

# Update:

# Liver Disease and Pregnancy

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# Cirrhosis in women

## Incidence

- Cirrhosis in USA is *“less common in women (<40%) with lower mortality”*

38% on transplant list.

No incidence data for US women

UK incidence in women >50 years is 26 per 100,000

# Cirrhosis in women

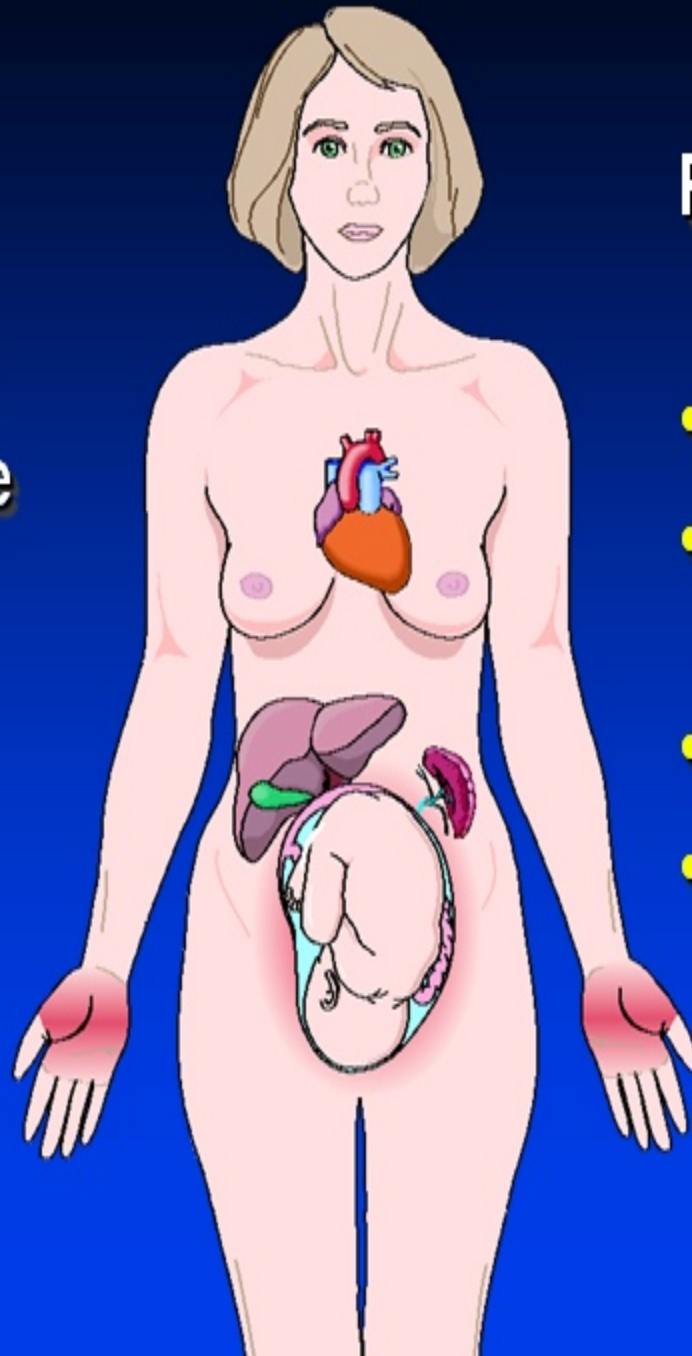
## Incidence and etiologies

- Frequency of underlying etiologies is different  
BUT generally clinical course and treatment is same
- Premenopausal female state associated with milder hepatitis C – most cirrhotics are menopausal or PMP.
- Slower fibrosis progression in hep C, hep B and PBC but more rapid in alcoholic liver disease *Poynard et al, 2003*
- Beware of smoking + alcohol in women with liver disease  
*Liu et al, 2009; Corpechot et al, 2012; Kamstrup Dam et al, 2013*

Females with  
cirrhosis during  
reproductive years

**0.045%** prevalence

- AiCAH
- PSC/PBC
- Wilson disease
- Viral hepatitis



Pregnancy

????

- **Fertility**
- **Risks to mother and fetus**
- **Breast feeding**
- **Posttransplant**

# Cirrhosis in women

## Fertility

Compensated cirrhosis, minimal portal hypertension

- $\pm$  menstrual periods and preserved fertility

Decompensated cirrhosis

- Hypothalamic-pituitary dysfunction leads to failure of ovulation, amenorrhea and infertility
- Menstrual history important
- Primary or secondary amenorrhea – conception unlikely
- Assisted conception has little success

# Cirrhosis in women

## Maternal risk of pregnancy: portal hypertension

- Pregnancy worsens portal hypertensive hemodynamics
- Maternal complications in 30-50% with 10-18% mortality
  - variceal bleeding – 20-45%, ↑ if pre-existing varices
    - Commonest cause of maternal death
    - Worse in 2<sup>nd</sup> trimester and postpartum period
  - postpartum hemorrhage 7-10%
  - rupture of SAA – 2.6%
  - ascites, SBP, HE, liver failure
- Risk correlates with degree of decompensation of cirrhosis
- Few data on optimal management in modern obstetric era.



# Cirrhosis in women

## Management of varices in pregnancy

No varices before pregnancy → EGD in second trimester

- Small varices – beta blockers ( fetal monitoring)
- Medium/large varices – beta blockers or endoscopic Rx
- High-risk varices – prophylactic band ligation

Large varices with previous GIB before conception

- endoscopic obliteration
- shunt ( surgical v. TIPS)
- delay pregnancy until after liver transplant

# Cirrhosis in women

## Management of varices in pregnancy

Moderate/large varices, no GIB (before or in 2nd trimester)

- beta blockers
- endoscopic therapy (prophylactic band ligation best if high-risk)

Acute bleeding – therapy same as non-pregnant except no vasopressin



# Cirrhosis in women

Maternal risk of pregnancy: disease flare

Pregnancy does not alter liver function in most patients

- Autoimmune hepatitis – flare in ~50%; poor outcome with persistent clinical activity and/or decompensated cirrhosis; maintain stable therapy.
- PSC, Wilson, hepatitis C, hepatitis B – no deterioration  
**BUT** continue therapy in Wilson, Hepatitis B

# Cirrhosis in women

## Management of pregnancy

Pregnancy possible in well-compensated, inactive cirrhosis on stable therapy but.....

- Pregnancy high-risk and counseling about maternal and fetal risks very important
- Coordinated care – high-risk obstetrician, hepatologist
- Early miscarriage rate (15-20%), termination rate (15-20%) and perinatal mortality (11-18%) all increased.
- Control of portal hypertension - EGD, ultrasound (SAA)
- Dietary sodium restriction to reduce portal pressure
- No contraindication to breast feeding ( except D-pen)

# Cirrhosis in women

## Contraception

Few data on effects of contraception in cirrhosis

- WHO expert Working Group 2008      Kapp et al, 2009

Compensated or mild, decompensated cirrhosis

No restriction on any hormonal contraception

Severe decompensated cirrhosis

No hormonal contraception

Unplanned pregnancies do occur and can be dangerous for mother

Tubal ligation after completion of child-bearing

# Cirrhosis in women

## Contraception

### Risk of HCC and the combined oral contraceptive (COC\*)

- WHO study 1989 – no link b/n COC and HCC
- No increase in HCC despite widespread use in hepatitis B and C  
Lam et al, 2005
- Meta-analysis –739 cases and 5223 controls  
no significant association with < 5 years use,  
longer use ??  
Maheshwari, 2007

\* COC has 99% efficacy

# Cirrhosis in women

## Choices of contraception

Present-day COC ( less oestrogen) safe

- oral or trans-dermal; 99% efficacy
- avoid in active hepatitis, BCS or decompensated cirrhosis

Intrauterine device ( IUD)

- Highest efficacy, no increase in infection risk
- Bleeding unlikely unless low platelets or coagulopathy

Progesterone-only preparations

- Minimal hepatic effects; depoProvera lasts 3 months

Barrier methods safe but less effective

# Hepatitis B

- universal screening of pregnant women for HBsAg has reduced perinatal transmission
- transmission is proportional maternal HBV DNA:
  - 10% if HBeAg -ve and HBeAb+ve
  - 90% if HBeAg +ve
- <3% transmission if Ig immunoprophylaxis and vaccine of infants, otherwise 40%
- transmission if acute HBV complicates pregnancy:
  - rare if during 1st trimester
  - 6% if during 2nd trimester
  - 67% if during 3rd trimester



# Chronic Liver Disease and Pregnancy

- **alcoholic liver disease:**
  - pregnancy rarely occurs
  - fetal alcohol syndrome
- **autoimmune hepatitis:**
  - fertility regained on treatment
  - continue immunosuppression
- **Wilson disease:**
  - fertility regained on treatment
  - continue chelation therapy
- **PBC:**
  - cholestasis may worsen - use urso

## Case

- 30 year old woman with hepatitis C comes to your office
- She and her husband would like to get pregnant

## Case (cont'd)

- Can you predict the natural history of her hepatitis C during pregnancy?
- Should she be treated with interferon and ribavirin before pregnancy?
- Can the patient get pregnant during or after treatment?
- When should her child be tested for HCV ?

# Hepatitis C

- Conte et al (Hepatology, 2000)
  - 15,250 consecutive deliveries
  - 370 HCV Ab+
  - 72% viremic

Mother	HCV RNA+	ALT levels proportion high ALT
1st month	61 (10-384)	56.4%
Third trimester	24 (8-337)	15 (4-43)
6 mos post delivery	63 (8-600)	14 (8-17)

# Hepatitis C

	Time from Delivery (months)				
	0	4	8	12	18
Total newborns					
(n)	366	167	161	155	103
anti-HCV+	366	151	102	25	9
	(100%)	(90%)	(63%)	(16%)	(9%)
HCV-RNA+	18	2	8	8	8
	(4.9%)			(5.1%)	
(became viremic)	0/6	6			

# Hepatitis C

- Transmission was confined to HCV RNA+ mothers
  - 2,150,000 +/- 1,045,010 copies/ml in those who transmitted
  - 2,038,375 +/- 983,456 copies/ml in those who did not transmit
- Transmission rate not affected by type of delivery
  - 1% of C-sections
  - 3% vaginal deliveries
- Transmission rate not affected by type of feeding
  - 2% breastfed infants
  - 2% infants fed artificially



# Case

- 35 year old female is underwent liver transplant 3 mos ago for ESLD secondary to hemochromatosis and alcohol
- patient wants to get pregnant
- currently on tacrolimus and prednisone; recently tapered off cellcept
- uncomplicated post transplant course
- amenorrhea x 5 years prior to transplant

# Cirrhosis in women

## Liver transplantation

<u>% female</u>	<u>2001</u>	<u>2011</u>	<u>2013 ( to date)</u>
Waiting list	42%	37.6%	38%
<u>Transplanted</u>	<u>35%</u>	<u>33.3%</u>	<u>35%</u>

SRTR data

### Moylan et al, 2008

- Women less likely to receive LT within 3 years of listing in pre- and post-MELD era
- Women more likely to die or become too sick for LT post-MELD

# Pregnancy After Liver Transplantation

- Normal menstrual function returns to 90% within 10 months after OLT
- Successful, with little risk to allograft function if timed and planned pregnancy
  - High risk of rejection if conceive within 6 mos of transplant
  - therefore recommend conception after 1st year
- Reproductive-aged recipients need contraception and preconception counseling
- Highest risk in those with preconceptional renal dysfunction

# Pregnancy After Liver Transplantation

- In general higher risk of:
  - preeclampsia (?CSA > tacrolimus)
    - NOT organ specific-ie seen also with kidney tx
  - worsening hypertension
  - preterm rupture of membranes
  - anemia
  - small for gestational age
  - preterm delivery
  - C-section
  - no increased incidence of gestational DM

# National Transplant Pregnancy Registry

- Established in 1991 to study outcomes of pregnancy after transplant
- Over 2000 recipients with 3000 pregnancies included
- Anyone can report a pregnancy, available online
- Last report: 450 pregnancies in 306 recipients, 76.9% live births (general population live birth rate 66.7%)

# Immunosuppression

- Do NOT stop all immunosuppression during pregnancy
  - Severe acute cellular rejection
  - Subsequent miscarriage
- 10% of pregnancies complicated by acute cellular rejection



# Immunosuppression Medication

- Tacrolimus category C, ok to use but levels must be monitored every 2-4 weeks since changes in P450 or plasma expansion can change levels quickly
  - Neonatal hyperkalemia and renal impairment possible
- Cyclosporine category C, but toxicities were seen at doses 2-5x higher than that used
- Prednisone category B, but infants with risk of hypoadrenalism
- Sirolimus category C: animal studies with increased risk of fetotoxicity
  - Can cause Azoospermia
- Azathioprine category D

# Immunosuppression Medication

- Mycophenolate mofetil NOT OK
  - Cellcept or Myfortic
  - Pregnancy category D
  - Serious congenital anomalies in 23%
    - Cleft lip/palate, microtia
  - Increased risk of spontaneous abortion in first trimester
  - FDA recommends two forms of birth control

# Factors resulting in favorable pregnancy

- Good general health for 2 years after transplant
- No graft rejection in past year
- Adequate and stable graft function
- No acute infections that might affect the fetus
- Maintenance immunosuppression at stable doses
- Patient compliance with treatment and follow up
- Normal blood pressure or blood pressure well controlled with one medication
- Normal allograft ultrasound results

# Factors that Worsen Pregnancy Outcomes

- Etiology of the original disease that resulted in transplant (risk of recurrence)
- Chronic allograft dysfunction
- Renal insufficiency
- Cardiopulmonary diseases
- Hypertension
- Diabetes mellitus
- Obesity
- Maternal infection with HBV, HCV, or CMV

# Complications that can Occur

- Maternal
  - pregnancy-induced hypertension
  - Intrauterine infections
  - Anemia
  - Pre-eclampsia
  - Cholestasis
  - Pyelonephritis
- Abnormal LFTs occur in 3-6%, usually in 3<sup>rd</sup> trimester, usually normalize

# Complications that can Occur

- Obstetric and Delivery:
  - Congenital CMV infection (highest in pregnancies occurring <6 months after transplant)
  - Perinatal infection with HBV or HCV

# Complications that can Occur

- Fetal:
  - Prematurity (40% of live births)
  - Intrauterine growth retardation (20%)
  - Prenatal infections
  - Birth defects (4-7%, slightly higher than general population)
  - Immune suppression

# Cirrhosis and Pregnancy

- reduction in fertility (50%) because of anovulatory menstrual cycles or amenorrhea
- reversible in most after liver transplantation within first year
- high risk of bleeding if portal hypertension and varices
- ? eradication with sclerotherapy or banding
- increased bleeding with delivery
- consider pregnancy after liver transplantation