Cholestasis in Pregnancy

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Faculty/Presenter Disclosure

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I have no relationships with for-profit or not-for-profit organizations.

Objectives of this Presentation

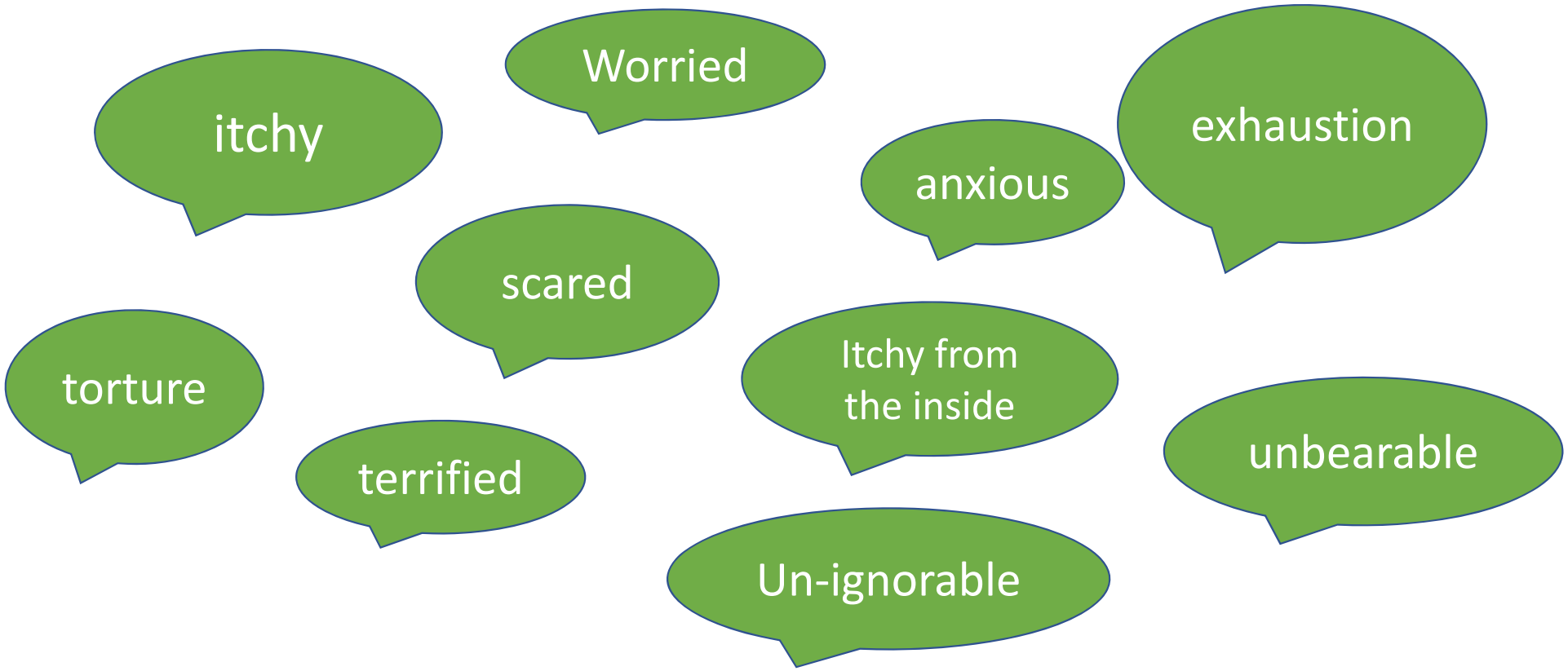
- Identify Signs and Symptoms of Cholestasis in Pregnancy.
- Select and interpret relevant investigations.
- Manage symptoms and plan for delivery based on current guidelines.
- Practice and evidence

Definition

“Cholestasis of Pregnancy is a multifactorial condition of pregnancy characterised by Pruritus in the absence of skin rash and accompanying abnormal LFTs with no other alternate diagnosis and resolves after birth.”

Green Top Guideline RCOG 2011 (8)

Living with Cholestasis in Pregnancy



Potential impact on fetal and maternal health

The fetus is at increased risk of :

- Stillbirth
- Preterm birth, highest rate associated to iatrogenic cause
- Increased risk of meconium in utero

The pregnant person is affected by:

- Pervasive itch causing fatigue, insomnia and distress
- The condition can result in reduced appetite
- Risk of depression and anxiety

Association of Severe Intrahepatic Cholestasis of Pregnancy with adverse pregnancy outcomes.

A Prospective Population Based Case Control Study -Hepatology. 2014 Apr; 59(4): 1482–1491. Published online 2014 Feb 26. doi: 10.1002/hep.26617 ref. (2)

Adverse outcome	Severe ICP	General Population
Preterm Labour	Singleton n= 669 risk of PTL 164/664 rate of 25% adj. OR 5.39, 95% CI 4.17-6.98	N= 2200 144/2200 rate of 6.5%
Neonatal admission	80/654 rate of 12% adj. OR 2.68 , 95% CI 1.97-3.65	123/2192 rate of 5.6%
Stillbirth	10/664 rate of 1.5 %	11/2205 rate of 0.5%

Identify Signs and Symptoms of Cholestasis in Pregnancy.

Pruritus

- Pruritus that commonly affects the extremities, the palms of hands and soles of feet.
- No accompanying rash, excessive scratching can cause excoriations.
- Symptoms are worse at night can result in insomnia

(1) A Deadly Itch. RCM Midwives Magazine 20th May 2010

(10) .Sebiha, Veli, Ozkan and Yildirim S. Review of a challenging clinical issue: intrahepatic cholestasis of pregnancy. World J Gastroent 2015:21(23):7134-7141

Less common signs

- Darkening of urine
- Pale stool
- Exhaustion
- Reduced appetite

(1) A Deadly Itch. RCM Midwives Magazine 20th May 2010

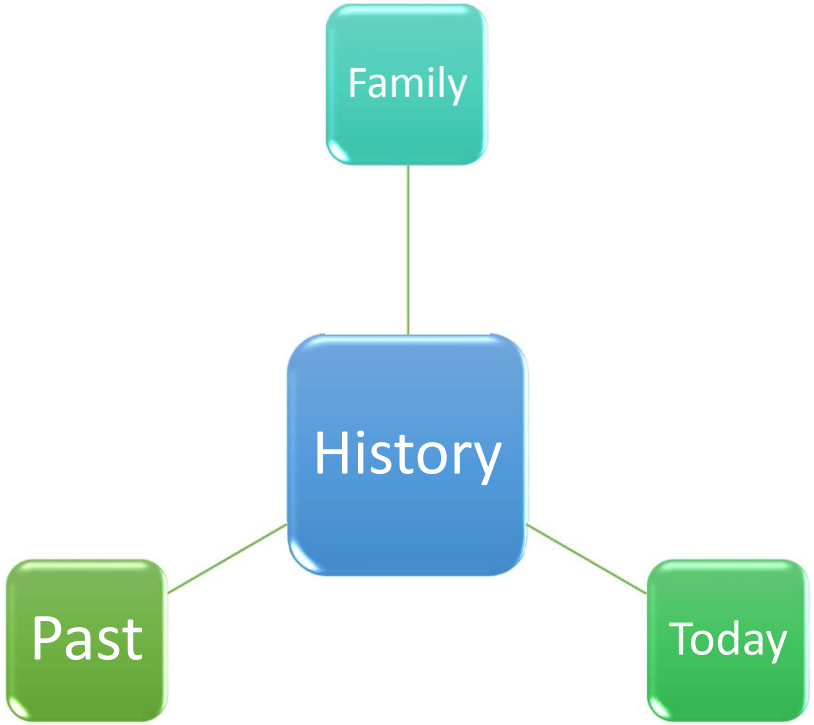
Rare Signs

- Jaundice
- Right upper quadrant pain
- Nausea

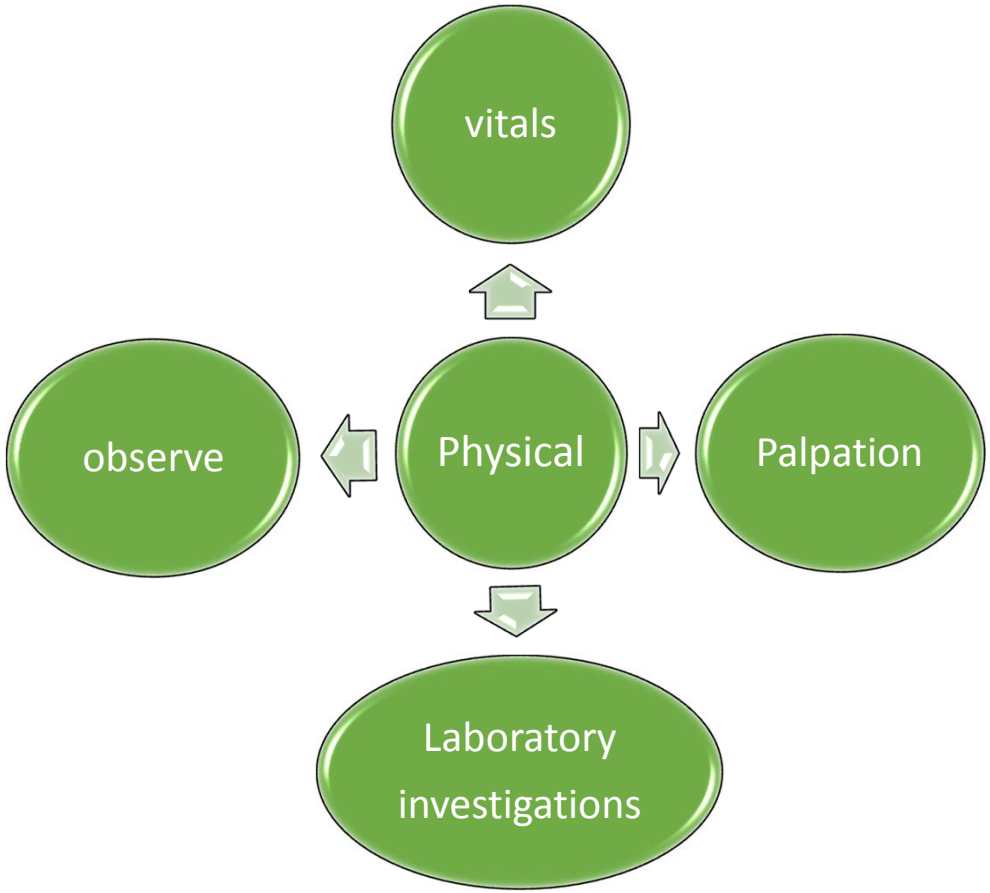
(1) A Deadly Itch. RCM Midwives Magazine 20th May 2010

Select and interpret relevant investigations

History



Physical


vitals
observe
Physical
Palpation
Laboratory investigations

Laboratory Investigations

- Liver function tests must include bile acids.
- Results strongly correlated with Cholestasis:

  ALT > 32 umols/l

  Bile acids > 10umols/l

  (3),(4)
- Other elevated LFTs may be aligned with other pathologies
- The upper limit of pregnancy specific-ranges are used as the reference range and is 20% below the non pregnant state. (3)

Pregnancy Specific reference ranges for LFTs in Pregnancy.

Liver Enzymes	Non-Pregnant	1st Trimester	2nd Trimester	3rd Trimester
AST (IU/l)	7-40	10-28	10-29	11-30
ALT (IU/l)	0-40	6-32	6-32	6-32
Bilirubin (umol/l)	0-17	4-16	3-13	3-14
GGT (IU/l)	11-50	5-37	5-43	3-41
Alk Phos (IU/l)	30-130	32-100	43-135	133-418
Bile Acid (umol/l)	5-10		5.3-5.7	5.6-6.5

Reference: https://www.researchgate.net/publication/24243142.Liver_function_test_and_pregnancy

Suggested Classification of severity of Cholestasis based on bile acid levels.

Severe

Bile Acids > 40 umols/l

Mild

Bile Acids < 40umols/l

ref- (4) (8)

of note bile acid testing is a non insured test- out of hospital cost is charged to the client.

Laboratory Investigations cont'd.

- Clotting screen

- Urea, electrolytes, creatinine and urates

- Serology for Hep A, Hep B and C. Epstein Barr virus and CMV
- Auto-antibodies
- Ultrasound of Liver and Gall Bladder

ref (13). Tran T, Ahn J, Reau N. Liver disease and pregnancy 2016: Am J Gastroent :111:176

Manage Symptoms and plan for Delivery based on current guidelines

Obstetric Care

Upon diagnosis

- The client should be counselled about the potential implications of this disorder.
- Recommend referral to a high risk Obstetric care provider.
- Low risk care providers can remain as part of the woman’s team in a supportive role.

Prenatal Monitoring

- Symptomatic with normal bile acids

  Repeat initial bloodwork every 10 to 14 days.

- Confirmed diagnosis

  Regular blood work assessing LFTs and bile acids.

  Instructing the woman on monitoring fetal activity.

  NSTs and ultrasounds for clinical reason not as a routine.

ref-(8).Obstetrics Cholestasis Green-Top Guideline No.43 April 2011

Non-Pharmacologic

- Avoid high fat diet.
- Tepid baths prn.
- Loose cotton clothing.
- To try and avoid scratching.
- Emotional health support strategies.

ref (12) 194https://www.smfm.org/publications/96-understanding-intrahepatic-cholestasis-of-pregnancy

Pharmacologic

Ursodeoxycholic acid (UDCA)

- **Mechanism**

  It is thought this hydrophilic acid replaces the endogenous hydrophobic acid which is thought to be causing the impairment of liver function. (12)

- **Clinical effect**

  Symptomatic relief of pruritus.

  Decreases elevated bile acids and LFTs.

- **Dose**- 500mg po bid up to max dose 500mg po tid for severe cases. (13)

- **Antihistamines.**
  Used to help alleviate itch probably more useful with aiding sleep.

- **Topical Emollients**
  There are different products prescribed aimed at the temporary relief of symptoms with varying success.

- In this community Health Care providers have been prescribing creams compounded with menthol is in common use.

Plan for Delivery

- When do we Induce ?

- Practice has ranged from 36 weeks to 38 weeks. Overall current consensus is after 37 completed weeks. (1)

- Fetal Prognosis is not directly linked with severity of signs and symptoms- studies do suggest that higher serum levels of bile acids may correlate with increased risk of mortality.

  ref – www.ncib.nlm.nih.gov.pmc/articles/PMC4476874 (13)

Informed Choice Counselling for elective early delivery.

- Active vs expectant management pros and cons for both.
- Mild cholestasis does not appear to have a negative influence on fetal outcomes.
- Elective induction at 37 weeks is stronger for severe Cholestasis in pregnancy.

In Summary

- Cholestasis in pregnancy increase risks of poor fetal outcomes
- Abnormal bile acids and alt helps confirm the diagnosis.
- UDCA reduces symptoms and can decrease elevations in bile acids.
- Induction at 37 weeks for severe ICP is reasonable
- Research is ongoing to develop evidenced based management and interventions.

Examples of Guidelines in existence.

- Green Top Guideline # 43,2011-RCOG.ORG.UK (8)
- Clinical Guideline for Diagnosis and Management – Royal Cornwall Hospital. NHS Trust uk (14)
- Society for Fetal Maternal Medicine – Understanding IHCP (12)
- UpToDate makes reference to Green Top Guideline #43
- ACG – American Journal of Gastroenterology –Liver Disease and Pregnancy 2016 (13)

Research

Research in this field is ongoing.

- What is not fully known is :

  Pathophysiology of Cholestasis In Pregnancy.

  How fetal death occurs .

  Prevention and intervention strategies that are evidenced based.

  Efficacy and risk of using UDCA and development of new therapies.

ref.(1)

Current Research

PITCH(Pregnancy Intervention Trial in Cholestasis) Study 2009-2011 a small pilot study comparing UDCA with placebo and early with late delivery.

received more funding to do a larger PITCH Study examining the efficacy of UDCA.2015

ref PITCH:ISRCTN37730443.

Heparin, rifampicin and nor-UDCA being studied for Obstetric Cholestasis.

http://www.britishlivertrust.org.uk/home/research/british-liver-trust-funded-research/ongoing-research.aspx

Table of Medications used historically in Cholestasis in Pregnancy

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4476874/table/T1/?report=objectonly

This link refers the reader to

Cholestyramine

S-adenosyl methionine

Dexamethasone

Phenobarbital

These therapies are not generally prescribed today.

References

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8.Obstetrics Cholestasis Green-Top Guideline No.43 April 2011

9.Reid R, Ivey KJ, Rencouret RH. Storey B. Fetal Complications of obstetric cholestasis. Br Med J. 1976 ;1:870-2

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12.194https://www.smfm.org/publications/96-understanding-intrahepatic-cholestasis-of-pregnancy
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14. Clinical Guideline for Diagnosis and Management – Royal Cornwall Hospital. NHS Trust uk