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:

Bilirubin	14 micromol/L	2-14
ALP	200 U/L	40-130
GGT	15 U/L	1-35
AST	630 U/L	8-35
ALT	550 U/L	8-40
Urine dipstick	1+ proteinuria	

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 hepatits

5) Pregnancy in patients with chronic liver disease

Note:

- Certain conditions morel 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:
    - **Serum ALP ⇑ 2-4x normal** levels (especially in 3rd trimester) with minimal ⇑ GGT suggesting ALP is from the placenta (and not liver)
    - Total and free bilirubin ⇓ throughout pregnancy
    - PT-INR unchanged
    - Serum fibrinogen ⇑ in late pregnancy
    - Thus any ⇑ aminotransferases, bilirubin or bile acid concentrations should prompt Ix
    - 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 hepatits

- 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)	Hepatits 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

	Perinatal transmission reported

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

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

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

- Prognosis:
  - **Good maternal outcome**
    - Pruritis disappears soon after delivery with rapid normalisation of LFTs
    - No hepatic sequelae
    - *Tends to recur* with subsequent pregnancies (60-70%)
  - **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

Preeclampsia (Mild/ Severe) No moderate! Systolic > 160 mmHg Diastolic > 110 mmHg (or both) > 20 weeks gestation Previously normotensive Note just absolute BP Sudden ⇑ important 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	Main risk factors - Nulliparity/ primagravid - Diabetes - PHx or FHx pre-eclampsia - Multiple gestation - Obesity - Age >40 or <18 - Partner with previous partner with pre-eclampsia New onset HT - Documented on at least 2 occasions - At least 6 hours apart but no longer than 7 days Proteinuria (≥ 0.3g/ day OR persistant 1+ on dipstick, may reach nephrotic range > 5g/day) Oedema (no longer a diagnostic criteria) 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 (⇑ 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 May persist > 12 weeks post-partum
Preeclampsia on chronic HT	
Gestational HT Systolic $\geq$ 140 Diastolic $\geq$ 90 (or both)	Usually mild HT with NO proteinuria Occurs in later part of pregnancy Resolves by 12 weeks post-partum
Eclampsia	Develop tonic clonic seizures Seizures not attributable to other causes (eg hypoglycaemia)

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)