Liver Disease in Women: Evaluation of Abnormal Liver Tests
UCSF Controversies in Women’s Health Symposium
Monika Sarkar, MD, MAS
UCSF Division of GI/Hepatology
December 9th, 2016

Outline:
- Outpatient evaluation
- The key players
- Why sex matters
- Primary care management

Approach to Women with Abnormal LFTS (Liver Function Tests)

Disclosures
- None
Which are tests of liver FUNCTION?

- Total bilirubin
- Albumin
- Prothrombin time/INR

But not:
- AST/ALT/Alkaline phosphatase

Approach to Women with Abnormal Liver Function Tests

What is “normal”?  

- Normal = mean of the distribution ± 2 SD of the “normal” population  
  - 5% of “normal” patients will have values outside of the normal range  
    - 2.5% above and 2.5% below

- Normal ALT varies by sex:  
  - ULN of ALT = 19U/L in women & 30 in men
  - Lower threshold than flagged by most labs!

Two general patterns of liver injury

- Hepatocellular: Predominately AST and ALT
  - Mild (1-100 U/L): Chronic viral hepatitis, alcohol, NASH, drug induced, hereditary, autoimmune
  - Moderate (100-300 U/L): As above
  - Severe (>1000 U/L): Acute viral hepatitis, autoimmune hepatitis

- Cholestatic: Predominately Tbilii and alk phos
  - Low (less than normal): Wilson’s Disease
  - Mild elevation: Biliary obstruction (ie stones)
  - Moderate elevation: Primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC)
  - Severe (>1000 IU/L): Malignant infiltration by tumor

Case

- 60 yo woman presents for new primary care evaluation
- Routine labs: Tbili 0.8, AST 120, ALT 90, AP 111 (ULN 95)
- One year ago: Tbili 0.6, AST 97, ALT 83, AP 120

Case- history

PMH: Hypertension, dyslipidemia, hypothyroidism, chronic back pain, recurrent UTIs

Menopausal history: Menopause at age 46 yo

Meds: HCTZ, pravastin, tylenol 2-3g 1-2x per week, macrobid, levothyroxine

SHx: Has one glass of wine per night, no tobacco use, IVDU x 1 in 1973

Physical Exam

VS: T 37.3  HR 72  BP 149/79  SaO2 99%  RA  BMI 35

General: overweight, interactive

CV: Normal

Respiratory: Normal

Abdominal: soft, central adiposity, non tender, no hepatosplenomegaly

Extremities: warm, no edema

Skin- no palmar erythema, no spider angioma, no acanthosis

Initial Labs

Albumin 3.8

HgAIC 6.3

Lipids: TG 161, HDL 40, LDL 101
Case - Moderate Hepatocellular Injury
(Tbili 0.8, AST 120, ALT 90, Alk phos 111)

What additional testing would you perform?

Risk for Hepatitis C?

PMH: Hypertension, hyperlipidemia, hypothyroidism, chronic back pain, recurrent UTIs

Menopausal history: Menopause at age 46 yo

Meds: HCTZ, pravastin, tylenol 2-3g 1-2x per week, macrobid, levothyroxine

SHx: Has one glass of wine per night, no tobacco use, IVDU x 1 in 1973

FHx: Mother with type 2 diabetes

ID: 60 yo woman, born in 1956

Baby Boomers

Does menopausal age matter in Hepatitis C?

- Liver cells incubated in estrogen make less collagen - anti-fibrotic role of estrogens
- Cross sectional data show:
  - More severe liver fibrosis in post compared to pre-menopausal women
  - HRT protects against hepatic fibrosis
  - Fibrosis progression more rapid in nulliparous women

More than 75 percent of American adults with hepatitis C are baby boomers

- Risk assessment misses 50% of infected patients
- Screen with HCV Ab
- Birth cohort testing is cost effective
**Accelerated HCV Fibrosis Begins in Peri-menopausal Years**

- n=405 HIV/HCV co-infected women, followed for 18 yrs
- Anti-mullerian hormone (AMH) measured every 6 months
- Assessed rate of fibrosis in each women
- Captured peri-menopause (within 5 years of AMH loss) and menopause
- Fibrosis starts to accelerate in peri-menopausal years

Sarkar et al, AASLD November 11, 2015

---

**Why Cure HCV?**

- High chance of cure (95-100%), tolerable side effects, short course
- Halt progression, cause regression of fibrosis
- Reduced risk of cirrhosis, liver cancer, and LT
- Decreased all cause mortality
- For early stage disease, 15 year survival higher in patients cured of HCV (93% vs 82%, p=0.003)
- Cost of therapy declining as more meds flood the market & shorter durations
- Decreased transmission in IDU
- Extrahepatic manifestations improve: cognitive function, quality of life, work productivity, insulin sensitivity


---

**Who Should Be Referred for HCV Treatment?**

- Our patient is HCV Ab negative!
Could This Be Medication Related?

60 yo woman
PMH: Hypertension, hyperlipidemia, hypothyroidism, chronic back pain, recurrent UTIs
Menopausal history: Menopause at age 46 yo
Meds: HCTZ, pravastin 10 yrs, tylenol 3g per day 1-2 times per week, macrobid x 3 months
SHx: Has one glass of wine per night, no tobacco use, IVDU x 1 in 1973
FHx: Mother with type 2 diabetes

Sex Differences in Drug-Induced Liver Injury

- Women more likely to have drug induced liver injury from a spectrum of agents\(^1,2\)
- Women account for ~70% of cases of drug induced acute liver failure (ALF)\(^2,3\)

Acetaminophen (APAP/tylenol) toxicity

- Most common cause of acute liver failure
- So why do hepatologists love tylenol for pain control?
  - ≤ 3g per day is safe for healthy livers
  - ≤ 2g per day is safe for cirrhotic livers
- Among 145 healthy adults taking 4 grams of APAP per day (RCT of different pain regimens):
  - 76% had at least one ALT > 40
  - 53% had peak ALT > 80
  - 39% had peak ALT > 120
  - Similar risk by sex

\(^1\)Navarro, NEJM 2006,
\(^2\)Reuben et al, Hepatology 2010,
\(^3\)Sarkar et al, AASLD November 11th, 2016

Watkins, JAMA 2006; livertox.nlm.nih.gov
Macrobid started 3 months ago, not the likely culprit

Statin Hepatotoxicity

- Mild elevations present - 3-15% of patients
- Higher elevations (ALT > 3xULN) in < 1%
- Dose dependent but typically self limited without dose reduction
- Clinically significant injury extremely rare
- Discontinue if ALT > 10xULN (ie ALT > 200 in women)

Might be statin related, but let’s rule out other causes

Additional Viral Testing

- HIV Ab - Recommended by CDC for all patients 13-64 yo
- Hepatitis B: HBsAg -, HBcAb IgG -, HBsAb - HBsAg: tests for chronic infection HBcAb IgG: tests for exposure to virus (past or current) HBcIgM: tests for acute hepatitis B HBsAb: tests for immunity to hepatitis B (cleared or vaccinated) HBeAg/eAb: characterizes chronic HBV
- Hepatitis A: HAV Ab IgG+ HAV Ab IgG: to assess immunity HAV Ab IgM: tests for acute hep A (AST/ALT 1000s, N/V/jaundice)
Additional testing

- Abdominal US with dopplers
  - smooth contour
  - normal spleen
  - patent hepatic vessels
  - hepatic steatosis
- Iron level 54, Tsat 21%, Ferritin 105

Could This Be Hereditary Hemochromatosis (HHC)?

- Most common genetic disorder among Caucasians
  - Prevalence: 1:250 individuals of Northern European descent
- Mutation in genes involved in iron regulation
- AASLD guidelines: suspect HHC in patients with transferrin saturation >45% AND elevated ferritin (>200 ug/L for women, >300 ug/L for men)
- Diagnose by HFE genotype (not needed in our patient)
- Elevated ferritin present in >20% of pts with nonalcoholic steatohepatitis (NASH)

Risk for Autoimmune Disease?

60 yo woman
PMH: Hypertension, hyperlipidemia, hypothyroidism, chronic back pain, recurrent UTIs
Meds: HCTZ, pravastin, tylenol PRN, macrobid, levothyroxine
SHx: Has one glass of wine per night, no tobacco use, IVDU x 1 in 1973
FHx: Mother with type 2 diabetes
**Autoimmune Liver Disease**

**Autoimmune Hepatitis**
- F:M = 4:1
- All ages
- Prevalence: ~ 15/100,000
- Hepatocellular pattern
  - Serologies: ANA, ASMA, and IgG level
  - Liver biopsy
  - No need for anti-LKM

**Primary Biliary Cholangitis (PBC)**
- F:M = 9:1
- Mean age 50s
- Prevalence: 40/100,000
- Cholestatic pattern
  - Elevated alk phos & AMA
  - Liver biopsy not required
  - ~ 5% of PBC pts are AMA neg


**Question**

What is *most likely* cause of abnormal liver tests?

1) Autoimmune hepatitis
2) Autoimmune hepatitis plus NAFLD
3) Nonalcoholic Fatty Liver Disease (NAFLD)

**Autoantibodies in NAFLD**

- Positive ANA > 1:160 or ASMA >1:40 present in ~ ¼ of patients with NAFLD
- Positive AMA ~ 8% patients with NAFLD
- Autoimmune markers are not associated with severity of NASH on liver biopsy

Vuppalanchi R et al., Hepatol Int 2011
**Risk for Fatty Liver Disease?**

PMH: Hypertension, dyslipidemia, hypothyroidism, chronic back pain, recurrent UTIs

Menopausal history: Menopause at age 46 yo

Meds: HCTZ, pravastin, tylenol PRN, macrobid

SHx: Has one glass of wine per night?, no tobacco use, IVDU x 1 in 1973

FHx: Mother with type 2 diabetes

Physical Exam: BMI 35

---

**Causes of Fatty Liver**

**Drugs and Toxins**
- Alcohol
- Corticosteroids
- Tamoxifen
- Amiodarone
- Industrial solvents

**Nutritional Syndromes**
- Small bowel bypass
- TPN
- Rapid weight loss

**Inherited Metabolic Diseases**
- Lipodystrophy
- Abetalipoproteinemia
- Wilson’s Disease

---

**Obesity Trends Among U.S. Adults 1990**

BMI ≥30, or ~30 lbs. overweight for 5’4” person
Obesity Trends Among U.S. Adults

2000

2010

Epidemiology

- What is the prevalence of NAFLD in the general population?
  - 30% - it is the #1 most common cause of chronic liver disease in the United States
- Prevalence of NAFLD in hyperlipidemia?
  - 50%
- Prevalence of NAFLD in DM2?
  - 70%
- Prevalence of NAFLD in morbid obesity?
  - 80-90%

NAFLD = Hepatic Manifestation of the Metabolic Syndrome

Chalasani et al., Am J Gastro 2012
**Natural History**

- NAFLD 30%
- NASH 5-15%
- NASH F>M ~15 million U.S. women
- Cirrhosis 20%
- Cirrhosis Related Complications...

40-60% over 5-7 yrs

*Rinella ME, JAMA 2015*

**Public Health Implications**

NASH will be leading cause of:

- Cirrhosis
- Hepatocellular Carcinoma
- Liver Transplant

...in less than 5 years

*Charlton et al., Gastro 2011; Wong et al Hepatology 2014*

---

**Does Menopause Matter in NAFLD?**

- Similar to other metabolic co-morbidities, risk of NAFLD increases after menopause.
- HRT is associated with lower risk of NAFLD in post-menopausal women.
- Severity of NASH fibrosis is greater in:
  1. post- vs pre-menopausal women
  2. women with earlier age at menopause


---

**1) What is the most common cause of death in patients with NAFLD?**

1. Cirrhosis with portal hypertensive complications
2. Hepatocellular carcinoma (HCC)
3. Cardiovascular disease
1) What is the most common cause of death in patients with NAFLD?

1. Cirrhosis with portal hypertensive complications
2. Hepatocellular carcinoma (HCC)
3. Cardiovascular disease

**Mortality in NAFLD**

- Eligible: 12,822 (817 NAFLD)
- F/U: 8.7 yrs (median)

Causes of death in NAFLD:
1) CV
2) Malignancy
3) Liver

**Independent Risk Factors for Clinically Significant CAD**

- n=317 elective coronary angiogram
- n=85 normal or mild CAD and n=232 clinically relevant CAD

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty Liver</td>
<td>8.48</td>
<td>4.39-16.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.54</td>
<td>1.47-5.91</td>
<td>0.002</td>
</tr>
<tr>
<td>Male Sex</td>
<td>2.31</td>
<td>1.19-4.48</td>
<td>0.014</td>
</tr>
<tr>
<td>HTN</td>
<td>1.63</td>
<td>0.90-2.98</td>
<td>0.106</td>
</tr>
<tr>
<td>LDL</td>
<td>0.99</td>
<td>0.99-1.00</td>
<td>0.201</td>
</tr>
</tbody>
</table>

Mirbagheri et al. Liver internat. 2007

**Additional High Risk Groups**

- Hypothyroidism
- Obstructive Sleep Apnea
- Hypopituitarism & Hypogonadism
- Polycystic Ovary Syndrome

AASLD Practice Guidelines NAFLD 2014
**PCOS Diagnostic Criteria**

- Hyperandrogenism
- Oligomenorrhea
- Polycystic Ovaries

**Rotterdam Criteria (2/3):**
1) Oligomenorrhea
2) Increased ovarian follicles #
3) Hyperandrogenism

Prevalence: ~10% of pre-menopausal women!

---

**Epidemiology: NAFLD in PCOS**

- ~50% of PCOS women have ultrasound evidence of NAFLD
  
- At least 1/3 have elevated liver tests
  
  ~ 60% with ALT > 19U/L

- Likely relates to overlapping metabolic risk factors...

---

**Metabolic Co-Morbidities in PCOS**

- 65-70% have insulin resistance
- 50% have metabolic syndrome: 7x higher than age matched non PCOS controls
- Glucose intolerance or DM2 develops by age 30 years in 30-50% of obese women

---

**PCOS Phenotypes Are Variable- May be Subtle**
Thin Women With PCOS Also Develop IR

Adapted from Dunaif A, et al. JCEM, 1996

PCOS in NAFLD

- n=71 pre-menopausal women with NAFLD: 43% diagnosed with PCOS
- Pre-menopausal women with NAFLD attending a liver clinic (n=14):
  - 71% diagnosed with PCOS
  - n=5 biopsied- all had steatohepatitis
- It is worth inquiring about menstrual cycles and hirsutism in your pre-menopausal patients with NAFLD

Testosterone Level in Pre-Menopausal Women Is Associated With Prevalent NAFLD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Testosterone (quintiles)</td>
<td>1.29 (1.10-1.53)</td>
<td>0.001</td>
</tr>
<tr>
<td>Δ Waist Circumference</td>
<td>1.07 (1.06-1.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ Triglycerides</td>
<td>1.14 (1.08-1.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ HOMA-IR</td>
<td>1.32 (1.23-1.42)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

2. Brzozowska et al, J Gastro Hep 2009

Back to our patient... Diagnosing NAFLD

Abdominal imaging with steatosis +/- elevated liver enzymes

Exclude other causes of liver disease

Sarkar et al, AASLD presentation, November 12th, 2016
What To Order in Primary Care Setting

- HIV Ab
- HAV IgG
- HBV sAg / sAb / cAb IgG
- HCV Ab

For hemochromatosis: Iron level, Tsat, ferritin

US with dopplers: assess for vessel patency, steatosis, cirrhosis, portal HTN

Reasonable in women (but can defer to hepatology):
- For autoimmune hepatitis: ANA, ASMA, and IgG level
- For primary biliary cholangitis: AMA

Referred to Hepatology

- Could alcohol look like this? Yes
- Doesn’t AST>ALT indicate alcohol? (AST 120/ALT 90)
  It might.
- AST: ALT > 2 is classic for alcoholic steatohepatitis

Alcoholic Liver Disease (ALD) in Women

- Women at higher risk for ALD than men: higher blood alcohol levels with same amount of alcohol intake
- Women are smaller, less total body water, & decreased gastric alcohol dehydrogenase
- Max recommended drinks per week: 7 in women vs 14 in men

Referred to Hepatology

- AST > ALT also suggests advanced scarring in NASH.

- Lots of fat
- Grade 2/3 inflammation
- Stage 3/4 scarring

Standard drink
- 12 fl oz of regular beer
- 8-9 oz of malt liquor (bowmore 12 oz glass)
- 5 oz of table wine
- 1.5 oz of 80 proof spirits (whiskey, gin, vodka, tequila, etc.)

NAFLD TREATMENT

Exercise

Moderate intensity aerobic activity 3-6 times per week for 1-3 months no weight change but:
- Improved AST/ALT
- Decreases hepatic fat on imaging
- No data on histologic benefits
- Long term maintenance difficult

Thoma C et al., J Hepatol 2012

Nutrition

- Ideal NAFLD diet not clear: Mediterranean, Paleo?
- Saturated fat and fructose stimulate hepatic lipid deposition
- Low-mod fat restriction with mod-high carb restriction for 1-6 months 4-14% decreased weight
- Improved AST/ALT, insulin resistance, and hepatic fat

Thoma C et al., J Hepatol 2012

The Whole Package: Diet, Exercise, Behavioral Modification

- 31 obese pts, randomized 2:1 in Lifestyle (LS) vs Structured Education (controls) for 48 wks
- LS lost 9.3% versus 0.2% in controls, p=0.003
- More histologic improvement in LS group (72% vs 30%, p=0.03)
- Weight loss of ≥7% associated with improved inflammation and scarring (p <0.05)

Porrat et al., Hepatology 2010
**MEDICATIONS FOR NASH**

- RTC: Adults with biopsy proven NASH
- Excluded DM and cirrhosis
- Randomized to pioglitazone (n=80), Vitamin E (n=84), or placebo (n=83) for 2 years
- **1° endpoint = Improved liver histology**

**PIVENS Trial: Pioglitazone, Vitamin E, or Placebo for Non Alcoholic Steatohepatitis**

- Improved liver histology

**Histologic Improvement in NASH**

<table>
<thead>
<tr>
<th></th>
<th>Vit E</th>
<th>Placebo</th>
<th>Pioglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Improved</td>
<td>43%</td>
<td>19%</td>
<td>34%</td>
</tr>
</tbody>
</table>

*P = 0.001*  
*P = 0.04*

**Pioglitazone in NASH**

- Side effect profile may limit use: CV events, CHF, weight gain 3-5kg in 70% pts, bladder cancer?, bone fractures in post menopausal women
- Longterm safety and efficacy in NASH unknown
Our Patient
- Started Vitamin E 800 IU/day.
- Joined gym and lost 10 pounds in 6 months.
- Repeat liver tests at one year:
  - AST 120 → 45
  - ALT 90 → 50
- Remains at risk for heart disease and progressive fibrosis...aggressive co-management by PCP and hepatology is key!

Summary (I)
- ALT: most sensitive marker of liver injury, ALT > 19U/L is abnormal in women
- PCP w/u: alcohol/medication history, viral serologies, iron studies, and abdominal US
- Hepatotoxicity is more common in women: NIH LiverTox website is great resource!
- Screen baby boomers with HCV Ab

Summary (II)
- Consider HCV treatment in patients without life-threatening comorbidities
- NAFLD is most common chronic liver disease, present in 1/3 Americans
- NASH is more common in women
- NASH and HCV fibrosis accelerate after menopause

Summary (III)
- CAD is #1 cause of death in NAFLD
- Women with PCOS have high risk for NAFLD
- Consider screening PCOS women for NAFLD
- Inquire about menstrual cycles and hirsutism in pre-menopausal women with NAFLD
- Resource permitting, consider hepatology evaluation for all patients with NAFLD
Thank you!

- Questions....

Happy Holidays!

monika.sarkar@ucsf.edu