81) A 39 year old primigravida at 32 weeks gestation presents with right upper quadrant pain and vomiting. Physical examination reveals poor peripheral perfusion, a pulse rate of 96/minute and blood pressure of 160/100 mmHg. There is tenderness in the right upper quadrant. Liver function tests show:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>14 micromol/L</td>
<td>2-14</td>
</tr>
<tr>
<td>ALP</td>
<td>200 U/L</td>
<td>40-130</td>
</tr>
<tr>
<td>GGT</td>
<td>15 U/L</td>
<td>1-35</td>
</tr>
<tr>
<td>AST</td>
<td>630 U/L</td>
<td>8-35</td>
</tr>
<tr>
<td>ALT</td>
<td>550 U/L</td>
<td>8-40</td>
</tr>
<tr>
<td>Urine dipstick</td>
<td>1+ proteinuria</td>
<td></td>
</tr>
</tbody>
</table>

The most likely cause for her abnormal liver function tests is:

A. Cholelithiasis
B. Acute fatty liver of pregnancy
C. Pre-eclampsia
D. Acute viral hepatitis
E. Cholestasis of pregnancy

Answer:

**Liver disease in pregnancy**

1) **Liver disease specific to pregnancy**
   - Cholestasis of pregnancy (Usually 2nd to 3rd trimester)
   - Acute fatty liver of pregnancy (2nd half of pregnancy, usually 3rd trimester)

2) **Multisystem disease in pregnancy with liver manifestations**
   - Pre-eclampsia +/- HELLP syndrome
   - Hyperemesis gravidarum (usually 1st trimester)

3) **Physiological changes of pregnancy which worsen severity/ predispose to certain liver disease**
   - Cholelithiasis
   - Hepatitis E
   - Thrombotic disease (eg Budd Chiari)

4) **Liver disease unrelated to pregnancy** which can occur during pregnancy
   - Acute viral hepatitis

5) **Pregnancy in patients with chronic liver disease**

Note:
- Certain conditions more likely during certain trimesters but there are always exceptions (can even occur or persist post-partum)
- Risk of recurrence with subsequent pregnancies
  - Hyperemesis gravidarum often recurs
  - Intrahepatic cholestasis recurs in up to 70% but may be milder
  - Acute fatty liver also recurs but frequency unknown
  - Pre-eclampsia tends to recur if severe or if developed early eg in 2nd trimester
Physiological changes in pregnancy
- Plasma volume ↑ by 50% from 6th to 36th week
- Simultaneous ↑ red cell mass but more gradual and to lesser extent -> Haemodilution
- Due to ↑ plasma volume: serum albumin ↓ as pregnancy advances
- Total lipids and cholesterol ↑ significantly during pregnancy
- Maternal cardiac output ↑ until 2nd trimester then plateaus till delivery, however absolute
  blood flow to liver unchanged (% cardiac output to liver relatively ↓)
- LFTs:
  o Serum ALP ↑ 2-4x normal levels (especially in 3rd trimester) with minimal ↑
    GGT suggesting ALP is from the placenta (and not liver)
  o Total and free bilirubin ↓ throughout pregnancy
  o PT-INR unchanged
  o Serum fibrinogen ↑ in late pregnancy
  o Thus any ↑ aminotransferases, bilirubin or bile acid concentrations should
    prompt Ix
  o Mild changes in ALP and albumin can be considered normal
Cholelithiasis
- Pregnancy is major risk factor for developing cholesterol gallstones
- Risk remains for 5 years post pregnancy then falls to baseline
- Risk ↑ with ↑ frequency and number of pregnancies
- Oestrogen induces ↑ cholesterol secretion, progesterone induces ↓ bile acid formation ->
  supersaturation of bile with cholesterol
- Pregnancy induces quantitative change in bile acids -> more hydrophobic acids are
  formed -> ↓ ability to solubilise cholesterol
- Progesterone leads to delayed GB emptying -> stasis
- Similar effect (though to lesser degree) seen in OCP and HRT
- Complications from gallstones eg cholecystitis, choledocholithiasis is uncommon but can
  often be managed conservatively
- If asymptomatic: do not treat
- If need surgery: safest in 2nd trimester (risk of premature labour ↓ and no uterine
  obstruction to gall bladder) but ideally laparoscopic cholecystectomy PRIOR pregnancy is
  best
**Acute Fatty Liver**
- Unique to human pregnancy
- Rare: 1 in 7000 to 16000 pregnancies
- Previously fatal unless early diagnosis and prompt delivery
- 2nd half of pregnancy, usually 3rd trimester

- **Microvesicular fatty infiltration** of hepatocytes
- Associated with enzyme deficiency: LCHAD (long chain 3-OH CoA dehydrogenase) which catalyzes the 3rd step of beta fatty acid oxidation in mitochondria
- Accumulation of long chain fatty acids (by placenta and foetus) is hepatotoxic

- Symptoms:
  - Nausea and vomiting (75%)
  - Abdominal pain, usually epigastric (50%)
  - Anorexia
  - Jaundice
  - Sx and signs of pre-eclampsia (50%)
  - Extrahepatic: infections, intra-abdominal bleeding, central DI (unknown reason)

- **Ix:**
  - LFTS mainly ↑ aminotransferases (mild to > 1000 U/L)
  - Non specific ↑ white cell count
  - Non specific thrombocytopenia +/- DIC
  - If severe: ↑ NH3 and hypoglycaemia +/- ARF and ↑ uric acid
  - Liver Bx: diagnostic but not usually performed (coagulopathy)
  - Need to exclude HELLP which has haemolysis

- **Rx:**
  - Maternal stabilisation
    - Glucose infusion
    - Correct coagulopathy (cryo better as less volume) +/- platelet transfusion
    - Haemofiltration/ HDx for ARF
    - Respiratory support
  - Delivery
    - Usually PT normalises shortly after
  - Rarely need liver transplant

- **Prognosis:**
  - Most, even severely ill, recover with support and have no hepatic sequelae
  - Can recur in subsequent pregnancies
### Acute viral hepatitis

- **Most common liver disease in pregnancy**

| Hepatitis A | Course of acute infection **similar to non-pregnant**  
|            | Severity worsens with ↑ age  
|            | If severe disease during 3rd trimester -> risk of preterm labour  
|            | Some associated complications  
|            | - PROM  
|            | - PV bleeding  
|            | - Placental separation  
|            | Good maternal and foetal outcome  
|            | **No evidence peri-natal transmission**  

| Hepatitis B | Acute infection during pregnancy has no ↑ mortality or teratogenicity  
|            | **Perinatal transmission** well documented especially:  
|            | - If acute infection in 3rd trimester  
|            | - If seropositive for HBSAg and HBeAg (suggests active replication)  
|            | If exposed during gestation:  
|            | - **Vaccinate**: no ↑ congenital anomalies  
|            | - Or passive immunisation with **immunoglobulins**  

| Hepatitis E | Usually mild and self-limiting illness in non-pregnant – faecal oral route  
|            | Endemic areas: developing world eg Pakistan, Africa, Mexico  
|            | Can be **very severe in pregnant** – especially 3rd trimester  
|            | - Can develop fulminant hepatitis with 20% mortality  
|            | - Ddx acute fatty liver of pregnancy, pre-eclampsia, HELLP, HSV hepatitis  
|            | - Dx via serology (research areas have HEV RNA PCR)  

| **Perinatal transmission -> acute hepatitis of neonate**  

| Herpes simplex hepatitis (HSV) | Hepatitis due to primary HSV infection  
|                                | Can be fulminant especially in 3rd trimester  
|                                | **Clues to dx:**  
|                                | - Vesicular rash  
|                                | - May have prodrome of fever/ URTI symptoms  
|                                | **Dx via serology/ cultures of vesicle fluid**  
|                                | **Ddx:** pre-eclampsia, acute fatty liver (but in this case delivery is not necessary)  
|                                | **Rx with acyclovir**  

| **Perinatal transmission during delivery**  

| Others | CMV/ EBV/ adenoviruses  
|        | - Usually self limiting with benign course  
|        | - Supportive care  

---

### Herpes simplex hepatitis (HSV)

**Hepatitis due to primary HSV infection**

**Can be fulminant especially in 3rd trimester**

**Clues to dx:**
- Vesicular rash
- May have prodrome of fever/ URTI symptoms

**Dx via serology/ cultures of vesicle fluid**

**Ddx:** pre-eclampsia, acute fatty liver (but in this case delivery is not necessary)

**Rx with acyclovir**

**Perinatal transmission during delivery**
Cholestasis of pregnancy
- Occurs 2nd to 3rd trimester
- Cause unclear but familial associations and related to pregnancy hormones (oestrogen levels peak at 3rd trimester, and more common in multiple pregnancies)

  - Symptoms:
    o Severe generalised pruritis, may be intolerable
    o Palms and soles worst
    o Worst at night
    o Often precedes laboratory abnormalities
    o Abdominal pain uncommon

  - Ix:
    o Serum total bile acid concentration ↑
    o ↑ cholic/chenodeoxycholic acid ratio
    o Modest ↑ bilirubin
    o ↑ ALP (but non-specific, given that placenta produces a lot)
    o Normal or mild ↑ GGT
    o ↑ aminotransferases, even up to 1000 U/L (need to ddx viral hepatitis)

  - Rx:
    o URSO (↑ bile flow)
    o Antihistamines
    o Cholestyramine
    o Delivery ASAP

  - Prognosis:
    o Good maternal outcome
      ▪ Pruritis disappears soon after delivery with rapid normalisation of LFTs
      ▪ No hepatic sequela
      ▪ Tends to recur with subsequent pregnancies (60-70%)
    o Foetal outcome poor
      ▪ Prematurity
      ▪ Meconium stained amniotic fluid
      ▪ Neonatal respiratory distress
      ▪ Death in utero (during last month of pregnancy)
### Hypertensive disorders of Pregnancy

- Complicates 10-20% all pregnancies
- Preeclampsia affects 3-14% all pregnancies

<table>
<thead>
<tr>
<th>Preeclampsia</th>
<th>Main risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Mild/Severe)</td>
<td>- Nulliparity/ primagravid</td>
</tr>
<tr>
<td>No moderate!</td>
<td>- Diabetes</td>
</tr>
<tr>
<td>Systolic &gt; 160 mmHg</td>
<td>- PHx or FHx pre-eclampsia</td>
</tr>
<tr>
<td>Diastolic &gt; 110 mmHg (or both)</td>
<td>- Multiple gestation</td>
</tr>
<tr>
<td>&gt; 20 weeks gestation</td>
<td>- Obesity</td>
</tr>
<tr>
<td>Previously normotensive</td>
<td>- Age &gt;40 or &lt;18</td>
</tr>
<tr>
<td>Note just absolute BP</td>
<td>- Partner with previous partner with pre-eclampsia</td>
</tr>
<tr>
<td>Sudden ⫸ important</td>
<td></td>
</tr>
</tbody>
</table>

If < 20 weeks
- Unusual
- Consider molar pregnancy

Main ddx:
- Pre-existing HT
- Gestational HT
- Exacerbation of renal dse
- Exacerbation of SLE
- TTP-HUS
- Acute fatty liver
- Autoimmune thrombocytopenia
- Gestational thrombocytopenia

### Haematological features:
- Thrombocytopenia: ⫸ platelet turnover in microthrombi
- PT-INR and fibrinogen should be normal unless DIC or liver dysfunction
- HELLP with microangiopathic haemolysis
- Liver dysfunction with vasospasm and microthrombi leading to RUQ pain and ⫸ AST/ALT and in severe cases: subcapsular haemorrhage/ rupture

### CNS:
- If seizures -> eclampsia
- Headache, blurred vision, transient cortical blindness

### ARF uncommon

### APO not infrequent

### Foetus and placenta
- Chronic hypoperfusion is the problem
- IUGR and oligohydramnios
- Placental abruption in 1% (more if severe)

### Maternal long term issues
- Risk of recurrence ( cif risk up to 65% in early + severe disease)
- → premenopausal cardiovascular risk (HT, IHD)
- One Israeli study reported → cancer risk (stomach, larynx, ovary and breast)

### Chronic HT
- Pre-existing HT
|                     | Either prior pregnancy or < 20 weeks gestation  
<table>
<thead>
<tr>
<th></th>
<th>May persist &gt; 12 weeks post-partum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preeclampsia on chronic HT</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Gestational HT</strong></td>
<td>Usually mild HT with NO proteinuria</td>
</tr>
<tr>
<td>Systolic ≥ 140</td>
<td>Occurs in later part of pregnancy</td>
</tr>
<tr>
<td>Diastolic ≥ 90</td>
<td>Resolves by 12 weeks post-partum</td>
</tr>
<tr>
<td>(or both)</td>
<td></td>
</tr>
<tr>
<td><strong>Eclampsia</strong></td>
<td>Develop tonic clonic seizures</td>
</tr>
<tr>
<td></td>
<td>Seizures not attributable to other causes (eg hypoglycaemia)</td>
</tr>
</tbody>
</table>

Finally going back to the question:
Primagravid > 20 weeks gestation  
Hypertensive  
RUQ pain  
Abnormal LFTs  
Proteinuria  
-> Has to be pre-eclampsia by definition (though I don’t really see why acute fatty liver can’t be a contender except that it is much rarer)