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ANEMIA IN PREGNANCY

Moderators : Dr. Hara Pattanaik, Dr. Shantha Kumari

Panel Members : Dr. Dipika Deka, Dr. Indrani Lodh, Dr. Poovathy Sreejayanth, Dr. N. Mahalakshmi

From left to right: Dr. Dipika Deka, Dr. Poovathy Sreejayanth, Dr. N. Mahalakshmi, Dr. Hara Pattanaik, Dr. Jaydeep Malhotra, Dr. Shantha Kumari, Dr. Indrani Lodh

Iron deficiency is one of the most common nutrient deficiencies among pregnant women. This is mainly because women during pregnancy, require iron to meet both, their own needs and those of the developing baby. In particular, the iron requirement increases significantly during pregnancy to cover the expansion of the erythrocyte mass during the second-trimester, and to enable placenta and fetal growth in the third-trimester.

It has been estimated that the demand for absorbed iron increases steadily during pregnancy: from 0.8 mg/day in the First-trimester to 4 mg in the second-trimester and 6 mg in the third-trimester. Further, the iron requirements may reach as much as 10 mg/d during the last 6–8 weeks of pregnancy. In the majority of cases, these requirements are not compensated for by diet alone. Hence, iron deficiency is a major health concern among pregnant women.

Iron deficiency is associated with significant problems of health for the mother and the fetus, such as maternal anemia, increased risk of preterm birth, low birth weight, delayed maturation, and cognitive abnormalities of the child. In this regard, various guidelines recommend using prophylactic oral iron supplementation during pregnancy to prevent iron deficiency. As a result, iron supplementation during pregnancy has become a common practice throughout the world.

Maternal iron supplements during pregnancy could improve outcomes for neonatal birth-weight and preterm birth. ***Iron supplementation reduces maternal anemia at term by 70%.*** *Women who receive iron supplements less frequently have low birth weight newborns and preterm babies. Also, women taking iron supplements appear to deliver slightly heavier babies.*

A study suggested that supplementation with iron at daily doses of between 60 and 100 mg appears to be the most beneficial for the health of mother and child.

Best wishes!

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Introduction

About two million people are affected with iron deficiency anemia, which is one of the most prevalent nutrient deficiencies in the world. According to World Health Organization (WHO), iron deficiency is estimated to cause 591,000 perinatal deaths and 115,000 maternal deaths globally. When maternal hemoglobin levels fall below 8.0 g/dL, there is usually a 2 to 3-fold increase in perinatal mortality rate, and 8–10 fold increase when maternal hemoglobin levels fall below 5.0 g/dL.[1]

Hemoglobin %	ICMR 2009	WHO 2011
Mild	8–10.9	10–10.9
Moderate	5–7.9	7–9.9
Severe	<5	4–6.9
Very severe		<4
ICMR: Indian Council of Medical Research; WHO: World Health Organization		

Causes of iron deficiency anemia[2]

- Low dietary intake
- Increased demand for iron, particularly in 2nd and 3rd trimester
- Malabsorption
- Multiple pregnancies, pre-pregnancy anemia, less spacing between births, early marriage, teenage pregnancies
- Infestation of hook worms
- History of menorrhagia: 20%–30%
- Morning sickness
- Drugs like aspirin/nonsteroidal anti-inflammatory drugs (NSAIDs)
- Colorectal cancer, polyp may cause increased loss

Symptoms

- Shortness of breath
- Lethargy
- Dizziness and fainting
- Palpitation
- Chest pain
- Headaches

Signs

- Pallor
- Tachycardia
- Soft ejection systolic murmur

History

Present

- Worms in stool
- Recurrent pregnancy at short intervals

Past

- Bleeding disorder
- Koch's, Malaria
- History of blood transfusions
- Chronic blood loss

Personal

- Dietary intake
- Food faddism
- Malabsorption, pica

General and systemic examination

- Pallor: Palate, nail, palm, vaginal mucosa, conjunctiva, tongue
- Glossitis, koilonychia, stomatitis
- Brittle hair, dryness/roughness of skin
- Pulse: Collapsing pulse
- Blood pressure: Postural hypotension
- Cardiovascular system: Tachycardia, tachypnea, hemic murmur
- Pedal edema
- Increased jugular venous pressure
- Look for septic focus

Laboratory diagnosis[3]

- Complete blood count
- Peripheral blood film
- To rule out thalassemia: Hemoglobin high-performance liquid chromatography
- Serum iron studies: Serum ferritin
- Complete urine examination
- Kidney function tests
- Liver function tests
- Stool for ova/cyst
- Ultrasound of whole abdomen

Parameter	Reference range	IDA
Hemoglobin	11%–14%	↓
Red blood cell count	4.0–5.2 million/cumm	↓
Mean corpuscular volume (MCV)	82–98 fL	↓
Mean corpuscular hemoglobin (MCH)	27–33 pg	↓
Mean corpuscular hemoglobin concentration (MCHC)	31%–35%	↓
Packed cell volume (PCV)	32%–40%	↓
Serum iron	50–150 mcg/dl	↓
Total iron-binding capacity (TIBC)	300–360 mcg/dl	↑
Red blood cell distribution width (RDW)	<14.5%	↑
Serum ferritin	15–150 mcg/l	↓
Transferrin saturation	25%–50%	↓
Transferrin receptor protein	4–9 mcg/l	↑
Red cell protoporphyrin	<30 mcg/dl	↑
Erythropoietin	15–20 U/l	↓[4]
Transferrin receptor protein	Best indicator • 3–5 fold rise in IDA • Not affected by infection or inflammation	
Red cell protoporphyrin	Values rise after 2–3 weeks, >70 µg/dL	
Peripheral blood film	• Microcytic, hypochromic • Poikilocytosis, polychromasia, Pencil cells • Raised red cell distribution width (Anisocytosis) • No s/o hemolysis • Hemoparasites	
Bone marrow (Not routinely done)	• Normoblastic • Reduction in stainable iron (gold standard) Indicated only when: • Failure of therapy • Hypoplastic/aplastic anemia • Kala azar	
sTfR- Ferritin ratio	• Indicates body iron stores • Ratio increases from <100 (adeq stores) to over 2000 during significant iron depletion, median: 500	

sTfR: soluble transferrin receptor; IDA: Iron deficiency anemia

Management of iron deficiency anemia

- Correcting iron deficiency
- Restoring iron reserve
- Correcting associated complicating factor

Choice of therapy

Depends on:

- Severity of anemia
- Duration of pregnancy
- Associated complicating factor

Prevention of anemia in pregnancy

- Daily oral iron and folic acid supplementation is recommended
- Deworming in 2nd trimester
- Delayed clamping of the umbilical cord at delivery (by 1-2 min) is an important step in the prevention of neonatal anemia[5]

Deworming in pregnancy

Where hookworms are endemic (prevalence 20%–30% or more), give anti-helminthic treatment once in the second-trimester of pregnancy. If hookworms are highly endemic (prevalence more than 50%), repeat anthelminthic treatment in the third-trimester of pregnancy.[6]

Drug and dose are as follows: Albendazole 400 mg single dose OR mebendazole 500 mg single dose or 100 mg twice daily for 3 days as oral tablet.

Iron supplementation in India

Ministry of Health, Government of India Recommendation – Indian National Iron Programme, April 2018 guidelines recommend intake of 100 mg elemental iron with 500 mcg of folic acid from 14th week for a period of 180 days and to be continued for 180 days post-partum.

	During pregnancy		Postpartum
	Prophylaxis	**Treatment**	
WHO	Daily 60 mg iron + 400 µg folic acid till term	Daily 120 mg iron + 400 µg folic acid till term	Daily 60 mg iron +400 µg folic acid for 3 months
MoHFW	Daily 100 mg iron + 500 µg folic acid for 6 months from 14th week onwards,180 tabs	**Mild anemia** • 2 IFA tablets/day for 100 days **Moderate anemia** • IV iron sucrose OR IV ferric carboxymaltose (FCM)* **Severe anemia** • Iron sucrose or FCM	Daily 100 mg iron + 500 µg folic acid for 6 months

WHO: World Health Organization; MoHFW: Ministry of Health and Family Welfare; * INIP April 2018 Anemia Mukt Bharat; IFA: Iron/Folic Acid

Oral iron preparations[7–9]

Iron preparation (100 mg)	% Elemental iron	Iron absorption %	Iron absorbed in mg*
Sodium feredetate	14	81%*	11.34
Ferrous sulphate	20	27%	5.4
Ferrous ascorbate	12	40%	4.8
Ferrous fumarate	33	27%	8.9
*Absorption of iron varies from patient to patient			

Sodium feredetate

- Sodium feredetate is effective in improving hemoglobin profile in pregnant anaemic women and it is tolerated well.[10]
- Moderate iron supplementation with sodium feredetate is beneficial in improving iron deficiency and oxidative stress, and it is better than ferrous sulfate.[11]
- Sodium feredetate is effective in reducing the prevalence of iron deficiency in women of child bearing age.[12]

Adverse effects of oral iron

- Constipation
- Bloating, diarrhoea, abdominal cramps
- Heartburn, nausea
- Dark stools
- Oxidative radical injury

Drug interactions of oral iron

- Oral iron decreases the absorption and efficacy of antibiotics (by forming insoluble complexes in gastrointestinal tract), levothyroxine, and methyldopa
- Iron absorption is decreased by antacids, H_2 receptor blockers, proton pump inhibitors, antibiotics, and calcium supplements

Parenteral iron

Indications	Contraindications
• Intolerance to oral iron • Malabsorption • Poor compliance • Routine supplementation to TPN • Patients on erythropoietin • No response to oral iron in 2 weeks (Hb rise/ reticulocyte count) • IDA in third-trimester	• Anemia not attributable to iron deficiency • Iron overload • Hypersensitivity to IV iron • Liver cirrhosis • Acute or chronic infection • First-trimester of pregnancy • Acute renal failure • H/o severe asthma, eczema or other atopic allergies

NHS 2008; IDA: iron deficiency anemia; TPN:total parenteral nutrition; Hb: hemoglobin.

Formula to calculate IV iron sucrose[13]

Body weight [kg] x (Target Hb – Actual Hb) [g/l] x 2.4 + Iron stores [mg]

Parenteral iron preparations

Parameters	Iron sucrose
Concentration	20 mg/ml
Test dose	+
Dosage (dilute in 0.9% normal saline)	100 mg over 5 mins IV injection
Maintenance dose	2–3 times a week
Diluent	0.9% sodium chloride
Total dose infusion	No
Bioavailability	+ +
Clearance	Unknown
Safety profile	Category B

Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Parameters	Injection ferric carboxymaltose (FCM)	Injection iron sucrose
Dose	1000 mg IV in 200 ml normal saline over 15–20 mins in one sitting. Minimum time 15 min.	100 mg IV in 100 ml normal saline (NS) in 15 to 20 mins thrice weekly OR 200 mg in 100 ml NS in 15 to 20 mins thrice weekly Total dose not to exceed 600 mg per week to avoid toxicity
Maximum dosage	1000 mg in a week	600 mg in a week
Number of visits	Less	More
Adverse events	• Injection site reaction • Transient hypophosphatemia	• Injection site reaction • Transient hypophosphatemia
Advantage	• Gradually releases iron, no acute toxicity • Deposits in reticuloendothelial system (RES), no oxidative stress • Can be given as rapid infusion	• Large dose should be avoided as it can cause iron toxicity • Causes oxidative stress • Slow infusion
Contraindications	• Hypersensitivity reactions • Hepatic impairment • Chronic infections like HIV, hepatitis • Iron overload disorders	• Hypersensitivity reactions • Hepatic impairment • Chronic infections like HIV, hepatitis • Iron overload disorders

HIV: human immunodeficiency virus.

- Ferric carboxymaltose (FCM) should only be administered when staff trained to evaluate and manage anaphylactic reactions are immediately available, and in an environment where full resuscitation facilities can be assured.
- Each patient should be observed for adverse effects for at least 30 minutes following each administration. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately.
- Facilities for cardio-respiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions should be available, including an injectable 1:1000 adrenaline solution.
- Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

Blood transfusion

Packed red cell transfusion may be indicated for pregnant women with severe anemia (Hb of 6 g/dL or less) close to due date or less than 7 g/dL if they have increased risk of blood loss at delivery.[5]

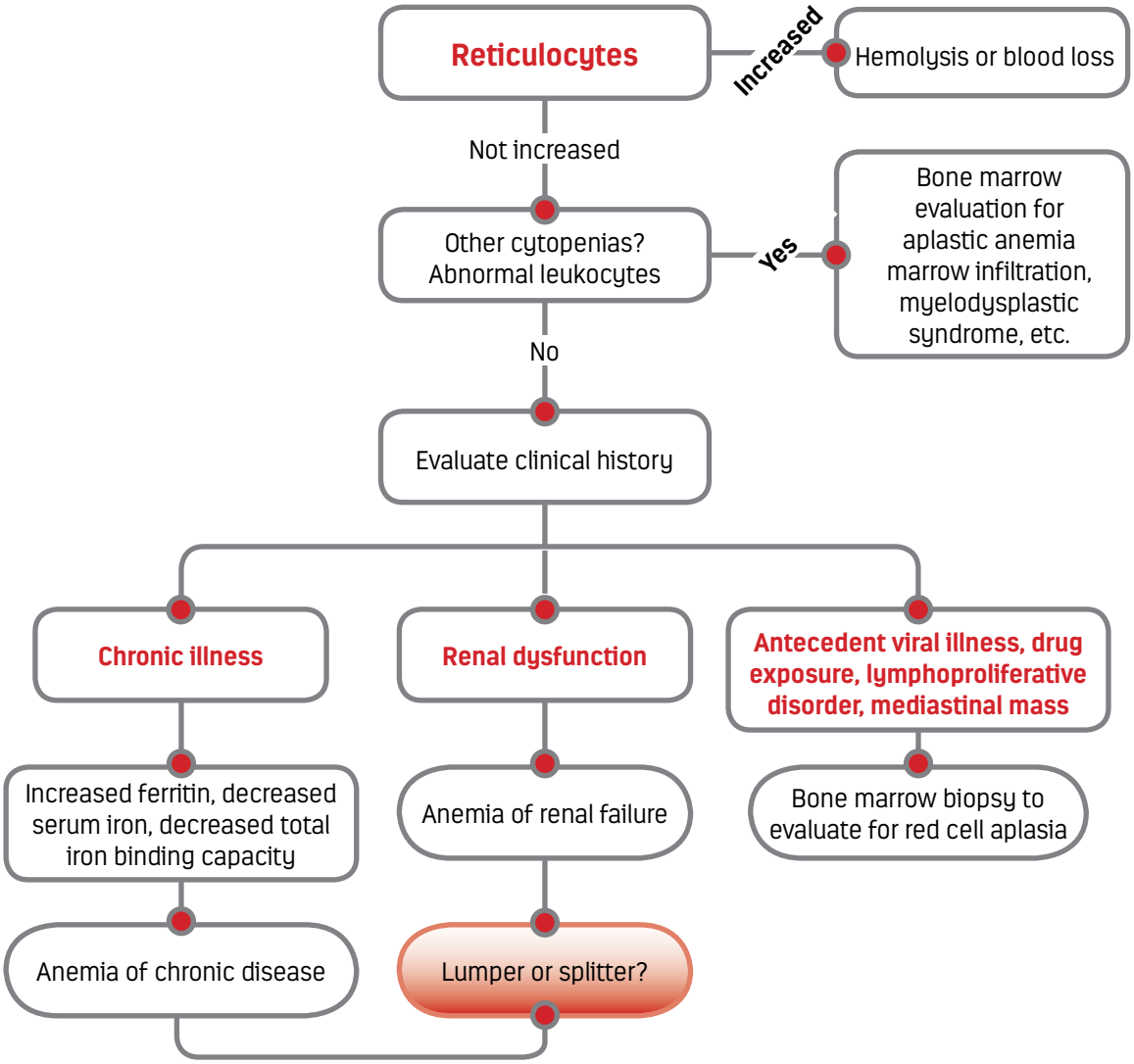
Indications

Antepartum period
1. **Pregnancy <34 weeks** a. Hb <5 g/dl with or without signs of cardiac failure or hypoxia b. 5–7 g/dl in presence of impending heart failure
2. **Pregnancy >34 weeks** a. Hb <7 g/dl even without signs of cardiac failure or hypoxia b. Severe anemia with decompensation
3. **Anemia not due to hematinic deficiency** a. Hemoglobinopathy or bone marrow failure syndromes b. Hematologist should always be consulted
4. **Acute hemorrhage** a. Always indicated if Hb <6 g/dl b. If the patient becomes hemodynamically unstable due to ongoing hemorrhage
Intrapartum period a. Hb<7 g/dl (in labor) b. Decision of blood transfusion depends on medical history or symptoms
Postpartum period a. Anemia with signs of shock/acute hemorrhage with signs of hemodynamic instability b. Hb <7 gm% (postpartum): Decision of blood transfusion depends on medical history or symptoms

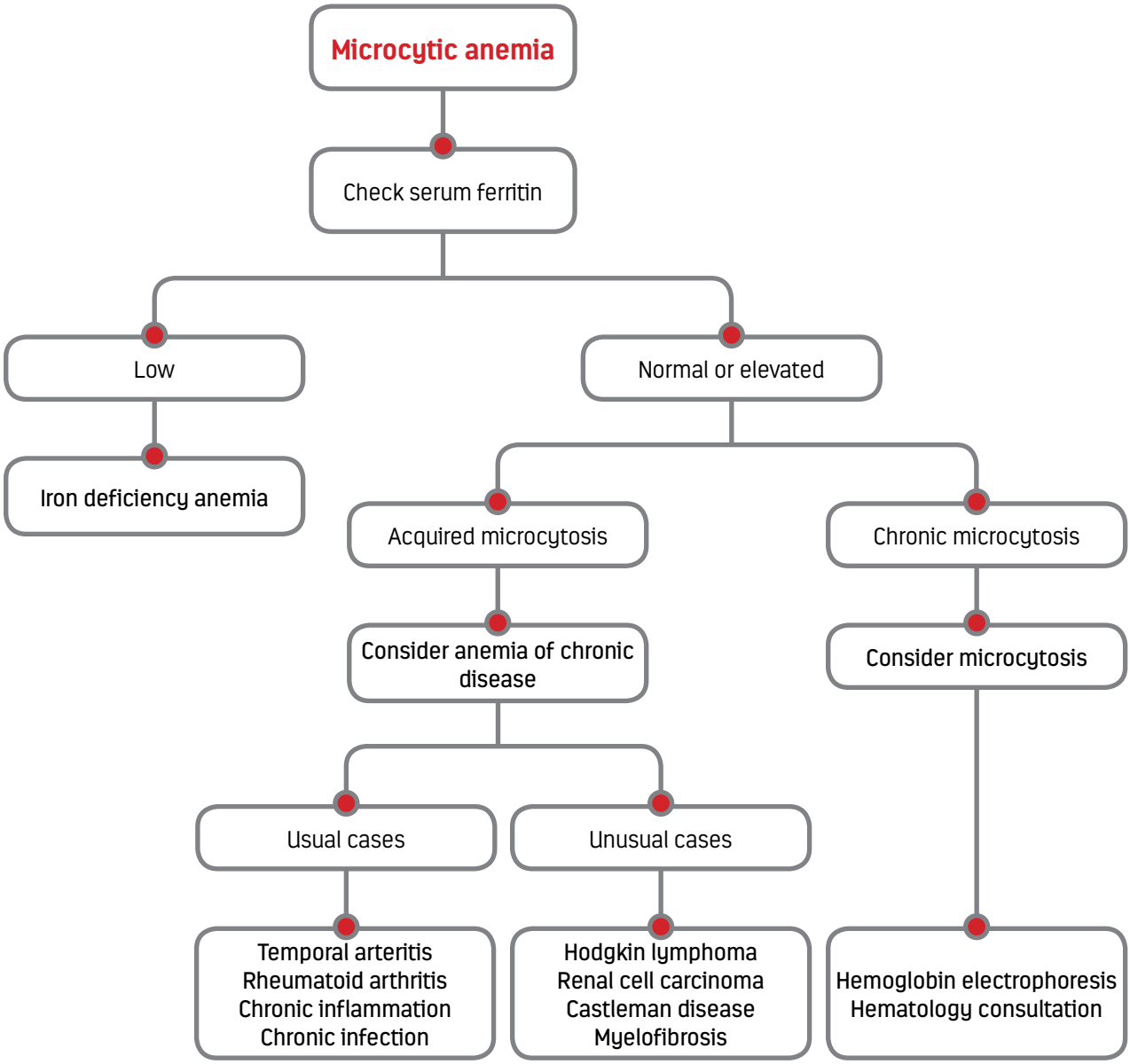
To summarize iron therapy in pregnancy and post-natal period

- Oral iron is ideal for prophylaxis and mild to moderate iron deficiency in pregnancy mostly up to 30 weeks
- If oral iron is not very effective /poor compliance/not tolerable, it is better to reassess the response to treatment by 3 to 4 weeks and opt for parenteral iron early rather than later
- Parenteral iron: Dextran molecule is no longer preferred for either IV or IM as safer and better option of iron sucrose IV is available
- Ferric carboxymaltose is not administered in antenatal period as studies are still awaited, but it is a wonderful option to treat post-natal anemia with single dose option

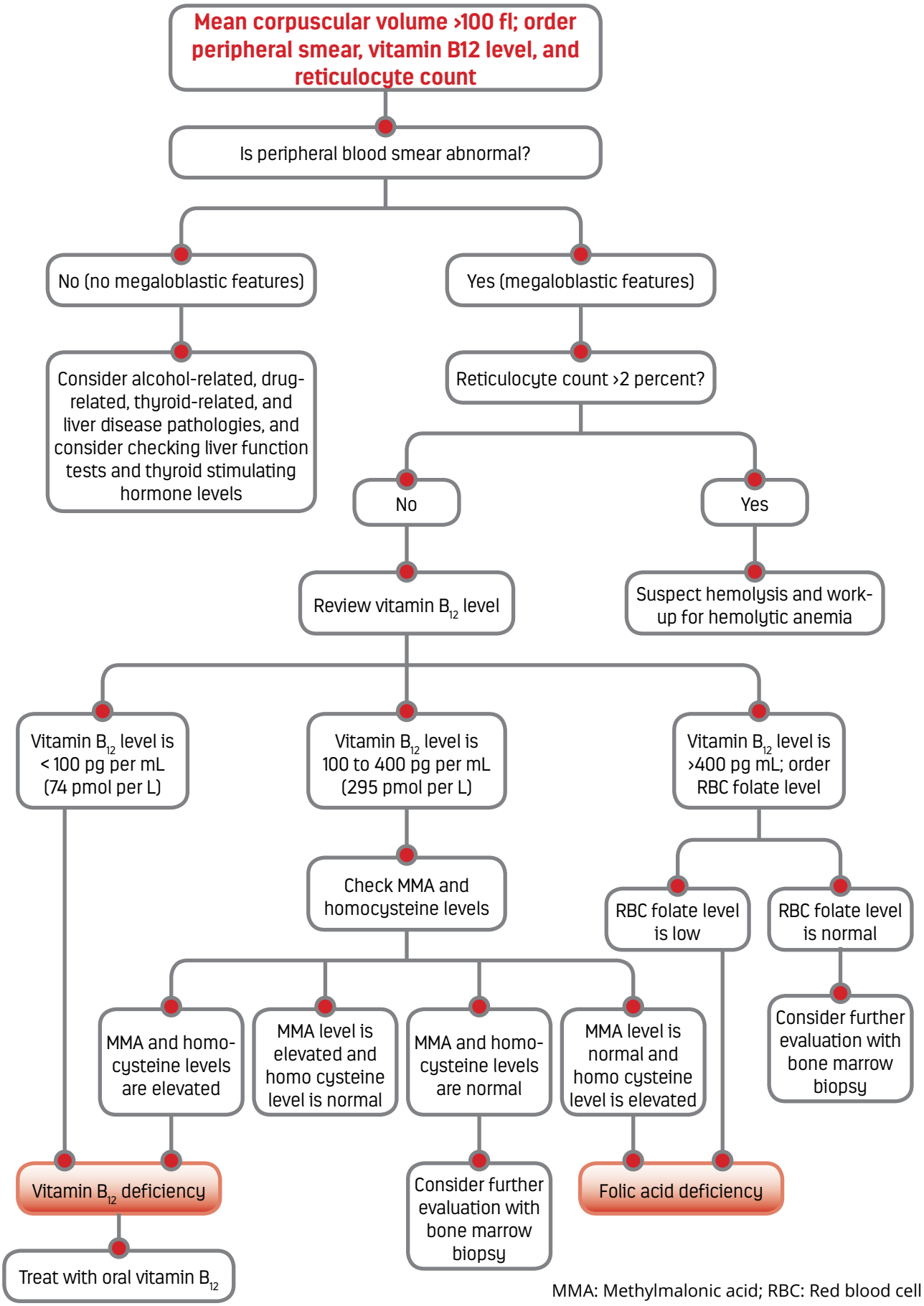
Algorithm for normocytic anemia



Algorithm for microcytic anemia



Algorithm for macrocytic anemia



MMA: Methylmalonic acid; RBC: Red blood cell

Summary

- Iron deficiency is associated with significant problems of health for the mother and the fetus, such as maternal anemia, increased risk of preterm birth, low birth weight, delayed maturation, and cognitive abnormalities of the child
- Anemia during pregnancy can be prevented with daily oral iron and folic acid supplementation, deworming in 2nd trimester and delayed clamping of the umbilical cord at delivery (by 1-2 min)
- The Indian National Iron Programme, April 2018 Guidelines recommend intake of 100 mg elemental iron with 500 mcg of folic acid from 14th week for a period of 180 days and to be continued for 180 days post-partum
- Sodium feredetate is effective in improving hemoglobin profile in pregnant anaemic women, improves iron deficiency and oxidative stress, and is well tolerated
- Packed red cell transfusion may be indicated for pregnant women with severe anemia having hemoglobin levels of ≤6 g/dL close to due date, or 7 g/dL if they have increased risk of blood loss at delivery

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CONSTIPATION IN PREGNANCY

Moderators : Dr. MC Patel, Dr. Parag Biniwale

Panel Members : Dr. Mahesh Jariwala, Dr. Papa Dasari, Dr. Lata Trivedi, Dr. Uma

From left to right: Dr. Lata Trivedi, Dr. MC Patel, Dr. Uma, Dr. Mahesh Jariwala

Constipation is a common medical problem all over the world. It is characterized by reduced defecation frequency, lumpy or hard stools, and straining. Various factors increase the morbidity rate of chronic constipation such as changes in diet, lifestyle, psychological, and socio-cultural factors. Constipation affects the quality of life of patients significantly. Pregnancy is a special period for a woman, both physiologically and physically. Pregnant women may have higher prevalence rates due to increased progesterone in the body, reduced exercise, and more protein and fat intake during pregnancy. It has also been shown that low fluid intake is linked to constipation in pregnancy, particularly in the third-trimester. Some medications, such as iron salts, taken during pregnancy have been also been associated constipation.

Mood disorders may also increase the prevalence of constipation. Pregnant women are most prone to developing constipation in the first two trimesters. Some women may suffer constipation before pregnancy, while others may experience it during pregnancy.

Pregnant women presenting with complaints of constipation may not require extensive evaluation and most of these patients respond to simple measures. The approaches to constipation during pregnancy are similar to women who are not pregnant except that special attention is given to the safety of the medication.

Severe constipation may result in fecal impaction, retention of urine, pain or abdominal discomfort, rectal bleeding and/or rectal prolapse.

The commonly used interventions to treat constipation during pregnancy include - bulk-forming laxatives, osmotic, and stimulant laxatives. Increased fibre and fluid intake, will also be useful for managing pregnant women suffering from constipation. There is a need to increase awareness about constipation in pregnancy, to avoid self-medication, and to consult obstetricians for early management and symptom relief.

Best wishes!

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Introduction

Constipation refers to difficulty in passing stool and infrequency of bowel motions, which is not secondary to an underlying cause. It can range from a low frequency of stools (<3 per week) to hard stools and/or difficulties in the evacuation of feces.[1]

Rome IV criteria for functional constipation[2]

1. Must include two or more of the following:
   a. Straining during more than one-fourth (25%) of defecations
   b. Lumpy or hard stools (Bristol stool form scale 1 or 2) more than one-fourth (25%) of defecations
   c. Sensation of incomplete evacuation more than one–fourth (25%) of defecations
   d. Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations
   e. Manual manoeuvres to facilitate more than one–fourth (25%) of defecations (such as digital evacuation, or support of the pelvic floor)
   f. Fewer than three spontaneous bowel movements per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome (IBS)

Rome IV—Bowel Disorders	Rome IV—Anorectal Disorders
1. Irritable bowel syndrome (IBS) a. IBS with predominant constipation b. IBS with predominant diarrhea c. IBS with mixed bowel habits d. IBS unclassified 2. Functional constipation 3. Functional diarrhea 4. Functional abdominal bloating/distension 5. Unspecified functional bowel disorder 6. Opioid-induced constipation	1. Fecal incontinence 2. Functional anorectal pain a. Levator ani syndrome b. Unspecified functional anorectal pain c. Proctalgia fugax 3. Functional defecation disorders a. Inadequate defecatory propulsion b. Dyssynergic defecation

How common is constipation in pregnant women?[3,4]

- 40% pregnant women suffer from constipation
- More common in those with a preconceptional history of constipation
- 1 in 4 pregnant women experience constipation
- Common during first- and second-trimester
- In the first- and second-trimester the prevalence of constipation in pregnant women varies between 35% and 39%
- In the third-trimester it is prevalent in 21% of the pregnant women and 17% in postpartum/ puerperal cases

Etio-pathogenesis[5,6]

- Hormonal changes, especially in the changes in the levels of progesterone during pregnancy reduce intestinal smooth muscle motility. Increasing serum levels of progesterone and somatostatin have also been shown to inhibit the secretion of motilin, a peptide hormone that stimulates smooth muscle motility. Another hormone, relaxin has inhibitory effects that acts on the myometrium and contributes to intestinal gut hypomotility. During pregnancy there is activation of the renin angiotensin system, as a result there is stimulation of sodium and water reabsorption from the renal tract and gut, ultimately leading to hardened stools. A slow forward passage of feces due to passive movements of the intestinal tract, hardened stools, and insufficient water and dietary fibre contribute constipation during pregnancy. Severe constipation may cause fecal impaction, retention of urine, pain or abdominal discomfort, rectal bleeding and/or rectal prolapse.

Other factors contributing to constipation in pregnancy:

- Reduced physical activity
- Changes in dietary habits - low fibres
- Pressure by gravid uterus
- Worry/anxiety
- Iron and calcium supplement
- Hormones: Thyroid dysfunction, diabetes mellitus
- Pelvic floor dysfunction

Complications of constipation

- Bleeding per rectum
- Hemorrhoids and anal fissures - due to straining
- Pelvic floor problems
- Fetal malpresentations and malposition at term due to loaded rectum
- Rarely – intestinal obstruction/rectal prolapse

Evaluation

Clinical evaluation

- History of water intake, medications used
- Disease conditions- hypothyroidism, diabetes
- History of decreased frequency of defecation[5]

Clinical examination

- Presence of loaded rectum

Characteristics of the faeces[5]

- An extensive evaluation is usually unnecessary for women who present with chronic constipation, or if constipation develops for the first time during pregnancy

Investigations

- Hemogram
- Thyroid Profile
- Ultrasound—3 D/4 D
- Stool : Ova cyst
- Proctoscopy

Management options

- Non-pharmacological interventions that are initially recommended include changes in diet (increasing fiber intake), water intake, and exercise.
- Pharmacological interventions are given if the non-pharmacological interventions fail or are insufficient. The pharmacological interventions include medications from different drug classes including lubricants, bulk-forming agents, osmotic laxatives, stimulant laxatives, stool softeners, and enemas and suppositories.[7]

Dietary modification

FOOD: Increase in fiber containing foods

- Dietary fiber is a polysaccharide with 10 or more monomeric units and is not hydrolyzed by endogenous enzymes in small intestine. Cereals, fruits, and vegetables are the good sources of dietary fiber
- Fiber containing short chain carbohydrates: Legumes/pulses nuts and seeds, wheat, rye, onions, garlic, and artichoke
- Fiber with long chain carbohydrates: Legumes/pulses, rye bread, barley, bananas, millets, oats, cooked and cooled pasta, potato, and rice

Recommended fiber intake during pregnancy

- American Pregnancy Association: 20–30 gm fiber/day[8]
- Institute of Medicine: 28 gm/day[9]
- British Nutrition foundation: 12–24 gm /day[10]

Fiber retains water and increases the bulk volume of stools

Fluid intake[11]

Pregnant women should be encouraged to increase their intake of water and other fluids to meet their bodies' needs.

- Water intake: 8–10 glasses of water each day

Juice intake: To be reduced

- Warm lemon juice early in the morning helps to relieve constipation
- Soup at the time of dinner
- Coffee, tea, cola, and other energy drinks- to be avoided

Increased water intake – First-line measure

Dietary modification for 3–7 days – if no effect – medication

Other measures

Change medication

- Iron formulation: Ferrous sulphate most commonly causes constipation
- Heme iron is non-constipating
- Calcium formulation: Carbonates
- Antihypertensives: Methyldopa, clonidine, propranolol, and calcium channel blockers (CCBs)
- Pain killers: Aspirin, ibuprofen

Exercise

10–15 min walk daily

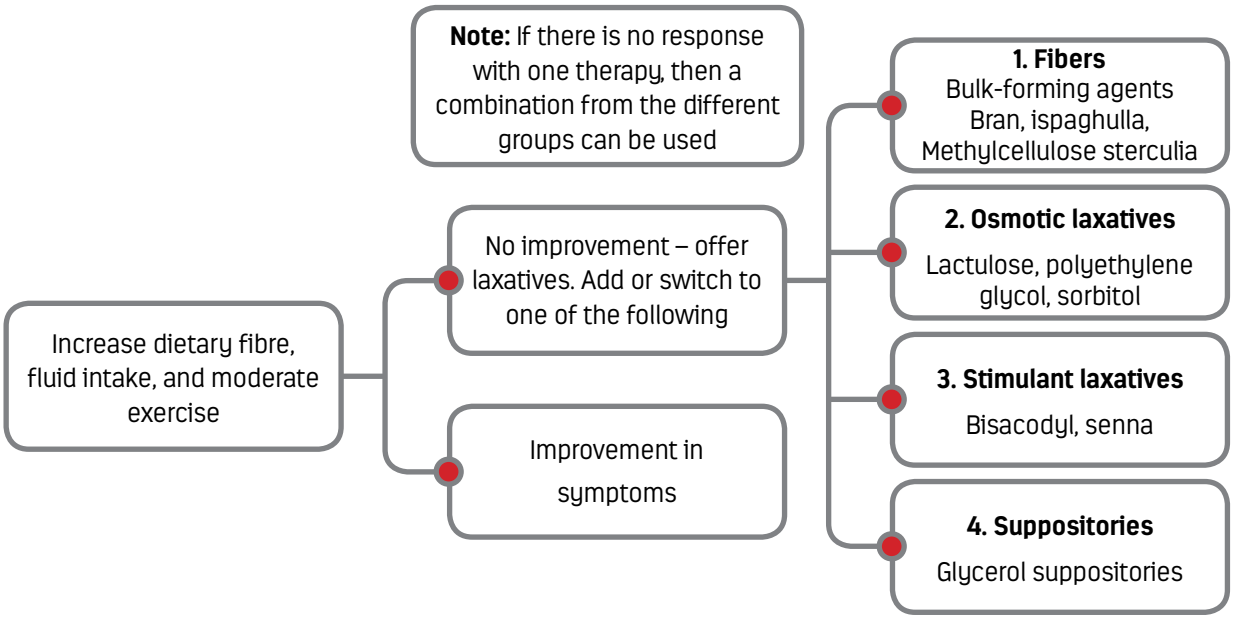
Aerobic exercise: Stimulates intestinal muscles, should be advised.

Yoga

Certain postures increase the blood flow to intestine and relieve constipation

Example: Konasana can be done during pregnancy

Pharmacological interventions[4]



Types of laxatives[12,13]

Treatment	Mechanism of action	Examples
Bulk-forming agents	Luminal water binding increases stool's bulk, making it easier to pass	Psyllium, bran
Osmotic laxatives	Increases osmolar tension, resulting in increased water collection, distention, peristalsis, and evacuation	Magnesium sulfate or citrate, lactulose, sorbitol, polyethylene glycol
Stimulant laxatives	Acts locally to stimulate colonic motility and decrease water absorption from large intestine	Bisacodyl, senna
Stool softeners	Stimulates net secretion of water, sodium, chloride, and potassium and inhibits net absorption of glucose and bicarbonate in the jejunum	Docusate sodium or calcium
Lubricant laxatives	Decreases surface tension of bowel's liquid contents so that more liquid remains in the stool, thereby facilitating evacuation and decreasing straining	Mineral oil

FDA classification of drugs used for constipation in pregnancy[12]		
Drug	**FDA class**	**Comments**
Bulk laxatives		
Psyllium	None	Considered safe
Methlycellulose	None	Considered safe
Osmotic agents		
Polyethylene glycol (PEG)	C	Inert, minimally absorbed, limited data, considered safe
Lactulose	B	Good safety and efficacy data available for use in constipation and lactation May cause bloating
Stimulants		
Senna	C	Not associated with increased risk of malformations, unpleasant side effects such as abdominal cramps[13]
Bisacodyl	B	Limited by cramping
Emollients/Lubricants		
Castor Oil	X	Premature uterine contractions
Prokinetics		
Tegaserod	B	Limited data in pregnancy, no teratogenic effects in rats; Suspended from the market in March 2007 with restricted availability as of July 2007
Lubiprostone (chloride channel activator)	C	No data in pregnant humans, no teratogenic effects in rabbits or rats

Safety of drugs in pregnancy[13-16]

Drugs	Type of study	Details	Outcomes
Psyllium	Surveillance	100>N<199 during First-trimester	No increased risk of malformations[13]
Docusate sodium	Prospective	N=116 anytime during pregnancy	No increased risk of malformations[13]
	Surveillance	N=473 during First-trimester	No increased risk of malformations (1/473=0.2%)[13]
		N=319 during First-trimester	
	Surveillance	N=232 during First-trimester	No increased risk of malformations (9/232=3.9%)[13]
Lactulose		N=6 adults given lactulose	Systemic bioavailability <3%[13]
		N=62 pregnant women	84% of physician reported a very good efficacy[14]
		N=106 women with constipation	Effective and safe in treating constipation[15]
		N=100 puerperal constipation	The efficiency of the lactulose groups was 92%[16]
Polyethylene glycol		N=11 adults given polyethylene glycol	Not absorbed[13]
Bisacodyl		N=12 adults given oral and rectal bisacodyl	Minimal absorption

Laxatives in pregnancy: Summary of published literature

Osmotic laxative[17]

Polyethylene glycol based plus electrolytes (PEG+E)

- Insufficient evidence
- Macrogol – Preferred
- Lactulose[13-16]
  - » Abundant data in pregnancy, lactation
  - » Good safety/efficacy
  - » Reduces straining and useful in treatment of hemorrhoids and anal fissure due to stool softening action

Stimulant laxatives or bulk forming laxatives[13]

- Both cause adverse side-effects
- Limited evidence for stimulant laxatives when compared to bulk forming laxatives.(side effects significantly more with stimulant laxatives)
- Adverse effects of stimulant laxatives (abdominal pain and diarrhea) limit the use in clinical practice

Bisacodyl and glycerin suppository

- Stool impaction
- When oral laxatives not effective

Contraindications

- First-trimester
- Intestinal obstruction
- Anal fissures

Recommendations/guidelines

NICE (2010)[18]

- Dietary modification
- No recommendations for non-improvement on dietary modifications

BNF (2010)[19]

- No improvement on diet & lifestyle modification

- Moderate doses of bulk forming laxatives

- Osmotic laxatives (lactulose)

- Stimulant laxative – (senna) last resort

Management of constipation during first-trimester[20]

- Challenging to treat
- First-line dietary modification
- Retroverted uterus can cause fecal impaction
- Senna is the last resort and it is not associated with congenital malformations

Experience in managing constipation during pregnancy

Remote case

Constipation after undergoing cerclage; A second gravida with incompetent os underwent cerclage at 20 weeks and experienced severe constipation which did not completely relieved over 10 days of dietary modification and local bisacodyl pessary. She resorted to bisacodyl oral tablets daily of 3 days and aborted. The cause of abortion was sent for investigation.

Recent case

A 4th gravida para1 A2, hypothyroid with threatened abortion with bicornuate uterus during the first-trimester experienced constipation. Problems were constant sensation to pass motion, discomfort, fear of pregnancy loss, and depression. Managed with dietary modification and lactulose was needed after a week. She was on vaginal progesterone. Pregnancy continued with progesterone support. Constipation relieved after 18 weeks of pregnancy.

Post-partum constipation

- Hemorrhoids, pain at the episiotomy site, effects of pregnancy hormones, and hematinics used in pregnancy can increase the risk of postpartum constipation.

Cochrane review: Clinical data for the usefulness of pharmacotherapy of post-partum constipation

Results from trials were inconsistent and there is insufficient evidence to make general conclusions about the effectiveness and safety of laxatives. Further rigorous trials are needed to assess the effectiveness and safety of laxatives during the post-partum period for preventing constipation. Trials assessing educational and behavioural interventions and positions that enhance defecation are also needed. Future trials should report on the following important outcomes: pain or straining on defecation; incidence of postpartum constipation, quality of life, time to first bowel movement after delivery, and adverse effects caused by the intervention such as: nausea or vomiting, pain and flatus.[21]

Lactulose[15-17,22]

- Lactulose is an effective and safe drug for treating postpartum constipation
- Oral lactulose is effective and safe, and it can be considered as the first-line therapy in treating chronic constipation during pregnancy.
- Lactulose offered good therapeutic benefit and it could be developed as an effective intervention to post-partum women with constipation.

Effects of laxatives on fetus-neonate[23]

- No deleterious effects due to laxatives as systemic absorption is very less
- There is one case report of maternal chronic use of docusate sodium throughout pregnancy, which was associated with symptomatic hypomagnesemia in the neonate.
- Risk of premature labour with stimulant laxatives

Side-effects on mother[13]

- Prolonged use of osmotic and stimulant laxatives might theoretically lead to electrolyte imbalances
- Prolonged use of lubricant laxatives–theoretical risk of reduction in absorption of fat soluble vitamins

Conclusion

- Constipation occurs in 11% to 38% of pregnant women.[5] The etiopathology of constipation during pregnancy involves, changes in hormones such as high progesterone and somatostatin levels, activation of the renin-angiotensin system, reduced physical activity, changes in dietary habits, pressure by gravid uterus, worries and anxiety, supplement use, thyroid dysfunction, diabetes mellitus, and pelvic floor dysfunction
- Certain medication can contribute to constipation such as increased vitamin, iron, and calcium supplementation[17]
- The first-line of therapy for constipation includes increasing dietary fibre, water intake, and moderate amounts of daily exercise
- If these are ineffective, laxatives are the second-line of therapy. Because most laxatives are not absorbed systemically, short-term use has not been, and is not expected to be, associated with an increased risk of malformations. However, as with the general population, it is recommended that osmotic and stimulant laxatives be used only in the short term or occasionally to avoid dehydration or electrolyte imbalances and the theoretical risk of "cathartic colon"
- The commonly used agents to treat constipation during pregnancy and postpartum that are effective and safe are Lactulose, Macrogol, and Glycerol suppositories

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ENDOMETRIOSIS

Moderators : Dr. Jayam Kannan, Dr. Bharti Dhorepatil

Panel Members : Dr. Seema Pandey, Dr. Charmila Ayyavoo, Dr. Sushma Gupta, Dr. Sasibala

From left to right: Dr. Sasibala, Dr. Jayam Kannan, Dr. Bharti Dhorepatil, Dr. Sushma Gupta, Dr. Seema Pandey,

Endometriosis, an inflammatory condition, is characterized by the presence of ectopic endometrial implants and it is often associated with infertility with or without pain. Endometriosis is prevalent among 25%–50% of infertile women, while about 30%–50% of women with endometriosis suffer from infertility. It is predominantly observed in women of reproductive age, and the associated symptoms can have severe impact on a woman's general physical, mental, and social well-being. Although many women may be asymptomatic, they typically present with pelvic pain, infertility, or an adnexal mass. It is therefore essential to note the complaints along with considering the concerns and anxieties as in other chronic diseases. A multifactorial mechanism is suggested to be involved in the cause of infertility associated with endometriosis.

Considering the clinical impact of endometriosis and effect on the quality of life, treatment is generally individualized. Despite adequate medical and/or surgical treatment, the pain symptoms may persist. Hence, a multi-disciplinary approach involving treatment of pain and counselling should be considered early in the treatment plan. However, since all forms of medical treatment available for endometriosis block ovarian function without a rebound in fertility, they are not indicated for infertility associated with endometriosis as a standalone option. Moreover, the issue of a woman's chances of spontaneous conception post-surgery is also complex. Research has shown that timely medical pretreatment—ovarian suppression with a gonadotropin-releasing hormone analogue—has favourable effects on assisted reproductive technology (ART) outcome in women with endometriosis.

Therefore, healthcare professionals need to consider the need for taking a biopsychosocial approach to endometriosis to tailor care to the needs of individual women.

With a thorough review of the literature assessing the causes and consequences of endometriosis, FOGSI committee presents the diagnostic approach and possible therapeutic measures for various stages of endometriosis that can be beneficial in improving the clinical outcomes.

Best wishes!

Dr. Jaideep Malhotra

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President 2018 - Federation of Obstetrics & Gynecological Societies of India (FOGSI)

Introduction

Endometriosis is an inflammatory disease associated with pelvic pain and infertility that is characterized by lesions of endometrial-like tissue outside of the uterus.[1]

Classification

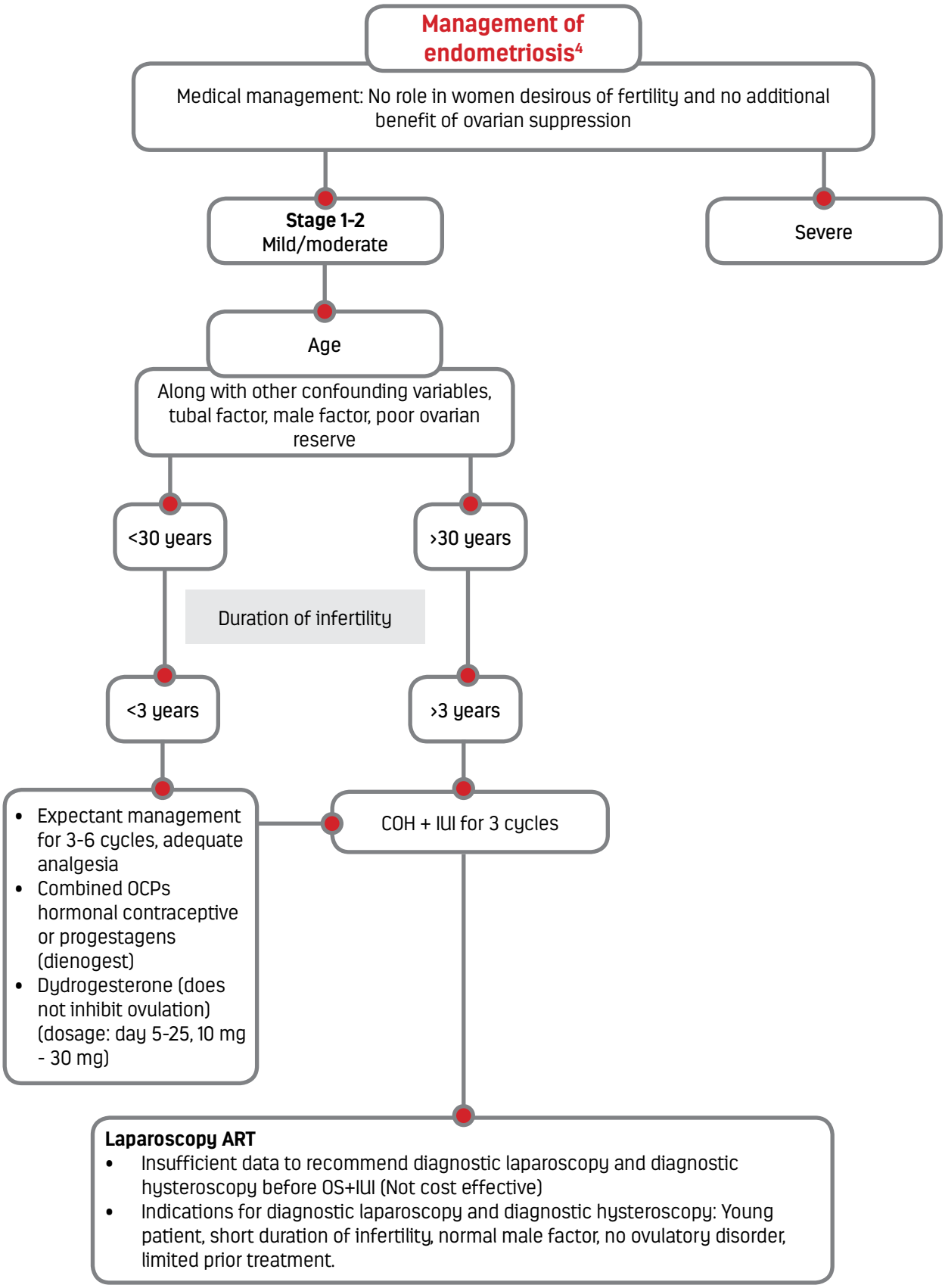
Mild, moderate, severe, and ovarian endometrioma (phenotypic classification).

Signs and symptoms

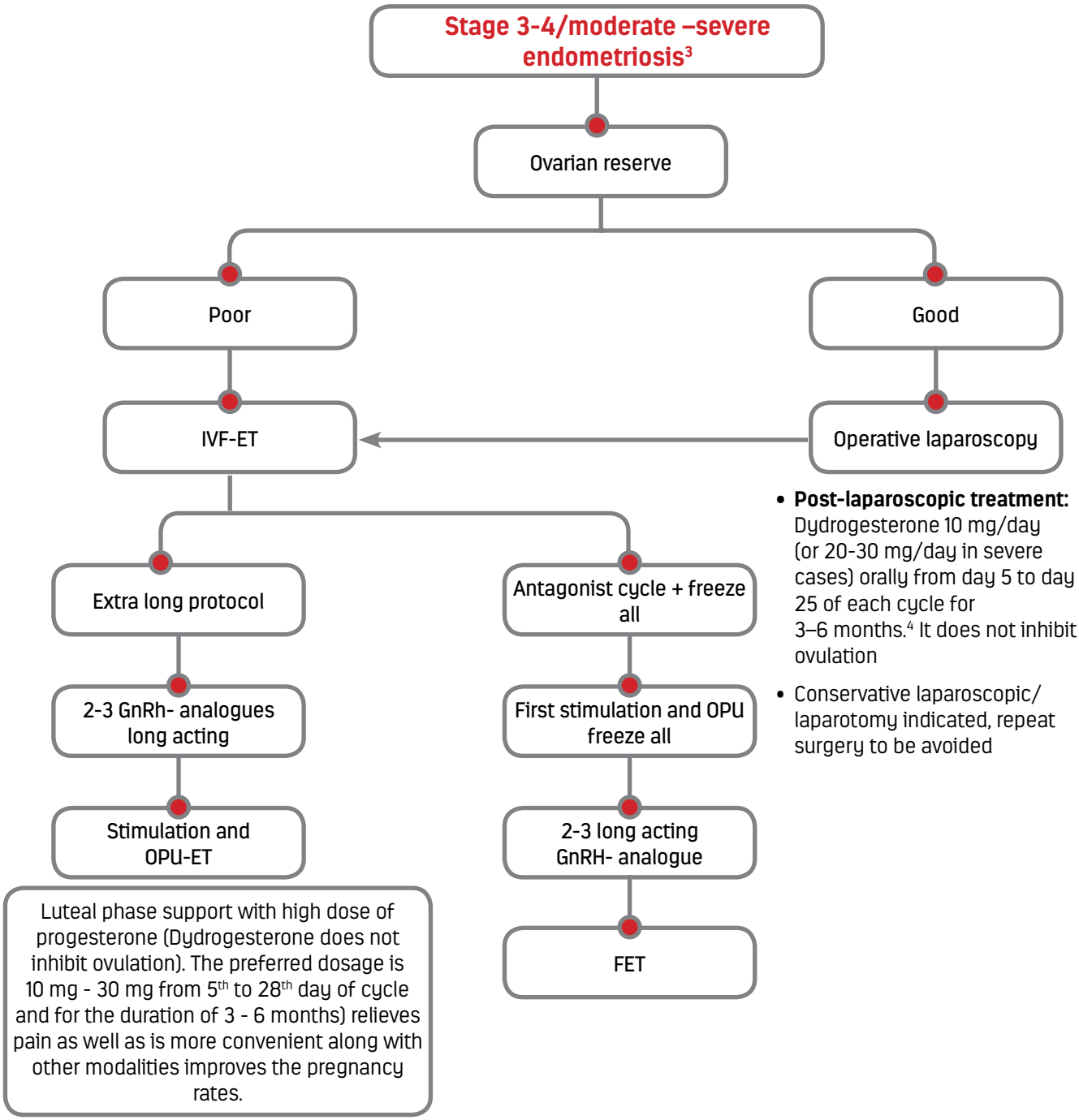
Pain, menstrual disturbances, and subfertility.

Diagnosis[2,3]

- Laparoscopy: Visual inspection by laparoscopy is the gold standard, unless disease is visible in the vagina or elsewhere
- Visual confirmation is adequate, but histopathological diagnosis of at least one area is recommended
- Positive histology confirms the diagnosis of endometriosis, negative histology does not exclude it
- For ovarian endometrioma (>4 cms in diameter), and in deeply infiltrating disease: Histology should be obtained to identify endometriosis and to exclude rare instances of malignancy
- TVS: Important in diagnosing ovarian endometriomas, but has no value in diagnosing peritoneal endometriosis. It is also useful if the bladder and rectum are involved
- Magnetic resonance imaging: No additional role
- Biochemical markers: No specific role [cancer antigen-125 (CA-125)]

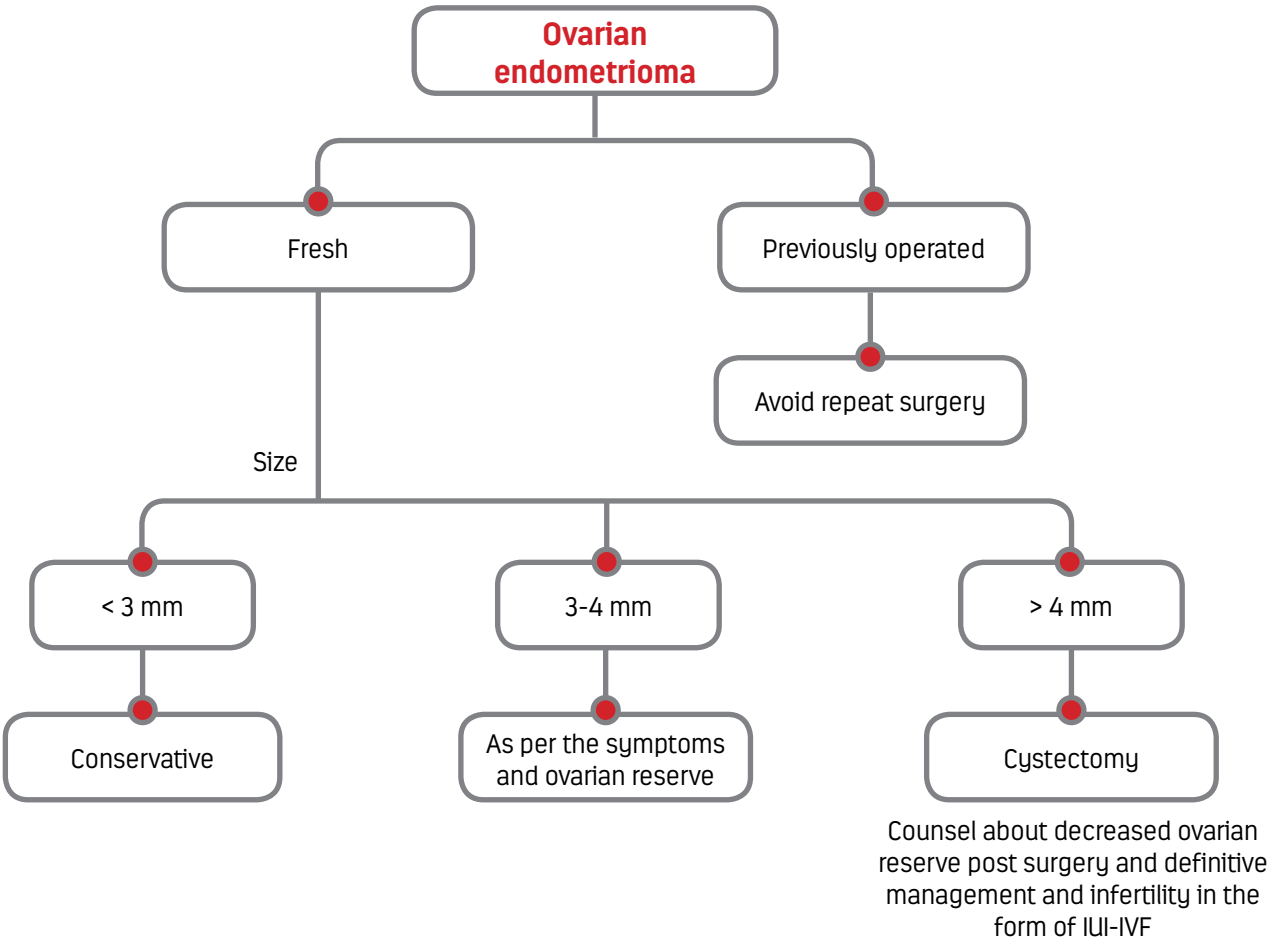


ART: Assisted reproductive technology; COH: Controlled ovarian hyperstimulation; IUI: Intrauterine insemination; OS: Ovarian stimulation



- **Post-laparoscopic treatment:** Dydrogesterone 10 mg/day (or 20-30 mg/day in severe cases) orally from day 5 to day 25 of each cycle for 3–6 months.[4] It does not inhibit ovulation
- Conservative laparoscopic/ laparotomy indicated, repeat surgery to be avoided

IVF-ET: In vitro fertilization and embryo transfer;
GnRh: Gonadotropin-releasing hormone;
OPU: Ovum pick-up.



Summary

- Endometriosis is classified as mild, moderate, severe, and ovarian endometrioma, associated with symptoms of pain, menstrual disturbances, and subfertility
- Obtaining histology is essential to identify endometriosis and to exclude rare instances of malignancy in deeply infiltrating disease and for ovarian endometrioma (>4 cms in diameter)
- Medical management of mild/moderate endometriosis includes adequate analgesia for 3–6 cycles. combined oral contraceptive pill (COCP) hormonal contraceptive or progestogens (dienogest) can be used. Dydrogesterone can be used on day 5–25 at dose of 10-30 mg
- Dydrogesterone 10 mg/day (or 20–30 mg/day in severe cases) orally from day 5 to day 25 of each cycle for 3–6 months can be administered post-laparoscopic treatment as it does not inhibit ovulation

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MALE INFERTILITY

Moderators : Dr. Anupam Gupta, Dr. Kishore Nadkarni

Panel Members : Dr. Anuradha Khar, Dr. Ragini Agrawal, Dr. Krishnendu Gupta, Dr. Rajalakshmi Walavalkar, Dr. Kannaki Utharaj

From left to right: Dr. Kannaki Utharaj, Dr. Anupam Gupta, Dr. Kishore Nadkarni, Dr. Ragini Agrawal, Dr. Krishnendu Gupta, Dr. Rajalakshmi Walavalkar, Dr. Anuradha Khar

Of the reproductive couples failing to achieve pregnancy within a 12-month period, abnormal semen parameters point to a male-infertility-associated factor in around 50% of the cases. A need has risen to determine the heterogeneous causes behind male infertility and to provide more personalized treatment of the condition.

Analysis of human semen has an important part in the male work-up schedule. It has been suggested that every male infertility work-up should begin with a thorough history, physical examination and at least two semen analyses. The new World Health Organization (WHO) manual for the examination and processing of human semen has specified a strict reference cut-offs in the previous editions. It has become a user-friendly laboratory manual with various new additions such as sperm cryopreservation techniques, the expansion of the section on sperm preparation and the inclusion of new appendices.

Amongst couples who have failed to achieve pregnancy, evaluating the fertility potential of the male partner represents an important part in the assessment. But, estimates have shown that it is not performed in at least 18% of cases. This not only compromises the fertility prognosis of the couple, but also misses an opportunity to improve health outcomes in male patients. Male infertility is associated with poorer overall health, increased cancer risk and decreased life expectancy.

Therefore, clinicians have a major role to play in maximizing the fertility potential and improving the overall health of the male patient.

The flowchart created by FOGSI guides through the process of causes involved, diagnosis with specific emphasis to semen analysis and management of male factor infertility, which can help to provide positive outcomes in couples trying to conceive.

Best wishes!

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Introduction

Infertility is a significant clinical problem, which affects 8%–12% of couples worldwide. Of all infertility cases, approximately 40%–50% are due to "male factor" infertility and as many as 2% of all men will exhibit suboptimal sperm parameters. According to the WHO, the overall prevalence of primary infertility in India ranges between 3.9% and 16.8%.

Among the Indian couples seeking treatment, the male factor is the cause in approximately 23% and nearly 50% of infertility is related to the reproductive anomalies or disorders in the male. The male factor infertility is an alteration in sperm concentration and/or motility and/or morphology in at least one sample of two sperm analyzes, collected 1 and 4 weeks apart. Male infertility is commonly due to deficiencies in the semen, and semen quality is used as a surrogate measure of male fecundity. An understanding of the hypothalamic-pituitary-gonadal (HPG) axis and the effect of estrogen excess is critical for the assessment and treatment of male infertility. The use of medical treatment has been associated with an increase in sperm production or motility, and is primarily focused on optimizing testosterone production from the Leydig cells, increasing follicle-stimulating hormone (FSH) levels to stimulate Sertoli cells and spermatogenesis, and normalize the testosterone to estrogen ratio.

Causes of male infertility[1]

Varicocele	12%
Primary idiopathic testicular failure	10%
Male accessory gland infection	7%
Abnormal sperm morphology	6%
Other seminal fluid abnormalities	4%
Immunological causes	3%
Sexual problems	2%
Azoospermia due to obstruction	1%
Endocrine and other problems	4%
No demonstrable cause	47%

Male factor – history[1]

History	Sexual history
• Undescended testis • H/o tobacco, alcohol, and drugs • H/o exposure and venereal diseases (VD) • H/o suggestive of filariasis • H/o trauma • H/o heat exposure • H/o any operation on testis • H/o of mumps and typhoid orchitis	• Problems of intercourse • Consummation of marriage • Erection, orgasm, ejaculation • Masturbation, frequency of intercourse • Use of lubrication, condom, contraceptive • Use of douche after intercourse
History of (H/o) all risk factors	

Examination[1]

- General examination for endocrinopathy
- Testicular size and position
- Look for Bayle's sign in ejaculatory duct
- Epididymis and Vas examination
- PR examination for seminal vesicles and prostrate
- Scrotal skin and penis, phimosis, hypospadias
- Varicocele, hydrocele, hernia

Physical examination

- General examination
- Masculinization
- Gynecomastia
- Secondary sexual characteristics
- Genital examination: Descent, testicular volume, testicular consistency
- Epididymis: Flat or turgid
- Presence of Vas deferens
- PR: Prostate and seminal vesicles

Investigations[1]

- Semen examination
  - » Minimum three reports
  - » Three days abstinence
  - » Count, mortality, and morphology
  - » Modified Kruger's criteria
  - » Viscosity and liquefaction
  - » Centrifuge and examine pellet in case of azoospermia

- Routine blood count for sugar and creatinine
- Blood group, venereal disease research laboratory (VDRL), human immunodeficiency virus (HIV), and surface antigen of the hepatitis B virus (HbSAg).
- Follicle stimulating hormone (FSH), Luteinizing hormone (LH), testosterone, and estradiol

Semen analysis

- The patient's seminogram is the central point of evaluation of male factor infertility
- A good standardized semen analysis report with an abstinence period of at least 2 days, is the most basic investigation
- In case of abnormal parameters, repeat (at least 3 at the interval of 7 days)
- Semen analysis has a sensitivity of 89.6 % and it is still relied on as marker for male infertility
- Serum FSH, and serum testosterone DNA fragmentation test also provide information regarding testicular function and sperm chromatin damage
- No single semen parameter is a powerful discriminator of fertility status
- Semen analysis reference ranges are not the minimal values required for conception
- Testicular volume as measured by an orchidometer is directly proportional to the number of seminiferous tubules present and more reliably predicts fertility status and androgen levels. The number of Sertoli cells during development predicts the sperm counts

Reference values[2]

WHO Laboratory manual for the examination and processing of human semen			
Semen parameters	**Old values**	**WHO 2010 values**	**Reference range**
Volume ml	2.0	1.5	1.5 (1.4–1.7)
pH	7.2–7.8	7.2	≥7.2
Concentration (x 10^6ml)	20	20	15 (12–16)
Total count	40	40	39 (33–46)
Progressive motility (%)	50	50	32 (31v34)
% Normal graph	30	-	4 (3.0–4.0)
Vitality (alive)	75	75	58 (53–63)
WBC (x 10^6)	1.0	1.0	<1.0
% Morphologically normal forms	20	50	<50

Sperm functional assessment (SFA) based treatment options

	Count	Choice of therapy
Mild oligospermia	5–12 million	IUI/IVF
Moderate oligospermia	2–5 million	ICSI/IVF/IUI
Severe oligospermia	<2 million	ICSI / IUI
Azoospermia	Nil	ICSI/IUI

Total motile count[3]

Concept of total motile count (TMC)

TMC = Count x Volume x % motility

Eg. 10 million/4ml/50% = 20 million

Total motile count of at least 5–8 million is needed to achieve pregnancy by natural methods or IUI.

A count less than value indicates for inevitable ART outcome i.e. IVF, ICSI, and sperm retrieval.

Oligoasthenoteratozoospermia (OATS)

- This category of sub-fertile males show abnormality in all three parameters of semen viz: Concentration, motility, and morphology
- Sperm concentration <12 million/ml
- Motility <25% grade IV
- Morphology <4% normal
- Common causes of OATS – varicocele, genital tract infections

Y chromosome micro deletion

- Yq microdeletion in the long arm are associated with spermatogenic failure.
- AZFa rare – Results in Sertoli cell only syndrome
- AZFb rare – Results in maturation arrest
- AZFc, d, e, f etc – 70% chance of sperm retrieval and is present in 10% men with NOA (non obstructive azoospermia)

Sperm DNA fragmentation tests

Indications

- Gross sperm defects
- Repeated treatment failures in spite of normal semen analysis
- It is a prognostic indicator and useful for ART counselling

Management of oxidative stress (OS)-related infertility

In >80% of males, medial treatment is effective.

General measures

- Lifestyle modification (smoking, poor diet, alcohol, obesity, and stress)
- Avoid activities that heat the scrotum
- Proper ventilation/use of personal protective equipment to reduce exposure to chemicals/ metals linked with OS
- Treatment of infections/varicocele
- Antioxidants, vitamins, and food supplementation

Antioxidants

- L-carnitine 1500 mg, co-enzyme Q_{10} 200 mg, and mix of multivitamins and minerals etc.
- Reduce oxidative stress, that scavenge free radicals thus reduce DNA fragmentation and damage to acrosome and mid piece
- Stimulate mitochondria, increase energy production, and stabilize cell membrane

Preferred combination

- L-Carnitine : 1500 mg
- Co-enzyme Q_{10} : 200 mg
- Mix of multi-vitamin, minerals, etc.

Selected male partners should be evaluated, if pregnancy is not achieved after 12 months of regular, unprotected sexual intercourse. A thorough history, physical examination, hormonal assessment, and semen analysis should be conducted. Advice about modifiable factors that have an impact on fertility is an important component in the management of patients desiring offspring. Hypogonadotropic hypogonadism with low FSH, low LH, and low testosterone or those with azoospermia or severe oligospermia should be treated with gonadotropin therapy with 2500 units of hCG thrice a week for 3 months and rFSH supplementation thrice a week induces spermatogenesis for next 3 months. Empirical anti-oxidant therapy may be given for up to two to three months and there is emerging evidence on the benefits of Co-Q_{10}, carnitine, acetyl levocarnitine in increasing sperm motility. Cryopreservation of human spermatozoa has overcome many limitations and now forms integral part of ART, althought good lab set up and experienced embryologist are essential.

- Empirical anti-oxidant therapy may be given for up to 2 to 3 months as the spermatogenesis cycle is of 63 days
- There is an emerging evidence on the benefits of Co-Q_{10}, carnitine, acetyl levocarnitine in increasing sperm motility

Azoospermia

- Detailed history
- Physical examination
- Hormonal profile
- Imaging: Sonography, vasography
- Genetic evaluation

How to distinguish between obstructive and non-obstructive azoospermia (OA)

- OA is characterized by normal testicular volume (18–24 ml), a turgid full epididymis, presence of vas deferens, a normal FSH, and a normal testicular histopathology. OA constitutes 40% of the cases of azoospermia
- Non obstructive azoospermia (NOA) is characterized by low volume or flabby testis, associated with mal-descent with elevated FSH and an altered testicular histopathology – Germ cell aplasia, maturation arrest, and hypospermatogenesis

Azoospermia: Sperm retrieval techniques

Technique	Acronym	Indication
Percutaneous epididymal sperm aspiration	PESA	• Obstructive cases only
Microsurgical epididymal sperm aspiration	MESA	• Obstructive cases only
Testicular sperm aspiration	TESA; testicular fine needle aspiration (TEFNA)	• Failed PESA in OA • Epididymal agenesis in congenital absence of the vas deferens (CAVD) cases • Favorable testicular histopathology in NOA • Previous successful TESA attempt in NOA
Testicular sperm extraction (singe or multiple biopsies)	TESE	• Failed PESA or TESA in OA • Non-obstructive cases
Microsurgical testicular sperm extraction	Micro-TESE	• Non-obstructive cases only

Hypogonadotropic hypogonadism

- Low FSH, low LH, low testosterone
- Small testis, 20%–30% volume, with azoospermia or severe oligospermia
- Gonadotropin therapy with 2500 units of hCG three times a week
- For 3 months and supplemented with rFSH 150 units three times a week is sufficient to induce spermatogenesis for next 3 months
- Borgress et al reported 80% of azoospermic men to have sperm in their ejaculate with above treatment. In a median time of 5 months
- Therapy should be started 6 months prior to planned fatherhood

Sperm cryopreservation

- Retrieved sperms are delicate, fragile, and sometimes immature with only a twitch to indicate its vitality
- Freezing and vitrification of retrieved sperms requires careful handling, a good lab set up and an experienced embryologist
- Testicular tissue vitrification is also challenging
- Thawing requires special attention
- Even a single sperm can be vitrified in a glass bead and used successfully after thawing

Conclusion

Selected male partners should be evaluated, if pregnancy is not achieved after 12 months of regular, unprotected sexual intercourse. A thorough history, physical examination, hormonal assessment, and semen analysis should be conducted. Advice about modifiable factors that have an impact on fertility is an important component in the management of patients desiring offspring. Hypogonadotropic hypogonadism with low FSH, low LH, and low testosterone or those with azoospermia or severe oligospermia should be treated with gonadotropin therapy with 2500 units of hCG thrice a week for 3 months and rFSH supplementation thrice a week induces spermatogenesis for next 3 months. Empirical anti-oxidant therapy may be given for up to two to three months and there is emerging evidence on the benefits of Co-Q_{10}, carnitine, acetyl levocarnitine in increasing sperm motility. Cryopreservation of human spermatozoa has overcome many limitations and now forms integral part of ART, althought good lab set up and experienced embryologist are essential.

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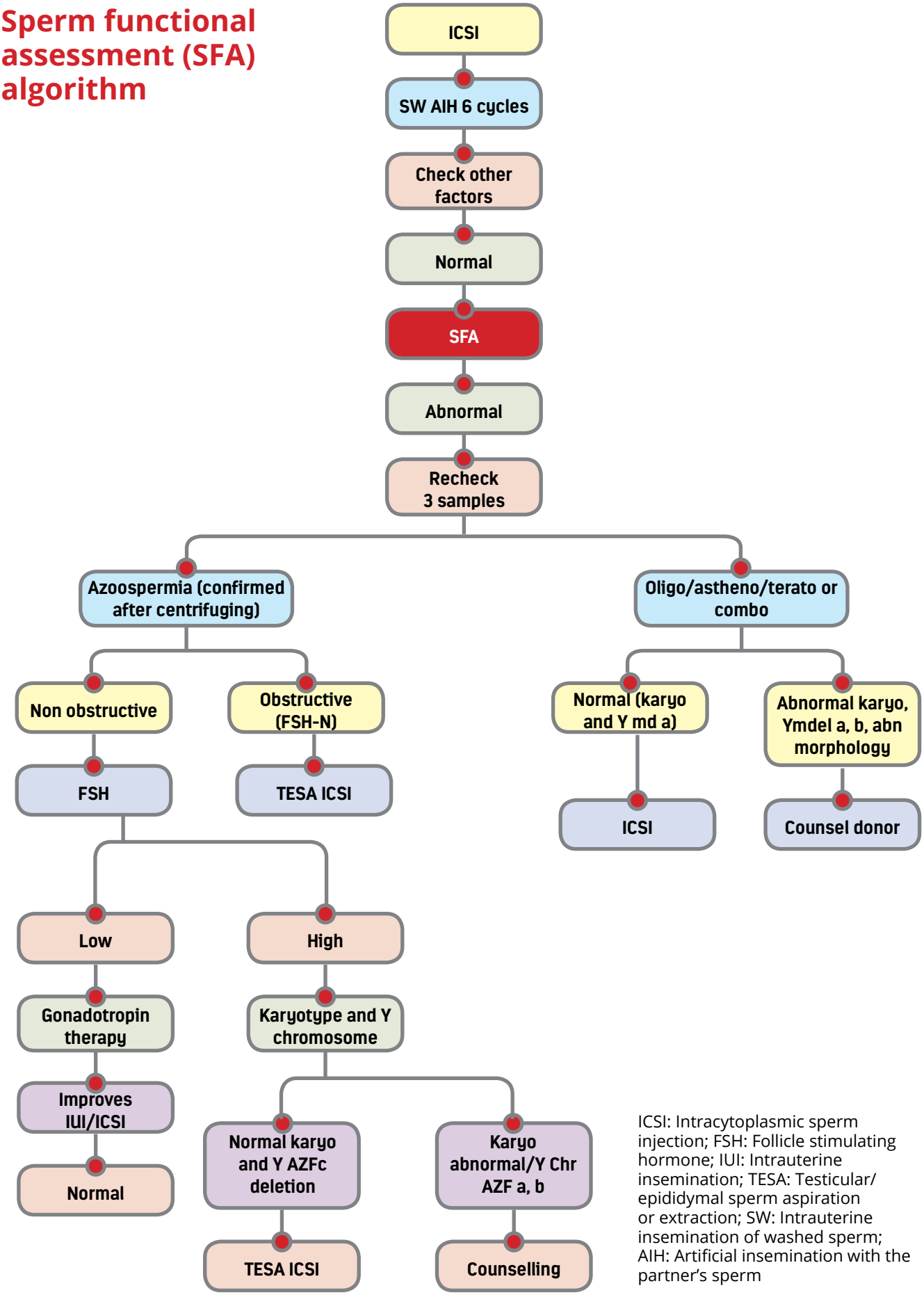
Sperm functional assessment (SFA) algorithm



ICSI: Intracytoplasmic sperm injection; FSH: Follicle stimulating hormone; IUI: Intrauterine insemination; TESA: Testicular/ epididymal sperm aspiration or extraction; SW: Intrauterine insemination of washed sperm; AIH: Artificial insemination with the partner's sperm

OVARIAN CYSTS

Moderators : Dr. Alka Kriplani, Dr. Maninder Ahuja

Panel Members : Dr. Ashish Kale, Dr. Bhagya lakshmi, Dr. Bharti Maheshwari, Dr. Vaishali Chavan, Dr. Rakhi Singh

From left to right: Dr. Maninder Ahuja, Dr. Vaishali Chavan, Dr. Alka Kriplani, Dr. Bhagya lakshmi, Dr. Bharti Maheshwari, Dr. Rakhi Singh, Dr. Ashish Kale

Ovarian cyst is a commonly occurring gynecological problem, and is categorized into follicular cysts and luteal cysts, or ovarian tumors (benign, malignant, and borderline). Around 10% of women have an operation during their lifetime for investigation of an ovarian mass. The ovarian masses are generally diagnosed in asymptomatic women who undergo imaging for other reasons, or for investigation of non-specific abdominal or pelvic pain. The cysts are typically benign in premenopausal women, but it is necessary to determine if further investigation is required. The overall incidence of a symptomatic ovarian cyst in a premenopausal female being malignant is approximately 1 in 1000, increasing to 3 in 1000 at the age of 50 years. The risk of ovarian cysts is higher in women having first-degree relatives with the same issue; estimates have shown a relative risk to first-degree relatives of 3.1.

Most of the ovarian cysts are considered asymptomatic and disappear spontaneously, but the larger ones may cause abdominal discomfort and may increase the frequency of urination. Ovarian cysts are associated with symptoms such as pelvic pain, dysmenorrheal, and dyspareunia. Other symptoms are nausea, vomiting, or breast tenderness, fullness and heaviness in the abdomen and frequency, and in difficulty emptying of the bladder. Treatment is not necessary for patients with clear, simple ovarian cysts diagnosed by ultrasound.

Management of ovarian cysts involves a conservative approach, surveillance, or surgery. Deciding an appropriate management strategy is based on the assessment of symptoms, ultrasound findings, menopausal status, RMI (if applicable) and risk factors. Usually, asymptomatic women with a simple ovarian cyst <5 cm resolve within three menstrual cycles, whereas a repeat ultrasound may be suggested for cysts of 5–7 cm, and surgery for cysts of >7 cm.

FOGSI committee presents the diagnostic approach and possible therapeutic interventions for dealing with various sizes and types of ovarian cysts in premenopausal and postmenopausal women.

Best wishes!

Dr. Jaideep Malhotra

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President 2018 - Federation of Obstetrics & Gynecological Societies of India (FOGSI)

Introduction

Ovarian cysts, also known as ovarian masses or adnexal masses, are frequently found in asymptomatic women. Ovarian cysts can be physiologic (having to do with ovulation) or neoplastic and can be benign, borderline (low malignant potential), or malignant. Ovarian cysts are sometimes found in the course of evaluating women for pelvic pain, though the cysts may or may not be the cause of the pain.

Patient may present with symptoms or without symptoms, diagnosed on routine ultrasound or pelvic examination. It can be present in a new born, young adolescents and adult perimenopause, menopause or pregnant women.

Presented with symptoms of pain in young patients	Ovarian cyst in the neonates	In pregnancy	Young adults
• Rule out by TVS Torsion of ovarian cyst • Hemorrhage and rupture • Acute differential diagnosis corpus luteum cyst – wait and watch • Other conditions - intervene	• In <8 years, 2% are malignant, and in >8 yrs, 33% are malignant • <2 cm, follow up • >2 cm, investigate further	• If diagnosed early in dating scan, rescan at 12-14 weeks • If more than 5 cms and likely to cause torsion or obstruction or risk of cancer which is low <1% • Operate in early second-trimester	• Functional cysts <5 cms, follow up–no role of oral contraceptives (OCP) for resolution • Can be PCOD • Can be dermoid • Epithelial cell tumours

Role of oral contraceptives

- Just for prevention
- Does not hasten resolution

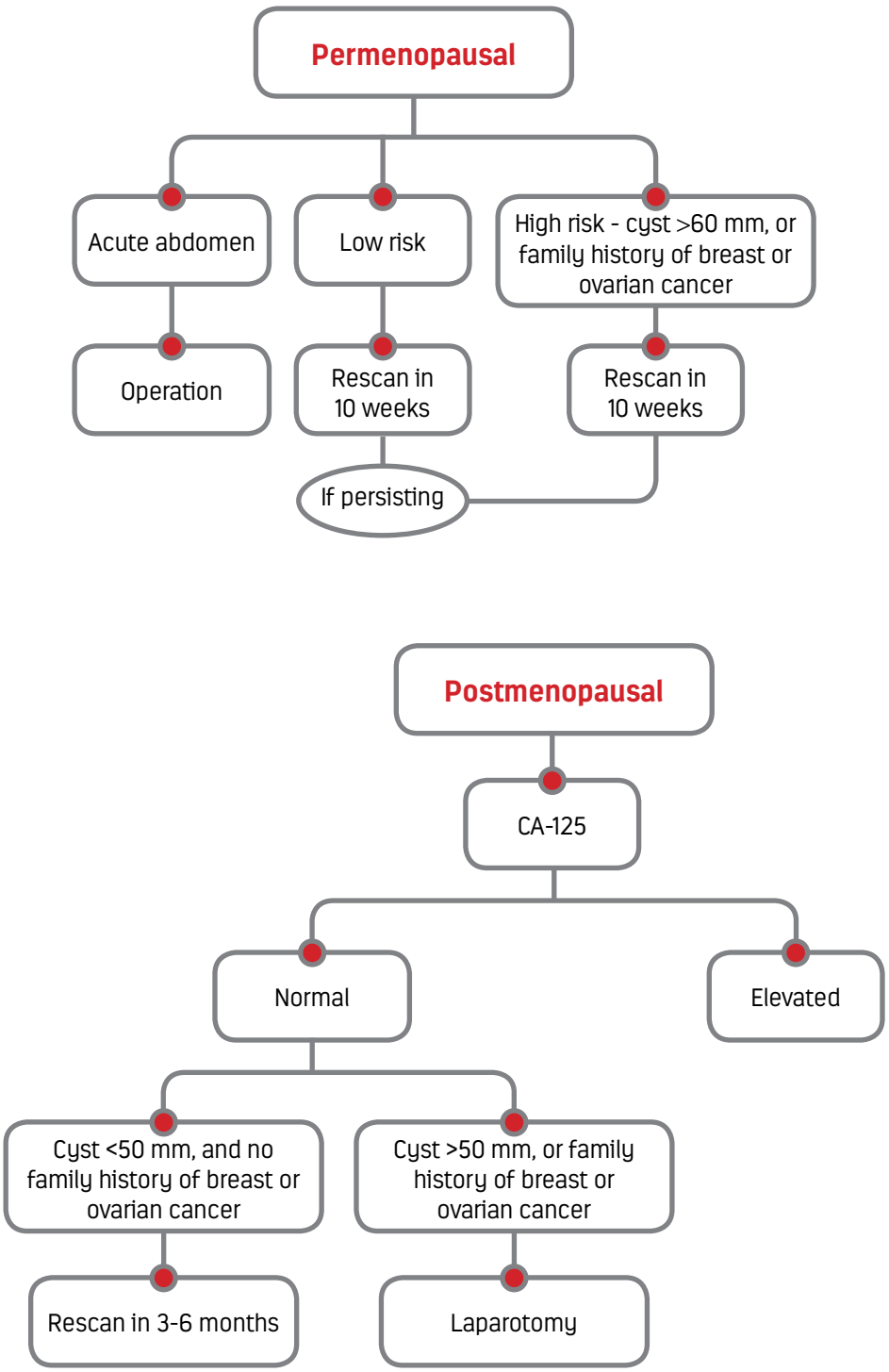
Polycystic ovarian syndrome (PCOS)

- The finding of multiple small (<1 cm) cysts in both ovaries (“string of pearls” appearance) on ultrasonography is indicative of PCOS, a condition unrelated to other ovarian cyst conditions. The “string of pearls” appearing cysts are a component of a multi-system syndrome, which usually also includes irregular ovulation and aspects of metabolic syndrome.

If cysts persist

After 3 to 6 months of treatment, no regression of size, then one can go for laparoscopic evaluation of cysts with pre-operative investigations such as CA-125.

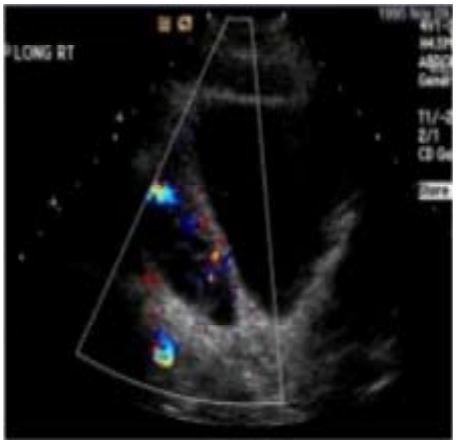
Algorithm for simple ovarian cyst[1]



CA-125: Cancer antigen 125

OVARIAN MASS IN POSTMENOPAUSAL WOMEN

Ovarian or non ovarian cysts



Adnexal mass is present

*first to do is try to identify the ovaries

The gonadal vessels lead to the lesion with no separately identifiable normal ovaries

*you are dealing with an ovarian lesion

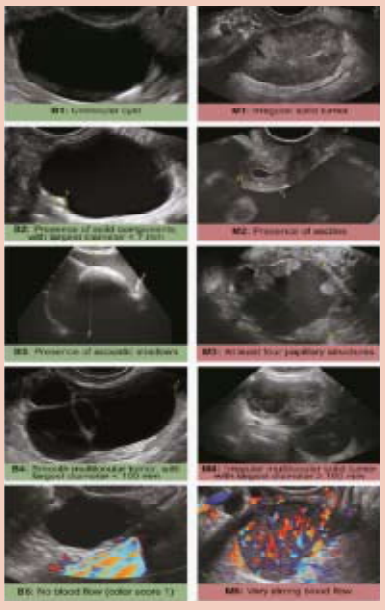
Both ovaries are separately identifiable from the lesion

*you are dealing with a non-ovarian cystic lesion

Assessment

- Pelvic transvaginal sonography (TVS) combined with abdominal ultrasound
- If ovarian mass, assess if benign or malignant
- Structures history or any malignancy in the family is very important
- If benign < 5 cms, wait and watch
- If > 5 cms but benign, can be treated laparoscopically
- Assess by MRI-1 index and CA-125
- Sonographic appearance of benign and malignant cysts is shown in the Table below[2]

Benign (B)-rules	Malignant (M)-rules
Unilocular cysts	Irregular solid tumour
Solid components <7 mm	Ascites
Acoustic shadowing	At least four papillary structures
Smooth multilocular <100 mm	Irregular multilocular solid tumour >100 mm
No blood flow	Very strong blood flow



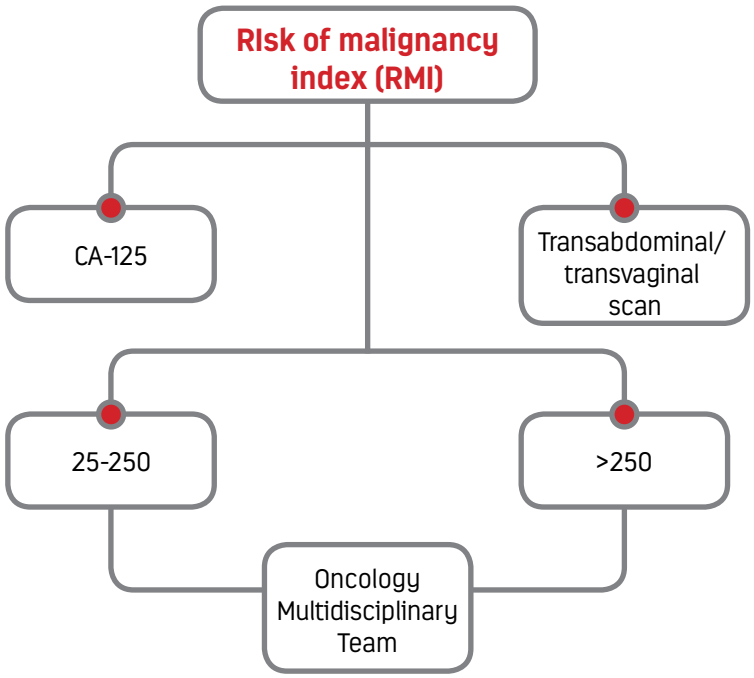
Risk of malignancy index (RMI)

RMI = U x M x CA-125 (U/ml) (Jacob's score)

M: Menopausal status; U: Ultrasound features of the lesion

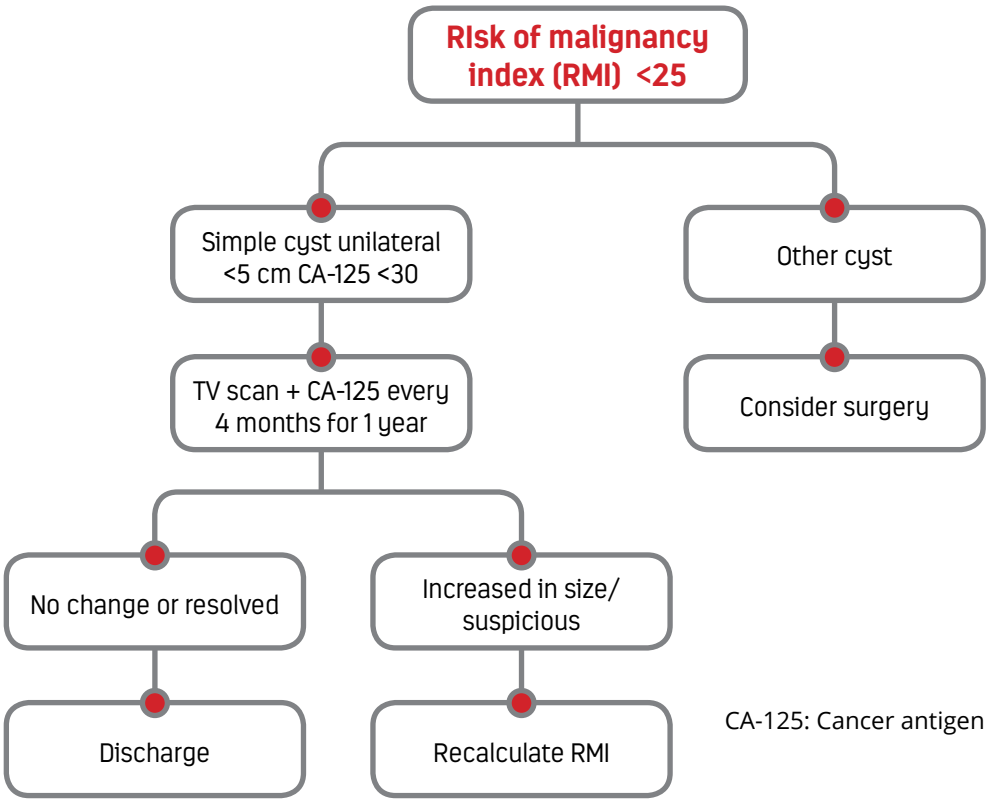
Ultrasound criteria (U score)	
Multilocular cyst	1
Solid areas	1
Bilateral lesions	1
Ascites	1
Intraabdominal metastases	1
U =0 (for an ultrasound score of 0); U=1 (for an ultrasound score of 1); U=3 (for an ultrasound score of 2-5); s-CA 125 (u/ml) (the actual value is used); The menopausal status is scored as 1 = premenopausal, 3 = postmenopausal	

Postmenopausal – Ovarian cyst



CA-125: Cancer antigen 125

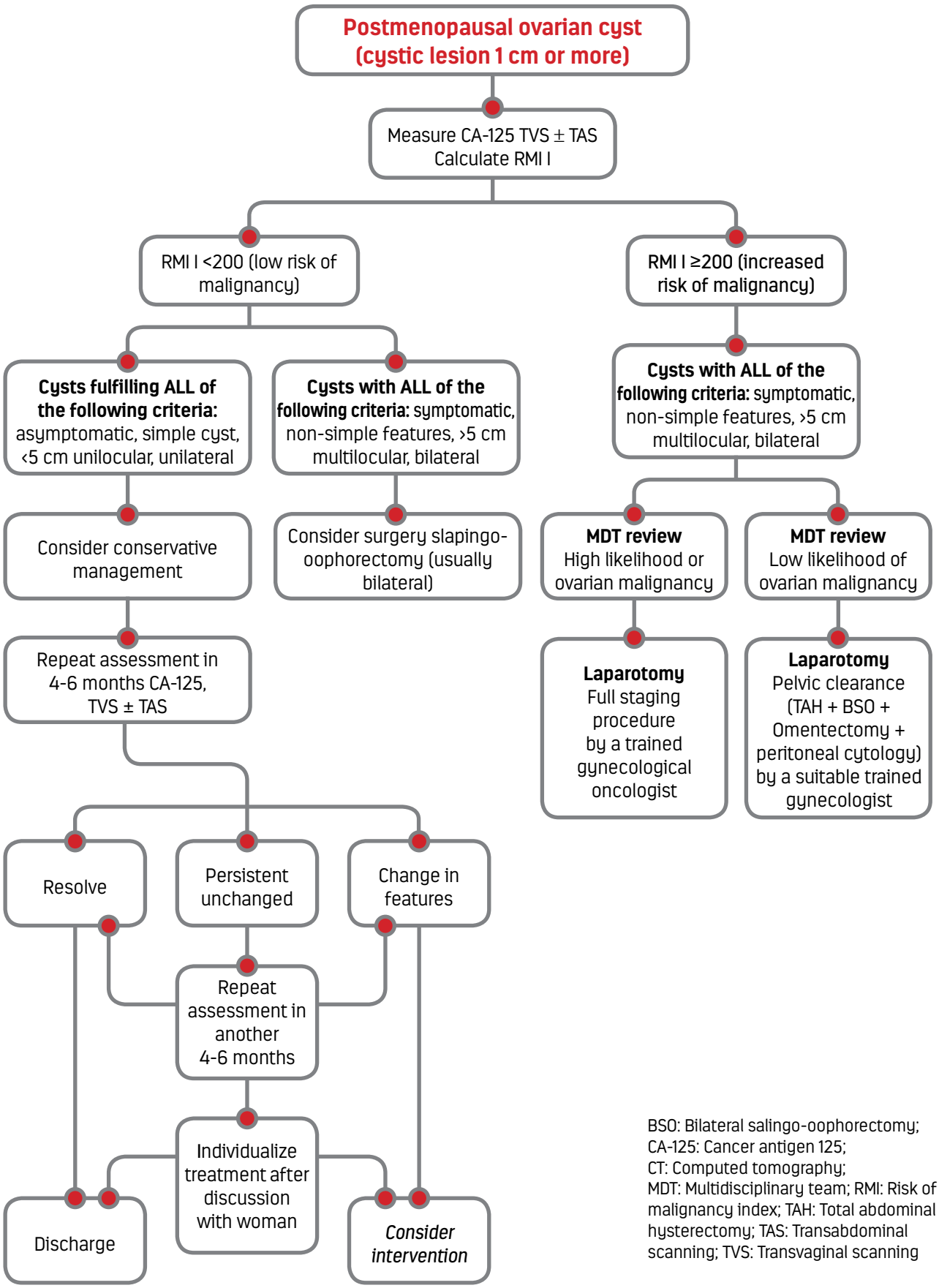
Postmenopausal – Ovarian cyst



CA-125: Cancer antigen 125

- Ultrasound-guided fine-needle aspiration and biopsy from the mass not recommended
- Ascitic fluid cytology can be done

Royal College of Obstetricians and Gynecologists (RCOG)[3]



BSO: Bilateral salingo-oophorectomy; CA-125: Cancer antigen 125; CT: Computed tomography; MDT: Multidisciplinary team; RMI: Risk of malignancy index; TAH: Total abdominal hysterectomy; TAS: Transabdominal scanning; TVS: Transvaginal scanning

Calculation of the RMI-I

The RMI-I combines three pre-surgical features. It is a product of the serum cancer antigen 125 (CA-125) level (IU/mL); the menopausal status (M) and an ultrasound score (U) as follows:

RMI = U x M x CA-125

- The ultrasound result is scored 1 point for each of the following characteristics: multilocular cysts, solid areas, metastases, ascites, and bilateral lesions.

  U = 0 (for an ultrasound score of 0)

  U = 1 (for an ultrasound score of 1)

  U = 3 (for an ultrasound score of 2 - 5)

- The menopausal status is scored as:

  1 = premenopausal

  3 = postmenopausal

  This guideline is directed at postmenopausal women and therefore all will be allocated the same score of 3 for menopausal status

- Serum CA-125 is measured in IU/mL and can vary between zero and hundreds or even thousands of units.

RCOG 2016[3]

- Clinicians should be aware of the different presentations and significance of ovarian cysts in postmenopausal women
- In postmenopausal women presenting with acute abdominal pain, the diagnosis of an ovarian cyst accident should be considered (e.g. torsion, rupture, hemorrhage)
- It is recommended that ovarian cysts in postmenopausal women should be initially assessed by measuring serum CA-125 level and transvaginal ultrasound scan
- A thorough medical history should be taken from the woman, with specific attention to risk factors and symptoms suggestive of ovarian malignancy, and a family history of ovarian, bowel or breast cancer
- Where family history is significant, referral to the Regional Cancer Genetics service should be considered
- Appropriate tests should be carried out in any postmenopausal woman with symptoms within the last 12 months suggesting irritable bowel syndrome (IBS), particularly in women over 50 years of age, or those with a significant family history of ovarian, bowel or breast cancer
- A full physical examination is essential and should include BMI, abdominal examination to detect ascites, any palpable mass, and vaginal examination
- CA-125 should be the only serum tumour marker used for primary evaluation as it allows to calculate RMI
- CA-125 levels should not be used in isolation to determine if a cyst is malignant
- While a very high value may assist in reaching the diagnosis, a normal value does not exclude ovarian cancer due to the nonspecific nature of the test

Use of other diagnostic methods[3]

- There is currently not enough evidence to support the routine clinical use of other tumour markers, such as human epididymis protein 4 (HE4), carcinoembryonic antigen (CEA), CDX2, cancer antigen 72-4 (CA72-4), cancer antigen 19-9 (CA19-9), alphafetoprotein (α-FP), lactate dehydrogenase (LDH), or beta-human chorionic gonadotrophin (B-hCG), to assess the risk of malignancy in postmenopausal ovarian cysts
- TVS is the single most effective way of evaluating ovarian cysts in postmenopausal women.
- Transabdominal ultrasound should not be used in isolation. It should be used to provide supplementary information to TVS particularly when an ovarian cyst is large or beyond the field of view of TVS
- On TVS, the morphological description and subjective assessment of the ultrasound features should be clearly documented to allow calculation of the risk of malignancy
- TVS scans should be performed using multifrequency probes by trained clinicians with expertise in gynecological imaging

Role of MRI[3]

- MRI should not be used routinely as the primary imaging tool for the initial assessment of ovarian cysts in postmenopausal women
- MRI should be used as the second-line imaging modality for the characterization of indeterminate ovarian cysts when ultrasound is inconclusive
- Colour flow Doppler studies are not essential for the routine initial assessment of ovarian cysts in postmenopausal women
- Spectral and pulse Doppler indices should not be used routinely (resistive index, pulsatility index, peak systolic velocity, and time-averaged maximum velocity) to differentiate benign from malignant ovarian cysts, as their use has not been associated with significant improvement in diagnostic accuracy over morphologic assessment by ultrasound scan
- Three-dimensional ultrasound morphologic assessment does not appear to improve the diagnosis of complex ovarian cysts, and its routine use is not recommended in the assessment of postmenopausal ovarian cysts
- CT, MRI, and positron emission tomography (PET)-CT scans are not recommended for the initial evaluation of ovarian cysts in postmenopausal women
- CT scan should not be used routinely as the primary imaging tool for the initial assessment of ovarian cysts in postmenopausal women because of its low specificity, its limited assessment of ovarian internal morphology and its use of ionising radiation
- If malignant disease is suspected, a CT scan of the abdomen and pelvis should be arranged, with onward referral to a gynecological oncology multidisciplinary team

Family history for risk of ovarian cancer[3]

She has a first-degree relative (mother, father, sister, brother, daughter, or son) affected by cancer within a family with:

- Two or more individuals with ovarian cancer, who are first-degree relatives of each other
- One individual with ovarian cancer at any age and one with breast cancer diagnosed under age 50 years, who are first-degree relatives of each other
- One relative with ovarian cancer at any age and two with breast cancer diagnosed under age 60 years, who are connected by first-degree relationships
- Three or more family members with colon cancer, or two with colon cancer and one with stomach, ovarian, endometrial, urinary tract, or small bowel cancer in two generations. One of these cancers must be diagnosed under age 50 years and affected relatives should be first-degree relatives of each other
- One individual with both breast and ovarian cancer

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2. Management of suspected ovarian masses in premenopausal women. Green–top Guideline No. 62. RCOG/ BSGE Joint Guideline I November 2011
3. RCOG. The Management of ovarian cysts in postmenopausal women. Green-top Guideline No. 34. July 2016

OVULATION INDUCTION

Moderators : Dr. Jaideep Malhotra,
Dr. Purnima Nadkarni

Panel Members : Dr. Selvapriya Saravanan, Dr. Pramya Nanjundan, Dr. Kavitha Gautham, Dr. Mahendra Soni, Dr. Jaishree Gajaraj

From left to right: Dr. Purnima Nadkarni, Dr. Pramya Nanjundan, Dr. Selvapriya Saravanan, Dr. Jaideep Malhotra, Dr. Mahendra Soni, Dr. Kavitha Gautham

Ovulation is the prime aspect of reproduction and is required for fertiity. Aberrations from normal ovarian function need to be identified, evaluated, and properly treated for conception. Ovulatory disorders can be identified in 20–30% of couples presenting with infertility. Ovulatory disorders are divided into two subgroups; a) ovulatory infertility that includes unexplained infertility, mild male factor infertility, and endometriosis grade 1 & 2; b) anovulatory infertility that includes WHO Group 1 (hypogonadotropic hypogonadism and hyperprolectinemia), WHO Group 2 (normogonadotropic-PCOS), WHO Group 3 (hypergonadotropic hypogonadism POF). Ovulation induction is the method of treating anovulatory as well as ovulatory infertility. The introduction of ovarian stimulation protocol for IVF is a major breakthrough which increases the pregnancy rate significantly. Induction of ovulation in ovulatory patient leads to multiple follicular development which enhances the possibility of fertilization. In anovulatory patient, it leads to monofolliculogenesis as well as multiple follicular development, thus enhances fertility. With the evolution of ovulation inducing drugs such as antiestrogens (CC), aromatase inhibitors (letrozole), and different formulations of gonadotropins (hMG, hpFSH, rFSH) not only there is increase in success of achieving live pregnancy but also increment of different complication (OHSS, premature LH surge, and HOMP), and cycle cancellation rate. To overcome various complication and to reduce cycle cancellation rate, GnRH analogue came into account to down regulate the cycle. As a infertility specialist what we really want to know in ovulation induction is, how to define the individualized treatment protocols for individual patient in order to increase pregnancy rate with less side effects and less physical, psychological, and financial burden.

Best wishes!

Dr. Jaideep Malhotra

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President 2018 - Federation of Obstetrics & Gynecological Societies of India (FOGSI)

Introduction

Ovulation induction is used for inducing ovulation in women who are anovulatory irrespective of their menstrual cycle regularity. Aim of ovulation induction is to stimulate the release of one or more egg a month.

Ovulation stimulation is done in a woman who ovulates spontaneously but has unexplained infertility or associated male factor infertility issues, which demands increasing the chance of conception. Aim of ovulation stimulation is to stimulate the production of multiple large follicles so that several eggs will be released.

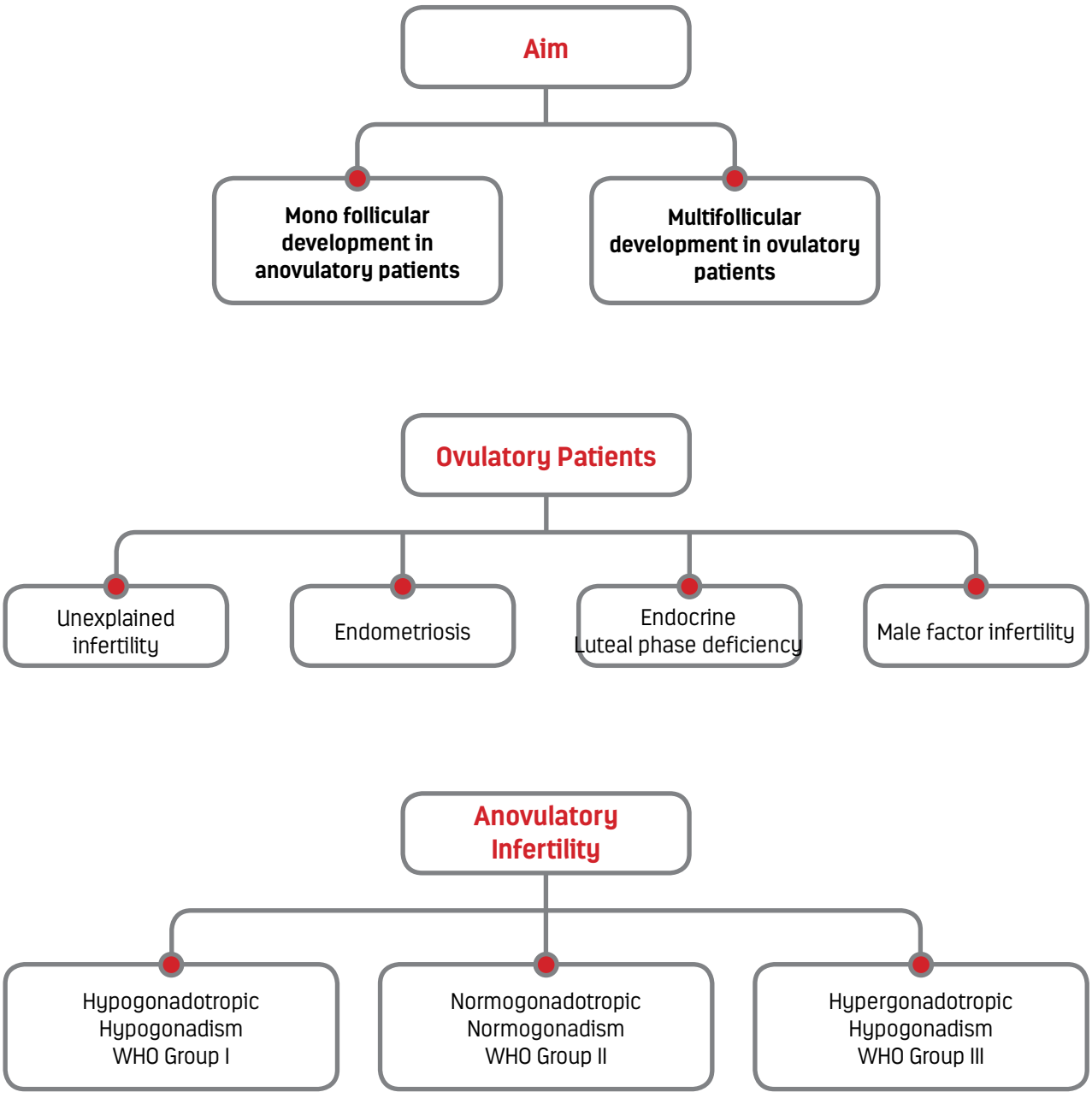
Controlled ovarian hyperstimulation (COH) is regulated super ovulation by turning off the patients own hypothalamic-pituitary-ovarian (HPO) SYSTEM (down regulation) followed by stimulation.

Aim of COH:

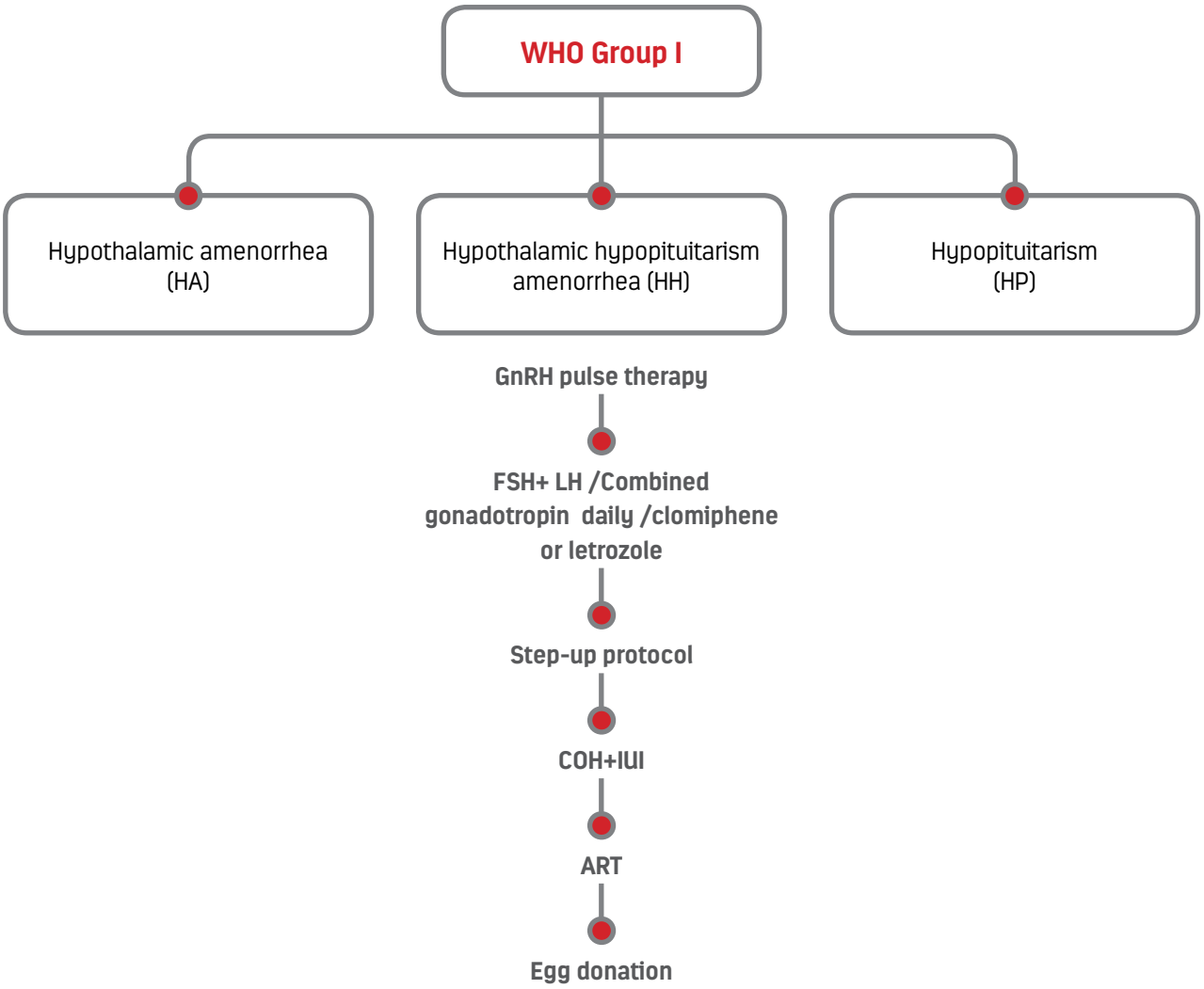
1. Recruiting multiple follicles
2. Control timing of ovulation (eggs can be surgically retrieved before they are ovulated)
3. Prevention of premature luteinizing hormone (LH) surge
4. To time the insemination
5. Increase the pregnancy rate

	Induction of ovulation	Ovarian stimulation	Controlled ovarian hyperstimulation (COH)
Patient	Anovulatory	Anovulatory ovulatory	Anovulatory ovulatory
Objective	One mature follicle	>1 but <4	Multiple
Example		IUI, unexplained infertility	IVF
Method	Stimulation	Stimulation	Down regulation Stimulation Prevent premature LH surge
LH: Luteinizing hormone; IUI: Intrauterine insemination; IVF: In vitro fertilisation			

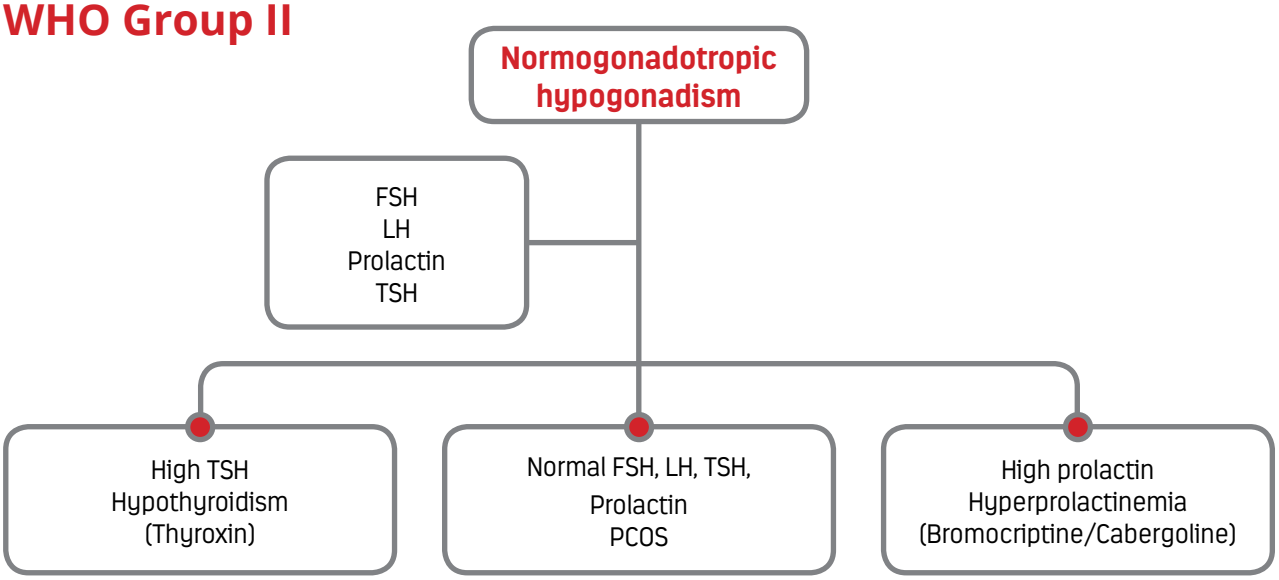
Ovulation induction[1]



Anovulatory infertility WHO Group I

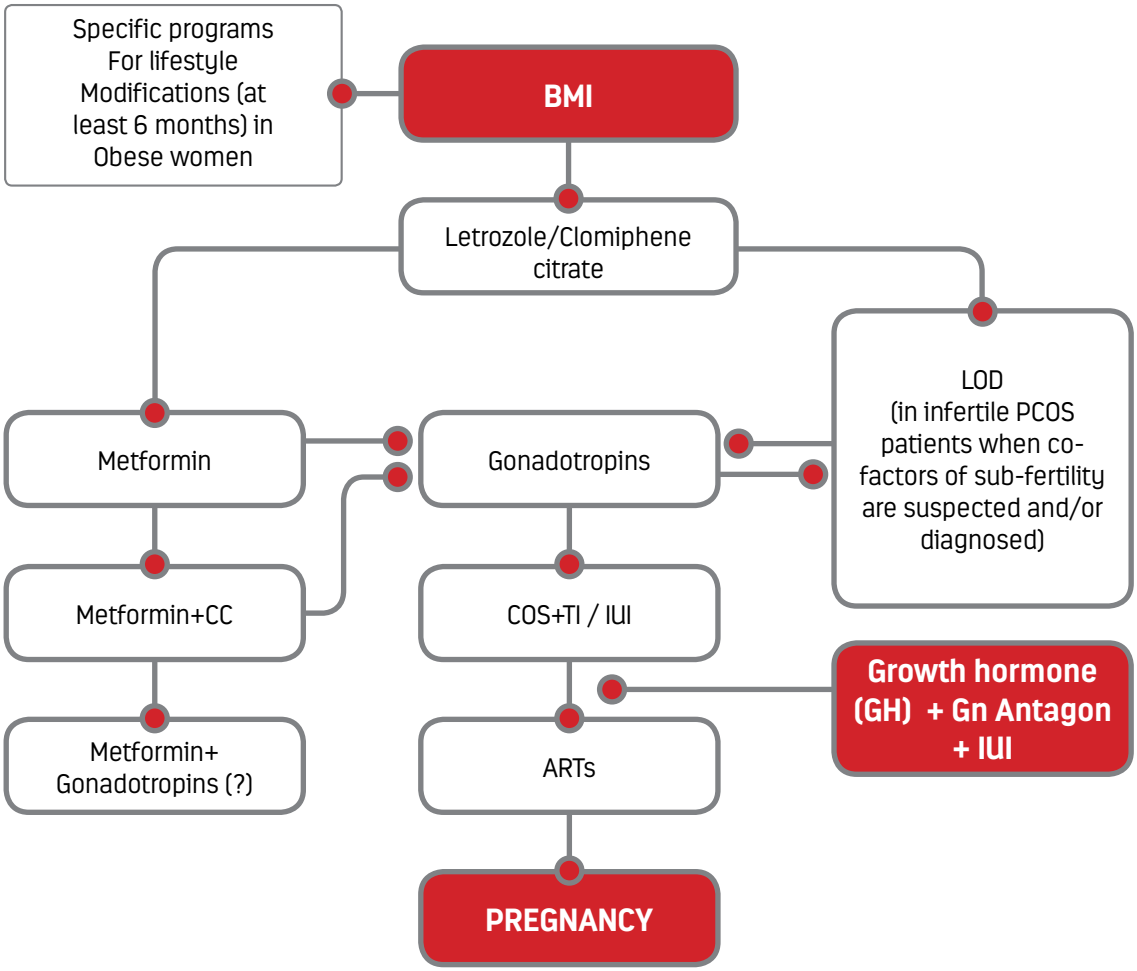


WHO Group II



FSH: Follicle stimulating hormone; LH: Luteinizing hormone; COH; Controlled ovarian hyperstimulation; TSH: Thyroid stimulating hormone; PCOS: Polycystic ovarian syndrome; GnRH: Gonadotropin-releasing hormone; ARTs: Assisted reproductive techniques; IUI: intra-uterine insemination

Ovulation induction in PCOS- Best Practices[2]



ARTs: Assisted reproductive techniques; BMI: body mass index; CC: clomiphene citrate; COS: controlled ovarian stimulation; IUI: intra-uterine insemination; LOD: laparoscopic ovarian drilling; TI: timed intercourse.

Palomba. Ovulation induction in PCOS. Fertil Steril. 2006.

Predictive markers for ovarian response[3]

AMH levels and antral follicle count (AFC) levels

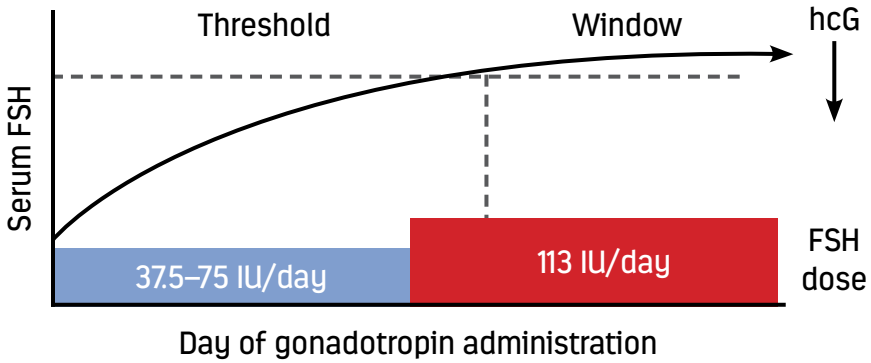
- ↑ In high responders
- ↓ In poor responders
- Anti-Müllerian hormone (AMH) – performed better in the prediction of excessive response to ovarian stimulation compared to follicle stimulating hormone (FSH), and AFC

AMH to be incorporated into work up protocols to predict patient's ovarian response to treatment.

Gonadotropins in WHO Group II

- WHO II anovulation is a common disorder in infertile woman. Induced ovulation with gonadotropins is usually a second-line therapy
- The effectiveness of gonadotropins is largely proven, but it requires experience and skill to get a singleton live birth, which is the ultimate goal of this therapy

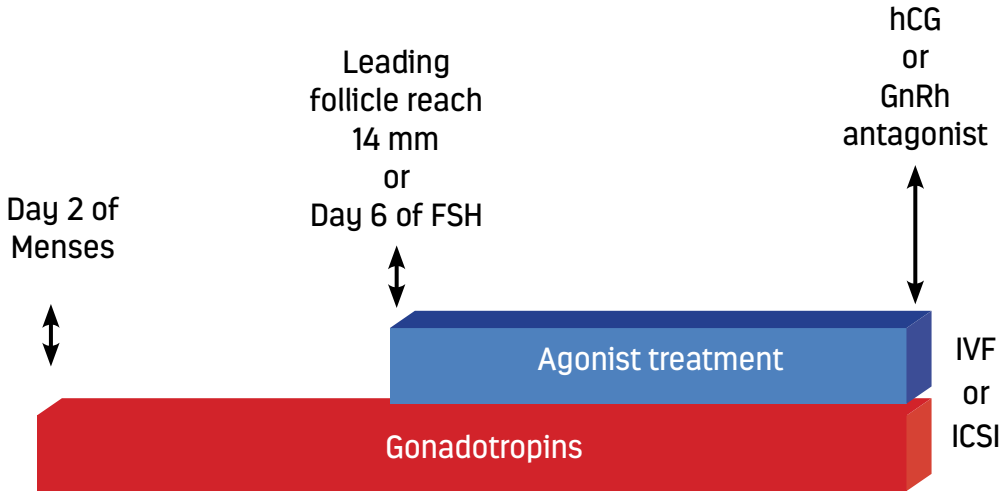
Protocols for the stimulation with gonadotropins Step-Up Protocol[1]



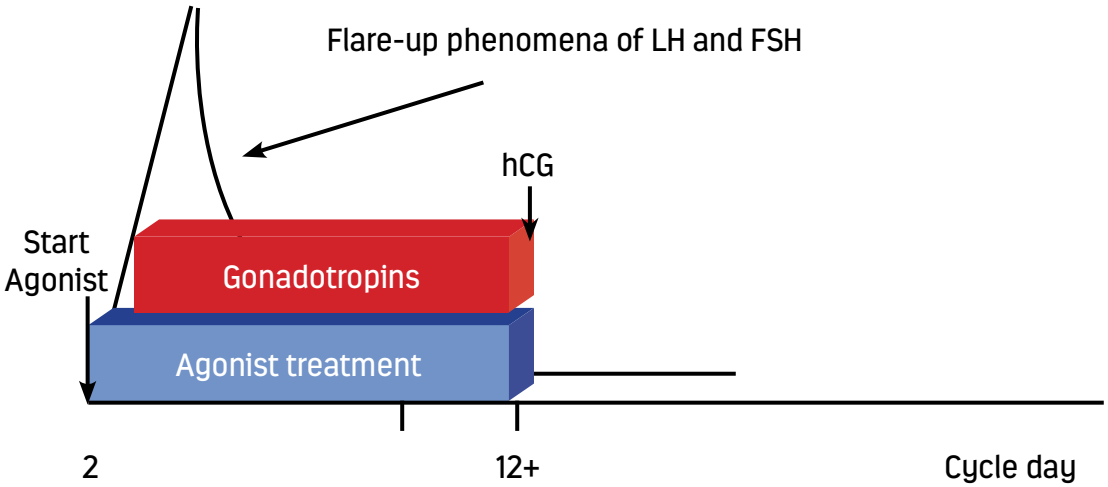
Adequate response –

- Follicular growth 2 mm/day
- Endometrial growth 1 mm/day
- If inadequate response
  - » Increase the dose by 37.5 – 50 IU after 7–10 day
  - » Chronic Low Dose Step up Protocol for high responders

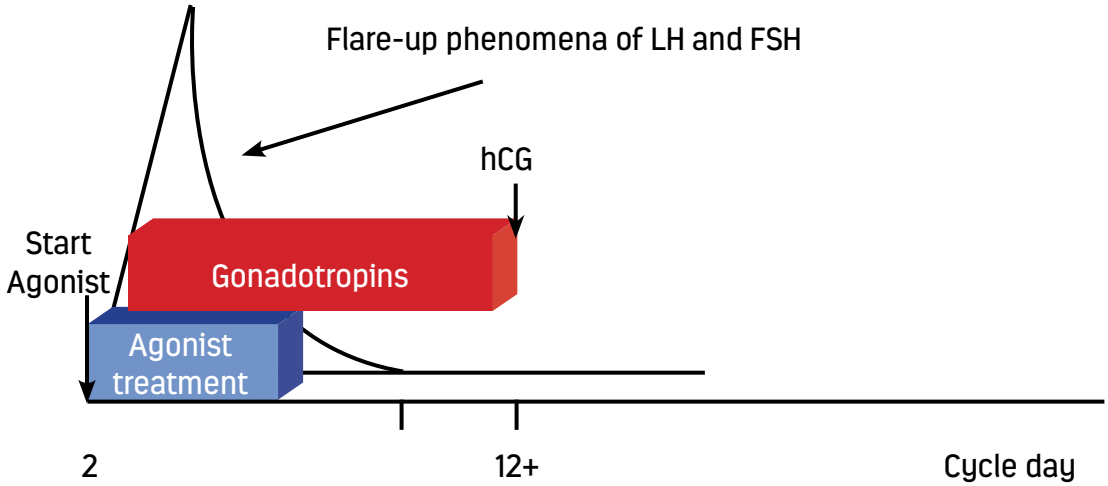
Treatment protocol with the GnRH antagonist[1]



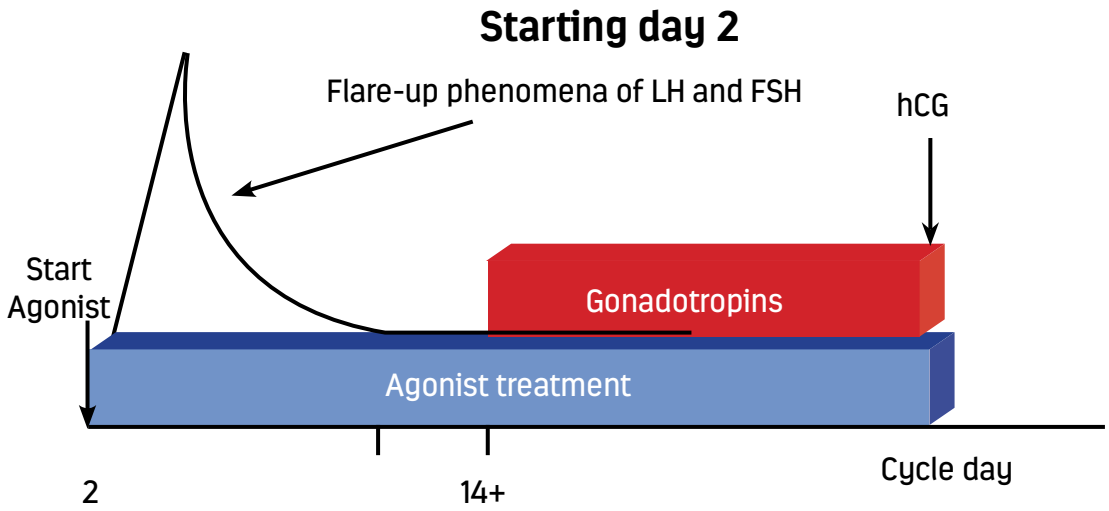
GnRH agonist short protocol[1]



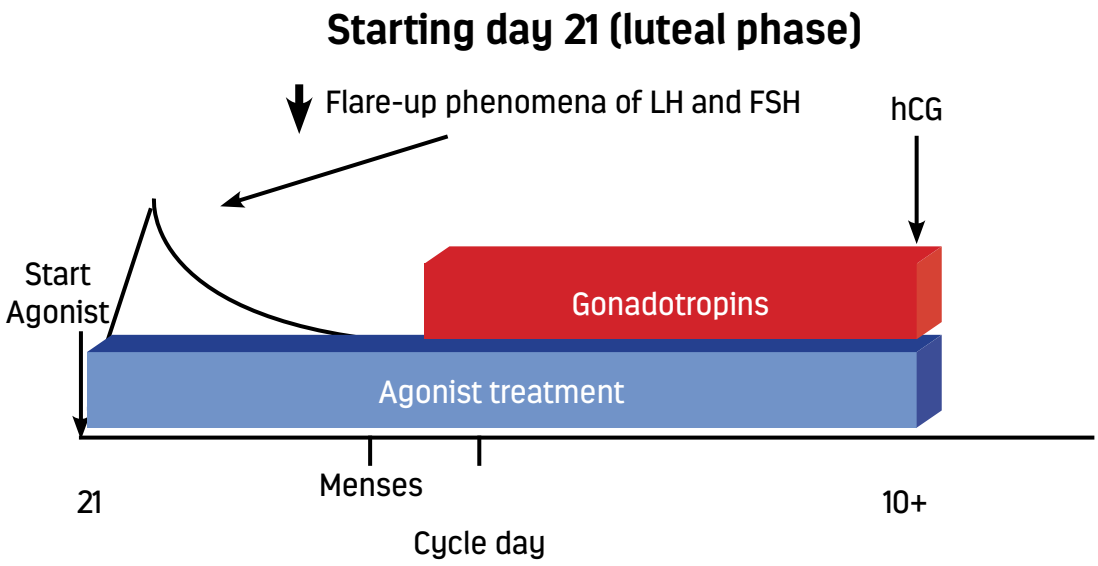
GnRH agonist ultra-short protocol[1]



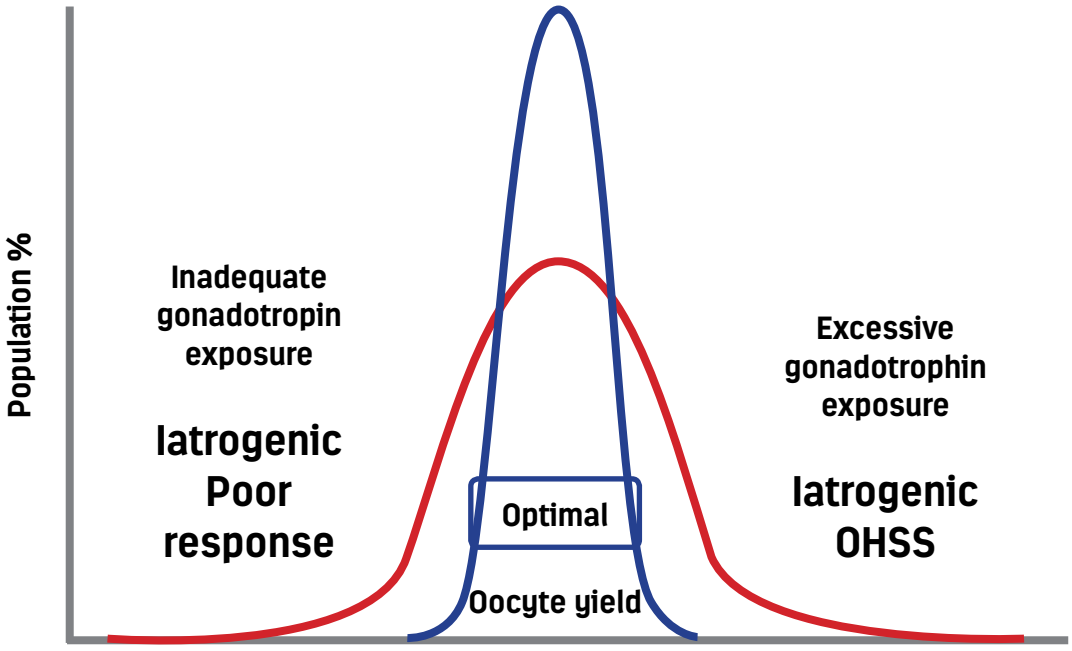
GnRH agonist long protocol[1]



GnRH agonist long protocol[1]

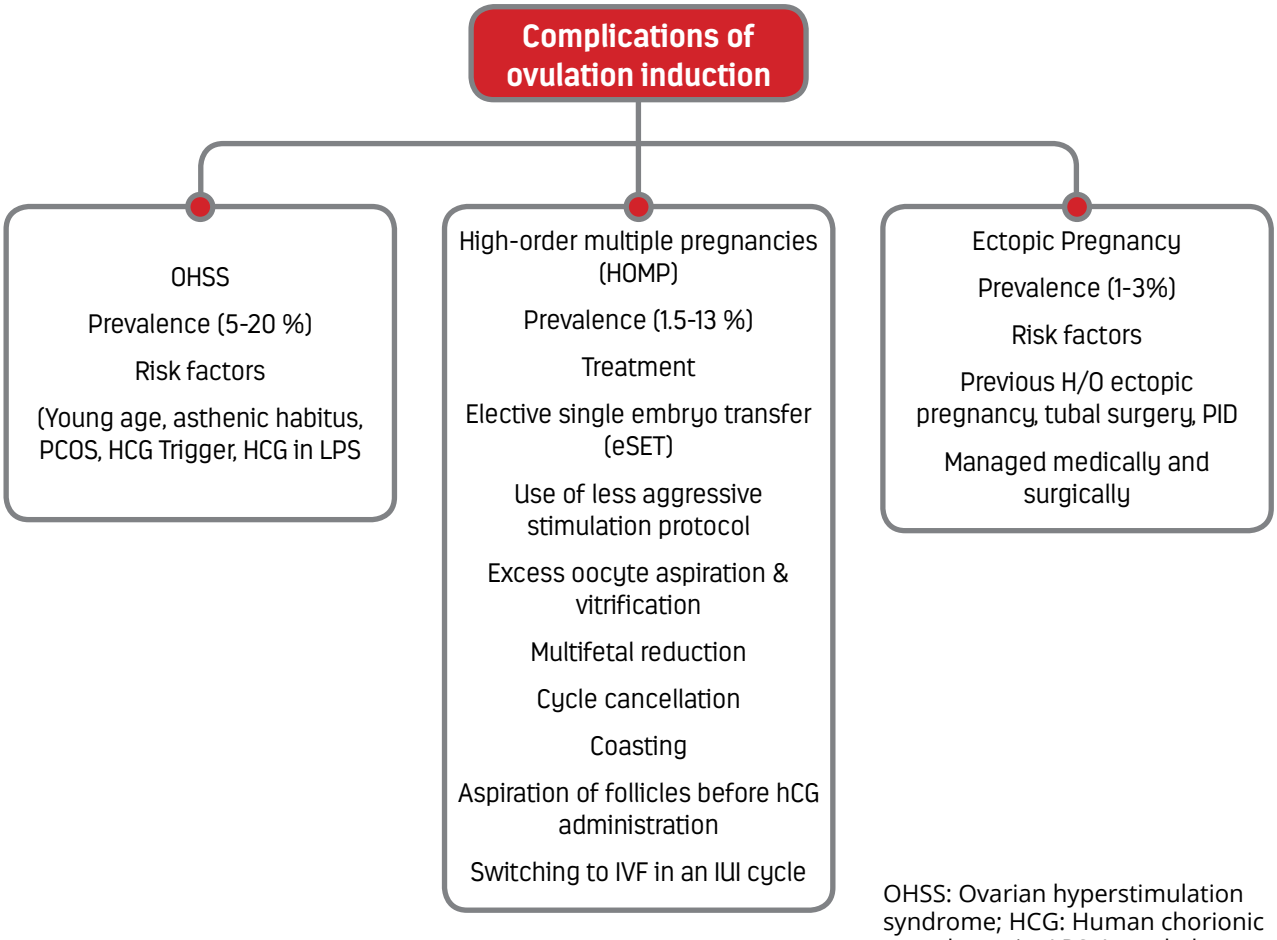


ICOS Goals

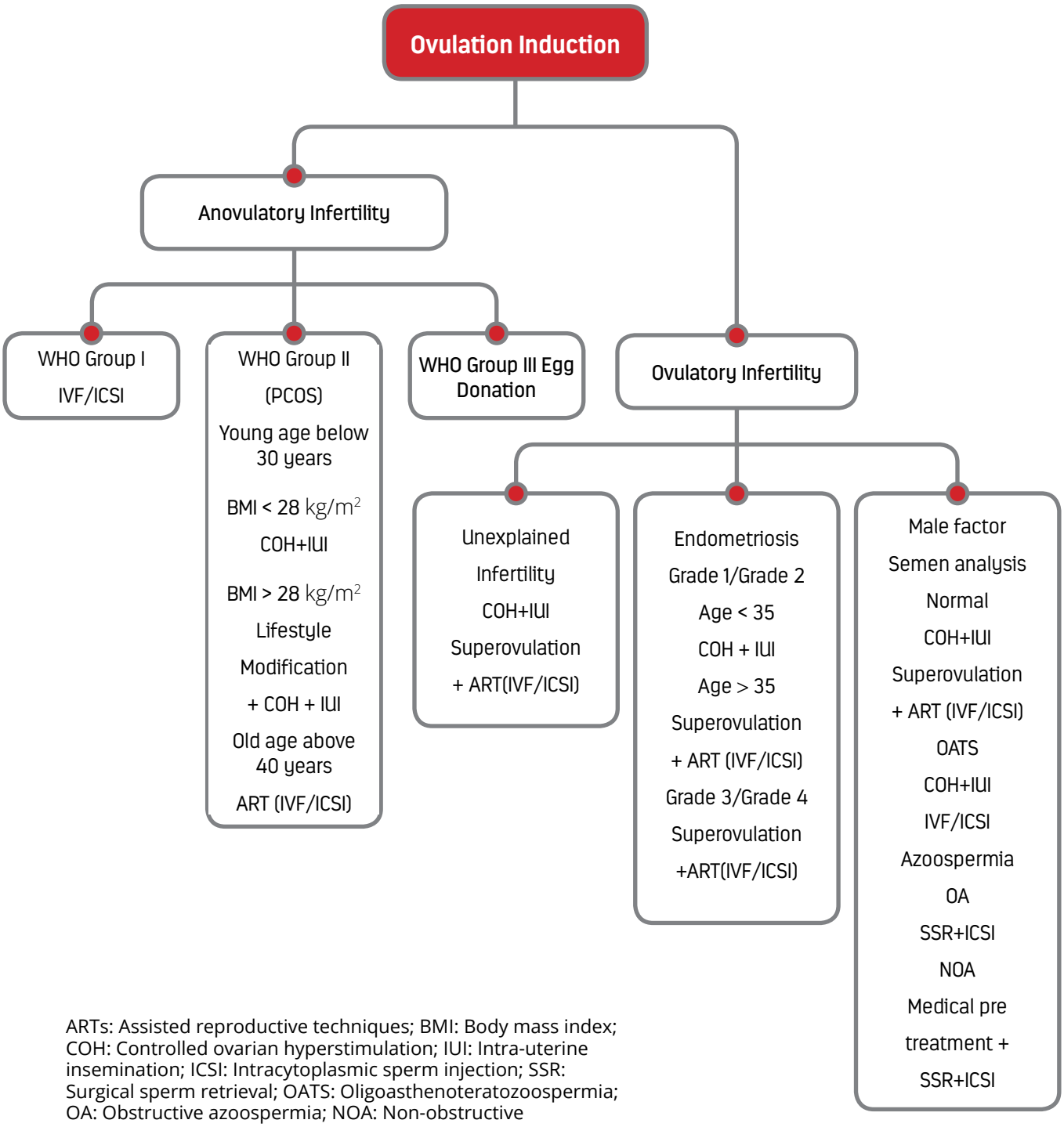


ICOS: Individualised controlled ovarian stimulation; OHSS: ovarian hyperstimulation syndrome

Determinants of ICOS (age, AMH, BMI, and AFC)		
Normal responder 1. Antagonist protocol 2. Long luteal phase protocol	**Hyper responder** 1. Antagonist 2. Minimal ovarian stimulation (MOS) protocol	**Poor responder** 1. Antagonist protocol 2. Microdose flare protocol 3. Modified natural cycle (MNC) protocol 4. MOS protocol with embryo banking



OHSS: Ovarian hyperstimulation syndrome; HCG: Human chorionic gonadotropin; LPS: Luteal phase support; PID: Pelvic inflammatory disease; IUI: Intrauterine insemination



ARTs: Assisted reproductive techniques; BMI: Body mass index; COH: Controlled ovarian hyperstimulation; IUI: Intra-uterine insemination; ICSI: Intracytoplasmic sperm injection; SSR: Surgical sperm retrieval; OATS: Oligoasthenoteratozoospermia; OA: Obstructive azoospermia; NOA: Non-obstructive azoospermia

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PREMATURE OVARIAN INSUFFICIENCY

Moderators : Dr. Pratima Mittal, Dr. Bhaskar Pal

Panel Members : Dr. Biswajyoti Guha, Dr. Shanthi Gunasingh

From left to right: Dr. Bhaskar Pal, Dr. Shanthi Gunasingh, Dr. Pratima Mittal, Dr. Biswajyoti Guha

Premature ovarian insufficiency (POI) is amenorrhoea due to the loss of ovarian function before the age of 40 years. POI can occur spontaneously or be secondary to medical therapies. POI is associated with cardiovascular morbidity, osteoporosis, and premature mortality.

Women with POI present in primary care with menstrual disturbance, menopausal symptoms, infertility and, often, significant psychosocial issues. The diagnosis of POI requires follicle-stimulating hormone (FSH) levels in the menopausal range on two occasions, at least four to six weeks apart in a woman aged <40 years, after more than 4 months of amenorrhoea or menstrual irregularity. It is estimated that spontaneous POI affects 1% of the female population.

The diagnosis is often distressing and women are likely to require psychological support. Hormone replacement therapy, unless contraindicated, is required and should be continued until the age of natural menopause.

The causes of POI are diverse and it can occur spontaneously or be secondary to medical therapies. The prevalence of POI due to medical therapies (e.g., chemotherapy, ionizing radiotherapy, and bilateral oophorectomy) may be more than 1%.

Infertility is a key feature of POI considering the loss of ovarian reserve. In women with spontaneous POI, about 5% can spontaneously ovulate and conceive and oocyte or embryo donations are the only reliable methods of achieving pregnancy. Fitness for pregnancy requires assessment in the preconception period as some women with POI may have high obstetric risk.

Women with POI may present with adverse psychosocial symptoms, and have higher levels of depression and anxiety, a more negative body image, decreased sexual function and reduced confidence, compared with premenopausal controls.

This guideline offers advice on the care of women with premature ovarian insufficiency, both primary and secondary.

Best wishes!

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Premature ovarian insufficiency criteria for diagnosis

The prevalence of premature ovarian insufficiency is 1% in general population.[1]

Criteria for diagnosis[2]

- Amenorrhea for > 4 months
- Two consecutive follicle-stimulating hormone (FSH) level >30 miu/ml in an interval of 1 month
- Less than 40 years of age
- Usually permanent but ovarian activity can resume and fertilty reversed in 5–10% of cases

Strategies to diminish incidence of premature ovarian failure[2]

- Lifestyle modifications
- Cessation of smoking
- Modified treatment of malignant lesions with an aim to minimize damage to ovaries

Understanding the etiology[2,3]

- Largely unknown
- X chromosomal disorders (Fragile X)
- Fragile X mental retardation 1 (FMR-1) permutations
- Turner & Turner Mosaic
- 46 XY gonadal dysgenesis
- Autoimmune causes
- Iatrogenic causes

History and differential diagnosis[2]

- Need to exclude
  - » Pregnancy
  - » Hypothalamic amenorrhoea
  - » Hyperprolactinaemia
  - » Polycystic ovary syndrome (PCOS)
  - » Genital tuberculosis
- Careful history to rule out Iatrogenic injury to ovary (CT/RT)
- Sheehan and Ashermann syndrome need to be excluded
- Family history

Investigations for diagnosis

- Urinary human chorionic gonadotropin (hCG)
- Serum prolactin and thyroid levels
- Serum FSH, luteinizing hormone (LH), and estradiol levels
- Serum dehydroepiandrosterone and serum testosterone if features of hyperandrogenism
- Ultrasonography to assess endometrial thickness (estrogen status), ovarian volume, and antral follicle count

Mandatory Investigations

- Chromosomal karyotype analysis
- Screening for thyroid antibodies (TPO-Ab)
- TSH should be measured every year
- Pelvic ultrasonography
- Routine screening for diabetes

Desirable investigations[4]

- FMR-1 premutation testing
- Screening for infections (screening for tuberculosis)
- Bone mineral density (desirable/mandatory)
- Autoimmune tests- adrenal and thyroid
- Screening for 21-OH antibody/adrenocortical antibodies (ACA) – referral to endocrinologist if positive
- Anti-mullerian hormone (AMH) – <0.3 ng/ml

Management[4]

- Education, counselling, and psychological support
- Prevention and treatment of estrogen deficiency with 17-beta estradiol plus oral dydrogesterone
- Maintain bone health: Diet, exercise, calcium, Vitamin D
- Contraception: Oral contraceptives as occasional chance of fertility though chances are very low. Hormone replacement is an added advantage
- Fertility preservation: Ovarian stimulation with oocyte retrieval followed by oocyte or embryo cryopreservation, ovarian tissue cryopreservation (experimental)
- Ovarian suppression with gonadotropin-releasing hormone (GnRH) prior to chemotherapy
- In-vitro fertilization (IVF) with donor oocytes

Hormone therapy[4]

- Estrogen till natural age of menopause for bone health, local symptoms, and cardioprotection (no breaks)
- If intact uterus, progesterone for 12–14 days a month
- Alternately, continuous combined preparation (better for endometrial protection)
- 17-beta estradiol preferred to estrogens (CEE), or ethinylestradiol (EE) due to less liver load
- Estrogen does not increase risk of breast cancer before menopause
- Transdermal estrogen preferred if risk of venous thromboembolism (VTE), migraine or obesity
- Oral progesterone/dydrogestone/medroxyprogesterone acetate (MPA) or levonorgestrel-releasing intrauterine system
- Oral contraceptive pills can be used but hormone therapy is better

- Local estrogen for urogenital symptoms
- Annual review if on hormone therapy, investigations prompted by clinical picture

Fertility interventions[4]

- No interventions are usually helpful
- Oocyte donation is probably the only option
- Oocyte donation from sisters have a higher rate of cycle cancellation
- IVF with donor oocytes
- Fertility preservation: Ovarian stimulation with oocyte retrieval followed by oocyte or embryo cryopreservation, ovarian tissue cryopreservation (experimental)
- Ovarian suppression with GnRH prior to chemotherapy

Bone health[4]

- Reduced bone mineral density (BMD) and therefore increased risk of fracture in life
- Estrogen therapy
- Bisphosphonates may also be considered
- BMD should be measured during diagnosis of premature ovarian failure and monitored by dual-energy x-ray absorptiometry (DEXA) scan. BMD needs to be repeated after 5 years

Screening of women with POF[4]

- Metabolic disorders
- Six to twelve months intervals with periodic testing of thyroid-stimulating hormone (TSH), calcium, and cortisol levels
- If antiadrenal antibodies are present, an adrenocorticotropic hormone (ACTH) stimulation test to assess adrenal reserve or referral to an endocrinologist is advised
- PAP smear and sonography (mammography) – desirable

Predictive criteria

- Very low AMH levels
- Fertile women receiving chemotherapy or radiotherapy

Implications on life expectancy[4]

- Untreated primary ovarian insufficiency has reduced life expectancy mainly due to cardiovascular problems
- Lifestyle advices need to be given

Obstetric risks

- Same as that of the general population
- Oocyte donation pregnancy are at a higher risk and managed in an appropriate setting
- Antenatal aneuploidy screening depending on the age of the donor

Cardiovascular and sexual health[4]

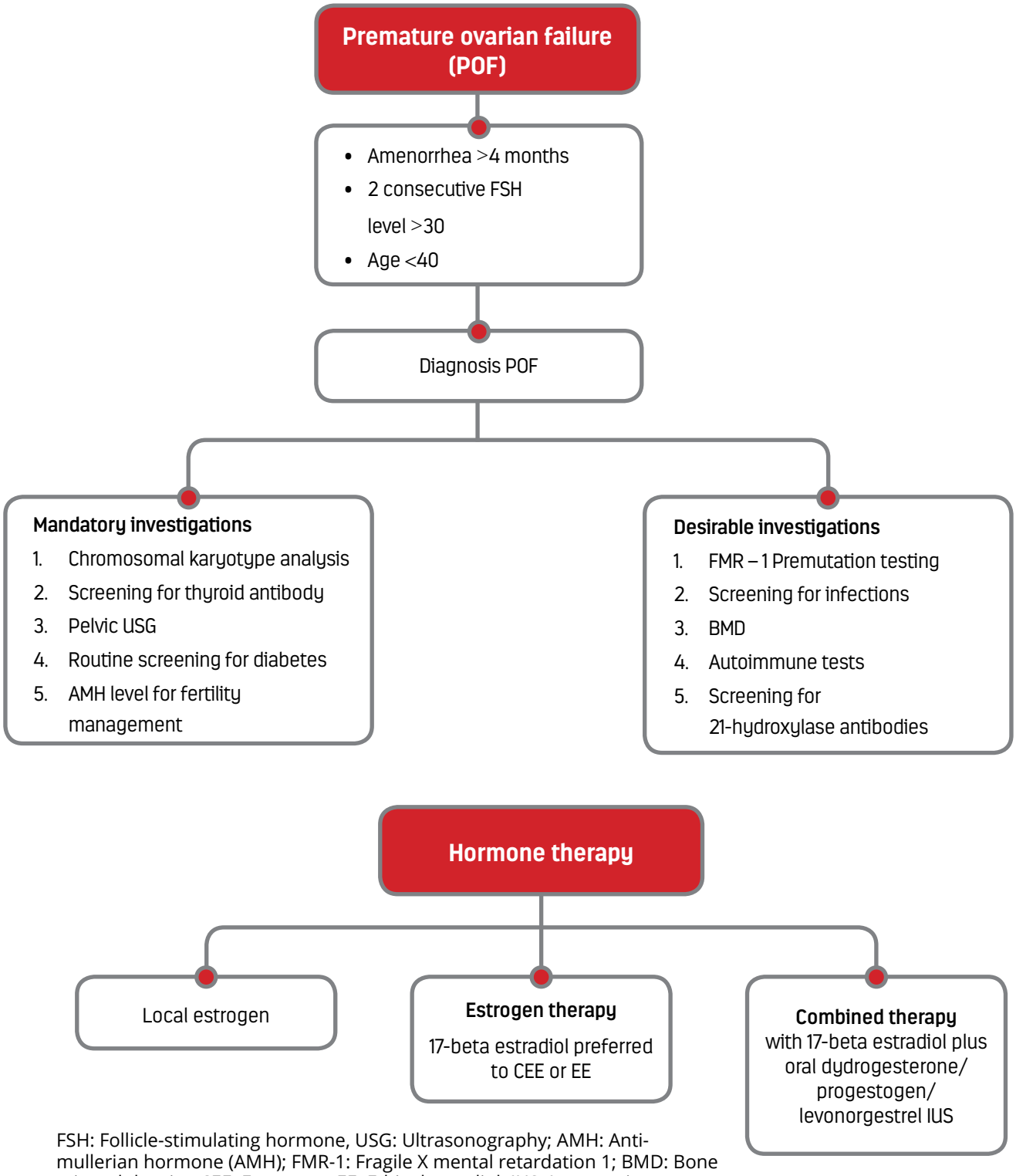
- Hormone replacement therapy with early premature ovarian failure (POF) is desirable for the prevention of cardiovascular diseases
- Estrogen replacement therapy (ERT) is strongly recommended to prevent dyspareunia
- Local estrogens and lubricants can also be used

Risk of hormone replacement[4]

- Not found to increase the risk of breast cancer
- Progestogen replacement should be routinely done in intact uterus

Options for hormone replacement

- 17-beta estradiol is preferred over estrogens (CEE) or ethinylestradiol (EE)
- Annual monitoring of patients on hormone replacement therapy should be done



FSH: Follicle-stimulating hormone, USG: Ultrasonography; AMH: Anti-mullerian hormone (AMH); FMR-1: Fragile X mental retardation 1; BMD: Bone mineral density; CEE: Estrogens; EE: Ethinylestradiol; IUS: Intrauterine system

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PRETERM LABOUR

Moderators : Prof. Meera Agnihotri,
Prof. Suchitra N. Pandit

Panel Members : Dr. Mala Raj, Dr. Jyoti Malik,
Dr. Deepa Ganesh

From left to right: Prof. Suchitra N. Pandit, Dr. Deepa Ganesh, Prof. Meera Agnihotri, Dr. Mala Raj, Dr. Jyoti Malik

Preterm labour complicates 5–10% of pregnancies and it is a leading cause of neonatal morbidity and mortality globally. Identifying a woman at high risk of preterm delivery remains a major challenge. Scoring systems based on socioeconomic status, obstetric or medical history, and antenatal events in the index pregnancy have shown a suboptimal correlation with subsequent preterm birth.

The single greatest risk factor for a preterm labour is a history of preterm labour, hence delivery cannot be reliably predicted in the first pregnancy. The risk of preterm delivery after one and two previous preterm deliveries has been given as 15% and 41%, respectively.

Investigations such as fetal fibronectin or cervical ultrasound can be used to identify women at high risk. A measurement of cervical length can be used as a predictor of preterm delivery.

The prevention of preterm labour is directed towards identification of women at risk. It includes screening and treatment for bacterial vaginosis, insertion of cerclage in appropriate women, and consideration of progesterone prophylaxis.

The management of preterm labour is directed towards establishing the cause, ensuring delivery under optimal conditions, and consideration of advantages and disadvantages of delaying delivery to increase gestational age. This requires appropriate assessment of women admitted to hospital to determine the optimal time for delivery. The presence of fetal compromise or intrauterine infection can hinder prolonging the pregnancy. An early gestational age and an uncomplicated preterm labour with intact membranes can mitigate a delay in delivery. The management decision should be based on a risk–benefit analysis for each women presenting with preterm labour.

The main pharmacological considerations are whether to administer antibiotics, steroids or tocolytics. The ultimate goal of management of preterm labour is not merely to prolong pregnancy but to improve neonatal outcome and to reduce morbidity and mortality.

Best wishes!

Dr. Jaideep Malhotra

MD, FICMCH, FICOG, FICS, FRCOG, FRCPI, FMAS
President 2018 - Federation of Obstetrics & Gynecological Societies of India (FOGSI)

Introduction

Magnitude of the problem

- Pre maturity is single biggest cause for neonatal morbidity and mortality and counts for 2/3rd of neonatal deaths.
- Preterm delivery affects almost 23% pregnancies in developing countries like India

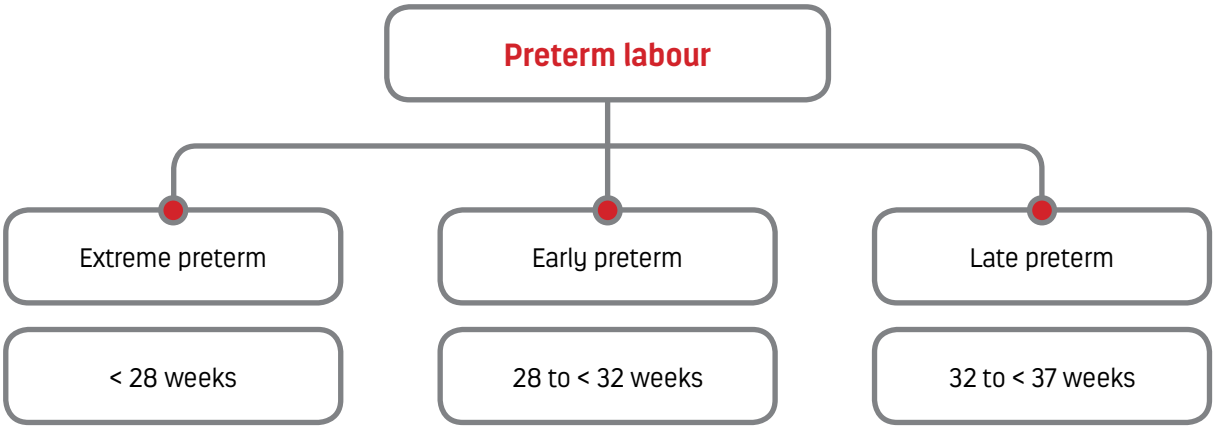
Aim should be to

- » **PREDICT**
- » **PREVENT**
- » **MANAGEMENT**

Definition and terminology

- **Preterm labour** is the onset of uterine contraction of adequate strength and frequency to cause progressive dilatation and effacement of cervix before 37 weeks of gestation (20 – 37 weeks)[2]
- **Lower limit:** Controversial 20 – 27 weeks as salvageability changes depending on NICU
- **Suspected/threatened preterm labour:** Uterine contractions without cervical dilatation
- **Diagnosed preterm labour:** Uterine contractions with cervical changes
- **Established preterm labour:** Uterine contractions plus progressive cervical dilatation of more than 4 cms

Working classifications[2]



The majority of the preterm infants belong to the late preterm subgroup

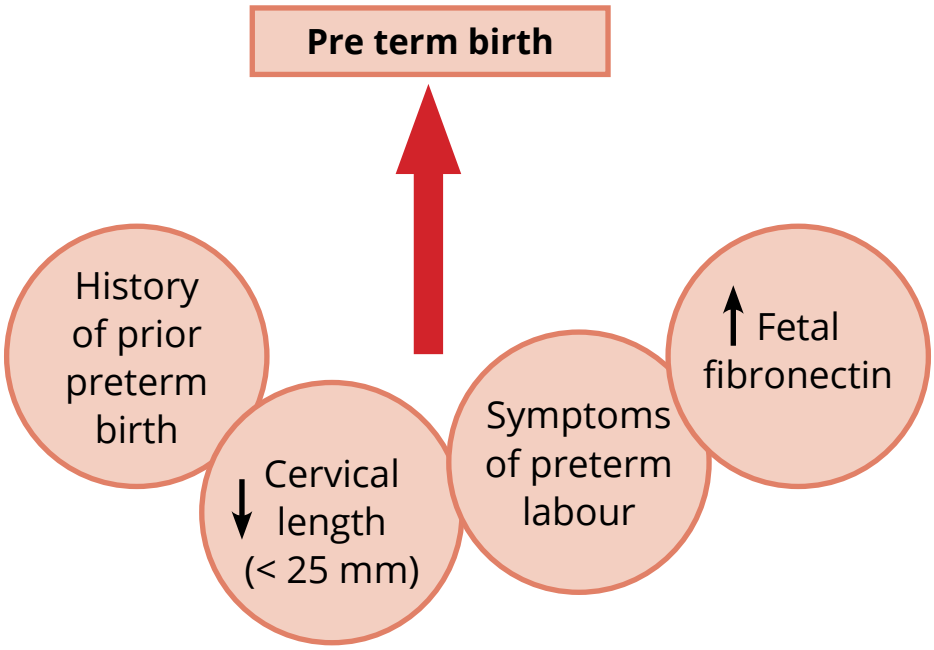
Clinical situations for preterm labour

Clinical situations	Percentage
Spontaneous preterm labour with intact membranes	35%
Indicated/planned preterm delivery » Maternal (e.g. pre - eclampsia) » Fetal (e.g. small for gestational age (SGA)/fetal compromise)	35%
Preterm premature rupture of membranes (PROM)	25%
Multiple pregnancy	15%

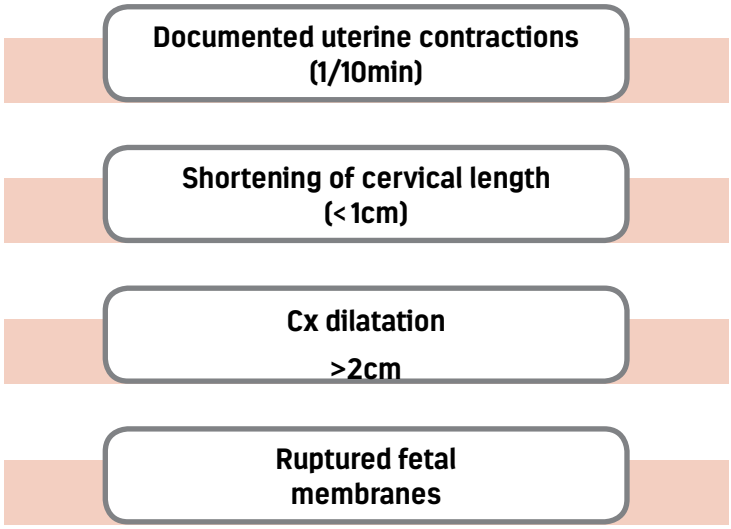
Risk factors for preterm birth[4]

Non-modifiable risk factors	Modifiable risk factors
• Prior preterm birth • Age < 18 years or > 40 years • Extremes of BMI (<19 kg/m^2 and >30 kg/m^2) • Low socioeconomic status • Cervical injury or anomaly • Uterine anomaly • Over distended uterus • Vaginal bleeding in pregnancy • Multiple pregnancy • Prior cervical surgery or loop • Fetal congenital anomalies	• Poor nutrition • Medical diseases (e.g anemia, diabetes) • Hypertension, thyroid problems, asthma, lupus) • Other infections (malaria, influenza, HIV) • Substance abuse: Tobacco/smoking alcohol/ drugs • Asystemic bacteriuria/urinary tract infection/ lower genital tract and periodontal Infections • Strenuous work/environment • Mental status (anxiety/stress/domestic violence) • Reduced immunity and susceptibility to infections • Responsible assisted reproductive technologies (ART) to reduce multiple pregnancy • Iatrogenic: Intrauterine growth restriction (IUGR)

Who is at risk of preterm labour?[4,5]



Criteria for preterm labour[6]



Signs and symptoms of preterm labour

- Frequent contractions (more than four per hour)
- Cramping
- Pelvic pressure
- Excessive vaginal discharge
- Backache and low back pain
- Non-specific symptoms

Prevention of preterm birth

Preconceptional advice in a patient with history of prior preterm birth[7]

- Folate supplementation
- Aim for desirable inter pregnancy interval (highest risk of PTB with interval <6 months)
- Balanced diet to improve nutrition status
- Physical fitness
- Maternal weight at least 40 Kg or BMI < 19 kg/m^2 and >30 Kg/m^2
- Optimize any medical disease (e.g. DM, hypertension, thyroid issues ,asthma, lupus, HIV)
- Avoid multiple gestations, (ART : placing fewer embryos)
- Pre-pregnancy vaccination (especially varicella, rubella, hepatitis B)
- Change over to safe medications once pregnant with no known teratogenic effect
- Avoid smoking, illicit drug and alcohol use
- Screen & treat STI (sexually transmitted infections)

Screen for domestic violence /stress at work or home

Component	Test	Treatment
Myometrium	Uterine monitor	Tocolysis
Cervix	Ultrasound	Cerclage
Membrane/decidua	Vaginal swab culture	Antibiotics
Immuno hormonal	Progesterone and Progesterone induced blocking factor (PIBF)	Progesterone therapy

Measurement of cervical length

Normal cervical length

Cervical length normally remains constant until the third-trimester.

Period of gestation	Endo cervical length
23 weeks	38 mm[8]
24 weeks	35 mm[9]
28 weeks	34 mm[9]

Definition of short cervix

Short cervical length is defined as less than 25 mm before 24 weeks (between 18 to 24 weeks) up to 28 weeks. Shorter the cervix longer is the risk of PTB (most powerful predictor of preterm labour)

Antenatal surveillance once diagnosed as preterm labour[7]

- Biochemical markers [fetal fibronectin (fFN) not available in India]
- Vigilant monitoring in patients with severe maternal diseases
- Progesterone support
- High vaginal swab for vaginal infection at 20 weeks
- Cervical encerclage if required
- Antenatal corticosteroid prophylaxis
- No evidence to support complete bed rest but,
  - » Rest from hectic work and advice increased periods of rest at home
- In utero transfer to higher centre with Neonatal Intensive Care Unit (NICU)

Indication for cervical cerclage

- History of 1st or 2nd trimester losses (painless dilatation, without labor or abruptio placenta)
- History of prior spontaneous preterm birth, cervical length of <25 mm before 32 weeks
- In previous history of cervical incompetence, a cerclage for painless dilation (Shirodkar or McDonald suture performed in early second-trimester after Nuchal translucency (NT) scan is of benefit. Transabdominal cervico - isthmic cerclage reserved for failed transcervical cerclage)
- Cervical dilation in the 2nd trimester in the present pregnancy
- Rescue cerclage is only for emergency use in early preterm labour before or at the limit of viability in case of cervical incompetence
- Select criteria carefully since cerclage in the presence of clinical or subclinical infection can result in significant maternal morbidity

Tocolytics

Indications of tocolytics		
Acute preterm labor	**Maintenance - acute preterm labor**	**Prophylaxis of preterm labor**
Completing a course of corticosteroids or in utero transfer Reduce the proportion of births occurring within 7 days	Oral and parenteral may be for maintenance therapy beyond 48–72 hours	Prophylaxis of preterm labor in women who are at high risk for Preterm labor

Tocolytic drugs

Name	Mechanism of action	Dosage	Side effects
Beta adrenergic receptor agonists Isoxsuprine	Maternal effects: Relaxes the uterus Uterine quiescence	40 mg in 500 mg ringer lactate 8 drops/min (0.04 mg/min). Drop rate will be increased by 8 drops/min every 15 min till uterus becomes quiet Isoxsuprine drip continued for 12 hours after uterine quiescence. Maximum dose not more than 0.5 mg/min Subsequently can be given orally (Tablets) 60-80 mg/day in divided doses	Maternal: Tachycardia, hypotension, palpitations, shortness of breath, chest discomfort, pulmonary edema, hypokalemia and hyperglycemia Contraindication: Maternal heart disease, diabetes. Drug Controller General of India (DCGI) approval for preterm labor India
Calcium channel blockers Nifedipine	Act by reducing influx of calcium ions in the cell membrane – reduces tone of smooth muscles	20 mg loading dose, then 10–20 mg every 4–6 h. Total dose not above 60 mg	Headache, nausea, transient hypotension, transient tachycardia fetal sudden demise Contraindication: cardiac disease, renal disease, maternal hypotension (< 90/50 mmHg)
Atosiban	Oxytocin antagonist	In bolus 6.75mg over 1 min followed by infusion of 18mg per hour for 3 hours, then 6mg per hour for up to 45 hours (Maximum 330mg)	Licensed for treatment of pre term labour
Indomethacin	Prostaglandin sythetase inhibitors	25-50mg orally followed by 25mg orally every 4-6 hours	Pre mature closer of ductus arteriosus Necrotizing Enterocolitis grade III & IV Intraventricular Hemorrhage Oligohydramnios
Beta-3 agonists (BRL37344)	Relaxation of uterus		Less cardiovascular side effects as compared to Ritodrine
Nitroglycerine	Smooth muscle relaxant	Transdermal patch 0.2 mg/hour and then add 0.1 mg/hour patch every hour	Hypotension, severe headache
Diaz-oxide	Inhibits contractility of arterial & venous smooth muscle	0.5mg/kg IV slowly in 15-30 minutes 1 ampoule of diazoxide is dissolved in 250 ml of half normal saline	Hypotension, tachycardia hyperglycemia, decreased utero placental blood flow.
Progesterogens 17 alpha-Hydroxy progesterone		250 mg IM weekly	

Why progestogens for preterm labor?

Most important single advance in last decade is the progesterone supplementation to prevent preterm labor in a patient with H/o 1 prior preterm birth (17α-hydroxy progesterone caproate approved by USFDA 2011)

Actions of progesterone

Tocolytic/ quiescent effect on uterus - blocks oxytocin effect of prostaglandin F2α and α-adrenergic stimulation

- Successful pregnancy depends on maternal tolerance of the fetal "semi-allograft". The protein progesterone-induced blocking factor (PIBF), by inducing a Th2 dominant cytokine production mediates the immunological effects of progesterone.
- Progesterone maintains a peaceful balance exist between "bad proinflammatory" Th1 and "good antinflammatory " Th2 cytokines. If Th1 cytokines overpower Th2, this leads to Preterm loss while Th2 predominance ensures a successful pregnancy

Progesterone is an important molecule to preserve and maintain successful pregnancy till term.

Guideline base approach for preterm birth prophylaxis

Indication	Formulation, dose, route	FDA (2011)	ACOG (2008)	SOGC (2008)
Previous preterm birth	17α-hydroxy progesterone 250 mg IM weekly New evidence is pointing to dydrogesterone for prevention of preterm labour	Approved Awaiting further approval	Approved	Recommended
Short cervical length during mid trimester (<15 mm)	Micronized progesterone 200 mg PV daily from GA 16 -20 to 34 - 37 wk Dydrogesterone 10mg twice daily	Not approved	May be considered	Recommended

FDA: US Food and Drug Administration; ACOG: American College of Obstetricians and Gynecologists; SOGC: The Society of Obstetricians and Gynecologists of Canada; GA: Age of gestation

Selected studies on progesterone supplementation for preterm labor delivery in singleton gestations

Study	Dosage	Remark	
Meis, 2003[1]	17α–hydroxyprogesterone caproate (250 mg weekly injections)	16-20 wks up to 36 weeks	A substantial reduction in the rate of recurrent preterm delivery among women who were at particularly high risk for preterm delivery and reduced the likelihood of several complications in their infants.
Saghafi N, 2011[2]	17α–hydroxyprogesterone caproate (250 mg weekly injections)	16 weeks up to maximum 37 weeks	Pregnant women with a history of preterm delivery was associated with a decrease in preterm delivery and improvement in birth weight.
Wajiha Shadab, 2018[3]	17α–hydroxyprogesterone caproate (250 mg weekly injections)	Till 37 weeks of gestation	17α-Hydroxyprogesterone was found to be an effective drug in preventing delivery before 37 weeks in women at risk.
Da Fonseca, 2003[4]	Vaginal progesterone (100 mg daily)	High risk women history of preterm labor	Prophylactic vaginal progesterone reduced the frequency of uterine contractions and the rate of preterm delivery in women at high risk for prematurity.
O'Brien, 2007[5]	Vaginal progesterone (90 mg daily)	24 weeks up to 34 weeks	Vaginal progesterone may reduce the rate of early preterm birth and improve neonatal outcome in women with a short sonographic cervical length.
Fonseca, 2007[6]	Micronized progesterone gel capsules (200 mg vaginally daily)	Asymptomatic women with short c/s length < 15 mm 24 - 34 weeks	In women with a short cervix, treatment with progesterone reduces the rate of spontaneous early preterm delivery.
Hassan, 2011[7]	Vaginal progesterone gel (90 mg daily)	Single gestation previous PTL 20–23 weeks. Up to 37 weeks	In women with a sonographic short cervix, vaginal progesterone gel was associated with a 45% reduction in the rate of preterm birth before 33 weeks of gestation and with improved neonatal outcome.

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Do's & don'ts in progesterone therapy

No role of progesterone therapy in normal healthy pregnant women for prevention of miscarriage

Progesterone has a role for luteal phase support in ART cycles

No Progesterone therapy for multiple pregnancy.

Adding one variety of progesterone with other does not give extra advantage

Use with caution in cardiovascular disease Impaired liver function & cholestasis

New thoughts[10]

- **Data suggest that dydrogesterone treatment of women at risk of preterm delivery results in increased PIBF production and interleukin 10 (IL-10) concentrations, and lowers concentrations of interferon gamma (IFNγ). So may be effective for prevention or treatment of preterm birth. Yet the exact role of progesterone as a maintenance therapy after the inhibition of preterm labor remains much to be discovered**
- **Further randomized control trials desired**

Steroids[4,11]

- Dexamethasone/betamethasone 24- 34 weeks mandatory unless active infection
- From 34–37 weeks recent data indicates reduction in respiratory morbidity
- Betamethasone 12 mg 24 hours apart (use propionate salt)
- Dexamethasone 6 mg 12 hourly 4 doses (preferred in patients with diabetes, pregnancy-induced hypertension)

Rescue course

- If pregnancy continues beyond 7 days after primary dose and if delivery is suspected within 7 days (delivery is imminent) then rescue course of betamethasone or dexamethasone can be given up to 34 weeks of gestation
- Repeated doses are not recommended
- **Aim for in-utero transfer whenever necessary after 1st dose of steroids to centre with neonatal intensive care unit (NICU)**

Antibiotics

Antibiotics are not routinely needed for all cases specially, with intact membranes.

Exceptions: infection

- If established labor (or imminent risk of preterm birth) give intrapartum group B streptococcal (GBS) prophylaxis regardless of GBS status or membrane status

If chorioamnionitis (membranes intact or ruptured)

- Ampicillin (or Amoxycillin) 2 g IV initial dose, then 1 g IV every 6 hours
- Gentamicin 5 mg/kg IV daily
- Metronidazole 500 mg IV every 12 hours

If penicillin hypersensitivity and chorioamnionitis:

- Clindamycin 600 mg IV every 8 hours and
- Gentamicin 5 mg/kg IV daily and
- Metronidazole 500 mg IV every 12 hours
- If labor does not ensue (and no evidence of chorioamnionitis) and membranes intact then cease antibiotics

Avoid Coamoxyclav

Magnesium sulfate for neuroprotection

- Magnesium sulfate reduces the severity and risk of cerebral palsy in neonates
- Gestational age 24–32 weeks
- Labor established or birth imminent
- Loading dose: 4 g IV bolus over 20 minutes
- Maintenance dose: 1 g/hour for 24 hours or until birth – whichever occurs first
- Delayed cord clamping up to 30s not more than 3 minutes except Rh negative mother and HIV+

Neuro protector/magnesium sulfate doses

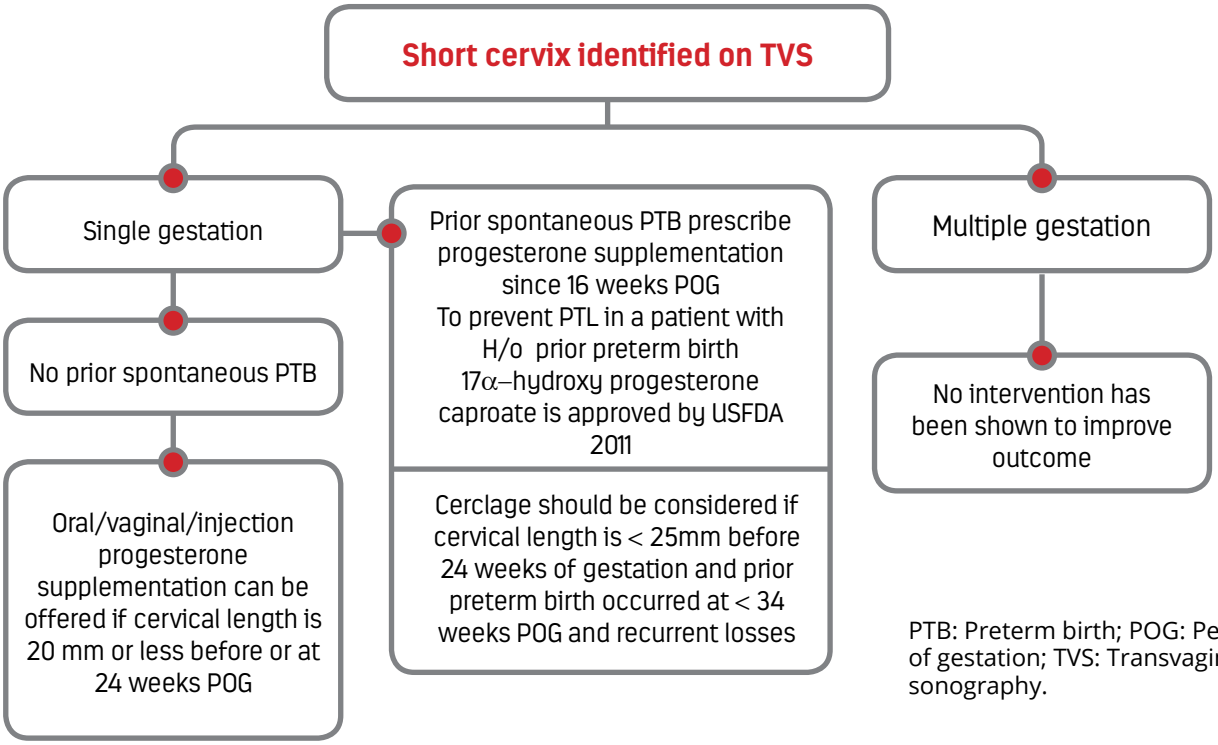
- Loading dose: 4g magnesium sulfate as a SLOW BOLUS over 15–30 minutes
- Maintenance dose: 1g/hr. for 24/hr.
- Monitor Respiratory rate 16 or more
- Patellar reflexes
- Urine output 25 ccs per hour

(Stop infusion if: RR<12, hypotension, loss of patellar reflexes and urine output <100ml in 4 hours)

Management of labour

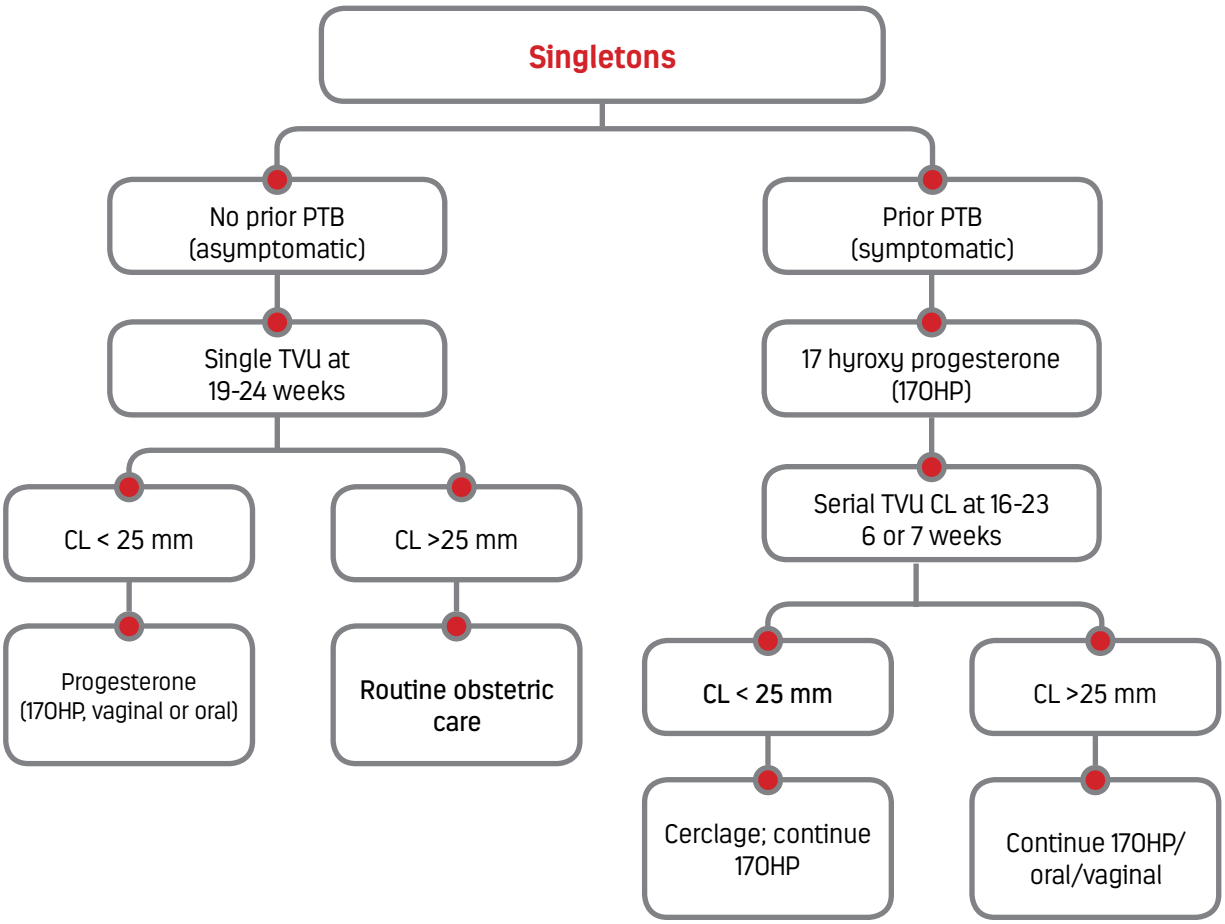
- Monitoring options: Continuous cardiotocography (CTG) or intermittent auscultation during labour.
- Vacuum extraction not used.
- Forceps can be used but with caution.
- Pre-maturity is not an indication for lower segment cesarean section (LSCS).
- Counseling for preterm LSCS in c/o breech malpresenations after discussing salvageability and NICU setup
- Cord-clamping wait for 30 sec. but not more than 3 minutes before cutting cord. Keeping baby below placental level.
- If baby needs immediate removal milking the cord is to be done

Management of short cervical length[12]

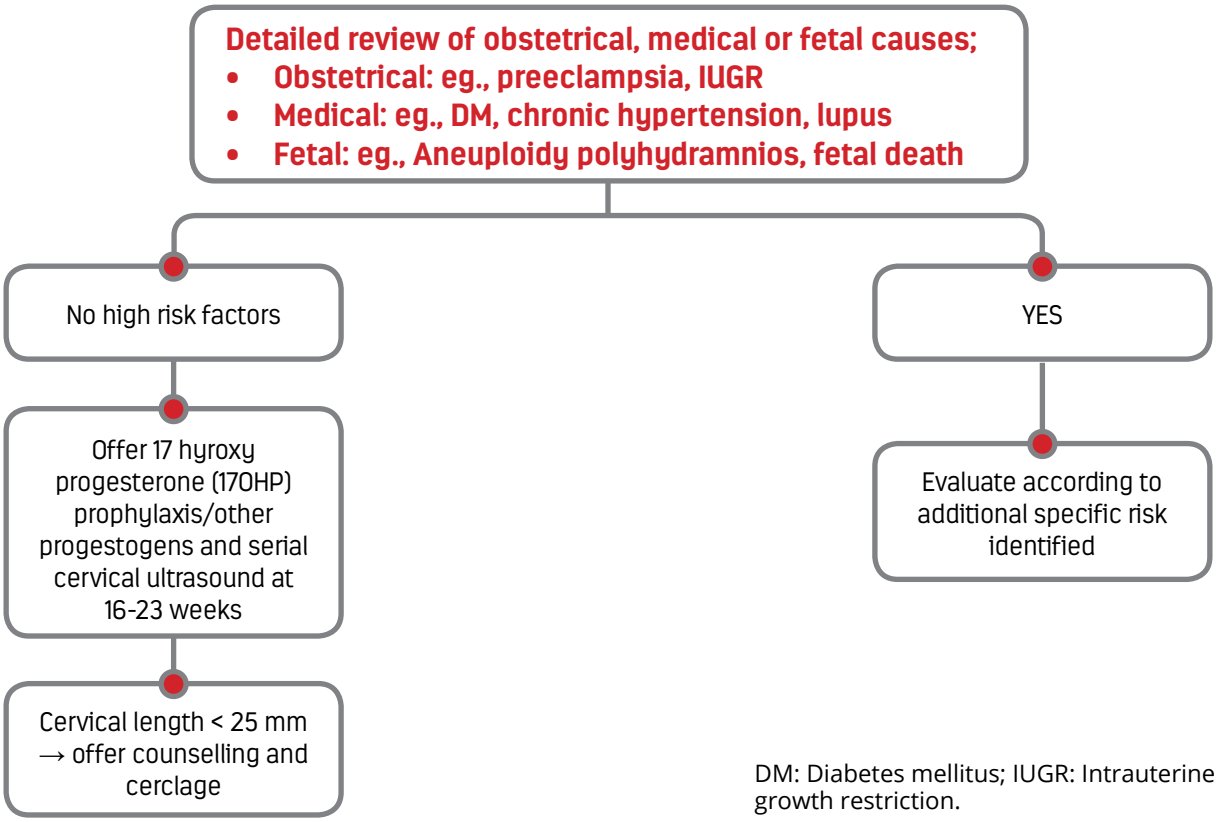


PTB: Preterm birth; POG: Period of gestation; TVS: Transvaginal sonography.

Progestogens in prevention of preterm labor



Management of women with H/o prior preterm birth



DM: Diabetes mellitus; IUGR: Intrauterine growth restriction.

Preterm labour: Summary of National Institute for Health and Care Excellence (NICE) guidance 2018

- To prevent preterm birth, offer a choice of either prophylactic vaginal progesterone or prophylactic cervical cerclage to women with
  - » H/o spontaneous preterm birth or mid-trimester loss between 16^{+0} and 34^{+0} weeks of pregnancy and
  - » TVS between 16^{+0} and 24^{+0} weeks of pregnancy, showing a cervical length of <25 mm.
- To diagnose preterm labour
  - » consider TVS measurement of cervical length to determine likelihood of birth within 48 hours for women who are ≥30+0 weeks pregnant and are in suspected preterm labour. If cervical length is >15 mm, explain that she is unlikely to be in preterm labour.
- To treat preterm labour
  - » Offer tocolysis, corticosteroids, or magnesium sulfate to women in PTL, including those with a cervical length of <15 mm, depending on gestation and clinical circumstances.

Conclusion

- Routine transvaginal cervical length assessment is not recommended in women at low risk
- Biochemical markers are no longer recommended as screening strategies
- H/o previous PTB and asymptomatic short cervix at the second-trimester are both strong predictors for PTB
- In asymptomatic short cervix in second-trimester, serial cervical length screening followed by treatment with progesterone is a cost effective strategy in preventing PTB
- Tocolytics to buy time for steroids, magnesium sulfate & inutero transfer
- Inj 17α-hydroxy progesterone, oral or vaginal, micronized progestogens, and dydrogesterone in high risk pregnancies have been used. Dydrogesterone due to its immunomodulatory properties during pregnancy mediated via PIBF seems promising. Large RCT awaited
- A very important intervention is giving antenatal steroid- Betamethasone 12 mg – 2 doses 24 hours apart, or dexamethasone 8 mg- 4 doses 12 hours apart. Rescue cortisone can be given
- Magnesium sulphate 28-32 weeks for neuroprotection
- Antibiotics, if and when indicated in selected cases
- In utero transfer to a higher centre with NICU

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MANAGEMENT OF PROLONGED LABOUR

Moderators : Dr. Lila Vyas, Dr. Shalini Rajaram

Panel Members : Dr. Nidhi Gupta, Dr. Shyamal Sett, Dr. Dibeyendu Banerjee, Dr. Abha Rani Sinha

From left to right: Dr. Shyamal Sett, Dr. Shalini Rajaram, Dr. Lila Vyas, Dr. Abha Rani Sinha, Dr. Nidhi Gupta

Management of prolonged labour decreases unnecessary induction and augmentation of labour, which in turn decreases amnionitis and rate of lower segment caesarean section. During the management of labour, consideration should be given to the woman's emotional and psychological needs, and encouragement to communicate their needs at any point of labour.

Prolonged labour is defined as the onset of rhythmical, regular, and painful uterine contractions accompanied by cervical dilatation and effacement where labour is longer than 24 hours. (WHO)

- *IA Latent phase of first stage of labour is the period, which is not necessarily continuous. It is defined as painful uterine contraction and cervical effacement with dilatation up to 4 cm.*
- *IB Active phase of first stage of labour is when regular painful contractions are associated with cervical dilatation of more than 4 cm. It should not last longer than 12 hours. Average duration in primipara woman is 8 hours, and in second and subsequent pregnancies is 5 hours.*
- *II stage of labour is divided into passive and active phases.*
  - » *In passive II stage, full dilatation of cervix occurs, and there is absence of involuntary expulsive efforts.*
  - » *In active II stage of labour, the presenting part is visible. Expulsive contractions are present with active maternal efforts. Duration of active second stage in primiparous woman is up to 3 hours after onset of active II stage, and in second and subsequent pregnancies up to 2 hours after onset of active II stage. (WHO)*

First, there must be a differentiation between false labour, and latent phase of labour. If there is no change in cervical dilatation or effacement, that means a woman may not be in labour. In such cases, antispasmodics such as camylofin, drotaverine, and hyoscine can be given to the patient. Camylofin according to present evidences, is one of the best available drugs. In clinical studies, camylofin provides superior results with just single dose compared to other molecules like drotaverine, hyoscine or valethamate bromide, and it does not affect uterine contractility.

Best wishes!

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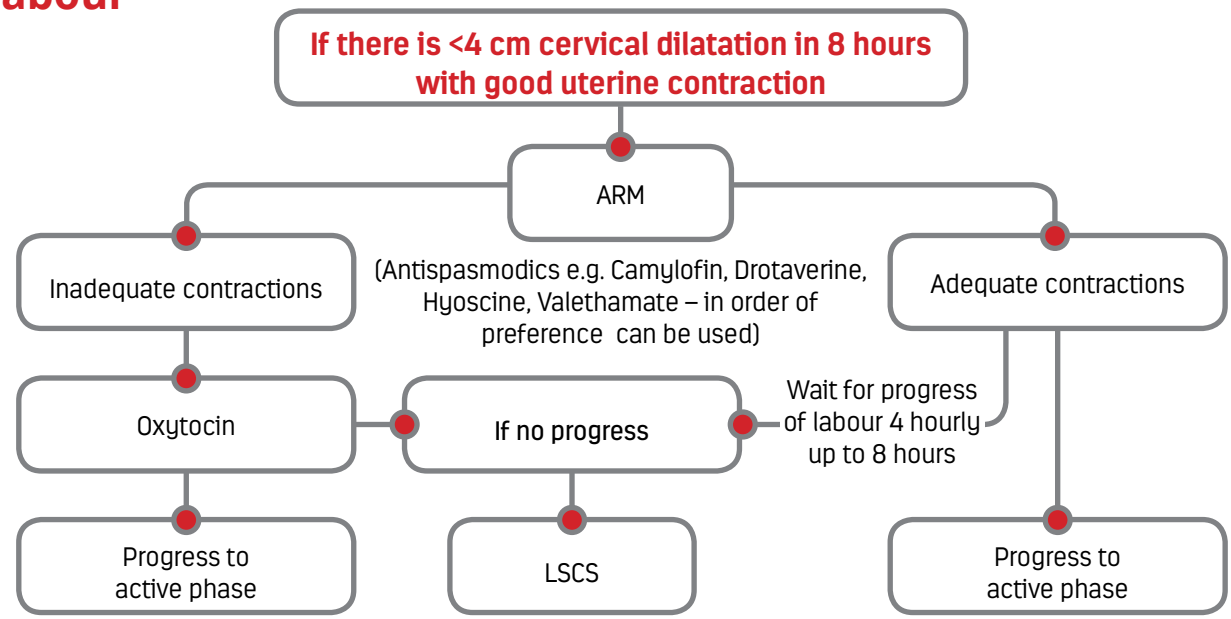
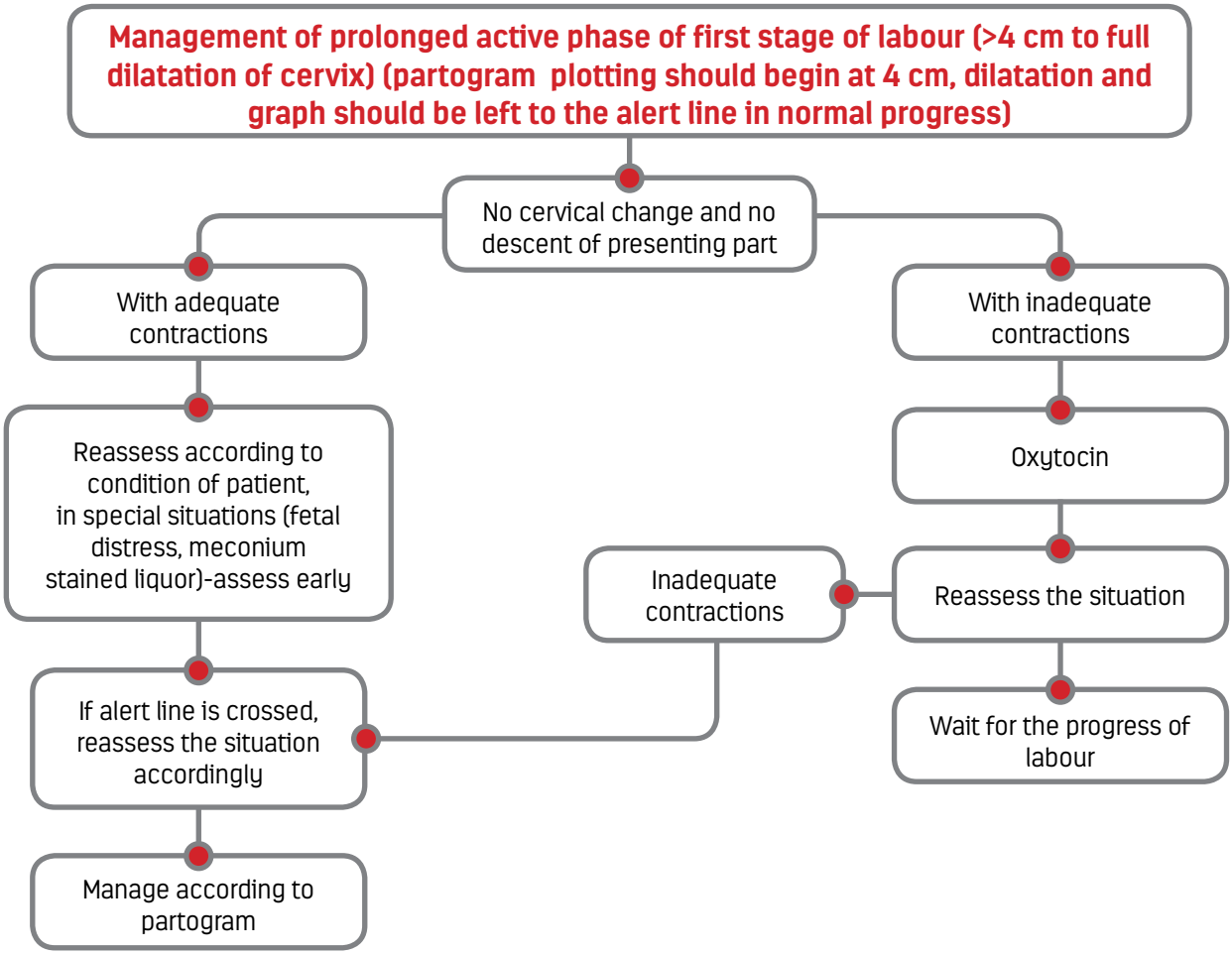
Management of prolonged latent phase of first stage of labour

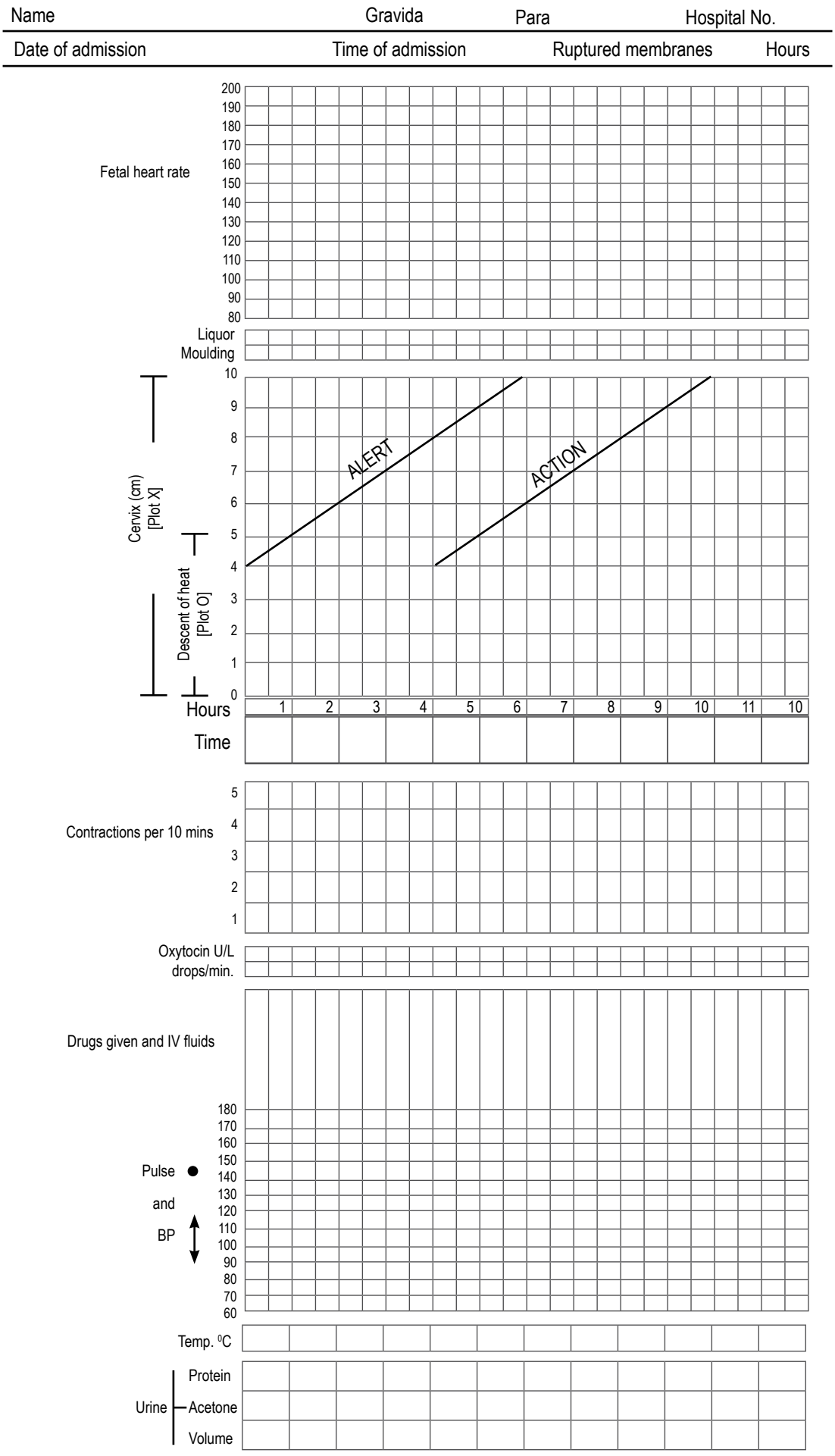


ARM: Artificial rupture of membranes; LSCS: Lower segment Cesarean section.

Management of prolonged active phase of first stage of labour



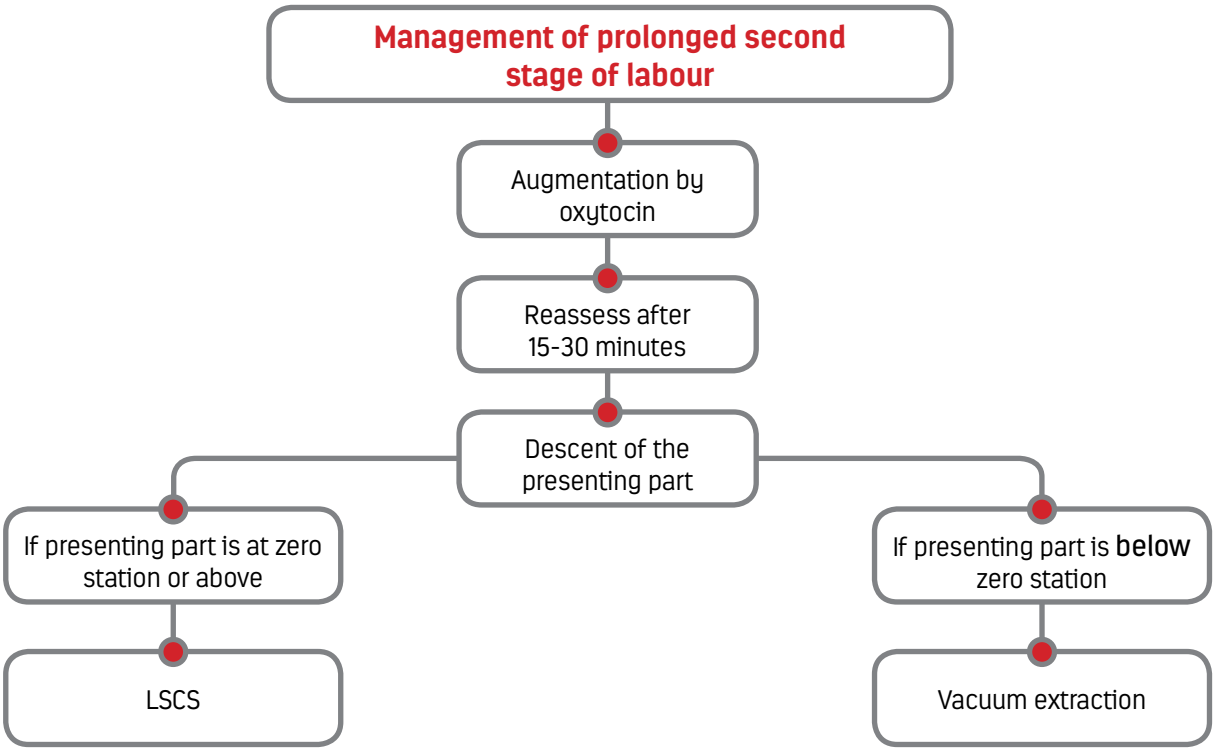
Partogram


Name
Gravida
Para
Hospital No.
Date of admission
Time of admission
Ruptured membranes
Hours
Fetal heart rate
200
190
180
170
160
150
140
130
120
110
100
90
80
Liquor
Moulding
Cervix (cm)
[Plot X]
Descent of head
[Plot O]
10
9
8
7
6
5
4
3
2
1
0
ALERT
ACTION
Hours
1
2
3
4
5
6
7
8
9
10
11
10
Time
Contractions per 10 mins
5
4
3
2
1
Oxytocin U/L
drops/min.
Drugs given and IV fluids
Pulse
and
BP
180
170
160
150
140
130
120
110
100
90
80
70
60
Temp. °C
Urine
Protein
Acetone
Volume

WHO partogram is used for monitoring the active phase of first stage of labour. This is helpful in diagnosing delay in the active phase of first stage of labour, so that a timely action can be taken. This decreases the incidence of obstructed labour, which is an important cause of maternal and perinatal morbidity.

The graph is plotted when a woman comes in at 4 cm or more of dilatation. Two straight lines are on the graph. Left one is alert line. In normal course of labour, graph should be left to alert line. If the alert line is crossed, then immediate reassessment of the woman and active intervention is required.

Management of prolonged second stage of labour



LSCS: Lower segment cesarean section

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RECURRENT MISCARRIAGE (RM): EVIDENCE BASED EVALUATION AND MANAGEMENT

Moderators : Dr. Nandita Palshetkar, Dr. Pratap Kumar

Panel Members : Dr. Nita Thakre, Dr. Vinita Singh, Dr. Alka Pandey, Dr. Shobha Gudi

From left to right: Dr. Alka Pandey, Dr. Pratap Kumar, Dr. Nandita Palshetkar, Dr. Vinita Singh, Dr. Nita Thakre, Dr. Shobha Gudi

Recurrent pregnancy loss (RPL) is a loss of three consecutive pregnancies prior to 20 weeks from the last menstrual period. Among patients without a history of a live birth, after two pregnancy losses, the risk of miscarriage in subsequent pregnancies increases. The accepted causes for recurrent pregnancy loss include parental chromosomal abnormalities, untreated hypothyroidism, uncontrolled diabetes mellitus, certain uterine anatomic abnormalities, and antiphospholipid antibody syndrome.

Diagnostic assessment for recurrent pregnancy loss should include maternal and paternal karyotypes, assessment of the uterine anatomy, and evaluation for thyroid dysfunction, antiphospholipid antibody syndrome, and selected thrombophilias. In some women, assessment should also include insulin resistance, ovarian reserves, antithyroid antibodies, and prolactin disorders.

Treatment is aimed at the treatable causes of RPL, which include surgical correction of anatomic abnormalities, in vitro fertilization with preimplantation genetic diagnosis, use of donor gametes, correction of endocrine disorders, and anticoagulation or folic acid supplementation. Progesterone is a well-established mediator essential for successful implantation of a fertilized ovum and maintenance of pregnancy. An inadequate progesterone secretion during the luteal phase may be responsible for causing miscarriage during the early weeks of pregnancy. The use of progesterone has been indicated to reduce miscarriage rate in women with at least 3 losses previously. Low-dose aspirin is observed to be beneficial for those with a history of losses at >13 weeks of gestation. Replacement of exogenous progesterone before 7 weeks' of gestation prevents the expected miscarriage.

Best wishes!

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Introduction

Recurrent miscarriage is traditionally defined as three or more consecutive miscarriages occurring before 20 weeks. Around 1% of fertile couples will experience recurrent early pregnancy loss.[1]

Incidence of pregnancy loss[2,3]

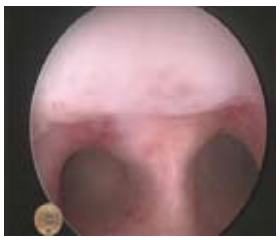
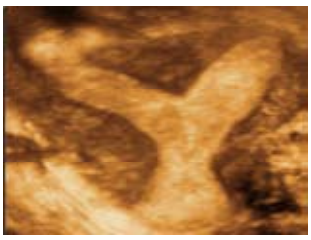
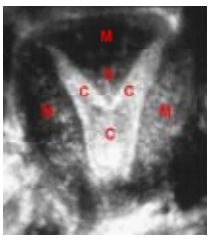
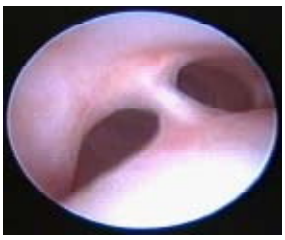
- Global risk of miscarriage for a clinically recognized pregnancy is 12%–15%
- Risk of recurrent miscarriage in reproductive age group is 1% of the population
- As the age advances, risk of miscarriage increases from 7%–15% (<30 years) to 40%–50% (>40 years)
- Around 3%–5% have chromosomal abnormalities in recurrent loss, but single pregnancy loss may be as high as 40%–50% (>40 years)
- Parental cytogenetic investigation
  - » The incidence of structural chromosome abnormalities, usually a balanced translocation is increased in couples with recurrent miscarriage
- Genetic factors
  - » Spontaneous early miscarriage rate is 50%–75%
  - » Only 5% of RPL will be due to genetic factors
  - » Balanced translocation are the most common parental chromosomal abnormalities

Causes of RPL[4]

- Parental chromosomal abnormalities
- Untreated hypothyroidism
- Uncontrolled diabetes mellitus
- Certain uterine anatomic abnormalities
- Antiphospholipid antibody syndrome
- Heritable and/or acquired thrombophilias
- Immunologic abnormalities
- Additional endocrine disorders
- Infections
- Environmental factors
- Half of all cases will remain unexplained after evaluation

Anatomical factors

- Only uterine septum has been proven to be the cause of RPL

Inherited thrombophilia

- Factor V Leiden deficiency, prothrombin mutation
- Less common, but more serious are protein C & S deficiency

No association and hence no need to test for the same.

Thyroid dysfunction and recurrent pregnancy loss

- ASRM: American Society for Reproductive Medicine, 2012 has clarified that thyroid stimulating hormone (TSH) above 2.5 mIU/L are outside the normal range and must be treated[5]
- TABLET (Trial of the efficacy and mechanism of levothyroxine treatment on pregnancy and neonatal outcome in women with thyroid antibodies) trial. Expected to be complete in 2018

Reference range of TSH	
Trimester	**TSH (mIU/L)**
1st trimester	0.1–2.5
2nd trimester	0.2–3
3rd trimester	0.3–3.5
TSH: Thyroid stimulating hormone	

Diabetes

Though it is not a direct cause of RPL, uncontrolled diabetes can be a cause of congenital anomaly. Blood sugar evaluation needs to be done.

Investigations and diagnosis

Coagulation investigations

- A testing for lupus anticoagulant (LAC) and
- Anticardiolipin antibodies (aCL), known collectively as antiphospholipid antibodies (APLA), to exclude an antiphospholipid syndrome (APS)[6]

Other specific assays

- Anti phosphatidyl serine antibody
- Anti-β2-glycoprotein-I antibody
  - » Always do both, lupus anticoagulant and aCL
  - » Repeat all positive results after 12 weeks
  - » If APLA is positive, heparin and aspirin to be started

Criteria for the diagnosis of antiphospholipid syndrome[8]

Clinical	Lab criteria
• Thrombosis • Pregnancy related morbidity	• aCL (IgG or IgM) • Lupus anticoagulant (on 2 or more occasions at least 6 weeks apart)

Presence of at least 1 clinical and 1 laboratory criteria.

Is parental karyotyping needed?

- Royal College of Obstetricians and Gynecologists (RCOG) 2011 – no longer recommended except when an unbalanced chromosome abnormality is reported in products of conception[7]
- American Society for Reproductive Medicine (ASRM) – recommends karyotyping[5]

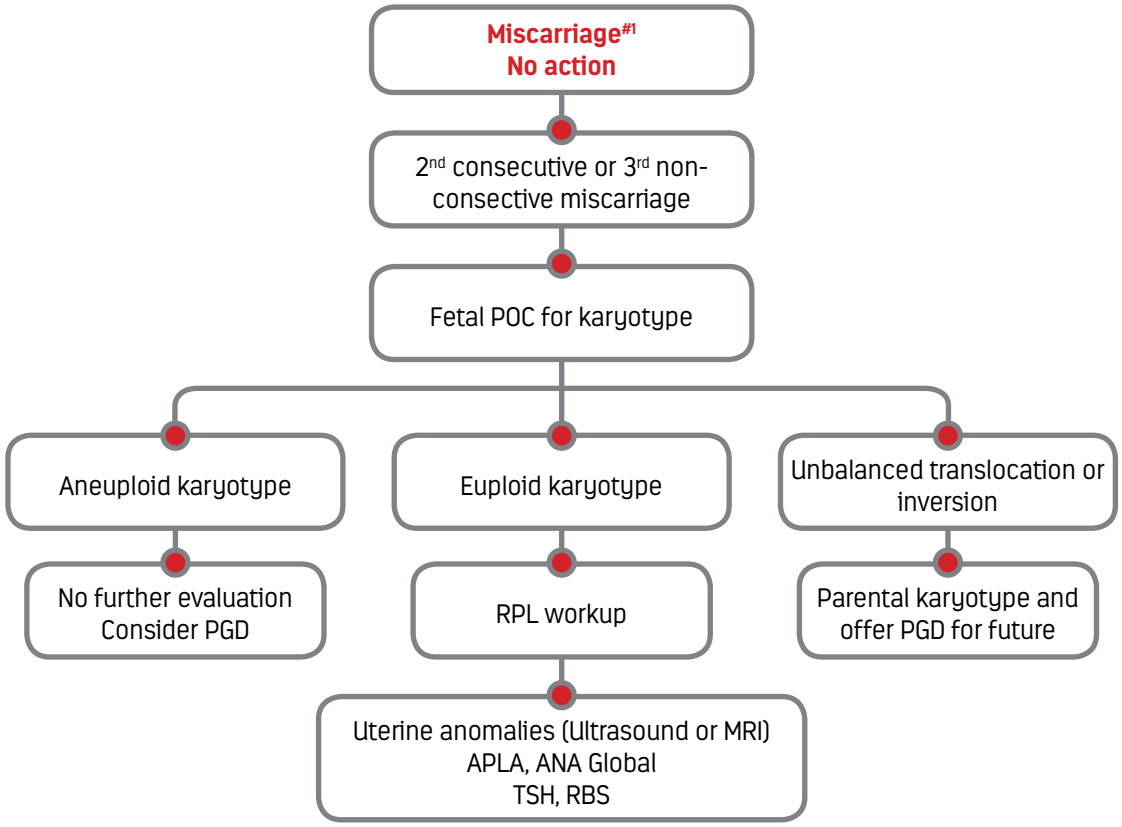
TORCH?

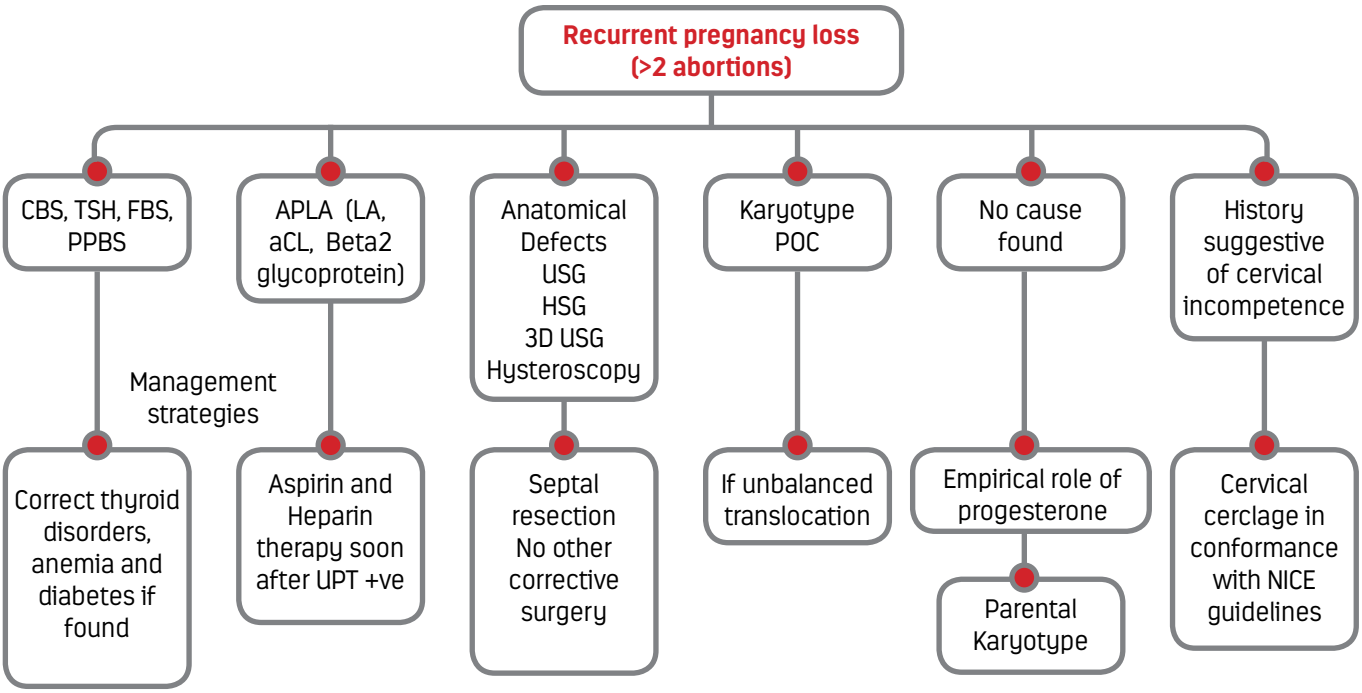
- Toxoplasmosis, Rubella, cytomegalovirus, herpes infections (TORCH) is not proved to be the cause and the performance of screening is invariably uninformative.

Recommendation for the testing of couples presenting with recurrent miscarriage (≥3 miscarriages)[9]

- Full blood count (blood sugar level and thyroid function tests)
- Antiphospholipid antibodies (LAC and aLC)
- Parental karyotype (after 2 miscarriages)
- Pelvic ultrasound [saline infusion sonohysterography (SIS)]
- Magnetic resonance imaging

Initial evaluation of recurrent pregnancy loss[9]



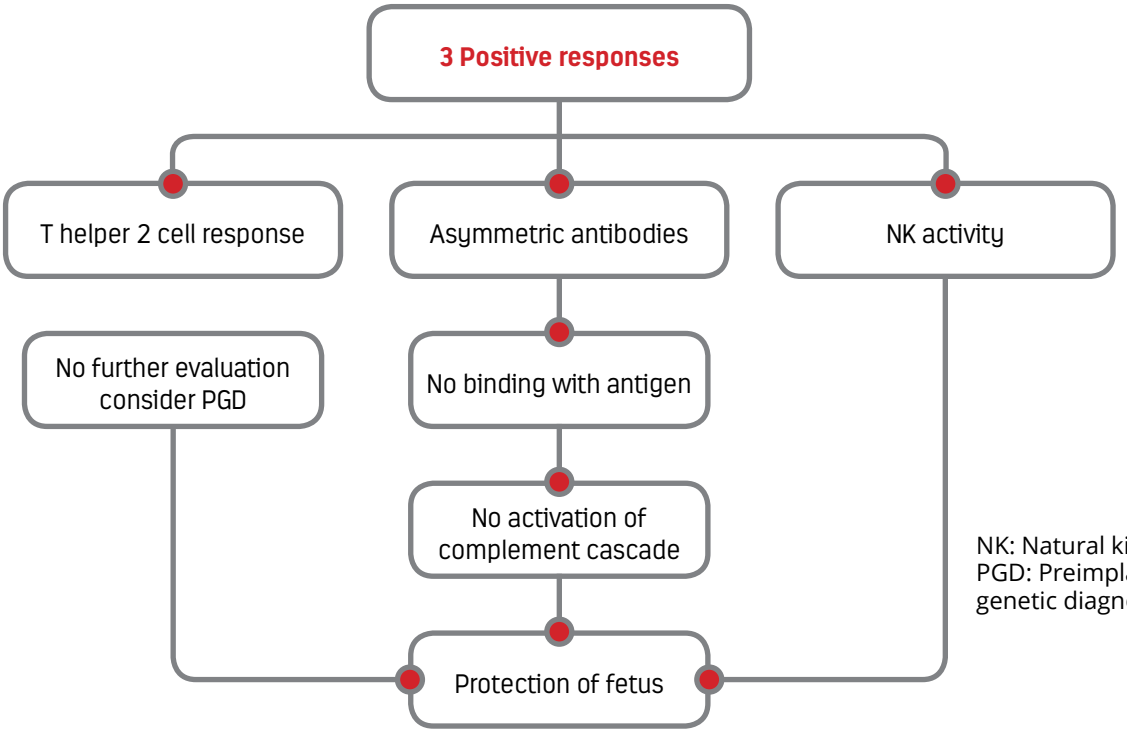


ANA: Anti nuclear antibodies; aCL: Anticardiolipin antibodies; APLA: Antiphospholipid antibodies; FBS: Fasting blood sugar; POC: Products of conception; PGD: Preimplantation genetic diagnosis; LA: Lupus anticoagulant; PPBS: Post prandial blood sugars; RPL: Recurrent pregnancy loss; TSH: Thyroid stimulating hormone; UPT: Urine pregnancy test; ; RBS: Random blood sugar; USG: Ultrasonography; HSG: Hysterosalpingogram; NICE: National Institute for Health and Care Excellence

Progesterone

- Dydrogesterone 10 mg BD till 20 weeks
- Micronized vaginal progesterone 200 mg BD till 20 weeks
- Progesterone (Oral route is preferred due to convenience)

Embryo protective immunomodulation[10]



NK: Natural killer cells; PGD: Preimplantation genetic diagnosis

Role of progestational agents

Progesterone was recognized early on to be one of the most important steroids required for the maintenance of pregnancy. Dydrogesterone shares similar biological properties with natural progesterone, and has high affinity for progesterone receptors (PRs). In contrast to progesterone, dydrogesterone is highly bioavailable after oral intake. In comparison with other progestogens, dydrogesterone has no relevant androgenic or antiandrogenic activity on the foetus, and can therefore be safely administered to mothers without the risk of causing foetal genital malformations.

Progestogens[11,12]

- Enhances implantation
- Modulates the cytokine balance
- Inhibits natural killer cell activity at the feto-maternal interface
- Inhibits the release of arachidonic acid
- Prevents myometrial contractility

Recent recommendations – ESHRE 2017

Vaginal progesterone during early pregnancy has no beneficial effects in women with unexplained RPL. There is some evidence that oral dydrogesterone initiated, when fetal heart action is confirmed, may be effective.[13]

Summary

Recurrent miscarriage is traditionally defined as three or more consecutive miscarriages occurring before 20 weeks. Around 1% of fertile couples will experience recurrent early pregnancy loss. About 12% to 15% pregnant women are at risk of miscarriage globally. This risk increases with advancing age from 40% to 50% in women over the age of 40.

Some of the common causes of recurrent pregnancy loss are chromosomal abnormalities, conditions such as hypothyroidism or diabetes, uterine anatomic abnormalities, antiphospholipid antibody syndrome, infections etc.

Various investigative and diagnostic tests are recommended including LAC, and aCL for determining coagulation abnormalities. Parental karyotyping is recommended to investigate chromosomal abnormalities especially after two miscarriages. Other tests recommended include full blood count, including levels of blood sugars and TSH.

Progesterone has an important role to play in the maintenance of pregnancy. Progesterone supplementation enhances implantation, balances cytokines, inhibits natural killer cell activity.

Dydrogesterone share the property of progesterone and is highly bioavailable after oral intake. It shows no relevant androgenic or antiandrogenic activity on the fetus. Prospective clinical trials, systematic reviews and meta-analyses have demonstrated that dydrogesterone significantly improves pregnancy outcomes in women with threatened miscarriage or with a history of miscarriage. Researchers have supported the use of dydrogesterone in women with RPL to improve pregnancy outcomes, such as a reduction in abortions and improved gestational age and baby weight at delivery.[15]

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SECONDARY AMENORRHEA

Moderators : Dr. PC Mahapatra, Dr. Suvarna Khadilkar

Panel Members : Dr. Vidya Thobbi, Dr. Tarini Taneja, Dr. Nidhi Gupta, Dr. B Ramesh

From left to right: Dr. Vidya Thobbi, Dr. PC Mahapatra, Dr. Suvarna Khadilkar, Dr. Tarini Taneja, Dr. B Ramesh, Dr. Nidhi Gupta

Amenorrhea is the absence of menstrual bleeding and a normal feature encountered in prepubertal, pregnant, and postmenopausal females. Secondary amenorrhea is the cessation of menses sometime after menarche has occurred; for three months or six months. Around 66% of the cases of secondary amenorrhea are associated with disorders occurring with a low or normal follicle stimulating hormone (FSH), such as weight loss/anorexia, chronic anovulation including polycystic ovarian syndrome (PCOS), hypothyroidism, Cushing syndrome, pituitary tumor, empty sella, and Sheehan syndrome. However, pregnancy needs to be excluded in all these cases.

Ideally, treatment is directed at correcting the underlying pathology to restore normal ovarian endocrine function and prevent the development of other chronic diseases.

Loss of menstrual regularity is an early sign of declining fertility and impending premature ovarian failure, and has been associated with an increased risk of wrist and hip fractures related to decreased bone density. Moreover, women with PCOS have many long-term health issues, including higher risk of diabetes and cardiovascular diseases.

Therefore, loss of menstrual regularity is an indication for a careful review, since it may be the first clear symptom signalling the onset of a major illness or systemic disease. Hence, clinicians are required to take informed decisions and need not wait for a defined duration of amenorrhea to pass before taking corrective action.

The FOGSI team has created a diagnostic approach and management strategy for resolving the problem of secondary amenorrhea.

Best wishes!

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MD, FICMCH, FICOG, FICS, FRCOG, FRCP
President 2018 - Federation of Obstetrics & Gynecological Societies of India (FOGSI)

Introduction

Amenorrhea

- In a woman who has been menstruating, the absence of periods for a length of time equivalent to a total of at least 3 of the previous cycle intervals or 6 months without menses.

Oligomenorrhea

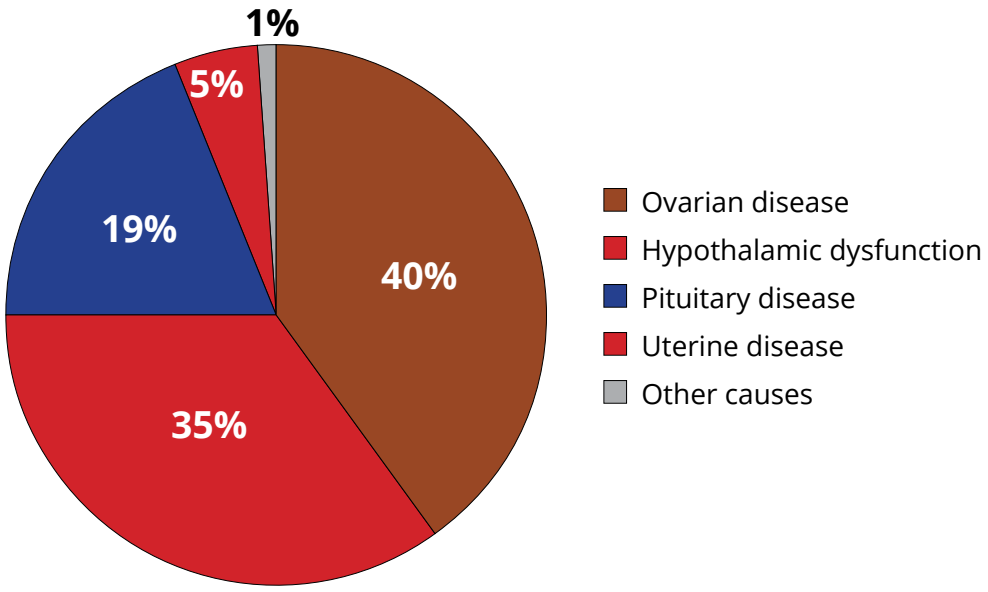
- Periods that occur at intervals of 35 days to 6 months with less than 9 cycles per year.

Etiology of secondary amenorrhea-common causes

- **Central nervous system disorders**
  - Chronic hypothalamic anovulation
  - Stress
  - Increased exercise levels
  - Anorexia nervosa
  - Head trauma
  - Space-occupying lesions, infections
- **Uterine abnormalities**
  - Asherman's syndrome
  - Cervical stenosis
- **Drug-induced amenorrhea**
  - Hormonal contraceptives
  - Gonadotropin-releasing hormone (GnRH) analogues
  - Antipsychotics, reserpine
- **Pituitary disorders**
  - Hyperprolactinemia
  - Prolactinoma
  - Medications
  - PCOS
  - Renal failure
  - Hypoprolactinemia
  - Pituitary resection
  - Sheehan's syndrome
- **Thyroid disorders**
  - Hyper-or hypothyroidism
- **Ovulation disorders**
  - PCOS
  - Premature ovarian failure

Etiology of secondary amenorrhea

After excluding pregnancy, the most common causes of secondary amenorrhea are:



History

Patients should be asked about:

- Eating and exercise patterns
- Changes in weight
- Previous menses (if any)
- Medication use
- Chronic illness
- Presence of galactorrhea
- Symptoms of androgen excess
- Abnormal thyroid function
- Vasomotor instability
- Taking a sexual history can help corroborate the results of, but not replace, the pregnancy test
- Family history should include age at menarche and presence of chronic disease
- Although it is normal for menses to be irregular in the first few years after menarche, the menstrual interval is not usually longer than 45 days

Physical examination

The physician should:

- Measure the patient's height, weight, and body mass index, and perform thyroid palpation.
- Tanner staging: Breast development is an excellent marker for ovarian estrogen production.
- Acne, virilization, or hirsutism may suggest hyperandrogenemia.
- Genital examination may reveal virilization, evidence of an outflow tract obstruction, or a missing or malformed organ.
- Thin vaginal mucosa is suggestive of low estrogen.
- Dysmorphic features such as a webbed neck or low hairline may suggest Turner syndrome.

Laboratory evaluation

The initial workup includes:

- Pregnancy test
- Serum luteinizing hormone, follicle-stimulating hormone, prolactin, and thyroid-stimulating hormone levels.
- If history or examination suggests a hyperandrogenic state, serum free and total testosterone and dehydroepiandrosterone sulfate concentrations are useful.
- If the patient is short in stature, a karyotype analysis should be performed to exclude Turner syndrome.
- If the presence of endogenous estradiol secretion is not evident from the physical examination (e.g., breast development), serum estradiol may be measured.
- A complete blood count and comprehensive metabolic panel may be useful, if history or examination is suggestive of chronic disease.

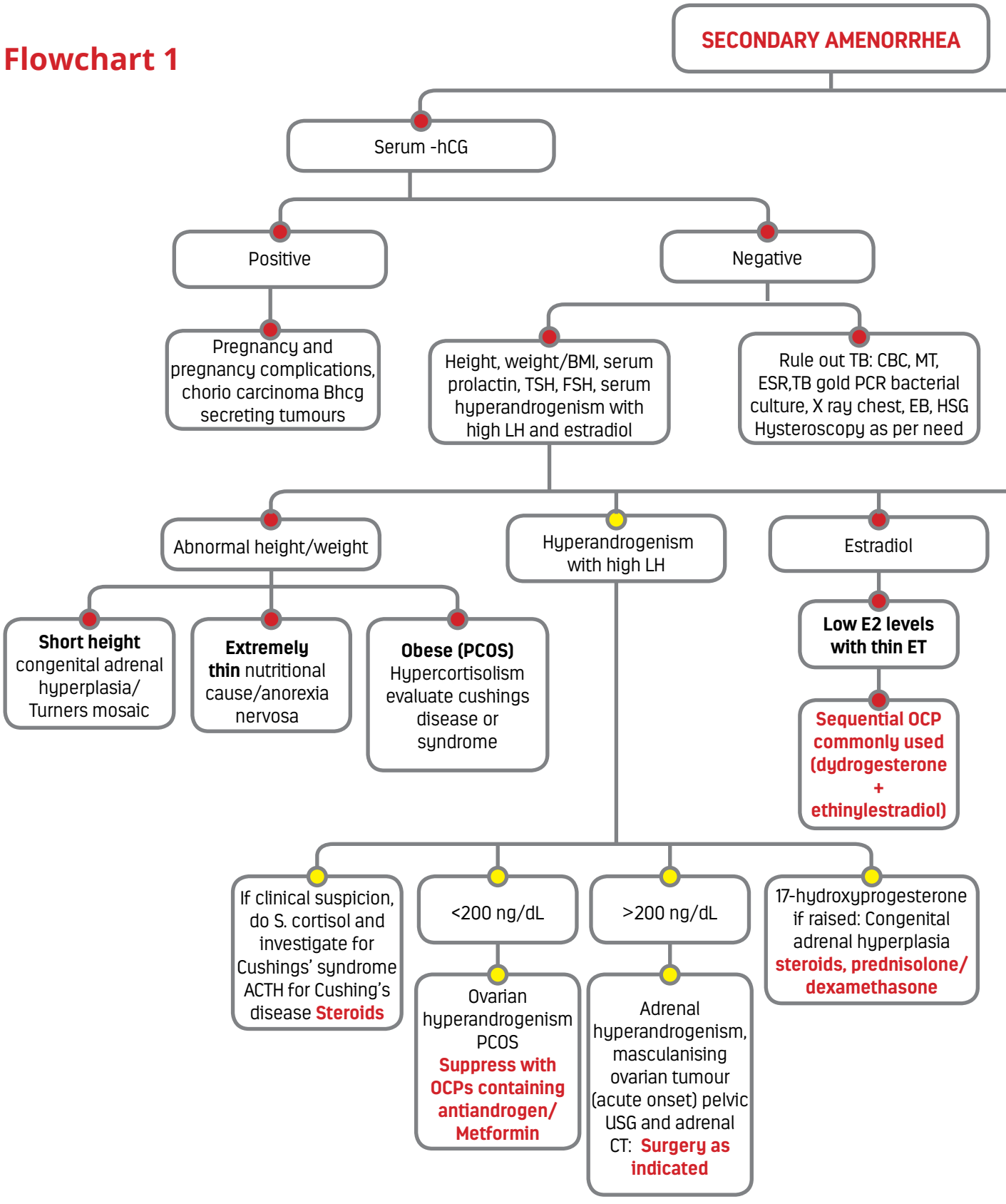
Further testing:

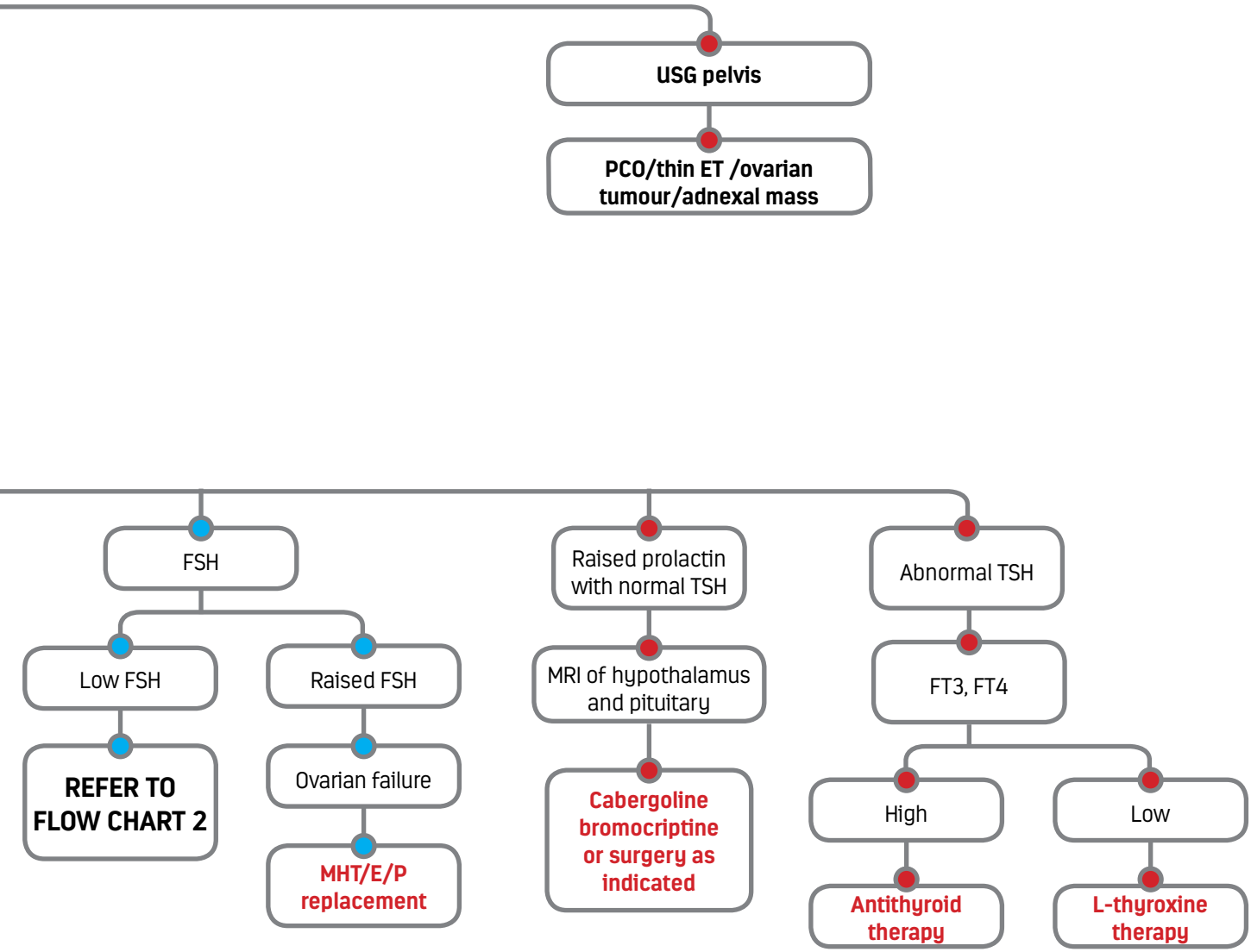
- Pelvic ultrasonography can help to confirm the presence or absence of a uterus, and can identify structural abnormalities of reproductive tract organs.
- If a pituitary tumor is suspected, magnetic resonance imaging (MRI) may be indicated.
- Hormonal challenge (e.g., medroxyprogesterone acetate, 10 mg orally per day for 7 to 10 days) with anticipation of a withdrawal bleed, to confirm functional anatomy and adequate estrogenization, has traditionally been central to the evaluation. Some experts defer this testing because its correlation with estrogen status is relatively unreliable.

Treatment goals

- Discovery and treatment of underlying disorder
- Hormone replacement for bone protection
- Menses every 1-3 months (To prevent endometrial hyperplasia and cancer)
- Need for contraception (rare)
- Achieve pregnancy
  - » Ovulation induction
  - » GnRH pump
  - » FSH/LH

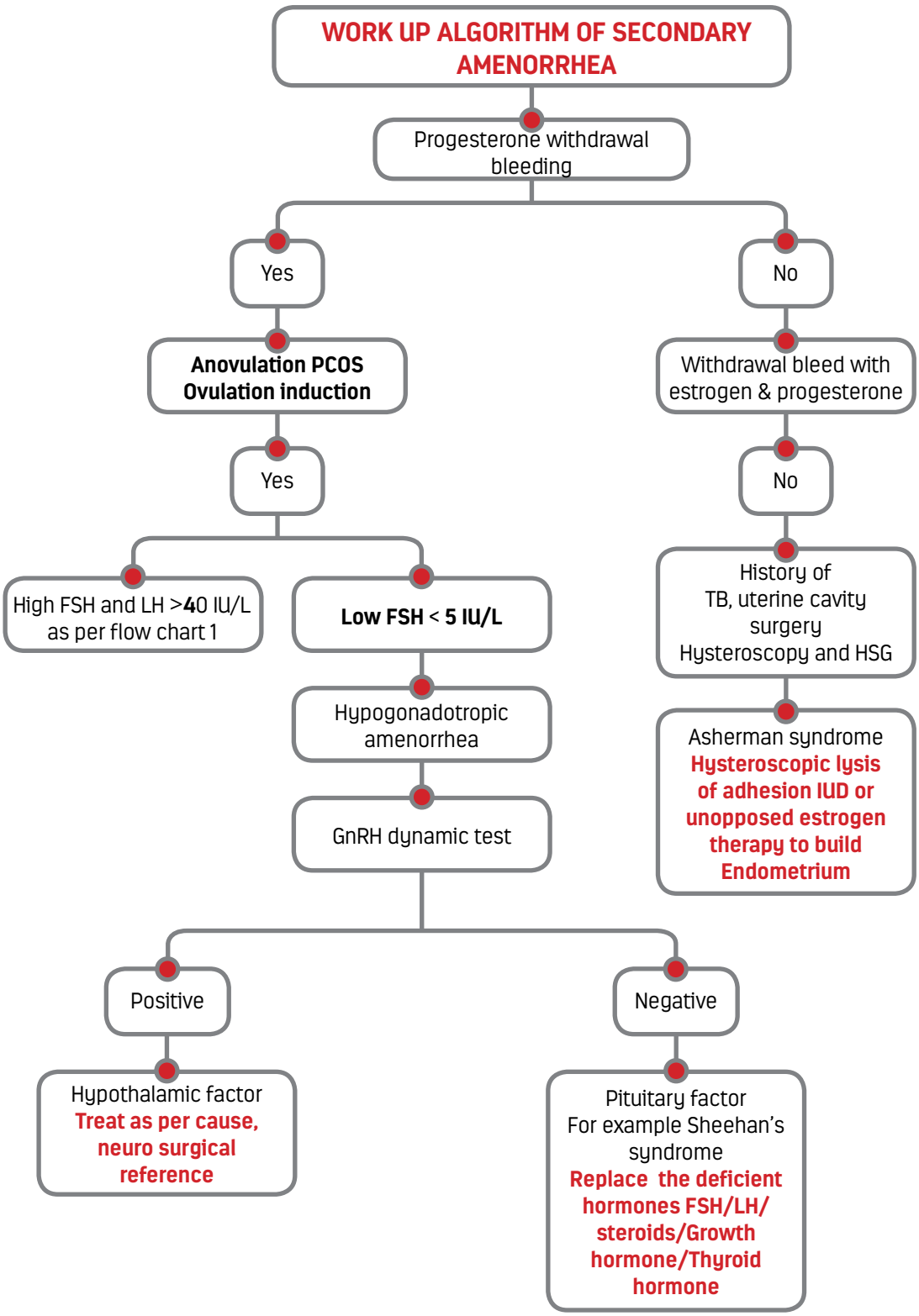
Flowchart 1


SECONDARY AMENORRHEA
Serum -hCG
Positive
Negative
Pregnancy and pregnancy complications, chorio carcinoma Bhcg secreting tumours
Height, weight/BMI, serum prolactin, TSH, FSH, serum hyperandrogenism with high LH and estradiol
Rule out TB: CBC, MT, ESR,TB gold PCR bacterial culture, X ray chest, EB, HSG Hysteroscopy as per need
Abnormal height/weight
Hyperandrogenism with high LH
Estradiol
Short height congenital adrenal hyperplasia/ Turners mosaic
Extremely thin nutritional cause/anorexia nervosa
Obese (PCOS) Hypercortisolism evaluate cushings disease or syndrome
Low E2 levels with thin ET
Sequential OCP commonly used (dydrogesterone + ethinylestradiol)
If clinical suspicion, do S. cortisol and investigate for Cushings' syndrome ACTH for Cushing's disease Steroids
<200 ng/dL
>200 ng/dL
17-hydroxyprogesterone if raised: Congenital adrenal hyperplasia steroids, prednisolone/ dexamethasone
Ovarian hyperandrogenism PCOS Suppress with OCPs containing antiandrogen/ Metformin
Adrenal hyperandrogenism, masculanising ovarian tumour (acute onset) pelvic USG and adrenal CT: Surgery as indicated



βhCG: Beta human chorionic gonadotropin; BMI: Body mass index;FSH: Follicle stimulating hormone; LH: Luteinizing hormone; TSH: Thyroid stimulating hormone; PCR: Polymerase chain reaction; ESR: Erythrocyte sedimentation rate; CBC: Complete blood count; PCR: Polymerase chain reaction; ESR: Erythrocyte sedimentation rate; HSG: Hysterosalpingographic; EB: Endometrial biopsy; PCOS: Polycystic ovarian syndrome; ACTH: Adrenocorticotropic hormone; OCP: Oral contraceptive pill; USG: Ultrasonography; CT: Computed tomography; MRI: Magnetic resonance imaging; TSH: Thyroid stimulating hormone; FT3: Free triiodothyronine; FT4: Free thyroxine; TB: Tuberculosis; MT: Mycobacterium tuberculosis; ET: Endometrial thickness; MHT: Menopausal hormone therapy.

Flowchart 2
Work up algorithm of secondary amenorrhea



FSH: Follicle stimulating hormone; LH: Luteinizing hormone; HSG: Hysterosalpingographic; TB: Tuberculosis; IUD: intrauterine device; GnRH: Gonadotropin-releasing hormone

Physiological	Clinical features	Investigations	Management
Pregnancy	Sexual history, married not using contraception,	UPT positive Serum beta HCG positive USG: /G-sac	As per desire of the patient continue the management
Puerperium	Recent delivery	High prolactin	Reassurance
Lactation	Continued Breast feeding	High prolactin	Reassurance Cabergoline if weaning/ stopping lactation
Menopause	Age >40, hot flushes, sweating, mood swings, loss of libido	High FSH Low estradiol Nil progesterone Estrogen: Androgen ratio reversed	If symptoms compromising quality of life, Hormonal therapy if not contraindicated, for shortest period and smallest possible dose

UPT: Urine pregnancy test; HCG: Human Chorionic Gonadotropin; USG: Ultrasonography; G-sac: Gestational sac; FSH: Follicle stimulating hormone

HPO axis Compartment and other glands	Name of conditions	History	Examination	Investigations	Management
Comp IV. Hypothalamus and central cause	Chronic hypothalamic anovulation	H/O factors suggestive of hypothalamic disease		Low FSH, Low LH	
	Stress	Stress			
	Increased exercise levels	Athletic profession		Leptin level alterations	
	Anorexia nervosa	Eating disorders, weight loss>25%, episodes of overeating or bulimia, behavioural abnormalities, high achiever family	Lanugo hair, bradycardia, overactivity, self induced vomiting.	GnRh -nil/ Low gonadotrophins + hypercortisolemia Hypokalemia and electrolyte imbalance ECG: ST- and T changes prolonged QTC interval Cardiac Dysrhythmias	Multi disciplinary management Individual and family psychotherapy Cognitive-behavioral therapy Hydration, correction of electrolyte abnormalities (eg, hypokalemia), Daily caloric intake 2600 cal /day; Prevent and treat life threatening complication
	Head trauma	H/O falls, accident blunt injury, surgery	Neurological deficit, vision problems	MRI/CT scan of the brain	Neuro surgical reference
	Space-occupying lesions,	Headaches, convulsion, weakness	Neurological deficit, vision problems	MRI/CT scan of the brain	Neuro surgical reference
	CNS Infections	Meningitis, tuberculosis and other infections		TB PCR, CSF examination	Neuro physician reference
	Constitutional delay	Family H/O late menarche (maternal side)	Short stature	Low gonadotrophins low estrogens	Counselling hormone therapy If psychological disturbances
	Septo-optic dysplasia Holoprosencephaly Encephalocele			MRI/CT scan brain	

H/O: History of; FSH: Follicle stimulating hormone; LH: Leutinizing hormone;
MRI: Magnetic resonance imaging; CT: Computerized tomography; TB: Tuberculosis;
PCR: Polymerase chain reaction; CSF: Cerebrospinal fluid

Comp III, Pituitary	Genetic conditions Congenital deficiency of hypothalamic or pituitary transcription factors (gonadotropin deficiency) Single-gene mutations (hypogonadotropic hypogonadism)			Low FSH, Low LH, Low TSH, Low Prolactin, GnRH stimulation test negative	
	Hyperprolactinemia Prolactinoma	Galactorrhea, Headaches, blurring of vision, lateral field defects		Raised prolactin with normal TSH Low or normal FSH, LH Low estradiol	
	Drug induced	H/O drugs antipsychotic , antacids, reserpine		Increased prolactin Normal FSH, LH	
	Panhypopituitarism	Extreme fatigability, poor quality of life		Low FSH, Low LH, low TSH, low prolactin, low estrogen	
	Cushing's disease			High ACTH levels and high cortisol	
	Hormone secreting pituitary tumour			Specific high levels of hormones e.g, high FSH, high prolactin, high ACTH, high IGF	Surgery/steroids
Comp II, Ovarian	Polycystic ovarian disease	Hirsutism acne, symptoms of hyperandrogenism, persistent chronic anovulation, weight gain	Acanthosis nigricans Evidence of hirsutism	High LH FSH: normal to high FSH: LH - 1:3 or more High testosterone <200 ng High free androgen index USG: AFC >12 (Necklace pattern) Ovarian volume >10 cc	Life style modification, weight reduction Antiandrogen therapy, ovulation induction or contraception
	Masculinizing and other ovarian tumours	Rapid onset of hirsutism and virilism	Clitoromegaly e/o Hirsutism	Pelvic USG or CT scan, high testosterone >200 ng, DHEAS normal	Surgical removal
	Gonadal agenesis or dysgenesis (in the setting of Turner Syndrome mosaic/ or other Ovotestis)	Short stature and other physical stigmata may be present		High Levels of FSH and LH, Low E2 Variable high testosterone if testis present, USG streak gonad, Karyotyping Turner mosaic or XX, XY	Hormone replacement therapy after epiphyseal closure, growth hormone therapy before

H/O: History of; FSH: Follicle stimulating hormone; LH: Leutinizing hormone;
CT: Computerized tomography; ACTH: Adrenocorticotropic hormone;
AFC: Antral follicular count; DHEAS: Dehydroepiandrosterone-sulfate.

	Primary or secondary ovarian failure Ovarian insufficiency Autoimmune Oophoritis Irradiation or surgery Iatrogenic	Suggestive history Pelvic irradiation, surgical removal. H/O excessive PCO drilling may be present		FSH > 40, low AMH <1, low estradiol, USG small size ovaries	Hormone replacement therapy Steroids for autoimmune conditions
	Chronic Anovulation	Any of the listed causes		Progesterone levels <4ng /ml USG no follicular development or rupture +ve PCT if estrogen priming -ve if no estrogen/ comp I disease	Treat specific cause Ovulation induction protocols As per requirement
Comp I uterine and outflow tract1286	Uterine syneche Tuberculosis	H/O TB, TB contact, D and C, hysteroscopic surgery		TB PCR of endometrium PCT negative O+P challenge test negative USG TB Gold test	AntiTB treatment IUCD, hysteroscopic lysis of syneche, estrogen therapy
	Cervical stenosis	Procedures on cervix, cone biopsy, cauterization		Inability to pass sound USG hematometra Eugonadism	Cervical dilatation
	Vaginal stenosis	Past vaginal procedures infections		USG hematocolpos Eugonadism	Vaginal dilatation, neovaginoplasty
	Iatrogenic: surgical procedures, TCRE, Endometrial ablation hysterectomy			PCT negative O+P CT negative USG thin endometrium	Reassurance
Thyroid	Hypothyroidism	Weight gain, intolerance to cold, edema feet past, H/O menstrual abnormality, swelling in neck		High ultraTSH > 4.5 IU TPO antibodies may be present Low FT4, FT3 Prolactin may be high	Levothyroxine 1.2 mcg/kg bodyweight
	hyperthyroidism	Weight loss palpitations, excessive sweating intolerance to heat, swelling in neck		High TT3, TT4 Low TSH <0.4 IU TPO antibodies/ TRab may be present	Antithyroid drugs, carbimazole, methimazole, propyl thiouracil if pregnancy is planned

H/O: History of; FSH: Follicle stimulating hormone; LH: Leutinizing hormone; TB: Tuberculosis; PCR: Polymerase chain reaction; PCT: Progesterone challenge test; TSH: Thyroid stimulating hormone; FT4: Free thyroxine; FT3: Free triiodothyronine; TPO: Thyroid peroxidase

Adrenal	Congenital adrenal hyperplasia: classic/ non-classic	Severe hirsutism, irregular menses, virilism, Non classic milder than classic		High 17-hydroxy progesterone High LH In classic – hyponatremia	Classic : steroid, Non classic observation / symptomatic treatment, ovulation induction
	Cushing syndrome or iatrogenic Cushings with injudicious use of steroids	Weight gain, puffy face	Striae, buffalo hump, central obesity, hypertension	High LH, High serum 8 am cortisol, High 24 hour urinary free cortisol, Dexamethasone suppression test positive, glucose intolerance	Steroids Endocrinology reference
	Addison disease (adrenal insufficiency)			24 hour urinary free cortisol, low serum 8 am cortisol low, ACTH stimulation test (short Syn-acthen)	Steroids, (hydrocortisone) Endocrinology reference
	Tumor (androgen-secreting)			Testosterone level >200ng	Surgical removal
Adipose tissue	Extreme obesity			High leptin level, high insulin level, high estrogen level	Weight reduction program: consider bariatric surgery for resistant morbid obesity
	Extreme low BMI			Chronic illnesses	High calories, nutrition, treat the cause
Systemic diseases	Severe liver disorders	Jaundice, cirrhosis , alcoholism, loss of appetite		High FSH, low estrogen	Disease specific treatment
	Renal failure				Disease specific treatment
	Severe diabetes mellitus	Family history, insulin resistance, severe metabolic syndrome		High blood sugar, High HbA1c >6, hyperinsulinemia, HOMA index	Antidiabetic agents and control of diabetes

H/O: History of; FSH: Follicle stimulating hormone; LH: Leutinizing hormone; HbA1c: Glycated hemoglobin; HOMA: Homeostatic model assessment; BMI: Body mass index

Key recommendations

Clinical recommendation	Evidence Rating
Pregnancy should be excluded in all patients presenting with amenorrhea.	C
In the evaluation of amenorrhea, hormone-induced withdrawal bleeding has poor sensitivity and specificity for ovarian function.	C
In patients with functional hypothalamic amenorrhea (especially with the female athlete triad), the primary treatment is weight restoration through nutritional rehabilitation and decreased exercise.	C
In patients with functional hypothalamic amenorrhea, combined oral contraceptives do not improve bone density and should not be used solely for this purpose.	C
Patients with polycystic ovary syndrome who are overweight should be evaluated for glucose intolerance, dyslipidemia, and overall cardiovascular risk.	C
Metformin may improve abnormal menstruation in patients with polycystic ovary syndrome.	A
Ultrasonography may be done initially in work up of all patients of secondary amenorrhea	C

A = Consistent, good-quality patient-oriented evidence; B = Inconsistent or limited-quality patient-oriented evidence; C = Consensus, disease-oriented evidence, usual practice, expert opinion, or case series.

Conclusion

Treatment goals of amenorrhea and oligomenorrhea include prevention of complications such as osteoporosis, endometrial hyperplasia, heart disease and preservation of fertility.

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1. Assessment of secondary amenorrhoea. BMJ Best practice. 2017
2. Secondary Amenorrhea. Family Practice Notebook. Available on: https://fpnotebook.com/Gyn/Menses/ScndryAmnrh.htm Assessed on: 31st July 2018

THYROID DISORDERS IN PREGNANCY

Moderators : Dr. Narendra Malhotra, Dr. Rishma Pai

Panel Members : Dr. Reena Wani, Dr. Rajendra Saraogi, Dr. N Palaniappan, Dr. Susheela Rani

From left to right: Dr. Narendra Malhotra, Dr. Reena Wani, Dr. Rishma Pai, Dr. Susheela Rani, Dr. N Palaniappan

The role of thyroid gland and the influence of thyroid disorders on pregnancy and offspring have attracted the interest of researchers and clinicians in recent years. Significant changes occur in maternal thyroid physiology during a normal pregnancy. There is an association between maternal thyroid dysfunction and adverse outcomes in the mother and fetus.

Hypothyroidism is considered to be the most common endocrinopathy in pregnant women. The prevalence of hypothyroidism during pregnancy varies from 2.5% in the west to 11% in India. Overt hypothyroidism prevails in around 0.3%–0.5% of all pregnant women. Failure to diagnose and treat hypothyroidism may cause irreversible damage to the fetus.

Hyperthyroidism is a rare condition during pregnancy. Overt hyperthyroidism occurs when the serum thyroid-stimulating hormone (TSH) levels decline below the trimester-specific reference range. It prevails in around 0.1%–0.4% of pregnancies, and is associated with various risks such as spontaneous miscarriage, congestive heart failure, thyroid storm, preterm birth, pre-eclampsia, retarded fetal growth, and increased perinatal morbidity and mortality.

Thyroid abnormalities are often subclinical in nature and not easily detected without specific screening programs. The first-trimester of pregnancy is a critical time for euthyroidism in which production of endogenous fetal thyroid hormones have not begun, and the fetus is completely dependent on the supply of maternal thyroid hormones for its development. The estrogen stimulated increase in thyroxine-binding globulin or those after treatment with exogenous gonadotropins during early pregnancy increases the requirement of thyroid hormones. Therefore, women without sufficient thyroid reserves may be prone to gestational hypothyroidism. The guidelines differ between an aggressive case finding approach vs. universal screening for women with previous history of thyroid disease. Therefore, these guidelines provide recommendations for screening to diagnose and treat thyroid dysfunction in pregnant women.

Best wishes!

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Introduction

- Increase in serum thyroxine-binding globulin (TBG) concentration
- Stimulation of thyroid-stimulating hormone (TSH) receptor by human chorionic gonadotropin (HCG)
- Thyrotropic activity of HCG reduces the concentration of serum TSH
- Both serum total thyroxine (T_4) and triiodothyronine concentrations increase
- Later in pregnancy, serum TSH concentration steadily returns to normal range and free T_4 concentration declines

Hypothyroidism

- **Epidemiology**
  - » Most common endocrine disease
  - » Females > Males – 8 : 1
- **Presentation**
  - » Often unsuspected and grossly under diagnosed
  - » 90 % of the cases are primary hypothyroidism
  - » Menstrual irregularities, miscarriages, growth retardation
  - » Vague pains, anaemia, lethargy, weight gain
  - » In clear cut cases - typical signs and symptoms
  - » Low free T_4 and high TSH
  - » Easily treatable with oral levothyroxine

Etiology of maternal hypothyroidism

Primary causes[1,2]	Secondary causes[3]
• Iodine deficiency » Cruciferous vegetables » Soy and millet » Cigarette smoking » Unclean drinking water » Deficiencies of selenium, iron, and vitamin A • Autoimmunity • Thyroidectomy • Radio ablation of the gland • External irradiation • Biosynthetic defect in iodine organification • Drugs	• Pituitary disease • Hypothalamic disease

1. Smallridge RC, et al. J Clin Endocrinol Metab. 2001;86(6):2349–53. **2.** Marwaha R, et al. JAPI. 2011;59(supplement):7–10.
3. Baskin HJ, et al. Endocr Pract. 2002;8(6):457–69.

Etiology of fetal hypothyroidism

Causes[1]
• Thyroid-binding inhibitory immunoglobulin (TBII)- Transient • Congenital • Antithyroid drugs • Prematurity
1. Smallridge RC, et al. J Clin Endocrinol Metab. 2001;86(6):2349-2353.

Clinical features of hypothyroidism

• Fatigue	• Irregular or heavy menses and infertility
• Constipation	• Hoarseness
• Weight gain from fluid retention	• Myalgias
• Memory loss and mental impairment	• Goiter
• Dry skin and cold intolerance	• Hyperlipidemia
• Decreased concentration	• Reflex delay, relaxation phase
• Yellow skin	• Bradycardia and hypothermia
• Depression	• Ataxia
• Coarseness or loss of hair	• Myxedema, fluid infiltration of tissues
Baskin HJ. Endocr Pract. 2002;8(6):457–69.	

Complications of hypothyroidism in pregnancy

Complications	Maternal	Fetal
Effect of hypothyroidism on general health	Anemia Congestive heart failure Antepartum depression	
Complications during the course of gestation	Eclampsia Pre-eclampsia Gestational hypertension Placental abruption	Growth restriction Increased perinatal mortality
Complications during delivery	Increased chances of cesarean section, preterm delivery	Miscarriage
Long-term complications	Postpartum depression Postpartum hypertension Lactation problems	Impaired neuropsychointellectual development
Galofre JC, et al. 2009;18(11):1847–56.		

Hyperthyroidism

Increased secretion of thyroid hormones.

Causes of hyperthyroidism
• Toxic diffuse goiter (Graves' disease)
• Toxic adenoma
• Toxic multinodular goiter (Plummer's disease)
• Painful subacute thyroiditis
• Silent thyroiditis, including lymphocytic and postpartum thyroiditis
• Iodine-induced hyperthyroidism
• Excessive pituitary TSH or trophoblastic disease
• Excessive ingestion of thyroid hormones[1]
• HCG-associated transient thyrotoxicosis[2]
1. Baskin HJ, et al. Endocr Pract. 2002;8(6):457–69. 2. Rodien P. Hum Reprod Update. 2004;10(2):95–105.

Common symptoms

Symptoms
• It is difficult to differentiate hyperthyroid symptoms from hyperdynamic
• Nervousness and irritability
• Palpitations and tachycardia
• Heat intolerance or increased sweating
• Tremors, sudden paralysis
• Weight loss or gain, mental disturbances
• Changes in vision, photophobia, eye irritation, diplopia or exophthalmos
• Fatigue and muscle weakness
• Thyroid enlargement (depending on the cause)
• Pretibial myxedema (in patients with Graves' disease)[1]
• Changes in appetite
• Frequent bowel movements or diarrhea
• Lower extremity edema
1. Baskin HJ, et al. Endocr Pract. 2002;8(6):457–69.

What tests should be ordered?

As per the guidelines of the American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association (ATA), as well as the Indian Thyroid Society (ITS)

1. TSH alone if hypothyroidism is suspected
2. TSH and Free T_4 only if hyperthyroidism is suspected or for routine evaluation
3. Free T_3 if T_3 toxicosis is suspected
4. For follow-up of treatment, only TSH
5. Don't order for total T_4 or total T_3
6. Never order radioactive iodine uptake test in pregnancy or lactation

Which laboratory to choose?

1. Depends on the method of estimation of hormones
2. Equilibrium dialysis is the gold standard for TSH
3. Radio-immuno assay (RIA) – 3rd or 4th generation RIA is the best
4. Reliability of ELISA (enzyme-linked immunosorbent assay) is not adequate
5. Chemiluminescence immuno assay (CIA) – is the gold standard for free thyroxine (FT_4) but expensive and less widely available

Choose a laboratory which offers 3rd or 4th generation RIA method

Thyroid antibodies

- Anti-microsomal (TM) antibodies
- Anti-thyroglobulin (TG) antibodies
- Anti-thyroxine per oxidase (TPO) antibodies
- Anti-thyroxine antibodies
- Thyroid stimulating antibodies (TSA)
- **High titres TPO antibodies in Hashimotos & Reidle's thyroiditis**
- **Anti thyroxine antibodies in peripheral resistance to thyroxine**
- **TSA (Thyroid-stimulating immunoglobulins) in Graves' hyperthyroidism**

Prevalence of thyroid antibody

Antibody	General population	Hypothyroid	Autoimmune thyroiditis
Anti –TG	3%	35%–60%	12%–30 %
Anti –TPO	10%–15%	80%–99%	45%–80 %
Anti-TSH	1%–2%	6%–60%	70%–100 %
Anti –NIS	0%	25%	20%

Note: Testing for antibody is not required routinely – selected cases only
TG: thyroglobulin; TPO: thyroid peroxidase; TSH: thyroid-stimulating hormone; NIS: natrium/iodide symporter

Recommendations for thyroid screening and treatment in pregnancy[2,3]

- All pregnant and lactating women must ingest approximately 250 µg of iodine daily[4]
- **Universal screening is not recommended in most countries due to scarcity of data, and most of the available guidelines recommend screening of high-risk pregnant women, including our country (GOI 2014)**
- However, the **Indian Thyroid Society (ITS)[5] recommends screening of TSH levels in all pregnant women** at the time of their first visit, ideally during pre-pregnancy evaluation or as soon as pregnancy is confirmed

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National Guidelines for Screening of Hypothyroidism during Pregnancy

High risk factors for hypothyroidism

- Residing in an area of known moderate to severe iodine insufficiency (according to area mapping)
- Obesity (pre-pregnancy/First-trimester body mass index (BMI) ≥ 30 kg/m^2) [BMI= weight in kg/ height in m^2]
- History of prior thyroid dysfunction or prior thyroid surgery
- Symptoms of thyroid dysfunction or the presence of goiter
- History of thyroid dysfunction in first degree relative (parents/siblings/children)
- History of diagnosed mental retardation in family/previous births
- Known case of autoimmune diseases like Type I diabetes/systemic lupus
- Erythematosus (SLE)/rheumatoid arthritis (RA)/Addison's disease/coeliac disease, etc.
- History of recurrent miscarriages, pre-term delivery, intrauterine demise, pre-eclampsia/ eclampsia, abruptio placentae
- History of infertility (inability to conceive after one year of unprotected intercourse)
- Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast

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Government of India
December 2014

Trimester-specific reference ranges for TSH

- As defined in populations with optimal iodine intake, should be applied
- If trimester-specific reference ranges for TSH are not available in the laboratory, the following reference ranges are recommended:
  - First-trimester, 0.1–2.5 mIU/L
  - Second-trimester, 0.2–3.0 mIU/L
  - Third-trimester, 0.3–3.0 mIU/L
- Method-specific and trimester-specific reference ranges of serum FT_4 are required.

Indian scenario: Screen or not to screen?[6]

- The cost effectiveness of routine screening of all pregnant women is not yet proven; however, many authors suggest that screening for subclinical hypothyroidism in pregnancy will be a cost-effective strategy under a wide range of circumstances, as listed above and in GOI 2014 guidelines.
- Published Indian data are limited, but a prospective study by Misra et al from Orissa reported a 5.3% prevalence of subclinical hypothyroidism.
- Cooper hospital Mumbai Data of voluntary TSH screening in ANC first visit found 16.2% with abnormal TSH, of which 88% were elevated (hypothyroid)
- Data from a 5-year multicenter study by ICMR had reported an incidence of 1 in 900 for congenital hypothyroidism in newborns
- **In our set-up we feel that screening of all pregnant patients is a cost effective strategy, although it is not yet available free of cost through government programs everywhere. Pregnant women should be offered screening at booking visit and most of them opt to do so.**

Hypothyroidism treatment

- Treatment of overt hypothyroidism is recommended during pregnancy.
- **The recommended treatment is with administration of oral levothyroxine (LT_4). It is strongly recommended not to use other thyroid preparations such as T_3 or desiccated thyroid**
- The goal of LT_4 treatment is to normalize maternal serum TSH values within the trimester-specific pregnancy reference range.

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National Guidelines for Screening of Hypothyroidism during Pregnancy

Methodology for diagnosis

- **Blood/sample collection:** Venous blood samples should be taken with other antenatal care (ANC) investigations in a single sitting
- **Equipment:** Auto-analyser/semi auto-analyser
- **Analysis:** Samples will be analysed using Chemiluminescence assay/auto-analyser/semi auto-analyser

Protocol for management of hypothyroidism

- Drug of choice for treatment is levothyroxine sodium, which is available in the market as 'tablets' in different strengths. Levothyroxine is to be taken orally, in the morning on empty stomach. The patient should be asked not to take anything orally for at least half an hour after intake of the medicine.
- The strength required for this programme is 25, 50, 100 µg. It has to be supplied in moisture tight packages and should be stored at room temperature. Exposure to direct sun light or heat should be avoided at all times
- Levothyroxine sodium belongs to category A for use during pregnancy and can be used safely during pregnancy and lactation without any adverse effects on the mother or fetus

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Hypothyroidism

- In pregnant patients with treated hypothyroidism, maternal serum TSH should be monitored approximately **every 4 weeks** during the first half of pregnancy, because further LT4 dose adjustments are often required. TSH should be checked at least once between 26 and 32 weeks gestation.
- Following delivery, LT_4 should be **reduced to** the patient's **preconception dose**. Additional TSH testing should be performed at approximately 6 weeks postpartum.
- Treated hypothyroid patients (receiving LT_4), who are newly pregnant should **independently increase their dose of LT_4 by** ~25%–30% upon a missed menstrual cycle or positive urine pregnancy test and notify their caregiver promptly. One means of accomplishing this adjustment is to increase LT_4 from once daily dosing to a total of nine doses per week (29% increase).
- Treated hypothyroid patients (receiving LT_4) who are planning pregnancy should have their dose adjusted by their provider to optimize serum TSH values to <2.5 mIU/L preconception.

Sub clinical hypothyroidism (SCH)

- SCH has been associated with adverse maternal and fetal outcomes.
- Pregnant women with TSH concentrations >2.5 mU/L should be evaluated for thyroid peroxidase antibody (TPO Ab) status.
- Subclinical hypothyroidism in pregnancy should be approached as follows:
    - LT_4 therapy is recommended for
        - » TPO Ab-positive women with a TSH greater than the pregnancy-specific reference range
        - » TPO Ab-negative women with a TSH greater than 10.0 mU/L.
- Euthyroid women (not receiving LT_4) who are TPO Ab or Thyroglobulin antibody (Tg Ab) positive require monitoring for hypothyroidism during pregnancy.
- They should have measurement of serum TSH testing at time of pregnancy confirmation and every 4 weeks through mid-pregnancy and at least once between 26 and 32 weeks gestation.
- In women with adequately treated Hashimoto's thyroiditis, no other maternal or fetal thyroid testing is recommended beyond measurement of maternal thyroid function (such as serial fetal ultrasounds, antenatal testing, and/or umbilical blood sampling) unless for other pregnancy circumstances.

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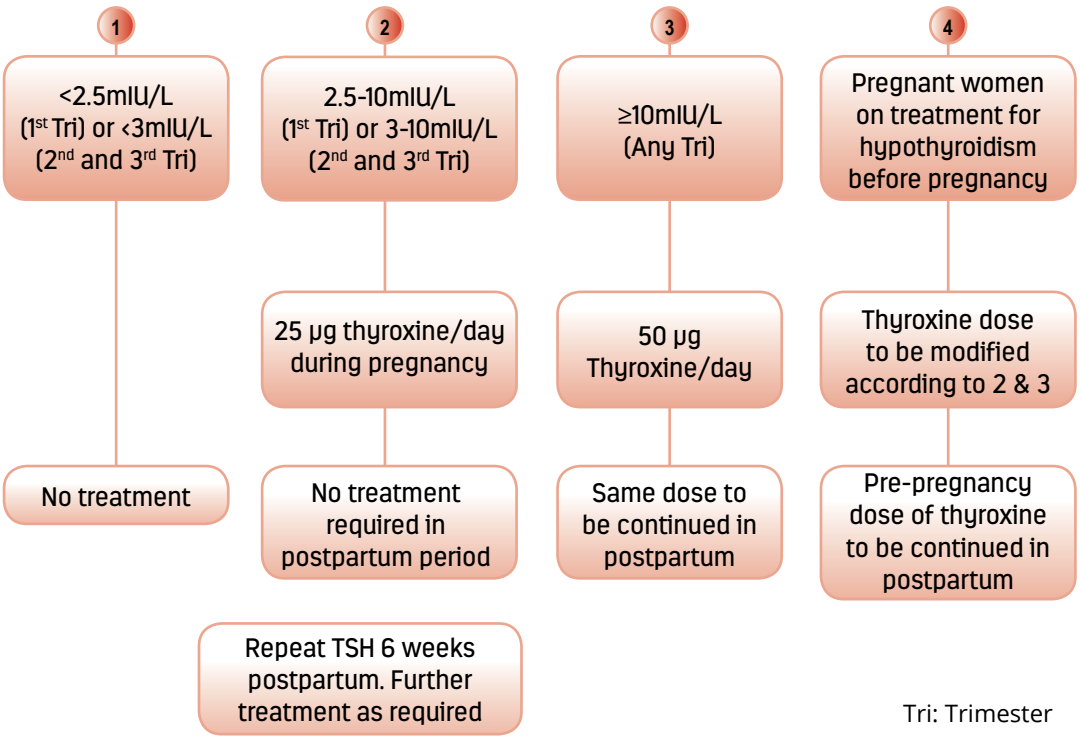
National Guidelines for Screening of Hypothyroidism during Pregnancy

Flowchart for treatment of hypothyroidism in pregnancy and postpartum period based on serum TSH values



Tri: Trimester

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The International Federation of Gynecology and Obstetrics (FIGO) recommendations

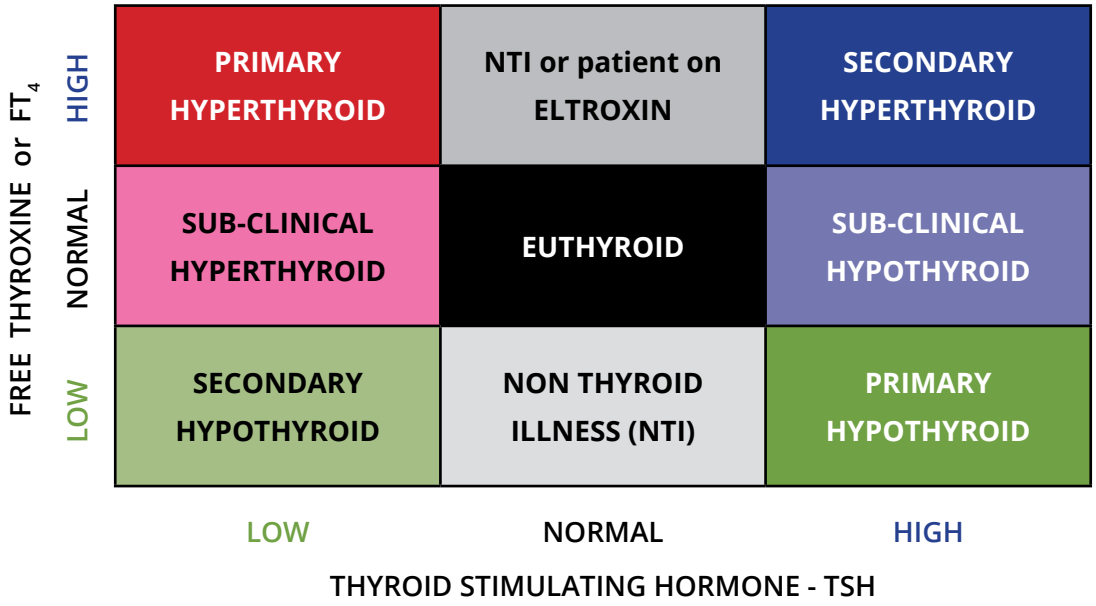
- Screening for thyroid function is recommended in the first-trimester particularly in countries with a deficient iodine diet and in patients with symptoms.
- TSH is the superior method for screening, T_4 and TPO Ab testing are not recommended for screening. Best reliable test for TSH is by CIA or 3rd generation RIA (Radio Immuno Assay). Thyroid test values change in pregnancy.
- Treatment for hypothyroidism is recommended when TSH levels are >2.5 mIU. Only L-thyroxine replacement therapy (dosage in table). Treating subclinical hypothroidism is debatable. Women on L-thyroxine before pregnancy should increase dosage by 30-50% when pregnant.

TSH	L-thyroxine starting dose
5-10 mIU/L	25-50 μg/day
10-20 mIU/L	50-75 μg/day
>20 mIU/L	75-100 μg/day

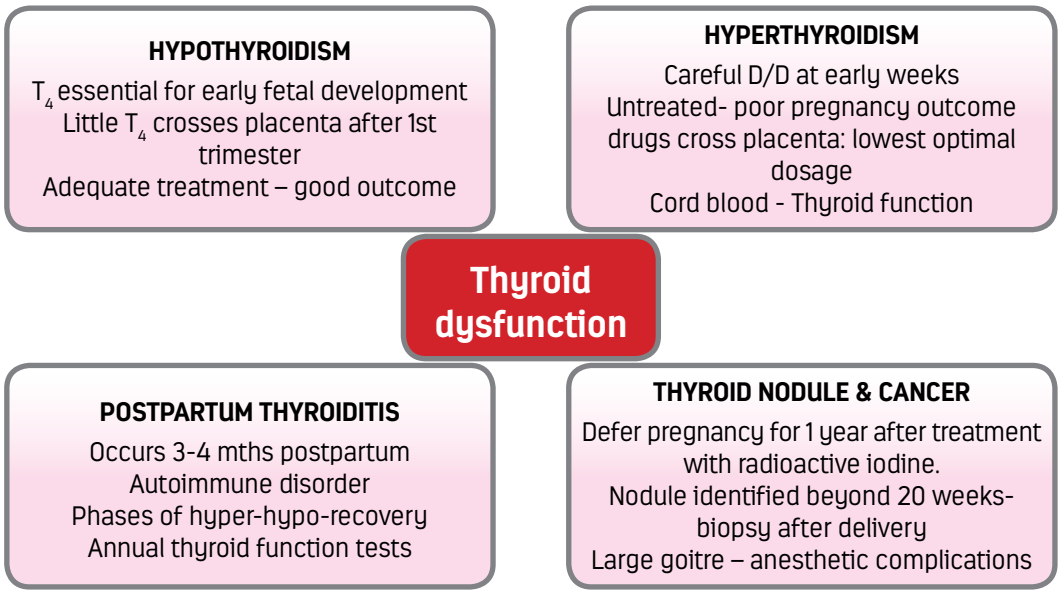
Thyrotoxicosis in pregnancy

- When TSH less than the reference range is detected in the First-trimester, a medical history, physical examination, and testing of maternal serum FT_4 or TT_4 should be performed. Measurement of TRAb and maternal total triiodothyronine (TT_3) may prove helpful in clarifying the etiology of thyrotoxicosis.
- Radioactive iodine (RAI) scanning or radioiodine uptake determination should not be performed in pregnancy.
- The appropriate management of abnormal maternal thyroid tests due to gestational transient thyrotoxicosis and/or hyperemesis gravidarum includes supportive therapy, management of dehydration, and hospitalization if needed. ATDs are not recommended, though β-blockers may be considered.
- In Grave's disease, propylthiouracil is preferred for treatment of hyperthyroidism in first-trimester. Patients on methimazole should be switched to propylthiouracil if pregnancy is confirmed in first-trimester. Following first-trimester, consideration should be given to switching to methimazole to decrease the risk of liver failure in the mother.
- In women being treated with anti-thyroid drugs (ATDs) in pregnancy, FT_4/TT_4 and TSH should be monitored approximately every 4 weeks.

Basic thyroid evaluation



Conclusions



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6. Wani R. Jalvee R. Screening and Clinical Management for Thyroid Disorders in Pregnancy. In: Kriplani A, Gupta S.(eds) FOGSI Focus- Preconceptional and Antenatal Care Update. Jan 2016.

Abbreviations

AACE: American Association of Clinical Endocrinologists
aCL: Anticardiolipin antibodies
ACOG: American College of Obstetricians and Gynecologists
SOGC: The Society of Obstetricians and Gynecologists of Canada
ACTH: Adrenocorticotropic hormone
AFC: Antral follicle count
a-FP: Alphafetoprotein
AIH: Artificial insemination with the partner's sperm
AMH: Anti-Müllerian hormone
ANA: Anti nuclear antibodies
APLA: Antiphospholipid antibodies
APS: Antiphospholipid syndrome
ARM: Artificial rupture of the membranes
ART: Assisted reproductive technique
ASRM: American Society for Reproductive Medicine
ATA: American Thyroid Association
BMD: Bone mineral density
BMI: Body mass index
BSO: Bilateral salingo-oophorectomy
CA-125: Cancer antigen-125
CAVD: Congenital absence of the vas deferens
CBC: Complete blood count
CC: Clomiphene citrate
CCBs: Calcium channel blockers
CEE: Estrogens
CIA: Chemiluminescence immuno assay
COH: Controlled ovarian hyperstimulation
CT: Computed tomography
CTG: Continuous cardiotocography
DCGI: Drug Controller General of India
DEXA: Dual-energy x-ray absorptiometry
DNA: Deoxyribonucleic acid
EB: Endometrial biopsy
ECG: Electrocardiography
EE: Ethinylestradiol
IUS: Intrauterine system
ERT: Estrogen replacement therapy
ESR: Erythrocyte sedimentation rate
FBS: Fasting blood sugar;
PCO: Products of conception
FDA: US Food and Drug Administration
FFN : Fetal fibronectin
FMR-1: Fragile X mental retardation 1
FSH: Follicle stimulating hormone
FT3: Free triiodothyronine
FT4: Free thyroxine
GA: Age of gestation
GBS: Group B streptococcal
GnRH: Gonadotropin-releasing hormone
H/o: History of
H2 receptor: Histamine receptor
Hb: Hemoglobin
HbSAg: Surface antigen of the hepatitis B virus
hCG: Human chorionic gonadotropin
HIV: Human immunodeficiency virus
HPO: Hypothalamic-Pituitary-Ovarian
HSG: Hysterosalpingographic
IBS: Irritable bowel syndrome
ICMR: Indian Council of Medical Research
ICOS: Individualised controlled ovarian stimulation
ICSI: Intracytoplasmic Sperm Injection
IDA: Iron deficiency anemia
IFA: Iron/Folic Acid
IFN: Interferon
IL-10: Interleukin 10
ITS: Indian Thyroid Society
IUGR: Intrauterine growth restriction
IUI: Intrauterine insemination
IV: Intravenous
IVF: *In vitro* fertilization
LAC: lupus anticoagulant
LDH: Lactate dehydrogenase
LH: Luteinizing hormone

LOD: Laparoscopic ovarian drilling
LPD: Luteal phase deficiency
LSCS: Lower segment caesarean section
MCH: Mean corpuscular hemoglobin
MCHC: Mean corpuscular hemoglobin concentration
MCV: Mean corpuscular volume
MDT: Multidisciplinary Team
MESA: Microsurgical epididymal sperm aspiration
MMA: Methylmalonic acid
MoHFW: Ministry of Health and Family Welfare
MPA: Medroxyprogesterone acetate
MRI: Magnetic resonance imaging
NICE: National Institute for Health and Care Excellence
NICU: Neonatal intensive care unit
NIS: Natrium/iodide symporter
NSAIDs: nonsteroidal anti-inflammatory drugs
NT scan: Nuchal translucency scan
OATS: Oligoasthenoteratozoospermia
OCP: Oral contraceptive pill
OHSS: Ovarian hyperstimulation syndrome
OS: Oxidative stress
PAP: Papanicolaou
PCOD: Polycystic ovarian disease
PCOS: Polycystic ovarian syndrome
PCR: Polymerase chain reaction
PCV: Packed cell volume
PESA: Percutaneous epididymal sperm aspiration
PET: Positron emission tomography
PGD: Preimplantation genetic diagnosis
pH: Hydrogen ion concentration of a solution
PIBF: Progesterone induced blocking factor
PID: Pelvic inflammatory disease
POF: Premature ovarian failure
PPBS: Post prandial blood sugars
PROM: Preterm premature rupture of membranes
PTB: Prevent preterm birth
PTL: Preterm labour
PV: Vaginal route
RBC: Red blood cell
RCT: Randomized controlled trial
RDW: Red blood cell distribution width
RES: Reticuloendothelial system
rFSH: Recombinant follicle stimulating hormone
RMI: Risk of malignancy index
RPL: Recurrent pregnancy loss
SFA: Sperm functional assessment
SSR: Surgical sperm retrieval
sTfR: Soluble transferrin receptor
STI: Sexually transmitted infections
SW: Intrauterine insemination of washed sperm
TA/TV: Transabdominal/transvaginal
TAH: Total abdominal hysterectomy
TAS: Transabdominal scanning
TEFNA: Testicular fine needle aspiration
TG: Thyroglobulin
Th cell: helper T cell
TI: Timed intercourse
TIBC: Total iron-binding capacity
TMC: Total motile count
TPN: Total parenteral nutrition
TPO: Thyroid peroxidase
TPO-Ab: Thyroid peroxidase antibodies
TSH: Thyroid stimulating hormone
TVS: Transvaginal scanning
UPT: Urine pregnancy test
USG: Ultrasonography
VD: Venereal diseases
VDRL: Venereal Disease Research Laboratory
VTE: Venous thromboembolism
WBC: White blood cells
WHO: World Health Organization