نحوه اپروچ به خانم ۳۱ ساله با شکایت خارش جنرالیزه مراجعه کننده به درمانگاه پزشکی خانواده

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Chief complaints

بیمار خانم ۳۱ ساله با شکایت خارش

Present illness

بیمار خانم باردار ۳۱ ساله، G3P2 که در هفته ۳۱ بارداری با شکایت خارش جنرالیزه به مرکز خدمات جامع سلامت مراجعه کرده است. پس از چک پروفایل آنزیم های کبدی بیمارجهت ارزیابی اولیه، افزایش AST و ALT رویت می شود که جهت ارزیابی های بیشتر و بستری توصیه به مراجعه به بیمارستان ضیائیان می شود. بیمار سابقه ۲ نوبت زایمان قبلی را نیز ذکر می کند که در هردو نوبت گذشته نیز خارش را تجربه کرده است. هر دو زایمان به روش طبیعی و ترم بوده است(پسر ۶ ساله و دختر ۱۱ ساله)

PMH: (-)

SH: (-)

AH: (-)

DH: (-)

HH: (-)

FH: (-)

Physical Examination

بیمار خانم میانسال هوشیار و اورینته – toxic - ill

ملتحمه pale نیست

اسکلرا icteric نیست – کاشکتیک نیست

V/S:

BP:120/70 RR:19 T:36.8 PR:87 SPO2:96 %

سمع قلب S1 و S2 بدون سوفل

سمع ریه نرمال و قرینه بدون کاهش صدا

شکم بدون دیستنشن، ارگانومگالی، اسکار جراحی، نرم بدون تندرس ریباند و گاردینگ

معاینه اندام‌ها: نرمال ، نبض‌ها پر و قرینه

ضایعات پوستی اولیه رویت نشد، تنها تعدادی ضایعه به صورت excoriations

Test				
Urea	20		WBC	8.7
Cr	0.88		RBC	4.26
AST	72	48	Hb	11.1
ALT	116	100	MCV	86.43
ALP	302		Plt	260
LDH	351	304	PT	13.4
U/A	WBC	0-1	INR	1
	RBC	2-3	PTT	25
	Bacteria	Rare		
	Others	Neg		

DDX

Disorder	Frequency	Characteristic Lesion	Adverse Pregnancy Effects	Treatment
Cholestasis of pregnancy	Common	No primary lesions, secondary excoriations from scratching	Increased perinatal morbidity	Antipruritics, cholestyramine, ursodeoxycholic acid
Pruritic urticarial papules and plaques of pregnancy (PUPPP)	Common	Erythematous pruritic papules or plaques; patchy or generalized on abdomen, thighs, buttocks, especially within striae, but with umbilical sparing	None	Antipruritics, emollients, topical corticosteroids, oral steroids if severe
Atopic eruptions of pregnancy (AEP)			None	
Eczema of pregnancy	Common	Dry, red scaly patches on extremity flexures, neck, face		
Prurigo of pregnancy	Common	1–5 mm pruritic red papules on extensor surfaces, trunk		
Pruritic folliculitis of pregnancy	Rare	Small red papules, sterile pustules on trunk		
Pemphigoid gestationis	Rare	Erythematous pruritic papules, plaques, vesicles, and bullae; abdomen often with umbilical involvement, extremities	Preterm birth, fetal-growth restriction, transient neonatal lesions	

Preexisting causes of hepatic impairment		
Viral hepatitis	Jaundice, nausea, vomiting, abdominal pain	Systemic symptoms, generally unwell, contacts
Primary biliary cirrhosis or primary sclerosing cholangitis	Pruritus, jaundice, lethargy, other autoimmune disorders	Symptoms before pregnancy; associated autoantibodies
Autoimmune hepatitis	Nausea, lethargy, jaundice, other autoimmune disorders	Symptoms before pregnancy; associated autoantibodies
Drug-induced liver injury	Pruritus, jaundice	Ingestion of drugs before onset of symptoms or biochemical abnormalities
Biliary obstruction	Abdominal pain, pale stools, dark urine	Liver ultrasound scan abnormalities
Venoocclusive disease	Abdominal pain, distension (ascites), jaundice, gastrointestinal bleeding	Thrombosis demonstrated on imaging, thrombophilia

Pregnancy-specific causes of hepatic impairment		
Acute fatty liver of pregnancy	Nausea, vomiting, headache, abdominal pain, polyuria, polydipsia in the third trimester	New nausea and vomiting in the third trimester are not caused by hyperemesis gravidarum Women with AFLP are more unwell and often have associated renal impairment, coagulopathy, hypoglycemia, and preeclampsia
Hemolysis, elevated liver enzymes and low platelets syndrome	Hypertension, proteinuria, headache, epigastric pain, visual disturbance in the second or third trimester	Hypertension and proteinuria are predominant features
Hyperemesis gravidarum	Nausea and vomiting in the first trimester	Presentation in early pregnancy, abnormal liver function test resolves with successful treatment

Evaluation of patients with pruritus

The key component of patient evaluation is the determination of the presence or absence of primary skin lesions. The presence of primary skin lesions suggests a dermatologic disorder. In patients who present without skin lesions or with only secondary skin lesions (eg, excoriations, hyperpigmentation, or lichenification), the possibility of systemic, neurologic, or psychogenic causes of itch must be considered.

Generalized pruritus without primary skin lesions

1) A detailed patient history is particularly important in patients with generalized pruritus who lack primary skin:

- History of thyroid disorders, liver disease, renal disease, HIV infection, or malignancy
- Presence of constitutional symptoms (eg, fever, weight loss, night sweats)
- Medication history
- Travel history
- Psychiatric and substance abuse history
- Pruritus in other household members (suggests scabies without identifiable skin lesions)

2) Physical examination should focus on looking for evidence of systemic disease. Findings of conjunctival pallor, thyromegaly, splenomegaly, or stigmata of liver disease should be sought out. Lymph nodes should be palpated for signs of lymphadenopathy.

3) typical initial evaluation includes:

- Complete blood count with differential to evaluate for evidence of malignancy, myeloproliferative disease, or iron deficiency
- Serum bilirubin, transaminases, and alkaline phosphatase to evaluate for evidence of liver disease
- Thyroid-stimulating hormone to evaluate for evidence of a thyroid disorder
- Blood urea nitrogen and creatinine to evaluate for renal disease
- Chest radiograph to evaluate for evidence of adenopathy

Evaluating pregnant patients with elevated liver biochemical and function tests:

Liver disease during pregnancy can be categorized by the following characteristics:

- Diseases unique to pregnancy:
  - primary liver diseases:
    - Intrahepatic cholestasis of pregnancy
    - Acute fatty liver of pregnancy
  - systemic diseases with hepatic manifestations :
    - HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)
    - Preeclampsia
    - Nausea and vomiting of pregnancy
- Diseases exacerbated by pregnancy:
  - gallstones
  - vascular diseases (eg, Budd-Chiari syndrome)
- Diseases coincidental to pregnancy:
  - acute viral hepatitis

Blood chemical constituent changes during pregnancy

	Nonpregnant adult	First trimester	Second trimester	Third trimester
Alanine aminotransferase (unit/L)	7 to 41	3 to 30	2 to 33	2 to 25
Albumin (g/dL)	4.1 to 5.3	3.1 to 5.1	2.6 to 4.5	2.3 to 4.2
Alkaline phosphatase (unit/L)	33 to 96	17 to 88	25 to 126	38 to 229
Alpha-1 antitrypsin (mg/dL)	100 to 200	225 to 323	273 to 391	327 to 487
Alpha-fetoprotein (ng/mL)	–	–	Approximately 130 to 400	Approximately 130 to 590
Ammonia (micrometer)	31.0 ± 3.2	–	–	27.3 ± 1.6
Amylase (unit/L)	20 to 96	24 to 83	16 to 73	15 to 81
Anion gap (mmol/L)	7 to 16	13 to 17	12 to 16	12 to 16
Aspartate aminotransferase (unit/L)	12 to 38	3 to 23	3 to 33	4 to 32
Bicarbonate (mmol/L)	22 to 30	20 to 24	20 to 24	20 to 24
Bilirubin, total (mg/dL)	0.3 to 1.3	0.1 to 0.4	0.1 to 0.8	0.1 to 1.1
Bilirubin, unconjugated (mg/dL)	0.2 to 0.9	0.1 to 0.5	0.1 to 0.4	0.1 to 0.5
Bilirubin, conjugated (mg/dL)	0.1 to 0.4	0.0 to 0.1	0.0 to 0.1	0.0 to 0.1
Bile acids (micromol/L)	0.3 to 4.8	0.0 to 4.9	0.0 to 9.1	0.0 to 11.3
CA-125 (microgram/mL)	7.2 to 27.0	2.2 to 268.0	12.0 to 25.1	16.8 to 43.8
Calcium, ionized (mg/dL)	4.5 to 5.3	4.5 to 5.1	4.4 to 5.0	4.4 to 5.3
Calcium, total (mg/dL)	8.7 to 10.2	8.8 to 10.6	8.2 to 9.0	8.2 to 9.7
Ceruloplasmin (mg/dL)	25 to 63	30 to 49	40 to 53	43 to 78
Chloride (mEq/L)	102 to 109	101 to 105	97 to 109	97 to 109
Creatinine (mg/dL)	0.5 to 0.9	0.4 to 0.7	0.4 to 0.8	0.4 to 0.9

Differential diagnosis based on initial evaluation

- Liver ultrasound with or without Doppler study:

1. biliary obstruction
2. vascular thrombosis
3. ascites

- Details of the patient's history (symptoms, medication use, comorbidities):

4. Severe nausea and vomiting during early pregnancy suggest hyperemesis
5. New onset hypertension and/or thrombocytopenia suggest preeclampsia with severe features or HELLP Syndrome
6. Abdominal pain, headache, nausea, and vomiting in the third trimester is concerning for acute fatty liver of pregnancy or HELLP syndrome
7. Pruritus (with or without increased total bilirubin) suggests intrahepatic cholestasis of pregnancy
8. History of potentially hepatotoxic medication and/or supplement use suggests drug-induced liver injury.
9. History of insulin resistance, polycystic ovarian syndrome, or dyslipidemia suggests increased risk for nonalcohol-associated fatty liver disease
10. History of recent alcohol use raises concern for alcohol-related liver disease

Introduction of ICP

Intrahepatic cholestasis of pregnancy (ICP) is characterized by pruritus and an elevation in serum bile acid concentrations, typically developing in the late second and/or third trimester and rapidly resolving after delivery. ICP is the most common liver disease unique to pregnancy. The incidence varies from <1 to 27.6 percent worldwide

Risk factors

- Seasonal occurrence: For unknown reasons, the disease occurs more commonly in the winter months in some countries (eg, Sweden, Finland, Chile)
- Past history of ICP
- Multiple gestation (twins 20.9 versus singletons 4.7 percent in one study; triplets 43 percent versus twins 14 percent in another study)
- Chronic hepatitis C virus infection
- Personal or family history of intrahepatic cholestasis
- Advanced maternal age

CLINICAL FINDINGS

Presentation:

The first symptom of ICP is typically pruritus. It is often generalized, but generally starts and predominates on the palms and soles and is worse at night. Right upper quadrant pain, nausea, poor appetite, sleep deprivation, or steatorrhea may occur. Pruritus and other symptoms usually develop during the late second or third trimester.

Encephalopathy or other stigmata of liver failure, if present, should initiate a search for other causes of liver disease.

CLINICAL FINDINGS

Physical examination:

Physical examination may show scratch marks, excoriations, and prurigo nodules secondary to scratching, but no primary skin lesions are associated with the disease. Jaundice occurs in 14 to 25 percent of patients, typically developing one to four weeks after the onset of itching. Jaundice without pruritus is rare and should prompt investigation of other causes.

Ultrasonography:

ICP is not associated with abnormalities on imaging (biliary ducts are not dilated, hepatic parenchyma appears normal).

Pathology:

Liver histopathology is characterized by cholestasis without inflammation. Bile plugs in hepatocytes and canaliculi predominate in zone 3. The portal tracts are unaffected. However, histopathology is rarely available as liver biopsy is not necessary for diagnosis.

CLINICAL FINDINGS

Laboratory findings:

Elevated bile acids – An increase in serum total bile acid concentration is the key laboratory finding (present

in >90 percent of affected pregnancies) and may be the first and only laboratory abnormality. Pruritus may precede laboratory abnormalities.

● The primary bile acids are cholic and chenodeoxycholic acids. Cholic and chenodeoxycholic acid levels are increased, but cholic acid increases more than chenodeoxycholic acid, resulting in a marked elevation of the cholic/chenodeoxycholic acid ratio compared with pregnant patients without ICP (3.4 versus 1.1).

CLINICAL FINDINGS

Other laboratory findings:

• Serum aminotransferases are increased in 60 percent of cases, usually less than two times the upper limit of normal, but may reach values greater than 1000 unit/L, making distinction from viral hepatitis important.

• Alkaline phosphatase is increased, possibly fourfold, but this is not specific for cholestasis during pregnancy due to expression of the placental isoenzyme.

• Total and direct bilirubin concentrations are increased in 25 percent of cases, although total bilirubin levels rarely exceed 6 mg/dL.

• Serum concentration of gamma-glutamyl transpeptidase (GGT) is usually normal but modestly elevated in 30 percent of cases.

• The prothrombin time is usually normal. When prolonged, it is typically secondary to vitamin K deficiency from fat malabsorption due to severe steatorrhea or secondary to use of bile acid sequestrants (such as cholestyramine), rather than liver dysfunction.

DIAGNOSIS

ICP should be suspected in any pregnant patient in the late second or third trimester with pruritus unrelated to a rash. The diagnosis is confirmed when pruritus is associated with elevated total serum bile acid levels, elevated aminotransferases, or both, and diseases that may produce similar laboratory findings and symptoms have been excluded. Because pruritus can precede the rise in serum bile acids by several weeks, we suggest repeating laboratory tests weekly if total bile acid and aminotransferase levels are initially normal. However, if ursodeoxycholic acid is started empirically, elevated bile acid and aminotransferase levels may never be detected. Severe cholestasis is consistently defined as a level over 40 micromol/L and accounts for about 20 percent of cases.

Two key clinical points in differential diagnosis include:

● Pruritus, the cardinal feature of ICP, helps distinguish ICP from other types of pregnancy-related disorders characterized by elevated aminotransferase levels (eg, HELLP syndrome [hemolysis, elevated liver enzymes, and low platelets], preeclampsia with severe features, acute fatty liver of pregnancy). However, ICP has been associated with development of preeclampsia and acute fatty liver of pregnancy.

● The lack of primary skin lesions in ICP helps to differentiate it from most pregnancy-specifc pruritic dermatoses and skin conditions unrelated to pregnancy.

FETAL EFFECTS

● Maternal bile acids cross the placenta. Transplacental gradients facilitate fetal clearance of bile acids in normal pregnancies, but are reversed in cholestatic pregnancies, which causes accumulation of bile acids in the fetus and amniotic fluid.

● Main complications are increased risks for fetal demise, meconium-stained amniotic fluid, preterm birth (spontaneous and iatrogenic), and neonatal respiratory distress syndrome (which appears to be associated with bile acids entering the lungs).

● Fetal death may be related to the sudden development of a fetal arrhythmia or vasospasm of the placental chorionic surface vessels induced by high levels of bile acids. Coexistent pregnancy complications (eg, gestational diabetes, preeclampsia) may also play a role.

● Bile acids appear to increase the expression of myometrial oxytocin receptors, which may explain the increase in preterm labor and spontaneous preterm birth. Pregnancies complicated by spontaneous preterm birth appear to have earlier onset of pruritus.

● Some controversy exists regarding the relationship between elevated total bile acids and birth weight ; however, fetal growth restriction and oligohydramnios are not features of the disease

MATERNAL TREATMENT

Goals

The management of ICP has two main goals:

● Reducing bothersome symptoms

● Reducing the risk of perinatal morbidity and mortality

Ursodeoxycholic acid

● we usually prescribe 300 mg three times a day (or 15 mg/kg per day) until delivery, but 300 mg twice daily (or 10 mg/kg per day) is also reasonable.

● Mild nausea and dizziness have been reported in up to 25 percent of patients.

● A decrease in pruritus within one to two weeks, and biochemical improvement within three to four weeks.

● If pruritus is not relieved to a tolerable level within about two weeks, the dose is titrated every week or two to a maximum dose of 21 mg/kg per day.

● UDCA appears to have modest maternal effects, but no significant fetal or newborn

benefits.

MATERNAL TREATMENT

● Clinical decision-making is based on the highest total bile acid level at any point during the pregnancy, maternal obstetrical history, and symptoms. Repeat evaluation of maternal total serum bile acid concentrations can be considered as often as weekly due to the significantly increased risk of stillbirth in patients with total bile acid concentrations ≥100 micromol/L, which would favor earlier delivery.

● We would not increase the UDCA dose to reduce elevated laboratory results if pruritus has been relieved and we would not revise the planned time of delivery if laboratory abnormalities improve.

● If a patient has persistent clinical findings consistent with ICP but total bile acid concentrations or aminotransferases are normal, we repeat testing as clinical symptoms can precede laboratory findings by several weeks. We would not start treatment unless there is biochemical evidence of ICP. If UDCA is started empirically, elevated bile acid and aminotransferase levels may never be detected.

● Postpartum, total bile acids and transaminases should be rechecked if the patient remains symptomatic.

Refractory cases

If the maximum dose of UDCA is reached and pruritus remains intolerable, one of the following drugs can be added:

● S-adenosyl-methionine –It is usually administered intravenously, which is inconvenient as prolonged

therapy is required. Oral SAMe (1600 mg/day) has been used to treat cholestasis in nonpregnant patients.

● Cholestyramine – Cholestyramine decreases ileal absorption of bile salts, thereby increasing their fecal

excretion. Cholestyramine is given orally in divided doses starting at 2 to 4 g per day and gradually increased

to a maximum dose of 16 g per day.

● Rifampin (also known as rifampicin) – It relieves pruritus in nonpregnant patients with pruritus associated with cholestasis, but potential adverse effects include nausea, decreased appetite, hemolytic anemia, renal failure, and hepatitis.

Other drugs

Alternative drugs may be considered in patients who are unable to take UDCA, but none have comparable efficacy:

● Hydroxyzine 25 mg orally every six to eight hours or chlorpheniramine 4 mg orally every four to six hours has been used to treat pruritus with minimal efficacy but provides sedation at night.

● Calamine lotion or aqueous cream with 2 percent menthol may also relieve pruritus. No trials have been performed in patients with ICP and none of these therapies improves laboratory abnormalities.

● Dexamethasone 12 mg orally per day does not improve pruritus or reduce the serum aminotransferase levels and is less effective than UDCA 1000 mg/day at reducing bilirubin and bile acids

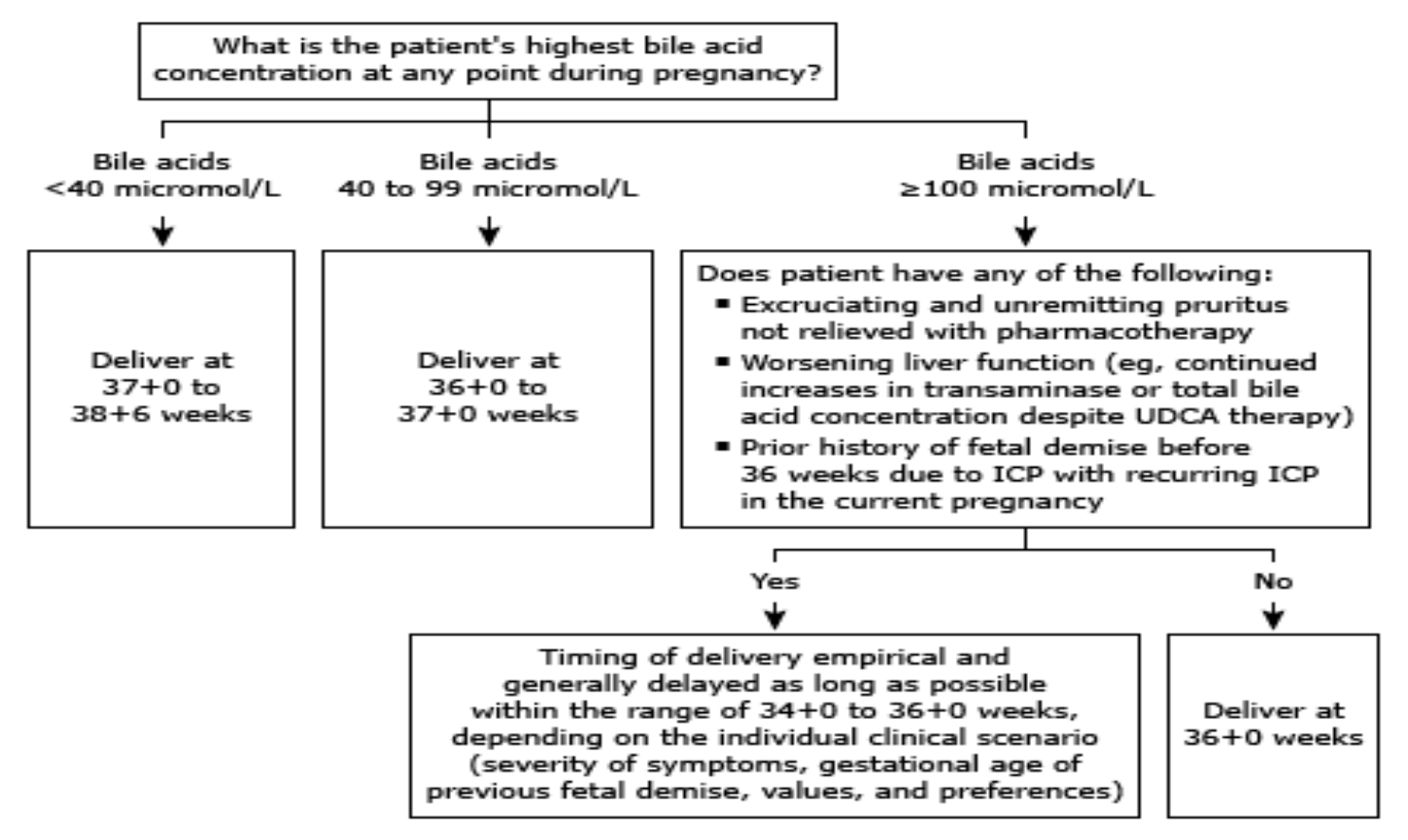
● Other treatments, including charcoal, ultraviolet light, herbal remedies, and phenobarbital, have been used, but few patients have been treated and with uncertain efficacy.

PREGNANCY MANAGEMENT

Antepartum fetal assessment:

We follow all pregnancies with ICP with twice weekly modified biophysical profiles.

Timing of delivery



Delivery

No special considerations related to delivery are required in patients with ICP. Continuous fetal monitoring during labor is indicated, given increased frequency of fetal death and nonfatal asphyxial events.

The risk for postpartum hemorrhage is not increased when ICP is managed with UDCA. Therefore, we do not routinely assess coagulation parameters or prescribe vitamin K before delivery. In rare refractory cases, the prothrombin time can be checked and vitamin K administered if it is prolonged.

MATERNAL OUTCOME

Postpartum course: Pruritus usually disappears in the “first few days after giving birth, accompanied by normalization of serum bile acid concentrations and other liver tests.

Breastfeeding: Breastfeeding should be encouraged for its maternal and infant benefits. ICP is not a contraindication to breastfeeding. Ursodeoxycholic acid (UDCA) is discontinued when labor begins. Low levels of UDCA have been found in breast milk, thus only small amounts will be ingested by the infant and are not expected to cause any adverse effects in breastfed infants.

Follow-up: We check liver biochemical tests and bile acid concentration after delivery if the patient remains symptomatic. If laboratory abnormalities do not return to normal, the patient should be referred to a hepatologist to assess for underlying hepatobiliary diseases.

Recurrence: Cholestasis recurs during subsequent pregnancies in 60 to 70 percent of patients with ICP. Recurrent episodes are variable in severity compared with the index pregnancy.

Contraception

- Any nonhormonal contraceptive may be used.
- Estrogen-progestin:

Estrogen-progestin contraception is an acceptable choice for individuals with a past history of ICP since the benefits generally outweigh the risks. Thus, combined hormonal contraceptives can be initiated after normalization of liver function tests. We also routinely check liver function tests after three or six months of such contraception. In patients with cholestasis related to past use of estrogen-progestin contraceptives, nonestrogen methods of contraception are preferred due to the increased risk for recurrent cholestasis.

- Progestin-only:

An acceptable choice for patients with a history of ICP or cholestasis related to use of estrogen-progestin contraceptives. The risk of recurrent cholestasis is low.

پ۱۶- مشکلات پوستی

علائم همراه	تشخیص احتمالی	اقدام
بثورات جلدی به همراه آبریزش از بینی، تب خفیف	بیماری های ویروسی (احتمالاً سرخجه)	ارجاع در اولین فرصت به متخصص عفونی یا زنان
پتشی، پورپورا، وزیکول، پاپول، پوسچول	بیماری خونی، بیماری پوستی	ارجاع غیر فوری به متخصص داخلی
خارش پوستی به ویژه کف پا (بیشتر در سه ماه سوم بارداری)	کلستاز بارداری	- درخواست تست های کبدی (ALP, AFP,ALT) - در صورت غیر طبیعی بودن نتایج آزمایش: ارجاع در اولین فرصت به متخصص زنان - در صورت طبیعی بودن نتایج آزمایش: • توصیه به مصرف کرم های مرطوب کننده • تجویز آنتی هیستامین خوراکی (قرص پرومتازین ۲۵ میلی گرم هر ۶ ساعت تا یک هفته) و در صورت عدم بهبود ارجاع در اولین فرصت به متخصص زنان

سطوح پیشگیری

۱. Primordial Prevention
۲. Primary prevention
۳. Secondary prevention
۴. Tertiary prevention
۵. Quaternary prevention

Primordial Prevention

آموزش و فرهنگ سازی به منظور جلوگیری از مصرف بیش از اندازه estrogen-progestin contraceptives، تشویق به دریافت میزان کافی سلنیوم از رژیم غذایی و ویتامین D از مسیر تماس مناسب با نور

Primary prevention

ارایه مشاوره توسط مراقبین سلامت و بهورزان برای کمک به ایجاد شیوه زندگی سالم

Secondary prevention

انجام آزمایشات بیس لاین کبدی در بیماران با سابقه قبلیICP و سایر بیماری های منجر به اختلال LFT برای تشخیص زود هنگام

Tertiary prevention

آموزش علایم و تظاهرات بالینی جهت افزایش آگاهی مردم و مراجعه جهت دریافت درمانهای موجود

فراهم کردن دسترسی به داروهای مورد نیاز جهت درمان ICP

Quaternary prevention

عدم انجام اقدامات تشخیصی درمانی غیر ضروری