Pregnancy related liver disease

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DISCLOSURES

No financial disclosures relevant to this presentation

QUESTION 1

In which trimester an acute fatty liver disease of pregnancy occurs

a. Second trimester

b. Third trimester

QUESTION 2

What is an additional therapy in intrahepatic cholestasis of pregnancy

a. Cholestyramine

b. Rifampicine

PREGNANCY RELATED LIVER DISEASE

Laboratory	Pregnancy
Hemoglobin	↓ (2nd trimester)
Leucocytes	↑
Thrombocytes	None
Bilirubin	None
Alkaline phosphatase	↑ (placenta, bone)
ALAT	None
ASAT	None
Albumin (g/L)	↓
GGT	None
Prothrombin time	None
Alpha-fetoprotein	↑

PREGNANCY RELATED LIVER DISEASE

- Hyperemesis gravidarum
- Intrahepatic cholestasis of pregnancy
- Pre-eclampsia
- HELLP
- Acute fatty liver disease of pregnancy

CASE

A 28 year old female, G2P1, 29+4 weeks of gestation, referred for itch, fluctuating abdominal pain and elevated liver function tests.

Medical history: Cholecystolithiasis

Physical examination:

RR 138/ 88, Pulse 84, T 37.2

Scratch marks on her skin and little jaundice

Laboratory results (GP):

Bilirubin 29 umol/l, ALAT 102 U/L, ASAT 66 U/L, Alkaline phosphatase 136 IU/L, gGT 56 U/L, Hemoglobin 7.3 mmol/L, Thrombocytes 140 x 10e9/L

Urine screening: protein +

LIVER DISEASE

- Pruritis gravidarum
- Hyperemesis gravidarum
- Intrahepatic cholestasis of pregnancy
- Pre-eclampsia
- HELLP
- Acute fatty liver disease of pregnancy
- Choledocholithiasis

CASE

Ultrasound

Normal homogenous liver, no dilatated bile ducts. Gallbladder: no evident stones. Normal vasculature with normal flow.

Laboratory results

Bilirubin 37 umol/l, ALAT 139 U/L, ASAT 80 U/L, Alkaline phosphatase 230 IU/L, gGT 99 U/L

Virology & immune serology negative.

CASE

Ultrasound

Normal homogenous liver, no dilatated bile ducts. Gallbladder: no evident stones. Normal vasculature with normal flow.

Laboratory results

Bilirubin 30 umol/l, ALAT 139 U/L, ASAT 80 U/L, Alkaline phosphatase 230 IU/L, gGT 99 U/L

Virology & immune serology negative.

Bile acids: 43 umol/L

=> Intrahepatic cholestasis of pregnancy

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

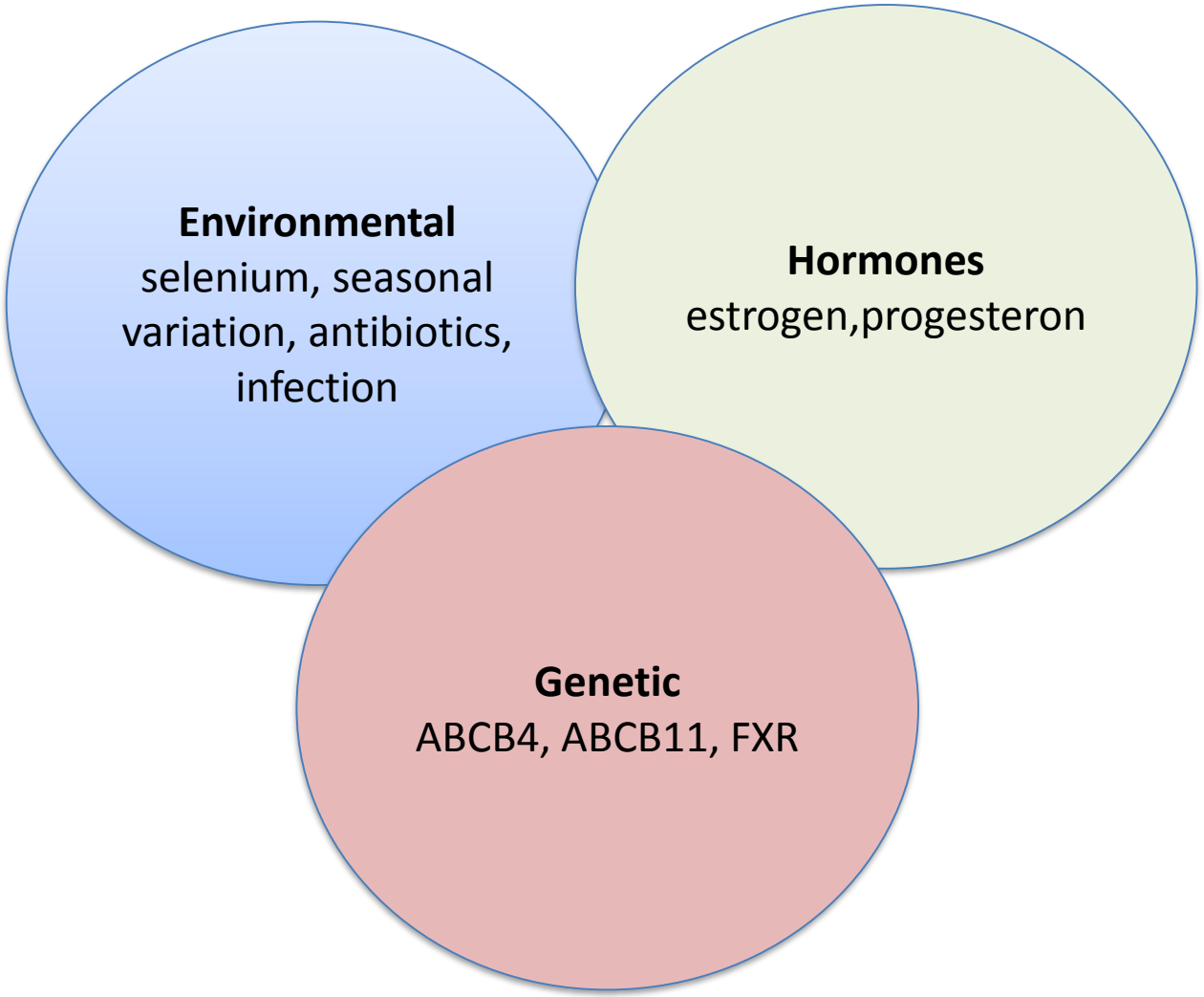
0,1% - 1.5% of pregnancies

Second-third trimester (25-32 weeks)

Clinical features
Generalised pruritis (palms, soles)
Jaundice (15%), steatorrhoe

Labatory findings
Serum bile acid ↑
Liverfunction tests ↑ (Transaminases, Alk phosphatase)

PATHOGENESIS



Wijampreecha Clin Res Hepatol 2017

CASE

Risk of complications?

FETAL COMPLICATIONS

- CTG abnormalities
- Meconium: 16-58%
- Spontaneous preterm labour: 30-40%
- Sudden Intra Uterine Death: 3.5%

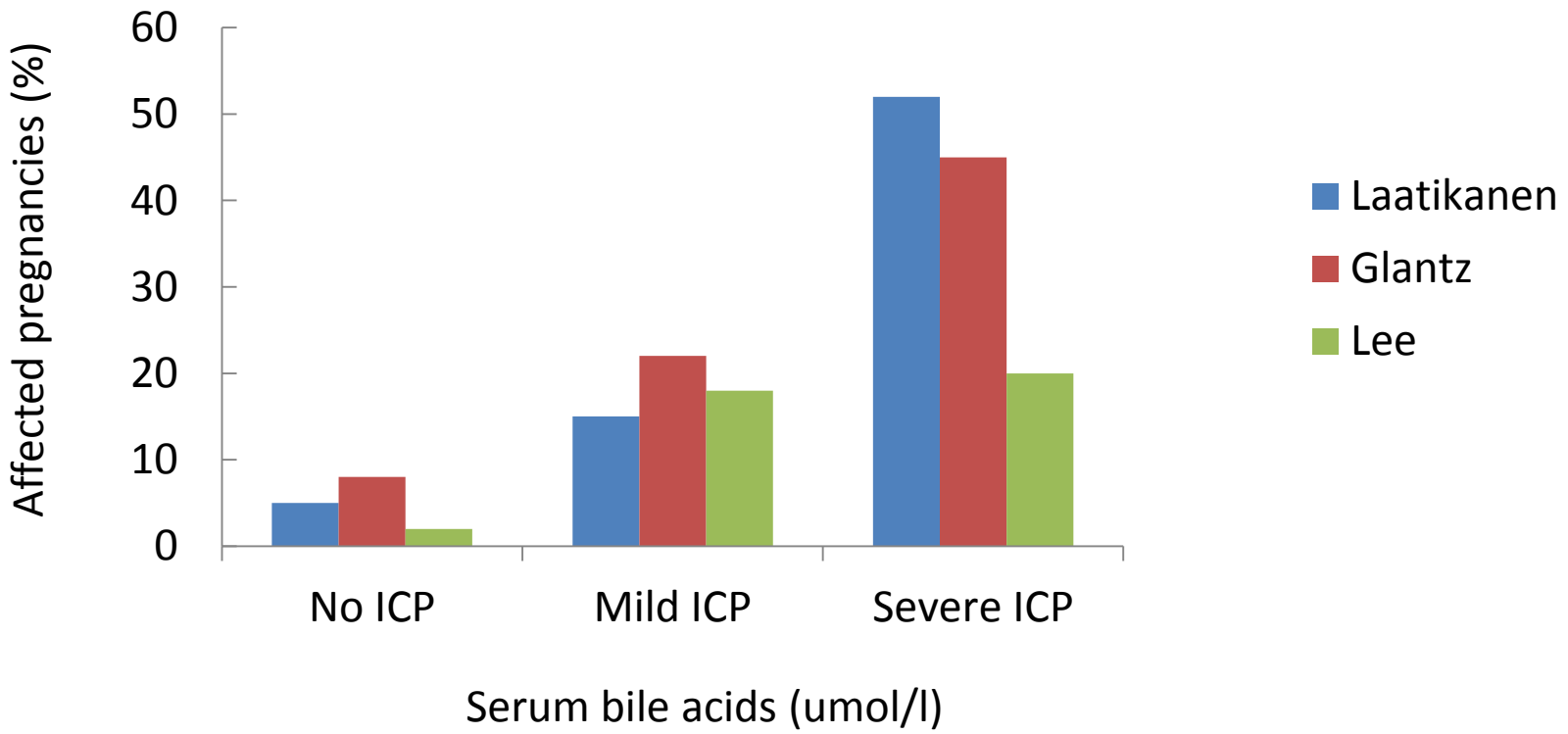
Lee, Am J Perinatol 2008
Glantz, Hepatology 2004

FETAL COMPLICATIONS: MECONIUM

No ICP < 10 umol/l

Mild 10-40 umol/l

Severe > 40 umol/l

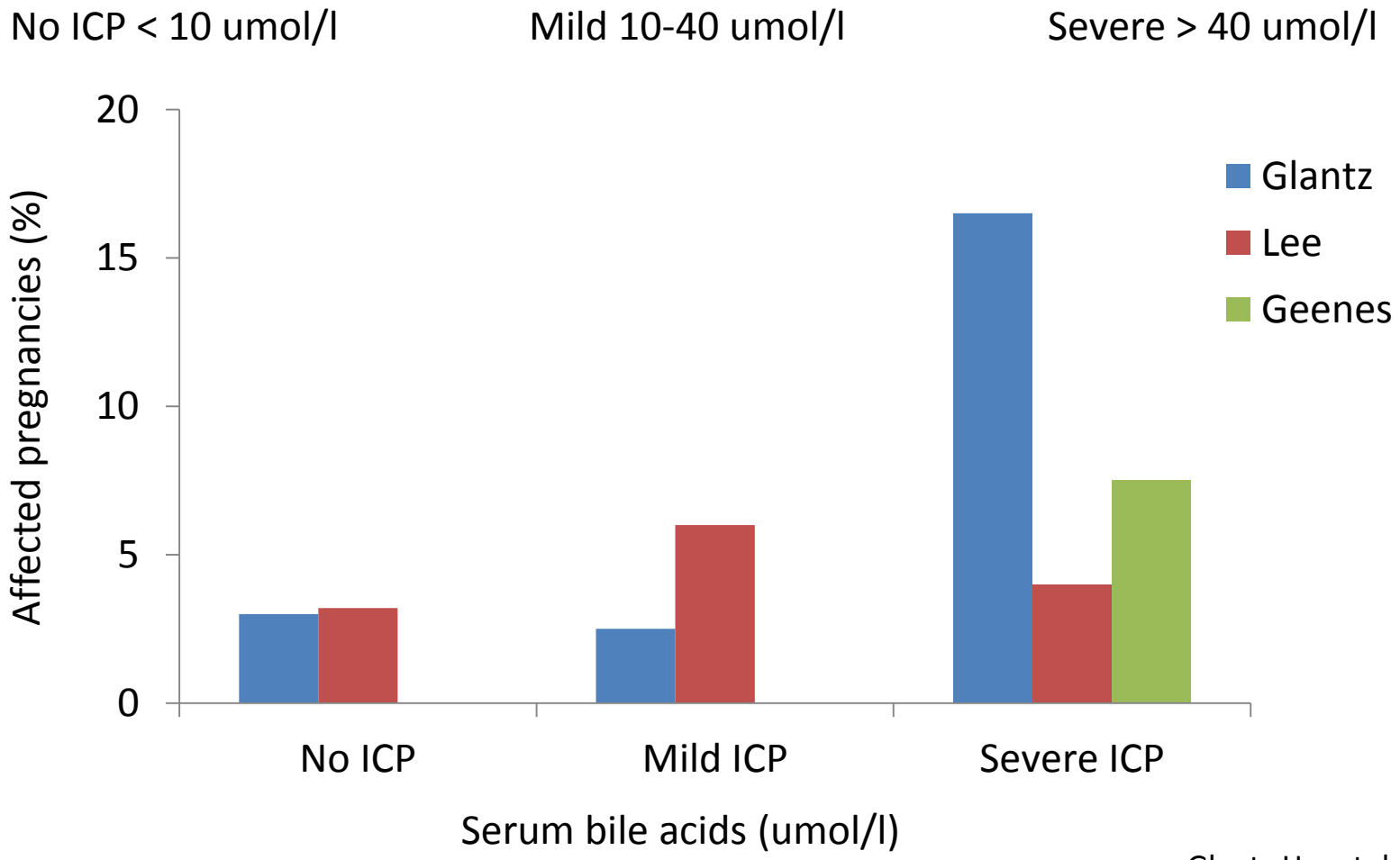


Laatikanen Int J Gynaecol 1984

Glantz Hepatology 2004

Lee J Perinatol 2006

FETAL COMPLICATIONS: PRETERM LABOUR



Glantz Hepatology 2004
Lee J Perinatol 2006
Geenes Hepatology 2014

MANAGEMENT

- Fetal monitoring
- Nutritional support, vitamin K
- Drugs

  Ursodeoxycholic acid 10-20 mg/kg
- Elective delivery at 37 weeks

Wood. Obstet Gynaecol Surv 2018
Gurung. Cochrane Database Syst Rev 2013

CASE

Started with Ursodeoxycholic acid

34+6 weeks of gestation

Ursodeoxycholic acid dose up to 20 mg/kg/day

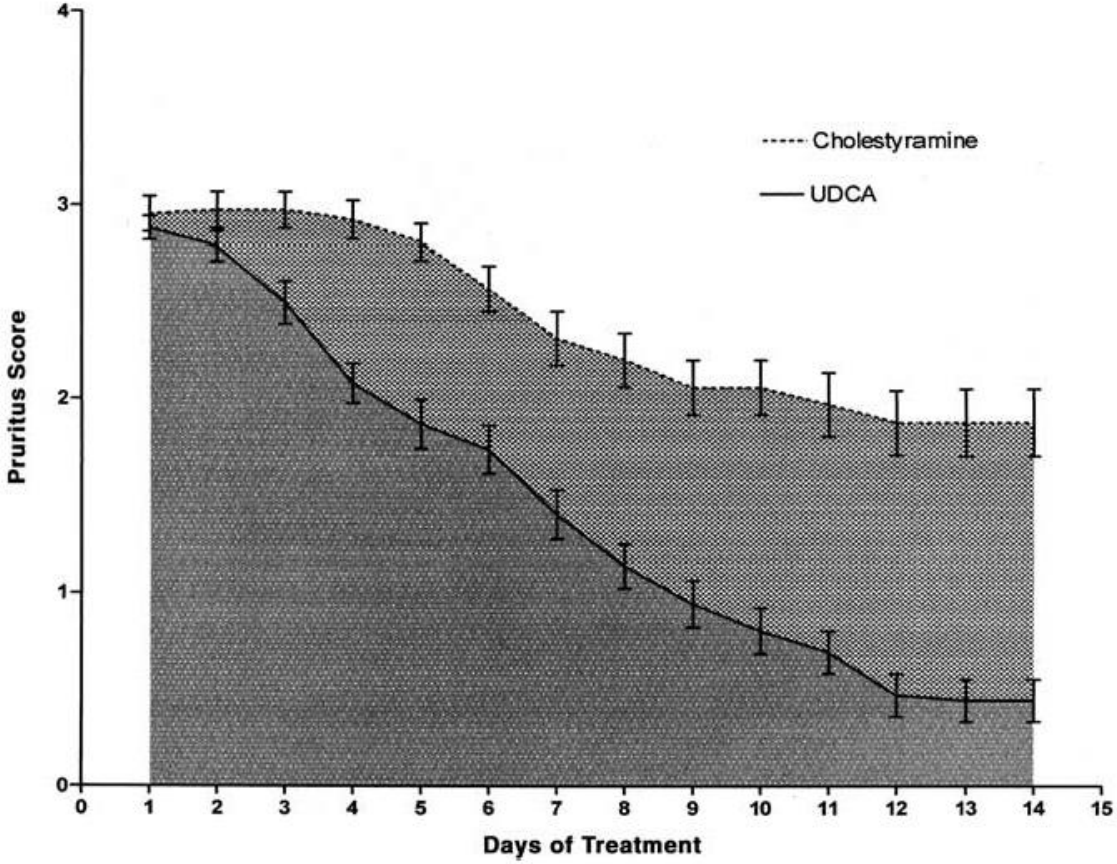
Laboratory results

Bilirubin 28 umol/l, ALAT 156 U/L, ASAT 99 U/L, Alkaline phosphatase 278 IU/L, gGT 104 U/L

Bile acids: 83 umol/L

Onbearable pruritus

MANAGEMENT: CHOLESTYRAMINE



Kondrackiene Gastroenterology 2005

MANAGEMENT: RIFAMPICINE

Retrospective cohort, 28 pregnancies in 27 women

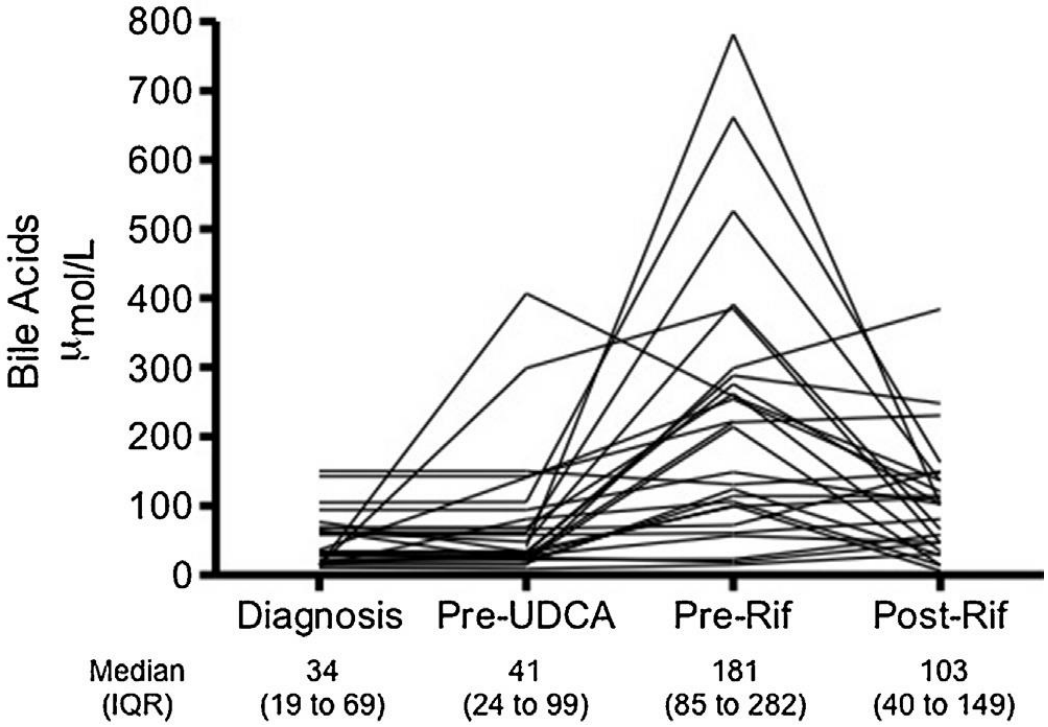
Add-on rifampicine 3rd trimester

Dosage: UDCA 500-1500 mg, rifampicine 300-1200 mg

Mean duration treatment rifampicine 2 weeks

Geenes European J Obst Gyn 2015

MANAGEMENT



Geenes European J Obst Gyn 2015

MANAGEMENT: RIFAMPICINE

14 (54%) reduction in bile acids

10 (38%) > 50% reduction in bile acids

4 (15%) > 50% reduction in ALT
3 (12%) > 50% reduction in bilirubin

10 (37%) reduction of pruritis

No predictors of respons on rifampicine

Geenes European J Obst Gyn 2015

MANAGEMENT

- Fetal monitoring
- Nutritional support, vitamin K
- Elective delivery at 37 weeks
- Drugs

  Ursodeoxycholic acid 10-20 mg/kg

  Rifampicine (3rd trimester)

  Cholestyramine: questionable

  ~~Dexamethason / s-adenosyl methionine: no role~~

Wood. Obstet Gynaecol Surv 2018

Gurung. Cochrane Database Syst Rev 2013

CASE

37+1 weeks of gestation delivery

Healthy girl, weight 2610 gram

APGAR score 9

Laboratory results normalised

PROGNOSIS

- Postnatal recovery (< 2 weeks)
- Recurrence subsequent pregnancy
- Increased risk hepatobiliary disease

HYPEREMESIS GRAVIDARUM

Excess vomiting, occuring in 0.3% of pregnancies

First trimester (4-10 weeks)

Pathogenesis: unknown

Hyperthyrodism, DM, cultural background, psychiatric

15-25% increased transaminases (up to 4x ULN)

Supportive therapy

PRE-ECLAMPSIA

De novo hypertension (≥ 140/90) & Proteinuria (≥ 300 mg/day)

Multisystem disorder, occurs in 3-5% of pregnancies

2nd-3rd trimester (20 weeks, 4 weeks postpartum)

Riskfactors:

- Previous pre-eclampsia
- Hypertension
- Diabetes
- Kidney or auto immune disease

PATHOGENESIS

Abnormal placentation

↓

Placental hypoperfusion

↓

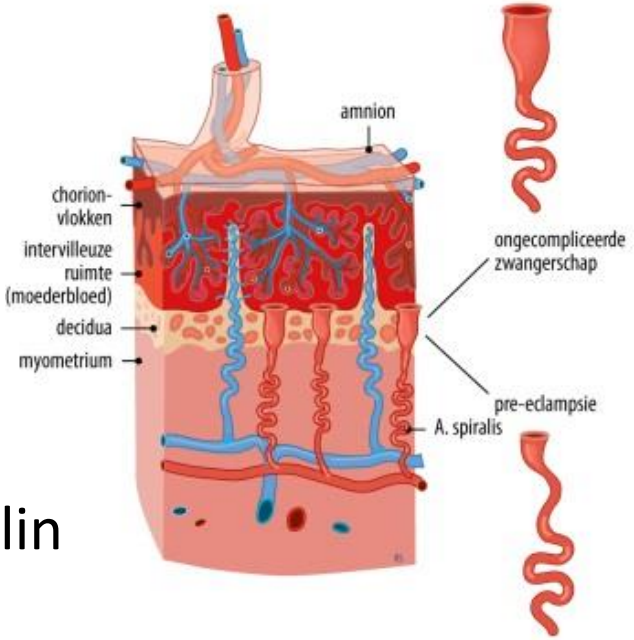
Release of NO, prostaglandines, endothelin

↓

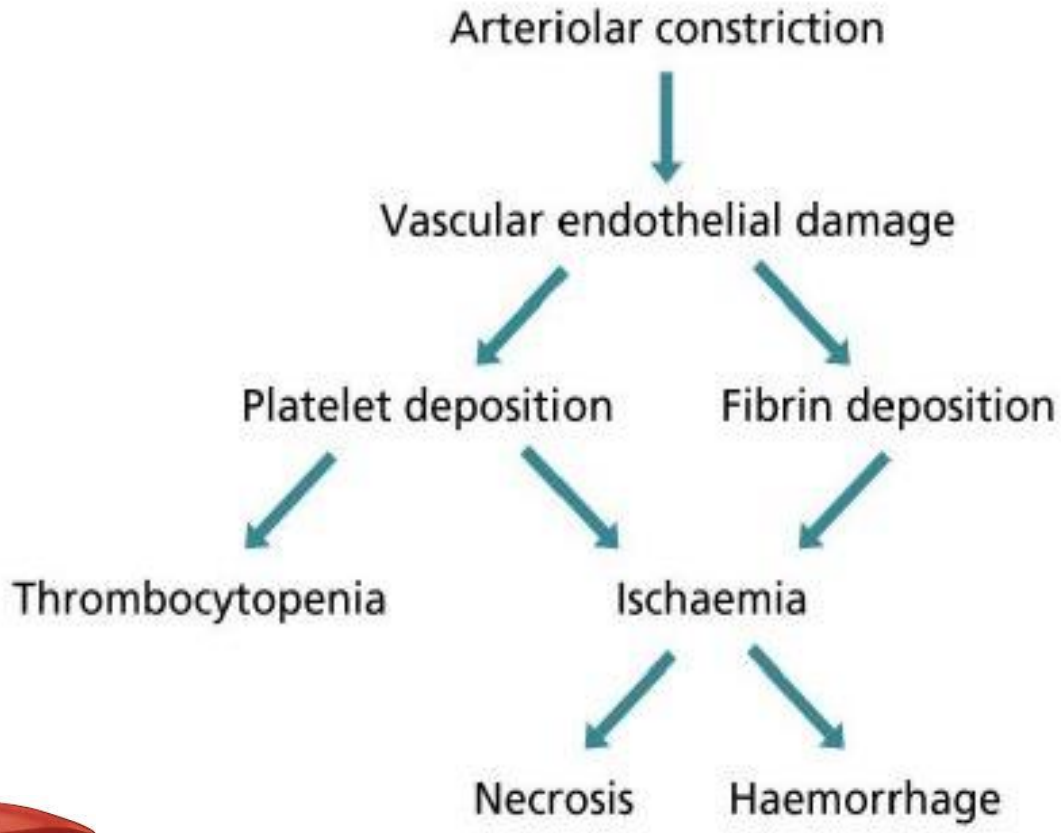
Endothelial dysfuntion, Platelet aggregation

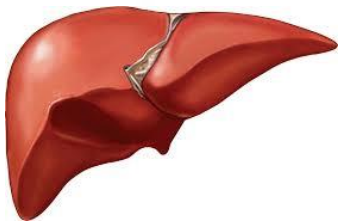
↓

Release fibrin: Fibrin deposition in small blood vessels



PATHOGENESIS LIVER





CLINICAL FEATURES

Mostly absent

Nausea, vomiting, headache

Right upper quadrant abdominal pain

Oedema

Liver involvement 30%

- elevated transaminases (5x ULN)
- severe disease

HELLP SYNDROME

Haemolysis **E**levated **L**iver enzymes **L**ow **P**latelets

Severe form of pre-eclampsia, occuring in 10%

2nd – 3rd trimester (week 27-36)

Riskfactors: advanced maternal age, multiparity, Caucasian

Pathogenesis: unknown, imbalance pro / antiangiogenic factors & proinflammatory cytokines

CLINICAL FEATURES

Significant number asymptomatic

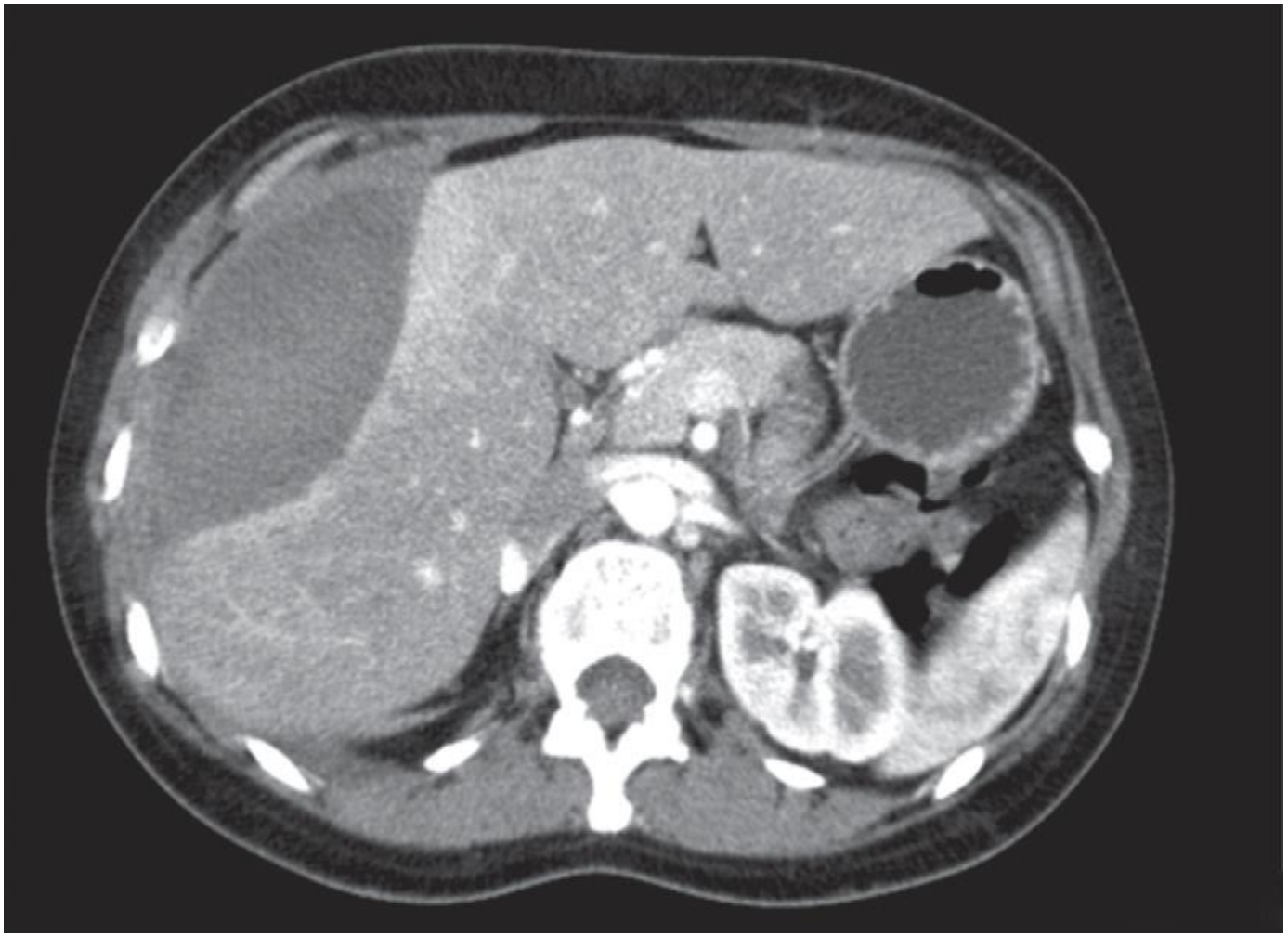
RUQ or epigastric pain	65%
Nausea & vomiting	35%
Headache	30%
Bleeding & jaundice	

Laboratory analysis

- Elevated transaminases (2-30 fold) & hyperbilirubinemia
- Hemolysis parameters
- DIC, PT

Imaging: abdominal pain, shoulder tip pain, hypotension

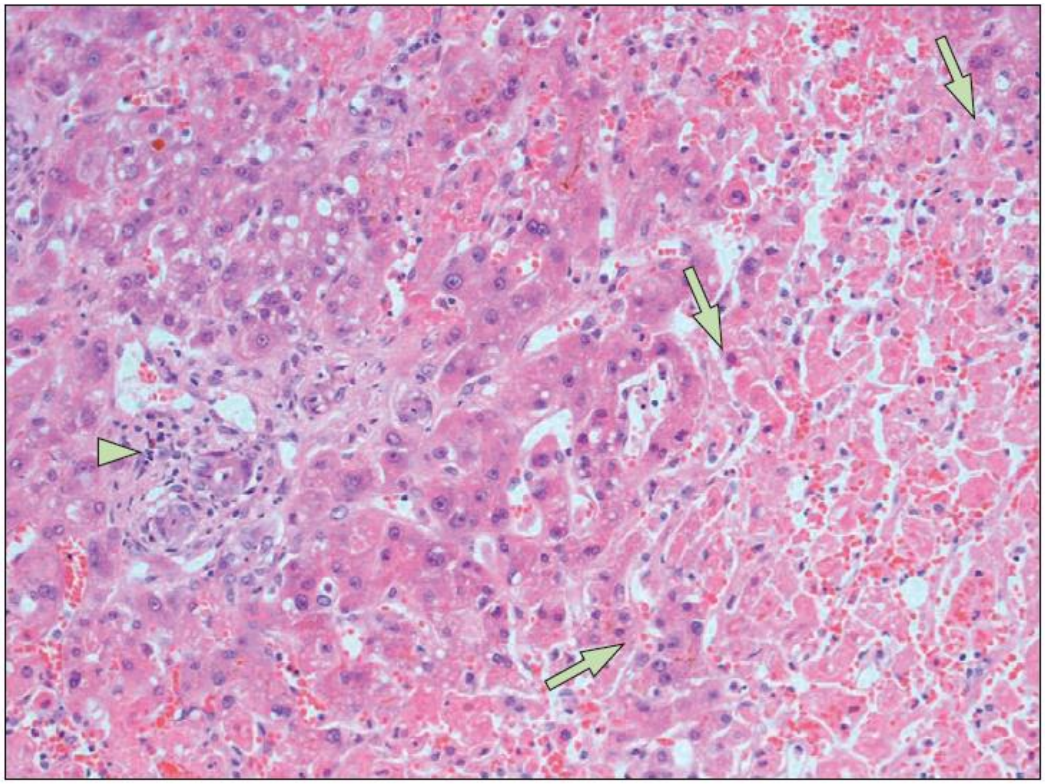
COMPLICATION



Joshi Lancet 2010

DIAGNOSIS

Biopsy not indicated



Periportal changes with haemorrhage, sinusoidal fibril deposition and necrosis

Joshi Lancet 2010

CLINICAL CLASSIFICATION SYSTEMS

Tennessee system

AST >70 IU/L

LDH >600 IU/L

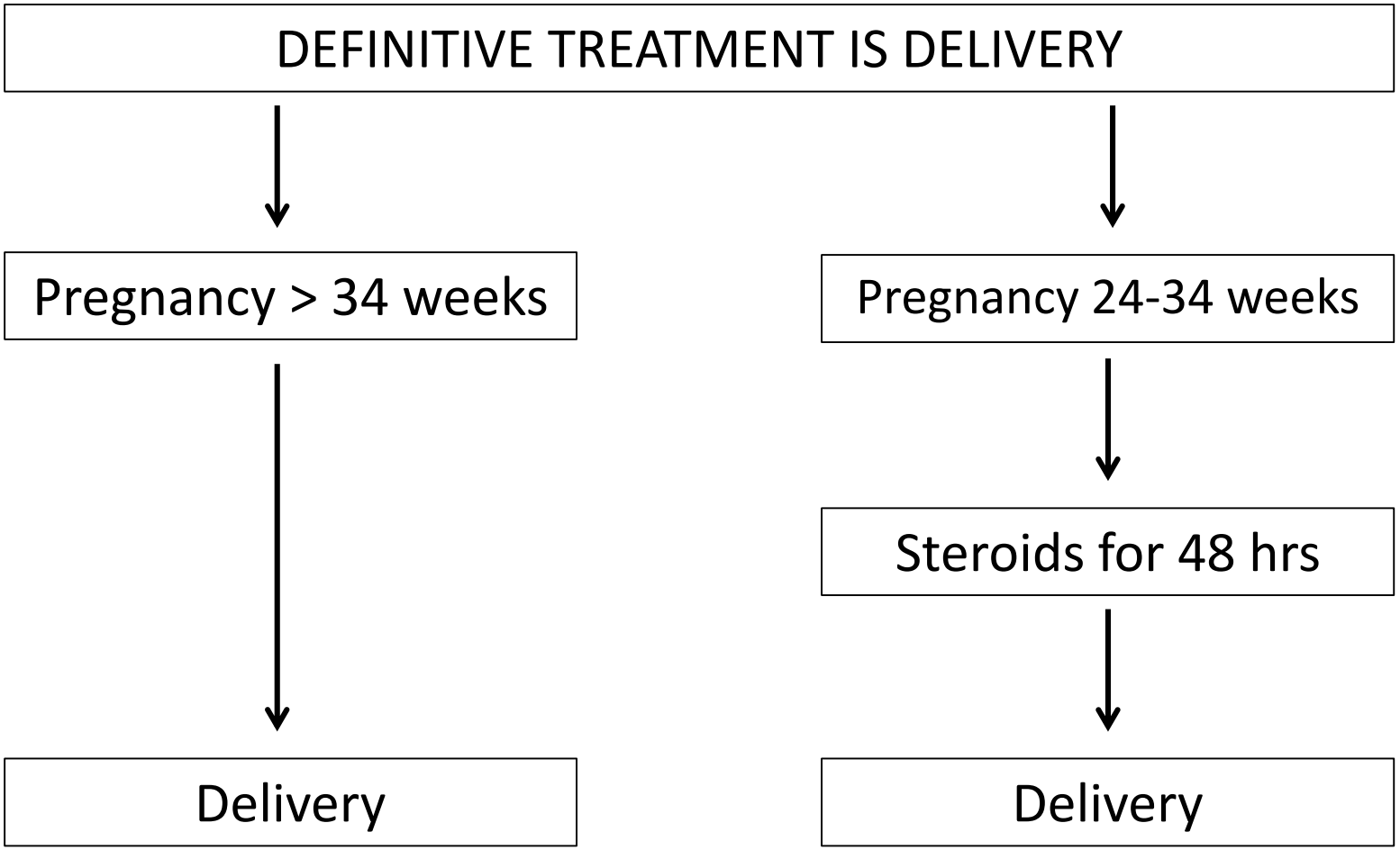
Thrombocytes $<100\times10^9$/L

Mississippi system

AST >40 IU/L and LDH >600 IU/L and:

- Class I: platelets $<50\times10^9$/L
- Class II: platelets $50–100\times10^9$/L
- Class III: platelets $100–150\times10^9$/L

MANAGEMENT


DEFINITIVE TREATMENT IS DELIVERY
Pregnancy > 34 weeks
Pregnancy 24-34 weeks
Steroids for 48 hrs
Delivery
Delivery

MANAGEMENT

Steroids: promote fetal lung maturity

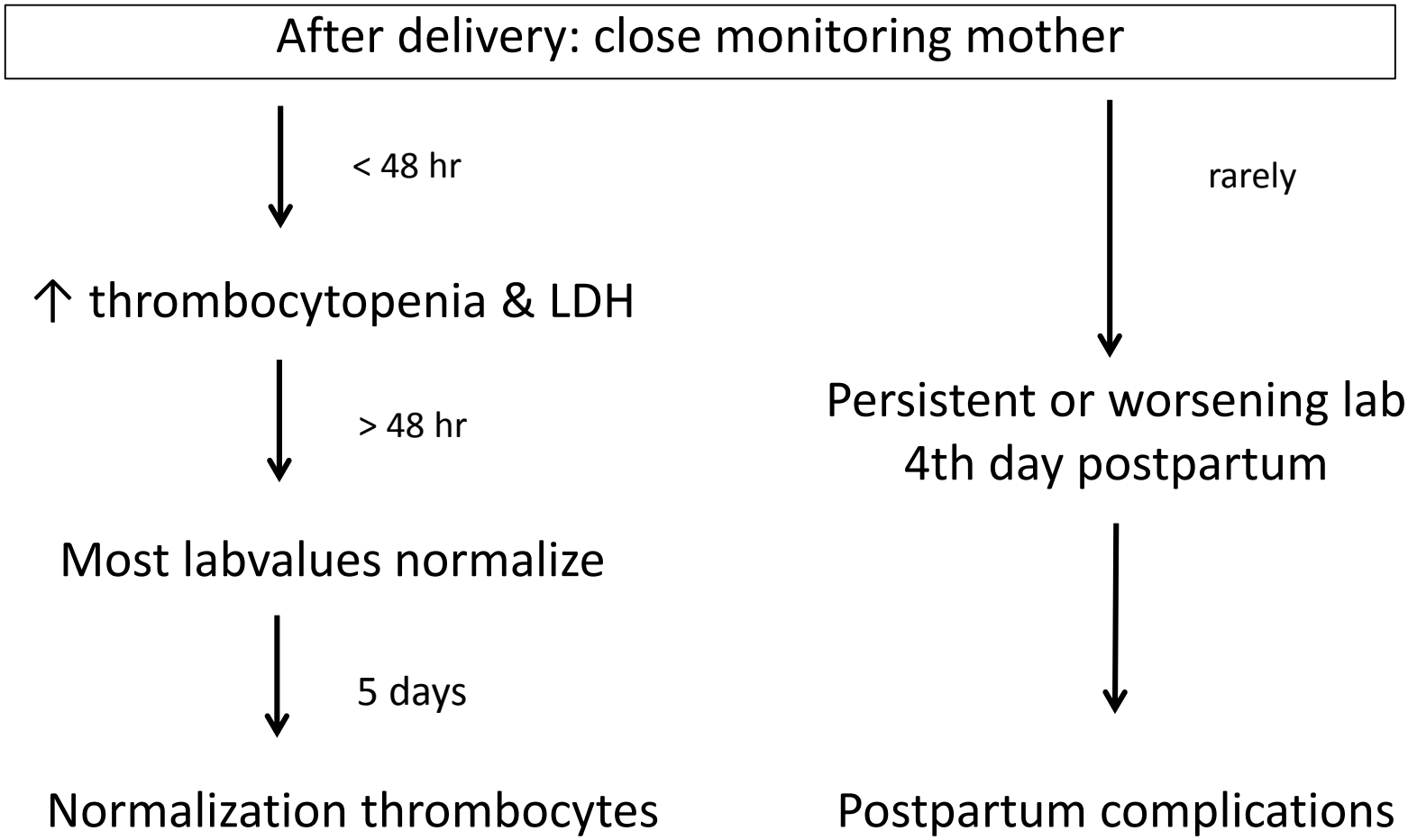
Cochrane review:

- Maternal effects
  - Improved platelet count & transaminases
  - No difference in mortality: RR 0.95, CI 0.28-3.21
  - No difference in morbidity: RR 0.27, CI 0.03-2.12

No evidence for other therapies: plasmaferesis, dialysis

Woudstra Cochrane Database Syst Rev 2014

PROGNOSIS


After delivery: close monitoring mother
< 48 hr
↑ thrombocytopenia & LDH
> 48 hr
Most labvalues normalize
5 days
Normalization thrombocytes
rarely
Persistent or worsening lab
4th day postpartum
Postpartum complications

ACUTE FATTY LIVER OF PREGNANCY

Rare, but serious complication of pregnancy

3rd trimester

Incidence 1: 20 000

High mortality

maternal: 18%

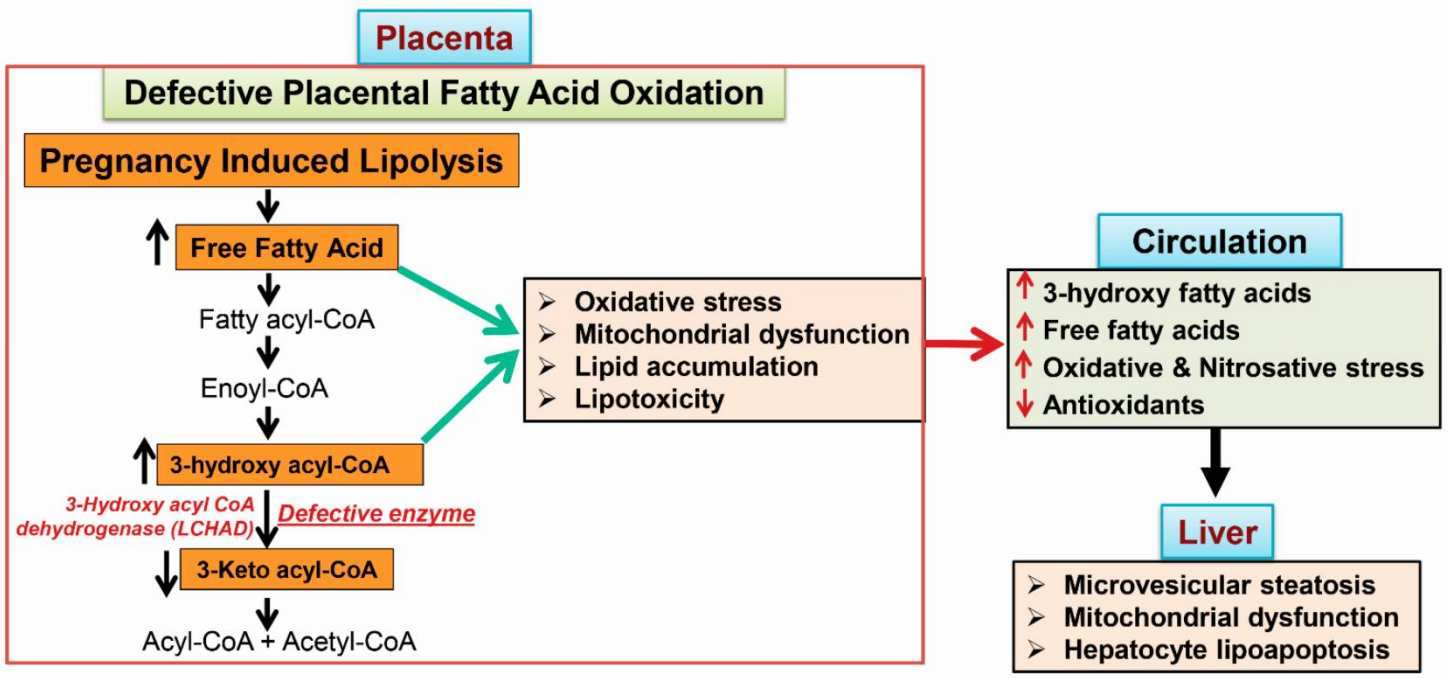
fetal: 23%

More common in nullparous, twin pregnancies, male infants

Knight. Gut 1999

PATHOGENESIS

Fetal homozygous mutation (1528G>C) in the gene for mitochondrial long-chain hydroxy acyl-CoA dehydrogenase (LCHAD).



Natarajan Int. J. Mol. Sci. **2018**

CLINICAL FEATURES

Usually after week 30 of gestation (35-36 week)
Gradual onset with nausea, vomiting, fatigue
Abdominal pain

Co-existing factors
Pre eclampsia (mild hypertension and mild proteinuria)

Signs of acute liver failure

- Jaundice
- Hypoglycemia
- Hepatic encephalopathy
- Coagulopathy

LABORATORY FINDINGS

Hyperbilirubinemia (> 85 umol/l)

Elevated transaminases (variable, usually 300-500)

Anemie, thrombocytopenia and leucocytosis

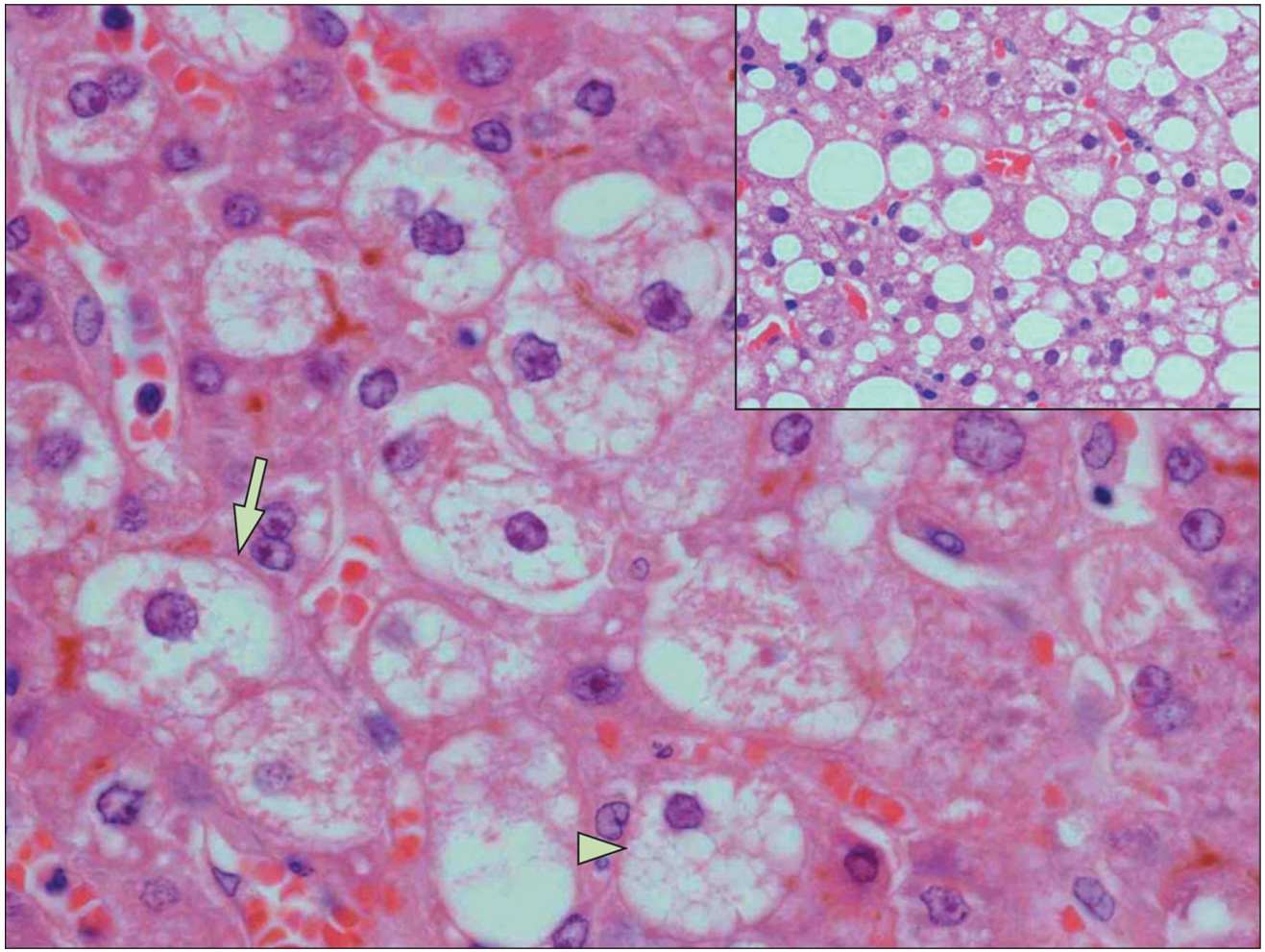
DIC, hypo albuminemia

Signs of mitochondrial failure (ammonia, lactate acid)

Complications

Ascites, renal dysfunction, respiratory failure, acute pancreatitis

LIVERBIOPSY



Westbrook Journal of Hepatology 2016

SWANSEA DIAGNOSTIC CRITERIA

Six or more features below in the absence of other aetiology
Vomiting
Abdominal pain
Polydipsia/polyuria
Encephalopathy
Bilirubin (> 14 umol/L)
Hypoglycaemia (4 mmol/L)
Leucocytosis (> 11 x 10^6/L)
Elevated uric acid (> 340 umol/L)
Elevated ammonia (> 42 IU/L)
Ascites or bright liver on USS
Elevated transaminases (> 42 IU/L)
Renal impairment (creantine > 150 umol/L)
Coagulopathy (PT > 14 s or APTT > 34 s)
Microvesicular steatosis on biopsy

MANAGEMENT

Early recognition & diagnosis + Rapid delivery fetus

Majority	→	2-3 days postpartum Improvement liver functon
Sometimes	→	Persistent lab abnormalities & May initially worse 1st postpartum week
Rarely	→	Progress to fulminant hepatic failure

Most patients improve 1 to 4 weeks postpartum

AFLP

Dutch data, 3 transplant centers, period 1979-2012

Ltx in 2 of 2445 (<0.1%) with AFLP

Aug 2004- aug 2006: 12 cases liver morbidity, no deaths

Incidence 3.2 / 10 000 deliveries

UK data, 229 hospitals, period feb 2005- aug 2006

57 women AFLP

1 LTX, 1 death

Ringers BJOG 2015

Knight Gut 2008

PREGNANCY RELATED LIVER DISEASE

	Trimester (week)	% Pregnancy	Liverfunction pattern	Histology	Therapy
Hyperemesis gravidarum	1 (4-10)	0.3	↑ ALT (2-5x)	-	Supportive
Intrahepatic cholestasis	2-3 (25-32)	0.1-1.5	↑ ALT (1.5-8x) ↑ bile acid (1.5-15x)	Cholestasis	Ursochol (Rifampicin)
Pre-eclampsia	2-3 (20->)	1-1.5	↑ ALT (2-5x)	Necrosis, bleeding	Delivery
HELLP	2-3 (27-36)	0.2-0.6	↑ ALT (2-30x) ↑ bili (1.5-10x)	Necrosis, bleeding	Delivery
AFLP	3 (35-36)	0.005-0.01	↑ ALT (3-15x) ↑ bili (4-15x)	Microvesiculair fatdeposition	Delivery

QUESTION 1

In which trimester an acute fatty liver disease of pregnancy occurs

a. Second trimester

b. Third trimester

QUESTION 2

What is an additional therapy in intrahepatic cholestasis of pregnancy

a. Cholestyramine

b. Rifampicine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