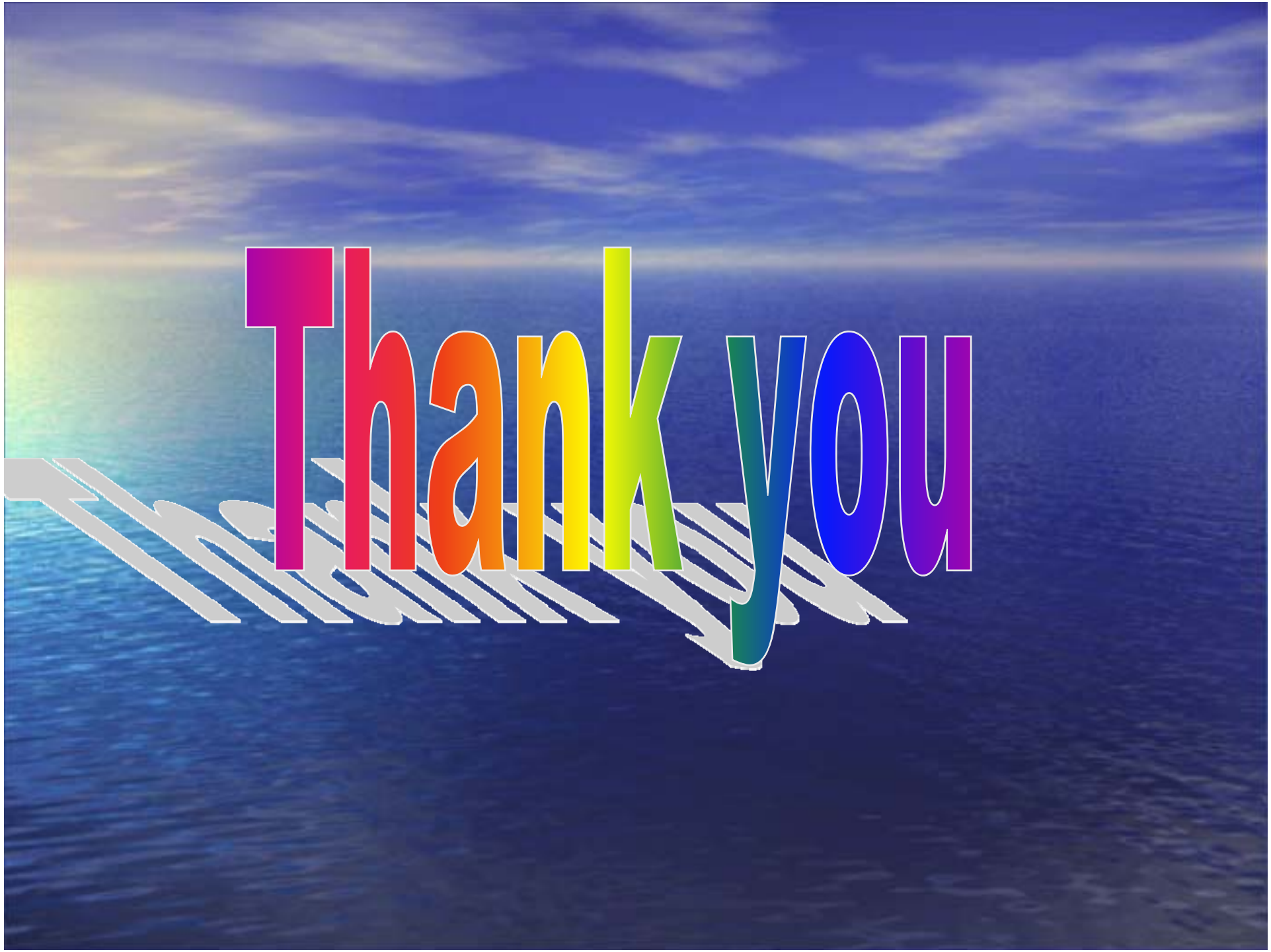
it seems convenient to maintain glucose infusions . Because of the risk of a sudden hypoglycemia until a full metabolic recovery is obtained.

- Treatment of AFLP begins with delivery. The route should be guided by obstetric indications. Cesarean section is not always necessary; vaginal delivery can be accomplished.

- With delivery, repair of the liver disease begins, the initial sign of improvement being a fall in prothrombin time elevation.
- The management should include maximal support in an intensive care unit by a team that includes both obstetri-cians and hepatologists. Liver transplantation for AFLP has been reported.

(Paternoster et al., 2004)

- There are no residua after AFLP, and complete recovery of the affected patient should be expected. Cases of recur-rent AFLP, as well as cases of nonketotic hypoglycemia in the offspring, have been reported.


Thank you