

Pregnancy and Liver Disease

Prof. Dr. Ömer ŞENTÜRK

Pregnancy and Liver Disease

Liver disease during pregnancy is rare, and pregnancy is rare in patients with chronic liver disease

There may be 3 possibilities of pregnancy and liver disease:

- I. Pregnancy-specific liver disease
- II. Liver disease that occurs during pregnancy who have previously had a normal liver
- III. Pregnancy with pre-existing liver disease

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I. Pregnancy-specific liver disease

- Hyperemesis gravidarum
- Preeclampsia
- HELLP syndrome
- Budd-Chiari syndrome
- Recurrent intrahepatic cholestasis of pregnancy
- Acute fatty liver of pregnancy
- Spontaneous rupture of the liver

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II. Liver disease that occurs during pregnancy who have previously had a normal liver

- Acute viral hepatitis
- Amebiases
- Gallstone
- Liver tumors
- Drug-related liver disease
- Budd-Chiari syndrome

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III. Pregnancy with pre-existing liver disease

- Those with mild hepatitis
- Those with cirrhosis or chronic active hepatitis
- Patients with portal hypertension due to portal vein thrombosis

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Pregnancy and Liver Disease

- There is no significant change in liver function in a normal pregnancy and the histological appearance of the liver is normal
- Arterial spider, palmar erythema and telangiectasia can be seen especially in third trimester
- These changes do not show liver disease and also disappear after birth
- **Hepatomegaly during pregnancy is an abnormal condition**

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Biochemical changes in pregnancy

Decreased	Increased	Unchanged
Hgb Albumin BUN Uric acid Globulin	Leukocyte Fibrinogen Ceruloplasmin Globulin Cholesterol Triglyceride Alkaline phosphatase AFP Bile acids	Transaminases PT GGT 5' Nucleotidase Bilirubin

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I. Pregnancy-specific liver disease

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Hyperemesis Gravidarum (HG)

- Nausea and vomiting frequently during the early stages of pregnancy, this situation rarely affects pregnancy
- Severe symptoms → malnutrition, dehydration and hepatic dysfunction
- Jaundice may be present (why?)(but, jaundice should not be attributed to a mild HG !)
- Before the diagnosis of hyperemesis gravidarum, drugs, viral hepatitis, and the normal bile duct of the liver should be revealed with USG

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Hyperemesis Gravidarum (HG)

- Risk factors;
 - Hyperthyroidism
 - Psychiatric disorders
 - Having diabetes before
 - Molar pregnancy
 - Multiple pregnancy

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Hyperemesis Gravidarum (HG)

- Treatment;
 - Liquid replacement, less-and frequent-eating (Naso-jejunal nutrition if necessary)
 - Prevention of vomiting with antihistamine or phenothiazines

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Preeclampsia-Eclampsia

- **Preeclampsia**; hypertension, proteinuria and peripheral edema
 - It can be seen in 5-10% of all pregnant women and is affected by 10-20% of the liver
 - In the first pregnancy, hypertensive pregnant, pregnant with organ transplant and those with procoagulant use pregnant → **more common**
 - More frequent after the 20th week of pregnancy
 - No symptoms suggestive of liver disease
 - Liver involvement is established by abnormal liver function tests
 - Transaminases < 500, B and AP moderate elevated

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Preeclampsia-Eclampsia

- **Eclampsia**; in addition to preeclampsia, there are convulsions and hyperreflexia
 - In eclampsia the liver can be damaged, hemorrhage and ischemic infarction can be seen
 - Clinically nausea-vomiting, right upper quadrant pain and sudden hypotension
 - Mortality rate for the mother is 50-75%, for the fetus 60%

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Preeclampsia-Eclampsia

Pathophysiology;

- Abnormal placental formation
 - Fetal ischemia and intrauterine growth retardation
- Local and systemic endothelial dysfunction
 - The release of soluble antiangiogenic factors
 - Reduction of VEGF and other angiogenic factors
 - Vasoconstriction
 - Increased sensitivity to vasoconstrictors
- Systemic endothelial damage, fibrin deposition, ischemic infarcts

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Preeclampsia-Eclampsia

Liver pathology: patchy ischemic necrosis and fibrin deposition

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Preeclampsia-Eclampsia

Treatment:

- Hepatic complications can be prevented by early diagnosis and treatment of preeclampsia
- If there is hepatic involvement and the fetus is mature, the delivery is terminated
- If the diagnosis is made in the early period of gestation;
 - Bed rest
 - Antihypertensive treatment
 - Mg sulphat

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HELLP Syndrome

- Hemolysis, elevated liver enzymes and low platelets
- It can be seen in 2-12% of cases with severe preeclampsia
- It is seen in ≈32nd week of pregnancy in patients with eclampsia (23-40 weeks)
- Diagnostic criteria:
 - H: Abnormal smear (microangiopathy), LDH > 600 U/L, I.Bilirubin ↑
 - EL: AST > 70 U/L, (AST/ALT increase, 10-20 times)
 - LP: Platelet < 150.000
 - Class 1: < 50 000
 - Class 2: 50-99 000
 - Class 3: 100-149 000

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HELLP Syndrome

Pathogenesis;

- Changes in platelet activation,
- Increase in proinflammatory cytokines,
- Segmental vasospasm with vascular endothelial damage,
- LCHD (long chain 3 hydroxyacyl coenzyme A dehydrogenase) defect

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HELLP Syndrome

■ Symptoms

- Nausea-vomiting, headache, right upper quadrant and epigastric pain
- Diastolic BP usually above 110 mmHg

■ Laboratory

- DIC findings
 - Low PLT, low fibrinogen, elevated fibrin degradation products and prolonged PT
- Findings of intravascular hemolysis
- Moderate increase in B and transaminases

■ Mortality; for the mother is 1-3%, perinatal 7-22%

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HELLP Syndrome

■ Recurres 4-19%

■ Pregnant women with HELLP syndrome are at risk for the following clinical conditions during their next pregnancy:

- Pre-eclampsia,
- Repeat HELLP,
- Premature,
- Intrauterine development retardation and
- Abruption placenta

■ There is no long-term negative effect on kidney function

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HELLP Syndrome

Treatment

A. Delivery

- >34 weeks pregnancy → delivery
- <34 weeks pregnancy → start to steroid, after 48 hours → delivery

B. Support treatment

- Antihypertensives
- Anticoagulant therapy

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HELLP Syndrome

Treatment

■ Antihypertensives

- **ACE inh. (C/D)**
 - First trimester exposure → congenital malformation
 - 2-3.trimester → oligohydramnios, anuri, hypotension, renal failure, death of the fetus
- **Beta blockers (C/D)**
 - Fetal bradycardia, hypotension, intrauterine growth retardation
- **Calcium channel blockers (C)**
 - Teratogenic and embryonic effects have been shown in animals (in humans?)

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HELLP Syndrome

Treatment

■ Anticoagulants

- **Aspirin [C (1-2.trimester)], [D (3.trimester)]**
 - Intrauterine growth retardation, salicylate intoxication, bleeding and neonatal acidosis
 - Use of aspirin near birth may cause premature closure of the ductus arteriosus
 - Low-dose aspirin (60-150 mg / day) can be safe in pregnancy
- **Enoxaparin (B)**
- **Heparin (C)**
 - Does not pass the placenta

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Budd-Chiari Sendromu

■ Hepatic venous thrombosis, which may lead to Budd-Chiari syndrome, may occur in pregnancy or puerperium

■ Mild cases are treated with diuretics

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Recurrent intrahepatic cholestasis of pregnancy

- It occurs between the 14th week and the birth (usually after the 30th week)
- Recurrence rate 58%
- It is spontaneous resolved until 2 weeks after birth
- **Etiyology**
 - Genetic factors
 - Metabolic factors
 - Estrogens
 - Twin pregnancy

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Recurrent intrahepatic cholestasis of pregnancy

- **Symptoms**
 - Pruritis (more at night)(100%)
 - Icter (25-50%)
 - Nause-vomiting (5-75%)
 - Abdominal pain (5-25%)
 - Malaise, anorexia
 - **No fever**

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Recurrent intrahepatic cholestasis of pregnancy

- **PE;**
 - Mild icter, itching scars and various skin lesions

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Recurrent intrahepatic cholestasis of pregnancy

■ Pathology

Cholestasis:

- sentrilobular cholestasis
- canalicular bile plugs
- accumulation of bile pigment in hepatocytes
- no inflammation or necrosis

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Recurrent intrahepatic cholestasis of pregnancy

- **Laboratory;**
 - Bile asid ↑ (x30-100)
 - Alkaline phosphatase ↑ (x1-2)
 - Cholesterol, triglycerides N or ↑
 - Bilirubine (<5mg/dl)
 - Transaminases ↑ (x1-4)
 - PT ↑
- **Liver biopsy is diagnostic, but rarely necessary**

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Recurrent intrahepatic cholestasis of pregnancy

■ Mortality/Morbidity

- Mother: 0
- Baby: premature, stillbirth, increase in perinatal mortality (0.4-1.4%)

■ Prognosis

- No long-term adverse effects on the liver
- Increased gallstones frequency
- May be precipitated by oral contraceptives
- Risk of premature birth, does not cause congenital abnormality
- 2/3 of the cases repeats in the next pregnancy

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Recurrent intrahepatic cholestasis of pregnancy

■ Staging;

- **Mild** = Bilirubin 0.58-2.28mg/dl
- **Severe** = Bilirubin \geq 2.34 mg/dl

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Recurrent intrahepatic cholestasis of pregnancy

■ Differential diagnosis;

- Viral hepatitis
 - Prodromal symptoms
 - Itching rare
 - Transaminases $\uparrow\uparrow\uparrow$
 - The agent can be shown by serological tests
- Biliary colic, cholecystitis
 - Abdominal pain
 - Fever, leukocytosis
- Gallstones
 - USG
- PBC
 - AMA positivity
 - The disease continues after birth

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Recurrent intrahepatic cholestasis of pregnancy

■ Treatment;

- Delivery
 - Mild disease \rightarrow **37.week**
 - Icter \rightarrow **36.week**
 - Fetal distress \rightarrow **immediately**
 - If the mother suffers from unresolved itching \rightarrow **early DELIVERY**
- UDCA (15mg/kg/gday)
- Cholestiramin, silymarin, SAME, deksametazon... ..

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Acute Fatty Liver of Pregnancy (AFLP)

- It is seen in the postpartum period with 26th week (usually > 32th week)
- It is seen in 1 out of every 1000 pregnant women
- Often there is a pregnancy toxemia
- It is more common:
 - Those who are pregnant with a boy,
 - In their first pregnancy,
 - Twin or more pregnancies

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Acute Fatty Liver of Pregnancy (AFLP)

■ Pathophysiology

- Microvesicular steatosis similar to Reye's syndrome
- Degradation of mitochondrial beta-oxidation of fatty acids \rightarrow fatty acid toxicity in mitochondria
- As a result, decreased ATP production and hepatic cell failure
- Trigger factors;
 - Genetic mutations affecting fatty acid metabolism (long-chain 3-hydroxy acyl CoA dehydrogenase deficiency)
 - Preeclampsia
 - Drugs that disrupt beta-oxidation or oxidative phosphorylation (such as aspirin and NSAIDs)
 - Inflammatory cytokines

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Acute Fatty Liver of Pregnancy (AFLP)

■ Symptoms

- Asymptomatic – Fulminant hepatic failure
- Approximately 50% of patients have preeclampsia
- Fever, headache, malaise, nausea, vomiting
- Epigastrium and right upper abdomen pain
- Jaundice, oliguria, uremia, encephalopathy
- GIS bleeding
- PE
 - Hypertension, edema and proteinuria

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Acute Fatty Liver of Pregnancy (AFLP)

■ Laboratory

- Leukocytosis, normal or decreased PLT, normochrome-normocytic anemia,
- 1-5 times increase in transaminases, increase in B with disease progression, AP ↑
- Glucose ↓, uric acid and ammonia ↑
- Coagulopathy (with or without DIC)
- PT / PTT normal or elevated
- Metabolic acidosis
- Renal dysfunction, oliguric renal failure

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Acute Fatty Liver of Pregnancy (AFLP)

■ Differential Diagnosis

- Acute viral hepatitis (fulminant form)...
 - Preeclampsia, leukocytosis, microangiopathic hemolysis, DIC → acute fatty liver of pregnancy
 - Increase in transaminases as progressive → fulminant hepatitis
- Alcoholic hepatitis ...
- Cholecystitis, cholangitis and pancreatitis

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Acute Fatty Liver of Pregnancy (AFLP)

■ Mortality

- Mother: 5-26%
- Baby: 9-32%

■ Morbidity

- Mother: 0
- Baby: LCHAD deficiency, hypoglycemia, hypotonia, striated and cardiac muscle dysfunction, growth retardation and sudden ex

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Acute Fatty Liver of Pregnancy (AFLP)

■ Diagnosis

- Definitive diagnosis: histological
 - Microvesicular fat infiltration (especially in Zone 3), mild portal inflammation and cholestasis
 - Sometimes the histological structure can be confused with viral hepatitis and preeclampsia
- Possible diagnosis
 - Clinical and lab tests
 - Imaging (USG, CT - oil infiltration)

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Acute Fatty Liver of Pregnancy (AFLP)

■ Treatment

- Depending on the stage at which the disease is defined
- If the diagnosis is confirmed **in the absence of any symptoms of deficiency**, the pregnancy is terminated
- Fresh frozen plasma and platelet infusion
- Early delivery
- The liver function quickly recovers right after birth
- With vaginal route or Sx birth in those near terme
- Liver Tx

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Spontaneous Rupture of The Liver

- Rupture of liver in pregnancy is rare

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II. Liver disease that occurs during pregnancy who have previously had a normal liver

- Acute viral hepatitis
- Gallstone
- Amebiases
- Liver tumors
- Drug induced liver disease
- Budd-Chiari syndrome

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Acute Viral Hepatitis

- Acute viral hepatitis most common liver disease causing jaundice during pregnancy
- Pregnancy does not increase susceptibility to acute viral hepatitis
- The course and outcome of viral hepatitis do not change in pregnancy
- Malnutrition may aggravate the prognosis

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Acute Viral Hepatitis

- Clinical features and LFT do not differ from non-pregnant women
- Hepatitis has different effects on fetus (abortus-premature birth)
- Does not cause congenital abnormality
- Treatment of viral hepatitis in pregnancy is done in non-pregnant women
- When Fulminant hepatic failure develops → Liver Tx

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Hepatitis B Virus

- Pregnancy is well tolerated in HBV carriers
- HBV reactivation during pregnancy or postpartum period is rare
- Intrauterine transmission of HBV is rare;
 - Women with acute type B hepatitis in the 1st and 2nd trimesters rarely pass the disease to their children (0-10%)
 - When there is an infection in the **third trimester**, the transition is around 60-70%

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Hepatitis B Virus

- Transition with amniocentesis is low (<4%)
- If prophylaxis is not performed and the mother is HBeAg (+), the risk of vertical transition is 90%
- Transition most often happens at birth

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Hepatitis B Virus

- If the mother HBV DNA < 100,000,000 IU/ml:
 - Neonatal immunoprophylaxis [HBIG + HBV immunization] prevents 95% transition
- If the mother is too infectious (HBV DNA > 100,000,000 IU/mL) despite **HBIG + HBV immunization**, transition risk **30-40%**
- Caesarean may reduce vertical passage, but:
 - Not indicated, because HBIG + HBV immunization highly effective

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Hepatitis B Virus

- If mother HBeAg (-) and HBV DNA >100 000 000 IU/mL
 - Infant has a risk of fulminant hepatitis B in life 2-4 months
- Mothers with HBV/HDV coinfection:
 - Can pass both infections to the baby
 - HBIG + HBV immunization can prevent both

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Hepatitis B Virus

■ Treatment

- Treatment is directed towards prophylaxis
- HB immunoglobulin within 12 hours of delivery (0,5ml)
- HB vaccination in 0,1,2 and 12th months
- Test after vaccination should be performed on 9-15th months
- Telbivudine and tenofovir are reliable during pregnancy
- Lamivudine can be safely used in 3.trimestir

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Hepatitis A Virus

- The transition to the baby was not shown
- It does not pose a risk for pregnancy

Hepatitis C Virus

- The transition to the baby may be (0-10%)
- Maternal viremia is important in the transition (HCV RNA positivity)
- Although the anti-HCV from the mother is lost in the baby, HCV viremia continues intermittantly

Hepatitis D Virus

- Transition to the baby is associated with HBV (coinfection)
- Fulminant course in pregnant women more
- Inhibition of transit is as in HBV infection

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Hepatitis E Virus

- Perinatal transit and chronic carriage are unknown
- Can make premature birth and abortion
- **Mortality 10-40%**

Other Viral Infections With Fetal Risk

- Measles
- CMV
- Polio
- HIV
- Herpes virus
- Coxackie B
- Parvo virus B 19 ...

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Gallstone

- Biliary sludge develops in 10-31% of pregnant women and gallstones develop in 2-3% of pregnant women
- The biliary sludge and gallbladder stones are associated with the number of birthdays;
 - ✓ %18 multiparous women
 - ✓ %8 nulliparous women
- Biliary pain can be seen in 28% of pregnant women with gallstone
- 60-90% of patients with biliary sludge and 20-30% of those with gallstones recover in the first postpartum period, and in the remaining group, biliary problems develop in the following years

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Gallstone

□ The etiology of bile sludge and stones are multifactorial:

- The increase in estrogen levels leads to an increase in cholesterol secretion and to the supersaturation of bile with cholesterol, which leads to biliary sludge and gallbladder stone formation
- An increase in progesterone levels leads to a decrease in gallbladder motility
- Increased fasting and postprandial gallbladder volume
- Reduction of gallbladder emptying time

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Gallstone

- Risk factors before pregnancy:
 - ✓ More than BMI
 - ✓ High leptin levels
 - ✓ Low HDL levels
 - ✓ Insulin resistance

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Gallstone

- Clinical presentation:
 - ✓ Biliary colic
 - ✓ Biliary pancreatitis
 - ✓ Acute cholecystitis
 - ✓ Right upper quadrant pain radiating to the back, shoulder and flank
 - ✓ Nausea-vomiting
 - ✓ Anorexia
 - ✓ Intolerance to fatty foods
 - ✓ Mild fever

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Gallstone

- Medical Treatment
 - Initially, conservative treatment is recommended (especially in 1st and 3rd trimesters) (surgical approach may cause abortion and premature birth)
 - Medical treatment; IV fluid and electrolyte treatment, bowel rest, pain therapy and broad-spectrum antibiotics

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Gallstone

- Surgery Treatment
 - Laparoscopic cholecystectomy is preferred in the second trimester (all patients who are symptomatic in 2nd trimester)
 - Pregnant women with recurrent biliary pain and complications (such as acute cholecystitis) should be treated surgically
 - Laparoscopic cholecystectomy is preferred for surgical treatment
 - ERCP can be performed in very carefully required cases (by exposure to a small amount of radiation)

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Other Liver Diseases

- Acute liver disease except viral hepatitis in pregnancy is rare
- Budd-Chiari syndrome can be seen due to hypercoagulability

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III. Pregnancy with pre-existing liver disease

1. Those with mild hepatitis
2. Those with cirrhosis or chronic active hepatitis
3. Patients with portal hypertension due to portal vein thrombosis

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1. Those with mild hepatitis

- Usually they have normal menstrual cycle
- They have normal fertility
- They do not carry any risk for pregnancy

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2. Those with cirrhosis or chronic active hepatitis

- Cirrhosis patients rarely become pregnant (because they are older, have amenorrhea or anovulatory cycle)
- Pregnancy occurs when inactive liver disease or liver function is good
- Pregnancy is more common in patients with cryptogenic cirrhosis or autoimmune hepatitis
- Spontaneous abortion has not increased (compared to non-cirrhosis)

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2. Those with cirrhosis or chronic active hepatitis

- Premature birth is seen in 1/5 of cirrhotic patients
- Increases premature risk when decompensation (jaundice, acid)
- Postpartum hemorrhage occurs in 3/4 of those with porto-systemic shunting
- Birth should be tried in the normal way, if necessary the second period (active delivery period) should be shortened with forceps

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2. Those with cirrhosis or chronic active hepatitis

- Caesarean section should be avoided
- Living babies have no special risk for congenital abnormalities and liver disease (if the mother is not HBV)
- Patients may require specific treatment due to underlying liver diseases during pregnancy

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2. Those with cirrhosis or chronic active hepatitis

- As a general rule, drug intake should be avoided, especially in 1st trimester
- Patients with autoimmune hepatitis should continue treatment with steroids
- Those with Willson disease should continue to receive penicillamine
- Liver functions may be impaired during pregnancy, bleeding from varicose veins

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2. Those with cirrhosis or chronic active hepatitis

- Gastrointestinal bleeding, hepatic coma and postpartum hemorrhage are the main causes of maternal mortality
- Permission to pregnancy in patients with cirrhosis?
- Although living babies do not carry the risk of congenital abnormalities, the risk of losing the baby increases
- Maternal mortality mean. 10%

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2. Those with cirrhosis or chronic active hepatitis

- Gastrointestinal bleeding, hepatic coma and postpartum hemorrhage are the main causes of maternal mortality
- Permission to pregnancy in patients with cirrhosis?
- Although living babies do not carry the risk of congenital abnormalities, the risk of losing the baby increases
- Maternal mortality mean. 10%

**Active or decompensated kc disease,
History of esophageal varices bleeding and
Patients over 30 yeras old
PREGNANCY SHOULD NOT BE ALLOWED**

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Otoimmune hepatitis

- Risk of exacerbation during pregnancy 21%, risk in the first 6 months after birth 52%
- The rate of stillbirth and perinatal mortality can be as high as 24%
- Monotherapy with prednisolone is recommended
- If pregnancy has occurred under treatment with prednisolone +AZA, this treatment is continued
- Premature rate with AZA treatment is 28%
- Esophageal varices should be checked, other autoimmune diseases should be reviewed

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Wilson disease

- Pregnancy in untreated patients is rare
- The disease does not worsen during pregnancy
- Treatment should be continued during pregnancy
- If the treatment is not maintained, there is a risk of stillbirth and fulminant liver failure
- Treatment with D-penicillamine (25-50% dose is reduced in the third trimester, vitamin B 6 deficiency is followed, it is not breast-fed under this treatment)
- Maternal and fetal complications with zinc acetate are very rare

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3. Extrahepatic Portal Hypertension

- The risk of spontaneous abortion has not increased and the risk of premature birth and perinatal mortality has increased
- Living children are normal
- Acute GI bleeding is the most common complication (≅ 50%)
- In contrast to patients with cirrhosis, the bleeding here is rarely fatal, and the treatment is conservative
- Postpartum bleeding is not frequent
- Birth is as in patients with cirrhosis

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