A FOGSI President's Initiative

TOG 6th CONCLAVE

By Dr. Nandita Palshetkar

TOG-6 ALGORITHMS

FEDERATION OF OBSTETRIC AND GYNAECOLOGICAL SOCIETIES OF INDIA TM

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सत्यमेव जयते

Dr. Harsh Vardhan,

Minister of Science & Technology, Earth Sciences Environment,
Forest & Climate Change, Government of India
appreciated TOG conclave and **Dr. Nandita Palshetkar,**
President, FOGSI for a unique Science Generating Platform.

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Dear FOGSIANs,

In this era of evidence-based medicine, Gynaecologists often must make decisions where neither evidence nor consensus exists. Fortunately, there is a growing body of evidence to assist in managing various conditions related to Obstetrics & Gynaecology. With the TOG-6 algorithms, the idea is to regularly create evidence and consensus based practical approach to the diagnosis and management of indications, thereby ensuring a higher quality of care to patients.

FOGSI & TOG-6 intends to bring the best talent across the country and get them to discuss, deliberate and create easy point of reference to practice better.

Hope you all will maximize from the TOG-6 algorithms and pass on further for the betterment of the community and the STREE in all. Our sincere gratitude to Abbott India Ltd. for their educational grant for the TOG-6 algorithms.

Best wishes!

Dr. Nandita Palshetkar

MD, FCPS, FICOG
President 2019 - Federation of Obstetrics & Gynecological Societies of India (FOGSI)

IMMUNIZATION IN PREGNANCY

FOGSI President : Dr. Nandita Palshetkar

Moderators : Dr. P. K. Shah, Dr. Bipin Pandit

Co-ordinators : Dr. Sheetal Punjabi

Panelists : Dr. Bakul Parekh (Paediatrician), Dr. Komal Chavan, Dr. Sneha Bhuyar, Dr. Elizabeth Jacob, Dr. Sherley Mathen

From left to right: Dr. Sherley Mathen, Dr. Elizabeth Jacob, Dr. Bakul Parekh, Dr. Bipin Pandit, Dr. P. K. Shah, Dr. Komal Chavan, Dr. Sneha Bhuyar, Dr. Sheetal Punjabi

> *It is rightly said that "Colostrum is the first immunization in an infant's life. With the advancement in science, in both disease causing micro-organisms and in the field of medicine, the unborn baby can be protected in the mother's womb by vaccinating the pregnant woman - a type of cocooning effect.*
>
> ***- Dr. Bakul Parekh (President - IAP)***

10 important points to ponder

1. Pregnant women are at an increased risk of severe illness and complications from some vaccine preventable illnesses e.g. influenza (flu).
2. Passive immunity by transplacental transfer of antibodies may protect vulnerable neonates.
3. When indicated, vaccination can be given anytime during pregnancy to decrease adverse pregnancy outcomes and perinatal outcomes.
4. Avoid pregnancy for at least 4 weeks after any vaccination.
5. The risk of vaccination during pregnancy is largely theoretical.
6. If vaccinated inadvertently during pregnancy with vaccine contraindicated during pregnancy or subject gets pregnant within 4 weeks of taking vaccination, no intervention in the form of MTP is required.
7. Avoid preferably in first trimester a vaccine with killed agents eg., cholera, inactivated typhoid, hepatitis B.
8. Live viral vaccines are contraindicated during pregnancy e.g. MMR, varicella, yellow fever, typhoid, Japanese encephalitis etc.
9. Cocooning: Strategy to vaccinate pregnant women in 3rd trimester or immediate postpartum and all those who are in close contacts of neonates and infants less than 12 months [Parents, grandparents, siblings, all health-care providers] with Tdap IIV to reduce risk of transmission in infant.
10. Small pox and yellow fever vaccinations are contraindicated during breastfeeding.

IAP: Indian Academy of Pediatrics; MTP: medical termination of pregnancy; MMR: Measles, mumps, and rubella; Tdap: tetanus, diphtheria, pertussis

Current vaccine recommendations for pregnant women

Vaccine	Type of vaccine	During pregnancy	Atleast one month before pregnancy	Immediate post-partum if not immunized earlier	Remarks
Vaccines recommended for all pregnant women					
Influenza Inactivated influenza vaccine IIV (QIV / TIV)[1,2]	Inactivated viral subunit vaccine	1 Dose at any gestational age preferrably between 27–36 weeks or during flu	YES	YES	Annually 1 dose during flu Practice Cocooning
Tetanus Diphtheria[1] Pertussis (Tdap/Td)[1]	Tetanus and diphtheria – Inactivated toxoids Acellular pertussis – Inactivated subunit vaccine	1 dose of Tdap during each pregnancy regardless of prior Tdap receipt at any time during pregnancy Preferrably between 27–36 weeks	YES	YES	Practice Cocooning
Tetanus toxoid vaccine (TT)[3]	Tetanus inactivated toxoid vaccine	First dose as soon as pregnancy detected. Second dose, 4–6 weeks after first dose WHO - 3rd dose given after 6 months of second dose. Protects her for 5 years	-	-	If she has received 2 TT in last pregnancy and gets pregnant again within 3 years, only 1 dose of TT

TIV: trivalent inactivated influenza vaccines; QIV: quadrivalent inactivated influenza vaccines; Tdap: tetanus, diphtheria, pertussis; Td: tetanus and diphtheria; WHO: World Health Organization

Vaccines contraindicated during pregnancy

Vaccine	Type of vaccine	During pregnancy			Remarks
Measles mumps rubella (MMR)[1,2]	Live-attenuated viral vaccine	CONTRAINDICATED	–	YES	1 dose immediately postpartum if rubella non-immune or susceptible to Rubella 1–2 doses, lifetime protection
Varicella vaccine for chickenpox (VAR)[1,2]	Live-attenuated viral vaccine	CONTRAINDICATED	–	YES	1 dose, immediately postpartum if varicella non-immune 2 doses, 6–8 weeks apart for lifetime protection
Influenza (LAV)[1]	Live-attenuated viral vaccine	CONTRAINDICATED	–	–	
Human Papilloma virus vaccine (HPV)[1]	Inactivated viral vaccine	CONTRAINDICATED	YES	YES	If found pregnant after initiating 3 dose series, remainder doses should be given after delivery
BCG	Live attenuated bacterial vaccine	CONTRAINDICATED	–	–	–
Polio vaccine - Oral polio vaccine (OPV) - Inactivated polio vaccine	Live attenuated vaccine	NOT RECOMMENDED	–	–	–
Cholera vaccine		NOT RECOMMENDED	–	–	–
Hemophilus influenza type B vaccine (Hib)		NOT RECOMMENDED	–	–	–
Zoster vaccine live (ZVL)	Live attenuated viral vaccine	NOT RECOMMENDED	–	–	–

BCG: Bacillus Calmette–Guérin

Vaccines recommended for pregnant women with risk factors/special circumstances

Vaccine	Type of vaccine	During pregnancy			Remarks
Hepatitis A vaccine (Hep A)[2]	Inactivated whole-cell viral vaccine	2 doses, 6 months apart if risk of infection outweighs theoretical risk of vaccine	YES	YES	2 lifetime doses
Hepatitis B vaccine (Hep B)	Inactivated viral recombinant subunit vaccine	3 doses over 6 months if previously unvaccinated or at high risk of exposure (Multiple sex partners in previous 6 months, treated for any STD, recent or current injection drug abuse, HBsAg positive partner, simply wants protection)	YES	YES	3 lifetime doses
Pneumococcal-13 valent conjugate vaccine (PCV 13)[1] Pneumococcal 23 valent polysaccharide vaccine (PPSV 23)[2]	Inactivated bacterial conjugate vaccine Inactivated bacterial polysachharide vaccine	1 dose if risk factor present eg. diabetes	YES	YES	–
Meningococcal serogroups A,C,W,Y vaccine (Men ACWY)[1,2] Meningococcal serogroup B Vaccine (Men B-4c MenB-FHbp)[1,2]	Inactivated bacterial polysachharide vaccine Inactivated bacterial polysachharide vaccine	1 dose if risk factor present	YES	YES	–
Yellow fever vaccine[2]	Live attenuated viral vaccine	1 dose if travelling to endemic region and risk of infection outweighs theoretical risk of vaccine	–	–	–
Japanese encephalitis vaccine	Live attenuated viral vaccine	1 dose if travelling to endemic region and risk of infection outweighs theoretical risk of vaccine	–	–	–
Typhoid vaccine	Live attenuated bacterial recombinant	NOT RECOMMENDED due to lack of data. In general, live vaccines like Ty21a are contraindicated in pregnancy. Vi polysaccharide vaccine should be given to pregnant women only if clearly needed.	–	–	–
Rabies vaccine[2]	Inactivated whole-cell viral vaccine	Post exposure prophylaxis (PEP) consider preexposure prophylaxis if risk of exposure very high e.g. Pets at home	YES IF INDI-CATED	–	–
Anthrax vaccine[2]	Inactivated bacterial subunit vaccine	Post Exposure Prophylaxis (PEP)	NO DATA	–	–
Recombinant Zoster vaccine (RZV)	Inactivated viral recombinant subunit vaccine	NOT RECCOMMENDED	–	YES IF INDICATED	–

STD: sexually transmitted diseases; HBsAg: hepatitis B virus surface antigen;

“Immunization by following a standard protocol can save the lives of many pregnant women and neonates who are vulnerable to such diseases. As the old proverb goes - prevention is better than cure.”

- Dr. Bakul Parekh (President - IAP)

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NAUSEA & VOMITING IN PREGNANCY

FOGSI President : Dr. Nandita Palshetkar

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Dr. Aswath Kumar

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Dr. Rakhi Singh
Dr. Abha Rani Sinha
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Introduction

Nausea and vomiting in pregnancy (NVP) is a very common disorder reported in 70%–80% of all pregnant women.[1] The symptoms usually begin 2–4 weeks after fertilization, peaks between 9 and 16 weeks and resolve by 22 weeks gestation. Ten percent of women may continue till delivery. The severe form of NVP is called hyperemesis gravidarum. The pathogenesis remains unclear and is multifactorial. The treatment is challenging and ranges from dietary modifications, medical management to hospitalization.

NVP should only be diagnosed when the onset is in the first trimester of pregnancy. The other causes of nausea and vomiting should be excluded. Hyperemesis gravidarum can be diagnosed when protracted nausea and vomiting are associated with a triad of symptoms: Weight loss of more than 5% of pre-pregnancy weight, dehydration, and electrolyte imbalance.[2]

Risk factors[1]

- Younger nullipara
- Under and overweight women
- Multiple pregnancy
- Molar pregnancy
- Socioeconomic factors – marital status, lower education
- Genetics
- History of hyperemesis gravidarum in previous pregnancy and family
- Female fetus

Etiopathogenesis

Hormonal stimulation

Human chorionic gonadotropin (hCG): The link between hCG and NVP is based on the temporal relationship between the peak symptoms of NVP and the peak levels of hCG production, both of which occur between 8 and 11 weeks of gestation. Higher urinary and serum hCG levels have been noted in NVP cases compared to asymptomatic woman. The extent of hCG stimulation may be modified by placental conditions that elevate its concentration (e.g., multiple gestation or molar gestation) and by hormone-receptor interactions modifying the effect of the hormone.[3]

Furthermore, hCG has been shown to be a thyroid stimulator of pregnancy. Several studies have exhibited the correlation between transient hyperthyroidism and NVP. Due to cross reactivity between hCG and the thyroid stimulating hormone (TSH) receptor, thyroid dysfunction has been evaluated as a possible mechanism for NVP and hyperemesis gravidarum development.[1]

Estrogen and progesterone: The ovarian hormones, estrogen and progesterone, have been implicated in the pathogenesis of NVP and hyperemesis gravidarum. NVP is more common when estradiol levels are increased and less common when estradiol levels are decreased.[3] Estrogen contributes to hyperemesis gravidarum by triggering the production of nitric oxide via nitrogen oxidase synthetase, which in turn relaxes smooth muscle slowing gastric intestinal transit time and gastric emptying. Cigarette smoking is associated with lower levels of hCG and estradiol, thereby lowering the risk of hyperemesis gravidarum in smokers.[3]

Progesterone in combination with estrogen may also elevate the risk for NVP. Progesterone reduces smooth muscle contractility and may alter gastric emptying, leading to increased nausea and vomiting.[1]

Prostaglandin E2 (PGE2) and leptin: The role of placental PGE2 has been implicated in the pathogenesis of NVP due to its effect on gastric smooth muscle. Additionally, hCG has been shown to stimulate placental PGE2 which peaks between 9 and 12 weeks of gestation. A study conducted by North et al. has reported higher maternal serum PGE2 levels during periods of nausea and vomiting in early pregnancy compared to asymptomatic periods.[4]

Serum leptin levels have been found to be significantly higher in patients with hyperemesis gravidarum compared to healthy pregnant controls. Leptin may contribute to hyperemesis gravidarum by increasing hCG secretion by the paracrine action of the placenta or by decreasing appetite and promoting more severe nausea and vomiting.[5,6]

Immune system dysregulation

Hyperemesis gravidarum has been associated with abnormal regulation of the immune system. The normal shift in pregnancy wherein T-helper cell types move into T-helper cell type 1 is exaggerated in hyperemesis gravidarum resulting in increased release of interleukin (IL)-4 as well as tumor necrosis factor-alpha. Furthermore, elevated levels of IL-6, immunoglobulin G (IgG), IgM, complement levels, and lymphocyte counts have been reported in women with hyperemesis gravidarum.[1]

Gastrointestinal motility

Few studies have shown a correlation between alterations in the lower esophageal sphincter (LES) resting pressure/esophageal peristalsis and NVP. Estrogen and progesterone are the triggers of esophageal dysmotility in pregnancy wherein estrogen serves as a primer and progesterone causes LES relaxation.[7] Higher levels of progesterone in pregnancy has also been linked with changes in gastric motility.

Helicobacter pylori (*H. pylori*) infection

Infection with *H. pylori* has been considered to play a role in the pathogenesis of hyperemesis gravidarum. In a study conducted by Bagis et al. histologic examination of the mucosal biopsy revealed that 95% of hyperemesis gravidarum patients tested positive for *H. pylori* compared with 50% in the control group.[8] *H. pylori* may exacerbate hormone-induced changes in the nerve and electric functioning of the stomach thereby increasing the risk for more severe nausea and vomiting.

Psychosocial factors

Previous studies have proposed that NVP may be a psychosomatic illness, in which vomiting represents intrapsychic conflicts. Few studies have speculated that NVP is a manifestation of a woman's subconscious attempt to reject an unwanted or undesired pregnancy.[1]

Although there are no definite psychogenic causes of hyperemesis gravidarum, the latter has been linked with psychological disturbances, namely neurotic tendencies, hysteria, rejection of femininity, rejection of pregnancy as well as depression and psychological stress related to poverty and marital conflicts.[9]

History

- Previous history of NVP/hyperemesis gravidarum.
- **History to exclude other causes:** Abdominal pain, urinary symptoms, infection, drug history, chronic *H. pylori* infection.
- **Quantify severity using PUQE score:** Nausea, vomiting, hypersalivation, spitting, loss of weight, inability to tolerate food and fluids, effect on quality of life.[10]

Circle the answer that best suits your situation from the beginning of your pregnancy	Points
1. On an average in a day, for how long do you feel nauseated or sick to your stomach?	
Not at all	1
≤ 1 hour	2
2 to 3 hour	3
4 to 6 hours	4
>6 hours	5
2. On an average in a day, how many times do you vomit or throw up?	
I did not throw up	1
1 to 2 times	2
3 to 4 times	3
5 to 6 times	4
≥ 7 times	5
3. On an average in a day, how many times do you have retching or dry heaves without bringing anything up?	
None	1
1 to 2 times	2
3 to 4 times	3
5 to 6 times	4
≥ 7 times	5

Total score: Mild NVP : ≤ 6; Moderate NVP: 7–12; Severe NVP: ≥ 13

Investigations

Nausea and vomiting in pregnancy

Mild

- Urine ketones
- Complete blood count
- Serum electrolytes

Severe

- Complete blood count
- Blood sugars
- Urine - ketones
- Serum electrolytes
- Blood urea
- Liver function tests
- Arterial blood gases
- Thyroid function tests
- Ultrasound of obstretics and abdomen

Maternal effect of NVP

- Significant detrimental effect on physical quality-of-life and work.
- Increased risk of preeclampsia.
- Increased feelings of depression, negative impact on employment, household duties, parenting and family relationships.
- Significant maternal morbidity due to dehydration, electrolyte and acid-base imbalance, nutritional deficiency, ketonuria, and loss of more than 5% of body weight.
- May lead to acute kidney injury, liver dysfunction, pneumomediastinum, ruptured esophagus, and Wernicke's encephalopathy.

Fetal effects

- No significant congenital anomalies have been demonstrated.
- Increased incidence of low birth weight, small for gestational age (SGA), and premature infants.

Management

Dietary modifications

- Eat small, frequent meals to avoid gastric distention.
- Avoid foods with strong odors/tastes, spicy food, caffeine.

- Increase protein and decrease high-fat and fried foods.
- Eat dry carbohydrates upon awakening, avoid late dinner.
- Try ginger, raspberry, and peppermint tea.
- Drink plenty of liquids, but only very small quantities at a time, between meals, rather than with meals.
- To take prenatal vitamins for one month before fertilization.

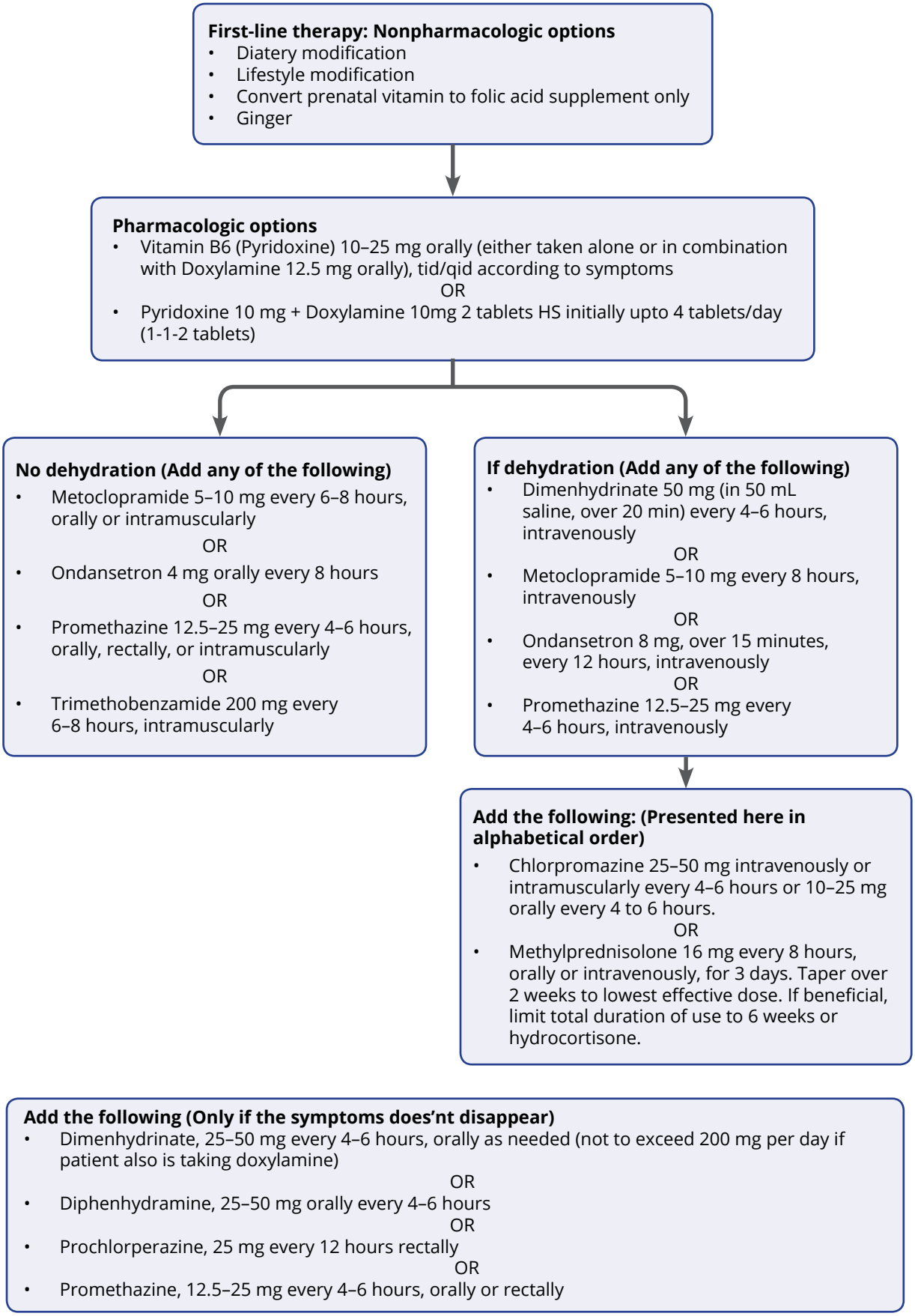
Lifestyle modifications

- Decrease or eliminate cigarette smoking.
- Brushing teeth after eating.
- Avoid lying supine for 2 hours after eating.
- Consider chewable prenatal vitamins.
- Straight posture to decrease stomach compression.
- Avoid mental stress and to keep mind occupied.

First-line treatment – Combination drugs (Doxylamine Succinate 10 mg + Pyridoxine Hydrochloride 10 mg)

- Category A drug.
- In NVP, it is the only approved combination by Central Durgs Standard Control Organisation (CDSCO).
- Delayed release medication.
- Should not be crushed or chewed. Food may affect absorption, so to increase the likelihood of maximum benefit tablets are best taken on an empty stomach.
- The initial starting dose is two tablets at bedtime. If symptoms are relieved, the next day this dosing schedule can be maintained. If symptoms persist, the dose can be increased to one tablet in the morning and two tablets at bedtime. If adequate relief still isn't obtained, the dose can be increased a final time to one tablet in the morning, one in mid-afternoon and two at bedtime. Four tablets is the maximum dose that can be taken each day.
- Not recommended in breast feeding women.
- It is recommended by the American College of Obstetricians and Gynecologists (ACOG) and Royal College of Obstetricians & Gynaecologists (RCOG) for treating NVP.

Algorithm: Management of NVP[11]



Pharmacological therapy

Early treatment of NVP is recommended to prevent the progression to hyperemesis gravidarum. The pharmacological therapies available for the treatment of NVP have been presented in table below.

Agents	Pregnancy category	CDSCO approval in NVP	Comments
Doxylamine Succinate 10 mg + Pyridoxine Hydrochloride 10 mg	Category A	Approved	• The combination of pyridoxine plus doxylamine is approved by the United States FDA for treatment of NVP in women who do not respond to lifestyle changes • Recommended as first-line pharmacotherapy for NVP • The pyridoxine-doxylamine combination has been found to be safe and does not cause adverse effects in the fetus
Dopamine antagonists • Metoclopramide • Phenothiazine medications (Promethazine, Prochlorperazine). • Droperidol	Category B	Not approved	• Side-effects of metoclopramide include dystonia, restlessness, somnolence. • In 2009 the FDA added a black box warning to metoclopramide due to the risk of tardive dyskinesia with chronic use • Side-effects of promethazine, prochlorperazine include drowsiness, decreased seizure threshold, akathisia • Side-effects of droperidol include drowsiness, dizziness, cardiac arrythmias. Droperidol bears a black box warning as it may cause QT prolongation and cardiac dysrhythmias
Antihistamines • Diphenhydramine • Dimenhydrinate	Category B	Not approved	• Side-effects include drowsiness, dizziness, HA, fatigue
Serotonin 5-hydroxy tryptamine type 3 (5-HT3) receptor antagonists • Ondansetron	Category B	Not approved	• Common adverse effects of ondansetron include headache, drowsiness, fatigue, and constipation • Ondansetron can prolong the QT interval, especially in patients with underlying heart problems, hypokalemia, or hypomagnesemia • There is insufficient data on fetal safety with ondansetron use • A possible association of ondansetron use in the first trimester and cleft palate has been reported, but the data is limited by a small sample size
Corticosteroids • Methylprednisolone	Category B	Not approved	• Side-effects include hyperglycemia, possible increased risk of oral facial clefts with first trimester use
H2 blockers • Ranitidine	Category B	Not approved	• Side-effects include HA, drowsiness, dizziness, diarrhea or constipation
Proton pump inhibitors • Lansoprazole • Esomeprazole	Category B	Not approved	• Side-effects include HA, nausea, diarrhea, fatigue

CDSCO: Central Durgs Standard Control Organisation; FDA: Food and Drug Administration; NVP: Nausea and vomiting in pregnancy

Clinical pharmacology of Doxylamine Succinate + Pyridoxine Hydrochloride

Mechanism of action:

- Doxylamine is a H_1 antihistamine. H_1 receptors are located in nucleus tractus solitarius, chemoreceptor trigger zone (CTZ) and vestibular apparatus which on stimulation promote nausea and vomiting. By blocking H_1 receptors, Doxylamine prevents vomiting.
- Pyridoxine: Vitamin B_6 serves as a co-factor for enzyme glutamate decarboxylase and increases the synthesis of gamma-aminobutyric acid (GABA), which serves as inhibitory neurotransmitter at CTZ.

Pharmacokinetics

The pharmacokinetics of delayed-release doxylamine succinate and pyridoxine hydrochloride has been characterized in healthy non-pregnant adult women.[12]

Absorption

- A single-dose (two tablets) and multiple-dose (four tablets daily), open-label study was conducted to assess the safety and pharmacokinetic profile of delayed-release doxylamine succinate and pyridoxine hydrochloride administered in healthy non-pregnant adult women. Single-doses (two tablets at bedtime) were administered on days 1 and 2. Multiple-doses (one tablet in the morning, one tablet in the afternoon and two tablets at bedtime) were administered on days 3-18.
- Blood samples for pharmacokinetic analysis were collected pre-and post-dose on days 2 and 18 as well as pre-dose prior to bedtime dose only (trough) on days 9, 10, 11, 16, 17, and 18.
- Doxylamine and pyridoxine are absorbed in the gastrointestinal tract, mainly in the jejunum.
- The maximum serum concentration (C_{max}) of doxylamine and pyridoxine are achieved within 7.5 and 5.5 hours, respectively.

Guideline recommendations

Below table showcases the recommendations of various guidelines for the management of NVP and hyperemesis gravidarum.

Guideline recommendations for the treatment of NVP and HG	
Guideline	**Recommendations**
American Congress of Obstetricians and Gynecologists[3]	• Pyridoxine (vitamin B6) and Doxylamine is recommended as the first-line agents when conservative treatment with dietary and lifestyle changes is unsuccessful[13] • Women with a history of NVP or HG in a prior pregnancy are advised to take a multivitamin at the time of the next conception
Royal College of Obstetrics and Gynecology[2]	• The combination of doxylamine and pyridoxine is significantly more effective than pyridoxine alone • There are safety and efficacy data for first-line antiemetics such as antihistamines (H_1 receptor antagonists) and phenothiazines and they should be prescribed when required for NVP and HG. • Combinations of different drugs should be used in women who do not respond to a single antiemetic • Metoclopramide is safe and effective, but because of the risk of extrapyramidal effects it should be used as second-line therapy • Data from the Swedish Medical and Birth Register has demonstrated a small increased risk of cardiovascular defects and cardiac septal defects (OR 1.62, 95% CI 1.04–2.14, and risk ratio 2.05, 95% CI 1.19–3.28, respectively) with ondansetron. Owing to these reasons, the use of ondansetron should be limited to patients who are not adequately managed on the aforementioned antiemetics and preferably used after the first trimester of pregnancy[14] • Enteral or parenteral treatment should be considered along with a multidisciplinary approach when all other medical therapies have failed
Drug Controller General of India (DCGI)	• The formulation of Doxylamine 10 mg and Pyridoxine 10 mg is approved in India for the treatment of NVP

NVP: Nausea and vomiting of pregnancy; HG: Hyperemesis gravidarum

Conclusion

- NVP is probably the most common disorder in pregnancy.
- It ranges in spectrum from mild to its pathologic form hyperemesis gravidarum.
- NVP significantly reduce the quality of life of the pregnant woman and has a large economic impact on patients, caregivers and society, yet this disorder is very often underestimated.
- Although the pathogenesis of NVP remains unclear, it is widely accepted that it is likely to be multifactorial.
- Doxylamine Succinate 10 mg + Pyridoxine Hydrochloride 10 mg is recommended by ACOG and RCOG in the management of NVP.
- Treatment with doxylamine–pyridoxine combination has demonstrated a significantly larger improvement in symptoms of nausea and vomiting of pregnancy on PUQE score and its safety has been demonstrated over 2,00,000 pregnant women hence should be considered as first-line treatment.
- Pre-emptive use of the delayed combination of doxylamine-pyridoxine can mitigate symptom severity among women who had experienced severe NVP in the previous pregnancy, hence should be considered in previous history of NVP.

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POSTPARTUM CARE AND CONTRACEPTION

FOGSI President : Dr. Nandita Palshetkar

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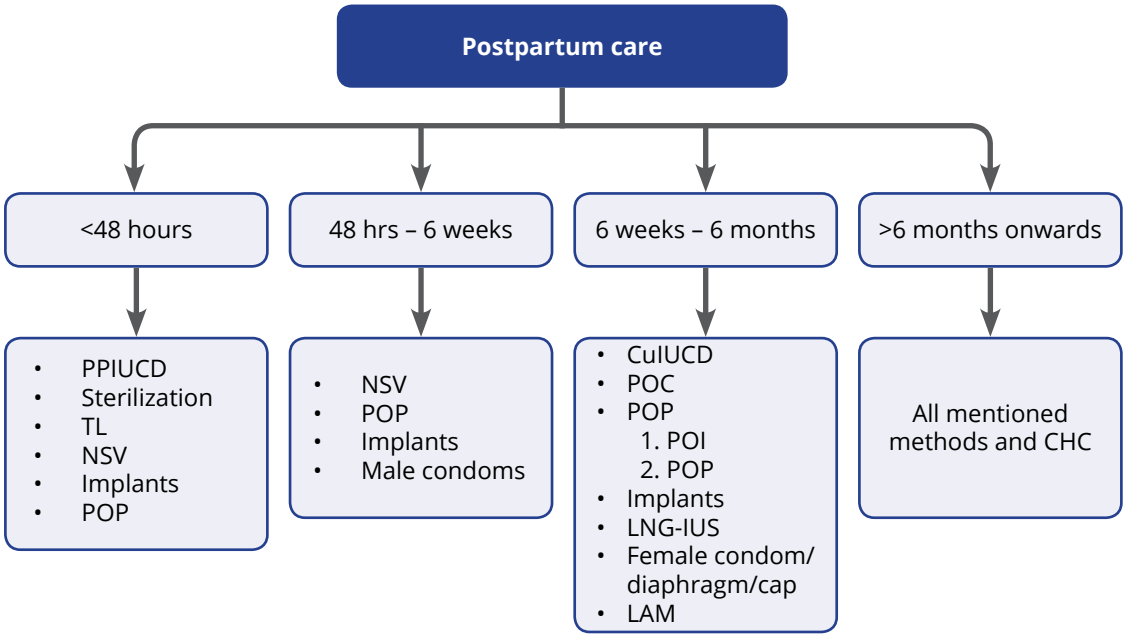
Panelists : Dr. Rajat Mohanty, Dr. Swarnalatha S, Dr. Basab Mukherjee, Dr. Shobha Gudi, Dr. Mandakini Megh, Dr. Kiran Kurtkoti, Dr. Punit Bhojani, Dr. Rajnikant Contractor, Dr. Radhamani K

From left to right: Dr. Punit Bhojani, Dr. Radhamani K, Dr. Swarnalatha S, Dr. Mandakini Megh, Dr. Basab Mukherjee, Dr. Rajat Mohanty, Dr. Rajnikant Contractor, Dr. Shobha Gudi, Dr. Kiran Kurtkoti

9 major points to ponder

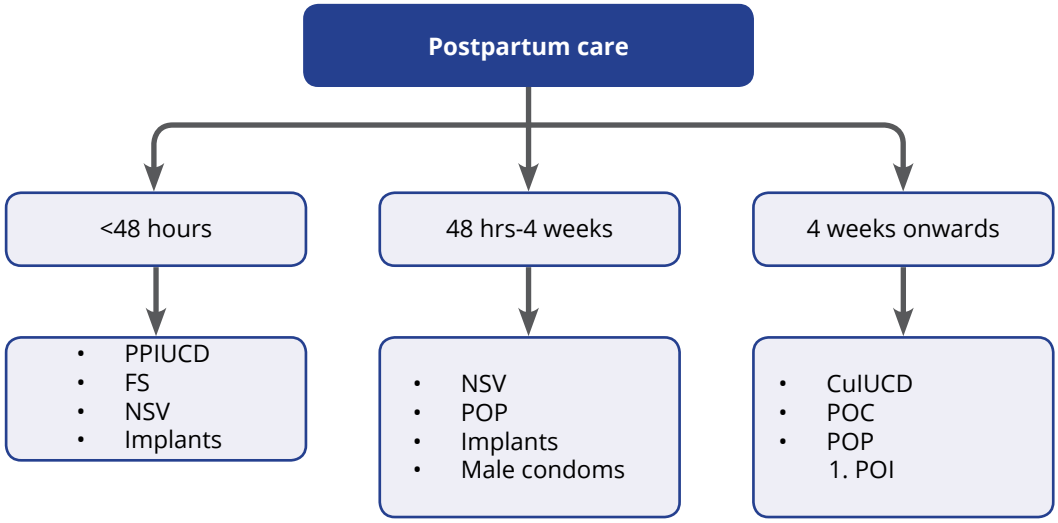
1. Holistic care provided to the parturient and the new born after childbirth extending to a period of 6-8 weeks and up to one year.
2. Though traditionally done at 6 weeks, the timing of the postpartum visit needs to be individualized and women-centred.
3. Appropriate advice on nutrition, breast feeding, exercise, emotional and psychological support should be provided.
4. Optimization of pre-existing medical disorders and ongoing medication.
5. Prevention, early diagnosis and treatment of immediate and delayed complications and early referral when necessary.
6. Discuss birth control methods for spacing/limiting family size. Ideally counselling for immediate postpartum contraception should start in the antenatal period.
7. Immunization and vaccination for the mother and neonate.
8. Lifestyle management, specially abdominal exercises and appropriate dietary modifications.
9. Calcium supplementation and hematinics to be considered.

Algorithm – PPCC in all breastfeeding



CuIUCD: copperIUCD; LAM: lactation amenorrhea method; LG-IUS: levonorgestrel-releasing intrauterine system; POC: progestogen-only contraceptive. POI: progestogen-only injectable; POP: progestogen-only pill; PPIUCD: Postpartum intrauterine contraceptive device; NSV: no scalpel vasectomy.

Algorithm – PPCC in non-breastfeding women



CuIUCD: copperIUCD; LG-IUS: Levonorgestrel-releasing intrauterine system; POC: progestogen-only contraceptive. POI: progestogen-only injectable; POP: Progestogen-only pill; PPIUCD: Postpartum Intrauterine Contraceptive Device; NSV: no scalpel vasectomy.

What is lactational amenorrhea method (LAM) ?

- Exclusively breastfeeding
- Menses has not returned
- Upto 6 months postpartum
- If any of these three criteria is not met: follow algorithm for breastfeeding women

Advantages of LAM

- Breastfeeding practices required by LAM have other health benefits for mother and baby.
- Bonding protects baby from disease, healthiest food for baby.
- Universally available.
- Can be used immediately after childbirth.

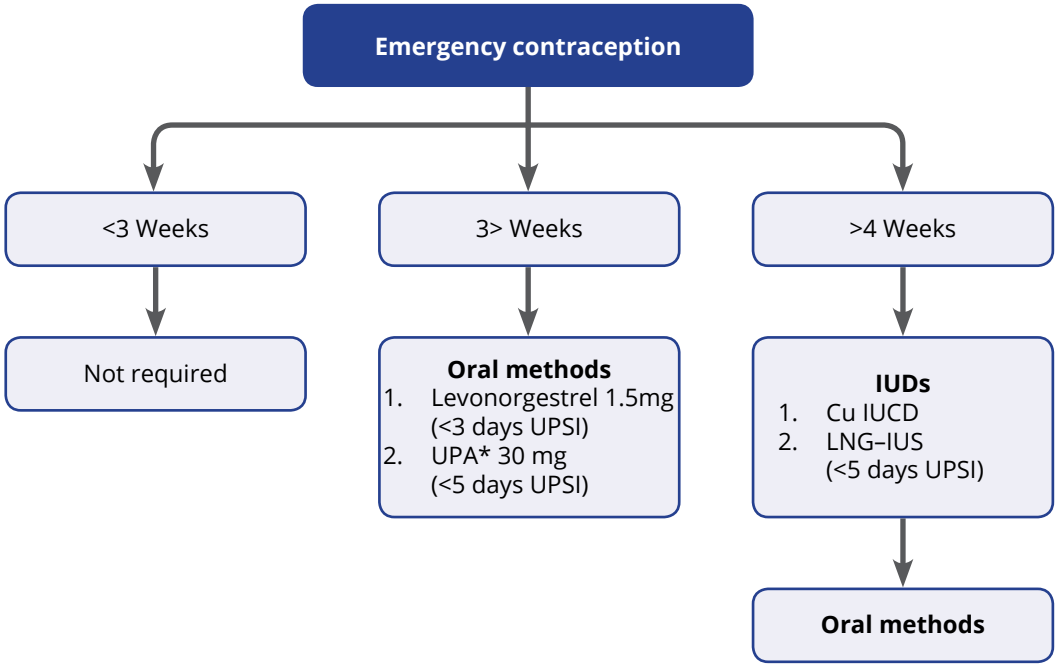
Emergency contraception (irrespective of breastfeeding status)

- Within 72 hrs of unprotected sexual intercourse (UPSI): Levonorgestrel (LNG) 1.5 mg single dose (after 3 weeks postpartum).
- Within 5 days of UPSI:

  1) Copper intrauterine device (Cu IUD)/levonorgestrel-releasing intrauterine system (LNG-IUS) (after 4 weeks postpartum)

  2) Ulipristal acetate 30mg (after 3 weeks postpartum)

  Avoid breastfeeding for 1 week within 5 days of UPSI
- Within 5 days > 3 weeks of birth of UPSI: Ulipristal acetate 30 mg



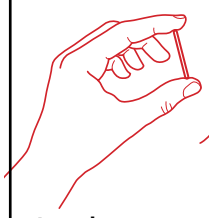
*Avoid breastfeeding for 1 week and discard milk
Cu IUD: Copper intrauterine device; LNG-IUS: levonorgestrel-releasing intrauterine system; UPA: ulipristal acetate; UPSI: unprotected sexual intercourse

Comparing typical effectiveness of contraceptive methods

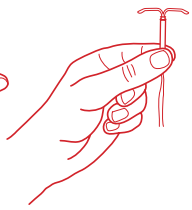
More effective

Less than 1 pregnancy per 100 women in one year

Reversible



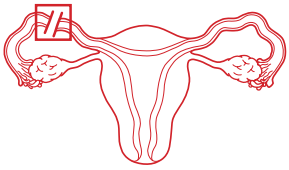
Implant



Intrauterine Device

Permanent

Male Sterilization



Female Sterilization

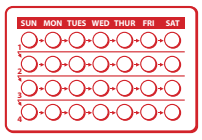
How to make your method most effective

After procedure, little or nothing to do or remember.

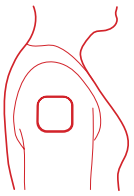
Vasectomy: Use another method for first 3 months.

6-12 pregnancies per 100 women in one year

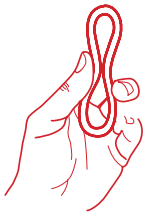
Injectable



Pill



Patch



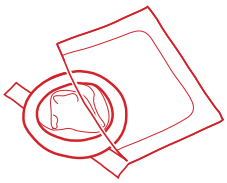
Ring

Diaphragm

Injectable: Get repeat injections on time.

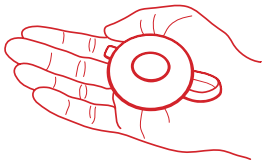
Pills: Take a pill each day. Patch, Ring: Keep in place, change on time.

Diaphragm: Use correctly every time you have sex

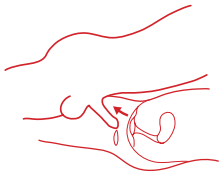


Male Condom

Female Condom



Sponge

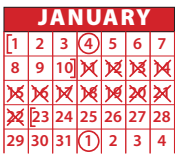


Withdrawal

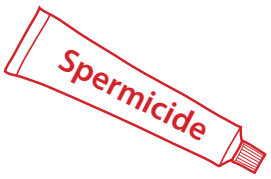
Condoms, sponge, withdrawal, spermicides: Use correctly every time you have sex.

Fertility awareness-based methods: Abstain or use condoms on fertile days. Newest methods (Standard Days Method and TwoDay Method) may be the easiest to use and consequently more effective

18 or more pregnancies per 100 women in one year



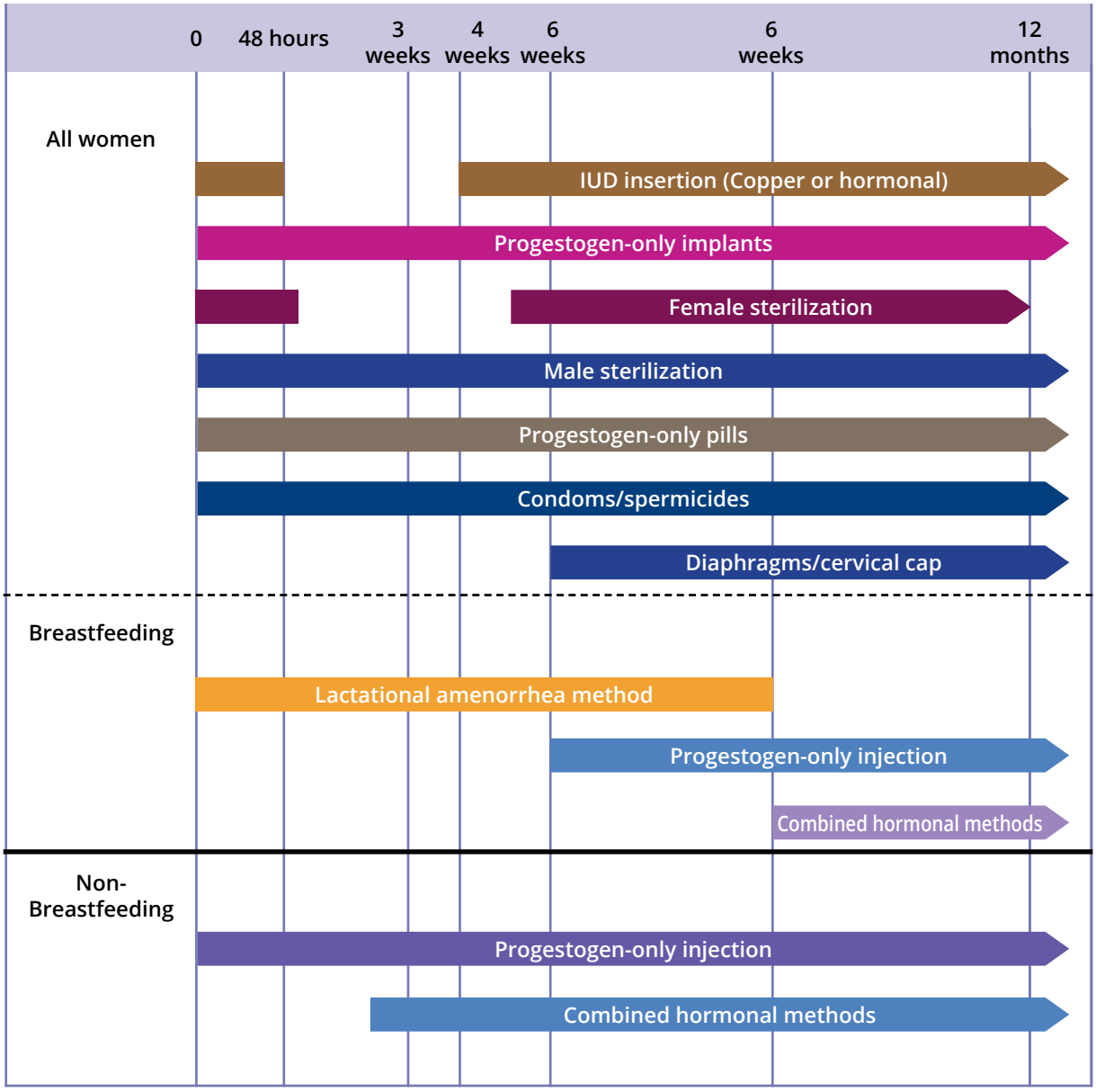
Fertility-Awareness Based Methods



Spermicide

Less effective

World Health Organization (WHO) Department of Reproductive Health and Research, Johns Hopkins Bloomberg School of Public Health/Center for Communication Programs (CCP). Knowledge for health project. Family planning: a global handbook for providers (2011 update). Baltimore, MD; Geneva, Switzerland: CCP and WHO; 2011; and Trussell J. Contraceptive failure in the United States. Contraception 2011;83:397–404.


0
48 hours
3 weeks
4 weeks
6 weeks
6 weeks
12 months
All women
IUD insertion (Copper or hormonal)
Progestogen-only implants
Female sterilization
Male sterilization
Progestogen-only pills
Condoms/spermicides
Diaphragms/cervical cap
Breastfeeding
Lactational amenorrhea method
Progestogen-only injection
Combined hormonal methods
Non-Breastfeeding
Progestogen-only injection
Combined hormonal methods

PREFACE

Preterm labour is the labor that starts before 37 weeks' of gestation. It is an important problem in obstetrics that affects 23% of pregnancies in India. It is considered as one of the most important risk factors for neonatal morbidity and mortality.

Preterm labour is a multifactorial problem and it's most common causes include ascending infection, multiple gestations, polyhydramnios, and uterine developmental malformations. Although the improved ability of obstetric care providers to identify pregnant women at risk for preterm delivery has increased, the overall incidence of preterm birth has remained unchanged for the past 30 years.

Among the various risk factors such as nutritional status, chronic diseases, and intrauterine malformation contributing to preterm labour, the strongest ones are multiple pregnancies and previous incidence of preterm delivery. In order to identify asymptomatic women at the risk of preterm delivery, cervical length assessment has been recommended to be performed in the second trimester of pregnancy. For a gynaecologist, knowledge of the molecular mechanisms responsible for the process of preterm labour and its early diagnosis is important. With a thorough review of the literature assessing the causes and consequences of preterm labour, FOGSI presents the following algorithm of diagnostic approach and possible preventive measures that provide a framework to improve the outcomes of preterm delivery.

Best wishes!

Dr. Nandita Palshetkar

MD, FCPS, FICOG
President 2019 - Federation of Obstetrics & Gynecological Societies of India (FOGSI)

PRETERM LABOUR

FOGSI President : Dr. Nandita Palshetkar

Moderators : Dr. Tushar Kar

Dr. Ameya Purandare

Co-ordinators : Dr. Jiteeka Thakkar

Panelists : Dr. Pratik Tambe, Dr. Vaishali Chavan, Dr. Selvapriya S, Dr. Sareena Gilvaz, Dr. Jeyarani Kamaraj, Dr. Ambujam K, Dr. Joshy Joseph N

From left to right: ***Standing*** **–** Standing - Dr. Joshy Joseph N, Dr. Vaishali Chavan, Dr. Pratik Tambe, Dr. Ambujam K, Dr. Nandita Palshetkar, Dr. Tushar Kar, Dr. Jeyarani Kamraj, Dr. Ameya Purandare,
Sitting **–** Dr. Sareena Gilvaz, Dr. Jiteeka Thakkar, Dr. Selvapriya

Background, scope, and extent

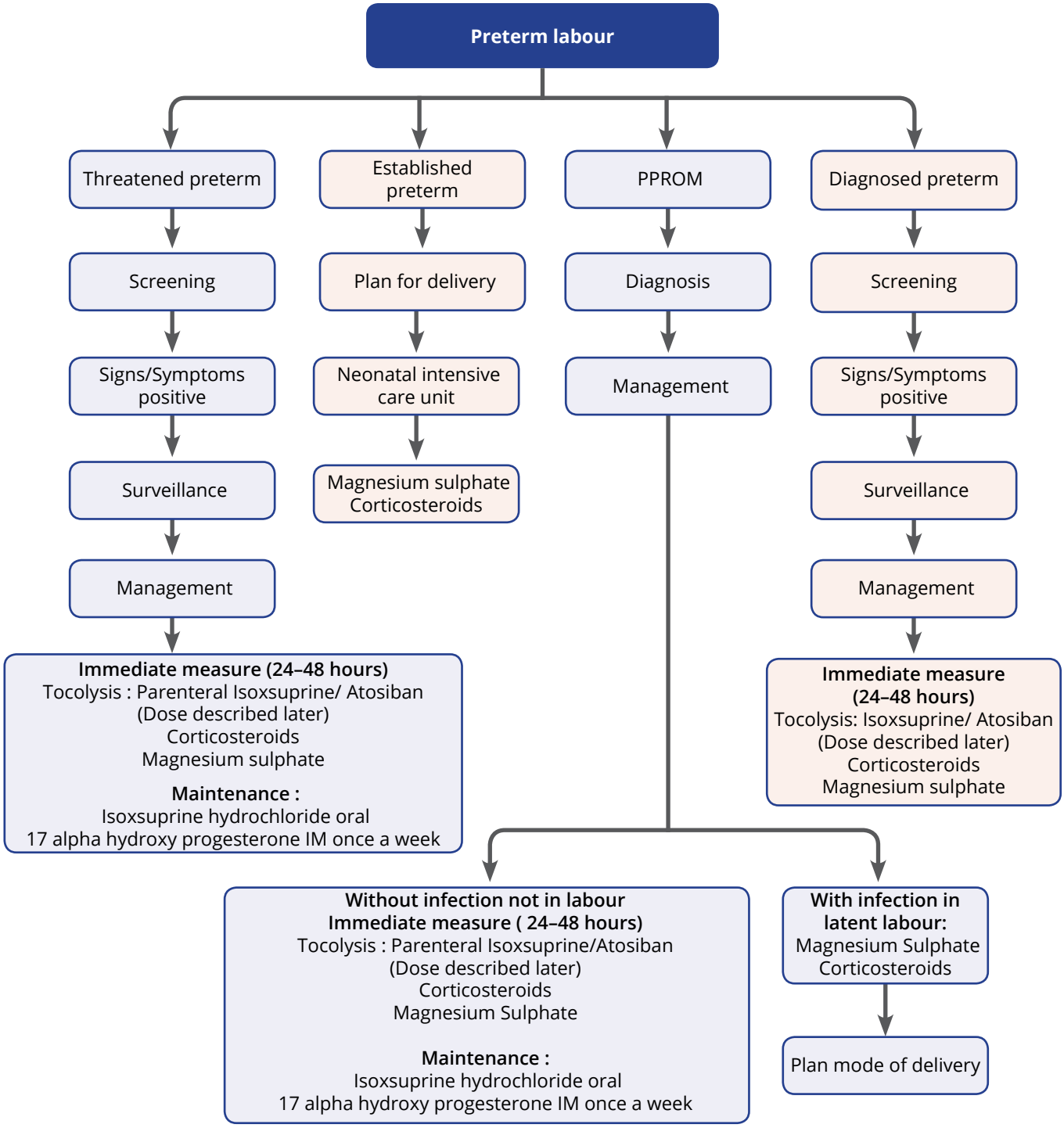
- Prevalence of preterm labour in India is 23.3%.[1]
- Over 35,00,000 annual preterm births in India.[2]
- Highest incidence in the world.

Definition of diagnosed, threatened and established preterm labour

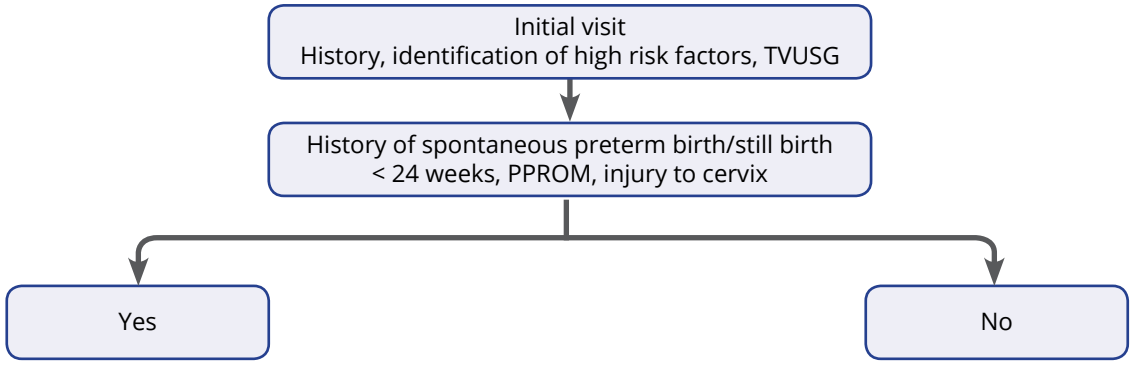
- Preterm is defined as babies born alive before 37 weeks of pregnancy are completed.[3]

Subcategory

- Extremely preterm: Less than 28 weeks.
- Very preterm: 28–32 weeks.
- Late preterm: 32–37 weeks.
- 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 more than 4 cm.[4]

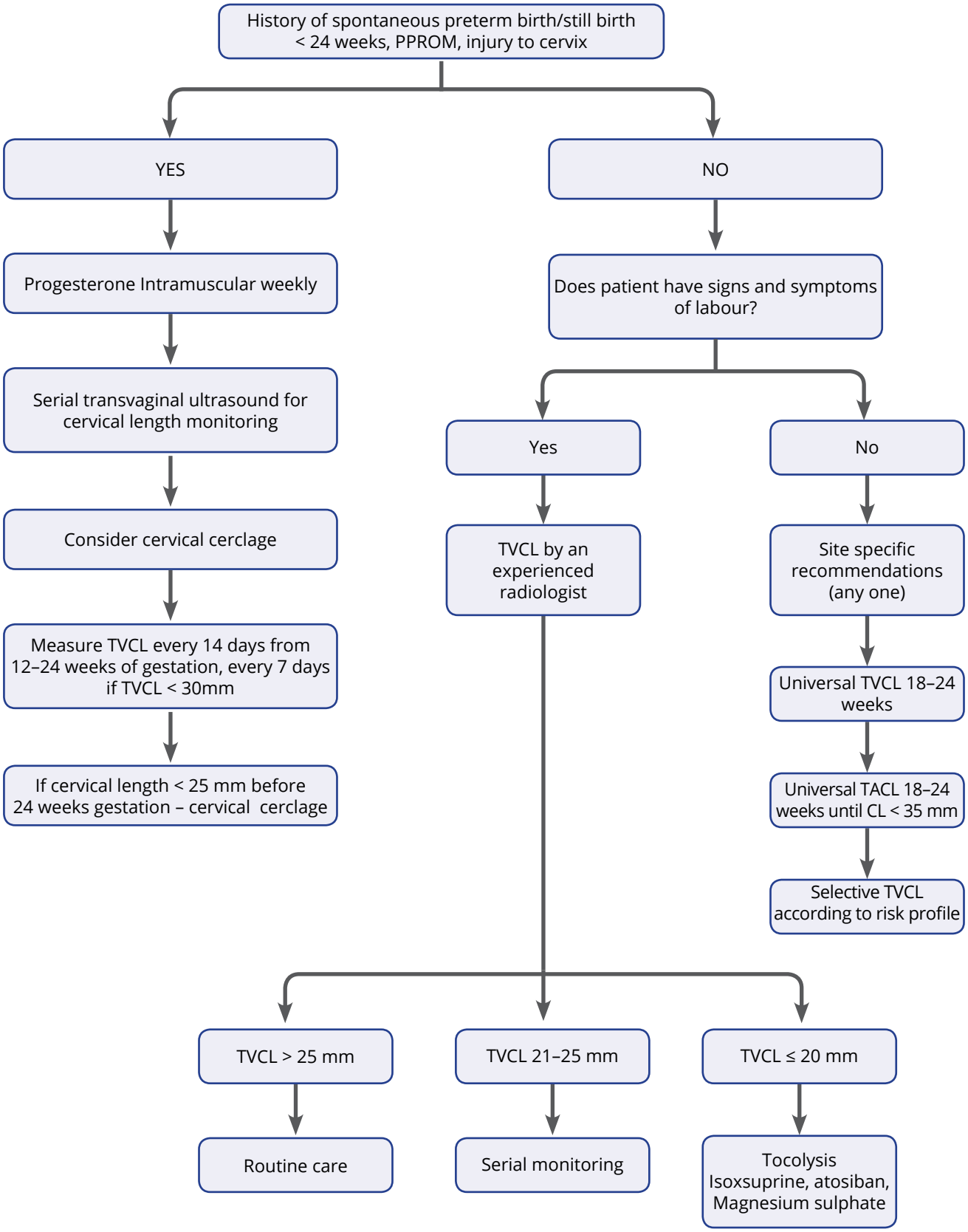


Algorithm for diagnosis and surveillance



PPROM: Preterm premature rupture of the membranes; TVUSG: Transvaginal ultrasound

Algorithm for further management



TVCL: Transvaginal cervical length; TACL: Transabdominal cervical length; CL: Cervical length; PPROM: Preterm premature rupture of the membranes.

Definition of preterm labour

- Defined as labour after 24 weeks gestation and before 37 weeks gestation.[5]

Recommendation: In Indian context

- Labour between 20 and 37 weeks of gestation.
- Medical Termination of Pregnancy Act covers abortion upto 20 weeks,[6] whereas in the UK, cut-off is 24 weeks.

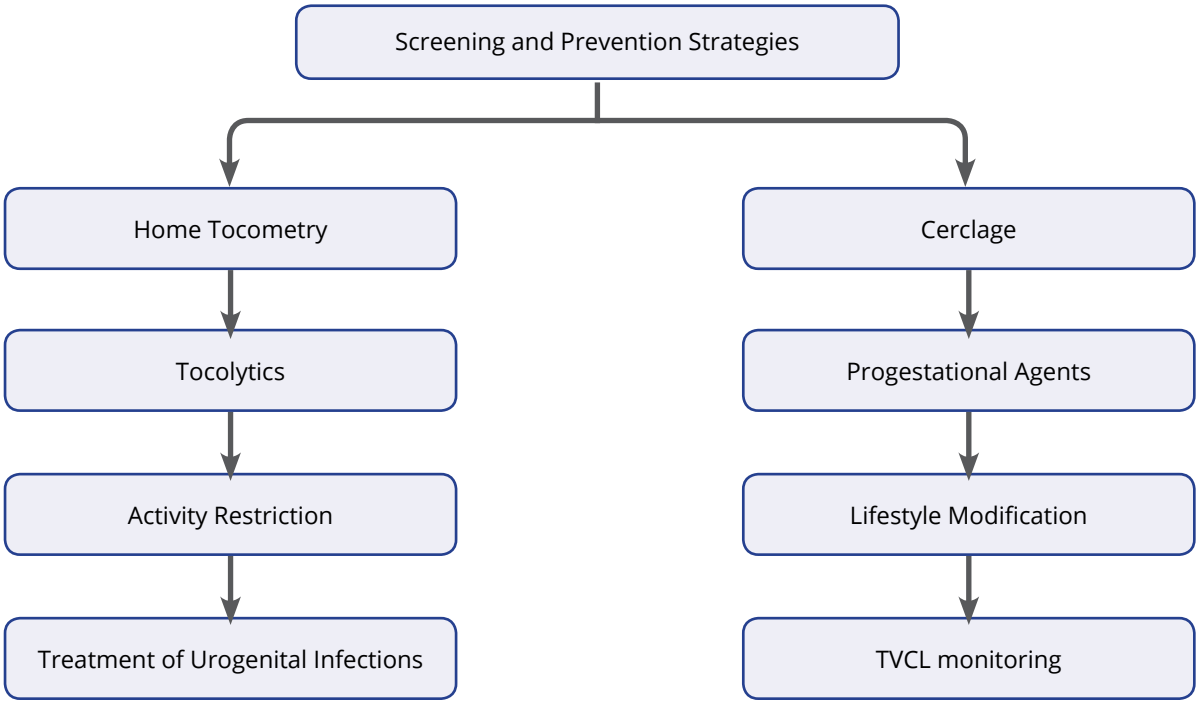
Screening

History	Modifiable risk factors
	Non–modifiable risk factors
Based on cervical length	Ultrasonography for cervical length
Per speculum examination/vaginal examination	Screening for vaginal infections and bacterial vaginosis

Risk factors for spontaneous preterm birth

Modifiable risk factors for spontaneous preterm birth[7]	
• Cigarette smoking • Illicit drug use • Anemia • Bacteriuria/urinary tract infection • Gingival disease • Strenuous work/work environment	Lower genital tract infections (including bacterial vaginosis, *Neisseria gonorrhoea*, *Chlamydia trachomatis*, Group B *Streptococcus*, *Ureaplasma urealyticum*, and *Trichomonas vaginalis*)
Non-modifiable risk factors for spontaneous preterm birth[7]	
• Prior preterm birth • Age <18 years or >40 years • Poor nutrition • Low prepregnancy weight • Low socioeconomic status • Absent prenatal care	• Cervical injury or anomaly • Uterine anomaly • Excessive uterine activity (?) • Premature cervical dilatation (<2 cm) or effacement (> 80%) • Overdistended uterus (twins, polyhydramnios) • Vaginal bleeding

Screening and prevention strategies



TACL: Transabdominal cervical length.

Utility of prevention strategies

Strategies that have limited or no proven efficacy
• Bed rest • Pelvic rest (avoidance of intercourse) • Intensive education and prenatal care • Screening and treatment of asymptomatic lower genital tract infections • Treatment of gingival disease • Empirical broad-spectrum antibiotic therapy
Strategies that may have some benefit
• Prevention and early diagnosis of sexually transmitted and genitourinary infections • Treatment of symptomatic lower genital tract infection • Cessation of smoking and illicit substance use • Prevention of multiple pregnancies • Elective (prophylactic) cervical cerclage, if indicated • Folic acid supplementation

Referral for cervical length screening

Women with a singleton pregnancy who can be offered referral for a single cervical length between 16–24 weeks gestation are:[8]

- Women with a history of mid-trimester loss or preterm birth between 16–34 weeks gestation.
- Women with a history of preterm prelabour rupture of membranes in a previous pregnancy.
- Women with a previous large loop excision of the transformation zone (LLETZ) of >10mm depth.

Who to offer screening

- Low risk population Suggested (as a part of Universal Screening)
- High risk population Recommended

When to offer screening

RCOG recommends 16–24 weeks.[5]

However, in high-risk populations it can be performed during the first trimester anomaly scan.

Universal cut-off for cervical length

- Transvaginal route: Recommended
- Cervical length: ≤ 25 mm[9]

Outcome of screening

- If an ultrasound shows a cervical length <25 mm the woman should have a discussion with her consultant about the risks and benefits of vaginal progesterone, cervical cerclage, or expectant management.[10]

Other screening tests

- Litmus paper test/nitrazine paper test
- Fetal fibronectin (fFN) levels[11,12]

fFN Level	N (%)	≤ 7 days	≤ 14 days	≤ 34 days
< 10 ng/ml	170 (57%)	1%	1.8%	1.5%
11–49 ng/ml	62 (21%)	0%	1.6%	8.2%
50–199 ng/ml	41 (14%)	0%	7.7%	11.5%
200–499 ng/ml	14 (5%)	14%	29%	33%
≥500 ng/ml	13 (4%)	38%	46%	75%

Fetal fibronectin levels

- Negative predictive value is excellent.
- Negative test implies negligible risk of preterm birth in next 7 days.
- Positive predictive values is equally good and levels > 200 should be used as a cut off for antenatal corticosteroids and in utero transfer.

Role of tocolysis[13]

- Administer corticosteroids to enhance pulmonary maturity.
- Reduce the severity of fetal respiratory distress syndrome.
- To reduce the risk of intraventricular hemorrhage.
- Facilitate transfer of the patient to a tertiary care center with NICU facilities.

Isoxsuprine

- First-line therapy according to American College of Obstetricians and Gynecologists (ACOG) recommendations.[14]
- Central Drugs Standard Control Organisation (CDSCO) approved drug in PTL.[14]
- IV infusion – 4 ampoules in 500 ml 5% dextrose/RL.
- Start with 08–10 drops per min, increase 8 drops every 15 min till the uterus become quiet.
- Maximum dose should not exceed more than 40 drops.
- Monitor the BP.
- Dose can be titrated as per the response of the patient.

IM injections	**Oral**
• Administered at the onset of premature labour, only if facilities for IV administration are not available and continued until control is obtained on symptoms of preterm labour • Dose is 10 mg every 1–2 hours	• Oral administration of isoxsuprine should be subsequent to IV or IM administration provided uterine activity has completely subsided • 60 to 80 mg daily in divided doses is the usual maintenance dose

Maintenance therapy of isoxsuprine hydrochloride

- Indian evidence suggests that isoxsuprine is superior with regards to maternal and fetal outcome when administered in appropriate doses.[1]

Evidence 1

- Jaju et al (Dec 2017), in a recently concluded study in Indian patients, reported that patients receiving oral dose of isoxsuprine with a maximum daily dose of up to 40 mg for an average of 23 days had a mean latency period of 37 days. Significant improvement in prolongation of delivery beyond 48 hours and perinatal outcomes were also noted amongst these patients on isoxsuprine versus other pharmacological agents.[14]

Evidence 2

- In study reported by V.K. Singh et al, isoxsuprine was initially administered intravenously, which was followed by maintenance oral therapy till 37 weeks of gestation. In this study, the mean latency period reported was 28 days, maximum being 70 days.[1]

Evidence 3

- Efficacy and safety of isoxsuprine hydrochloride as uterine relaxant in preterm labor - A prospective, open-label, non-comparative study- 2018 [presented as a poster in COGI (The Multidisciplinary Gynecology Congress, Controversies in Obstetrics, Gynecology & Infertility), London] isoxsuprine hydrochloride was continued till delivery/37 weeks of gestation.[16]
- Total latency period was 58.5±18.5 days.

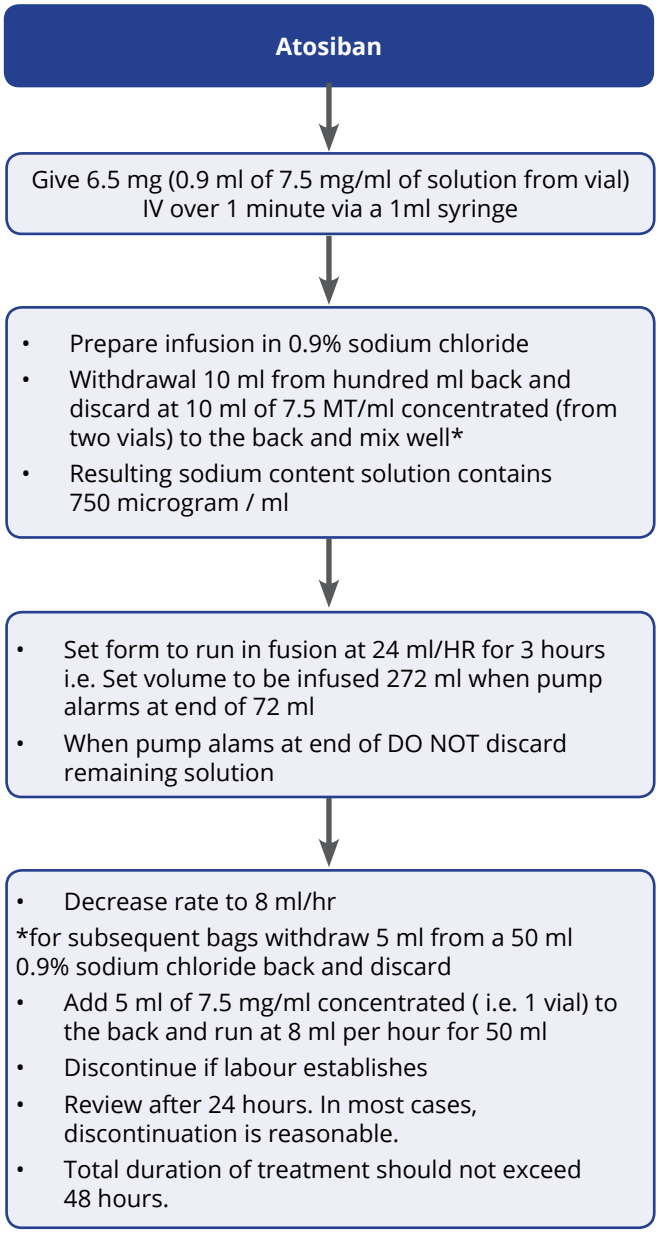
Evidence 4

- Comparison of isoxsuprine 10 mg and 40 mg for the management of preterm mothers: A prospective study.
- According to Dr. M Kavitha et al, the mean duration of prolongation of pregnancy in 10 mg group was 4 days and in 40 mg group was 15 days.[1]

Recent studies

Recent Indian studies have shown encouraging results when it was used in maintenance after the arrest of preterm labour, however clinician should decide the duration of therapy based on patients response.

Atosiban


Atosiban
Give 6.5 mg (0.9 ml of 7.5 mg/ml of solution from vial) IV over 1 minute via a 1ml syringe
• Prepare infusion in 0.9% sodium chloride
• Withdrawal 10 ml from hundred ml back and discard at 10 ml of 7.5 MT/ml concentrated (from two vials) to the back and mix well*
• Resulting sodium content solution contains 750 microgram / ml
• Set form to run in fusion at 24 ml/HR for 3 hours i.e. Set volume to be infused 272 ml when pump alarms at end of 72 ml
• When pump alams at end of DO NOT discard remaining solution
• Decrease rate to 8 ml/hr
*for subsequent bags withdraw 5 ml from a 50 ml 0.9% sodium chloride back and discard
• Add 5 ml of 7.5 mg/ml concentrated (i.e. 1 vial) to the back and run at 8 ml per hour for 50 ml
• Discontinue if labour establishes
• Review after 24 hours. In most cases, discontinuation is reasonable.
• Total duration of treatment should not exceed 48 hours.

Off label drugs used in the management of PTL

Some of the off label drugs used in preterm in India includes nifedipine, indomethacin, nitric oxide donors. Even though Western guidelines mentioned these agents in management of preterm labour in India, CDSCO has not approved its usage.

Neuroprotective agents

Magnesium sulphate

- Confers neuroprotection to the neonate and is used for this benefit.
- Offer intravenous magnesium sulphate for neuroprotection of the baby to women between 24+0 and 29+6 weeks of pregnancy who are:[4]
  - » in established preterm labour or
  - » having a planned preterm birth within 24 hours.

Dosage regime[18]

- A loading dose of 4 g (8 ml of 50% magnesium sulphate), diluted with 12 ml of saline 0.9% (total 20 ml), is given IV over 5–10 minutes using a 20 ml syringe.
- A maintenance dose of 10 g (20 ml magnesium sulphate), diluted with 30 ml of saline 0.9% (total 50 ml) is set up to deliver 1 gram per hour (5 ml/hr) using a syringe driver, until delivery.
- If delivery is imminent it is appropriate to give only the loading dose.
- For a planned lower segment Caesarean section delivery start the regime 4 hours prior to expected delivery time.

Role of prophylactic cervical cerclage

- Consider prophylactic cervical cerclage for women in whom a transvaginal ultrasound scan has been carried out between 16–24 weeks of pregnancy that reveals a cervical length of less than 25 mm and who have either:[4]
  - » Had preterm prelabour rupture of membranes in a previous pregnancy or
  - » A history of cervical trauma.

Progesterone

- Indications: Short cervix on transvaginal ultrasound.
- 17-OH-progesterone 250 mg IM once weekly is recommended in high-risk preterm labour.[7]

Maternal antenatal corticosteroids

- For women between 23+0 and 23+6 weeks of pregnancy who are in suspected or established preterm labour, are having a planned preterm birth or have PPROM discuss with the woman (and her family members or carers as appropriate) the use of maternal corticosteroids in the context of her individual circumstances.[4]

- Consider maternal antenatal corticosteroids 24+0 and 25+6 weeks of pregnancy who are in suspected or established, or having a planned preterm birth or have PPROM.

- Offer maternal antenatal corticosteroids 26+0 and 33+6 weeks of pregnancy who are in suspected or established preterm labour, are having a planned preterm birth or have PPROM.[4]

Choice of agent

- Dexamethasone or betamethasone either can be used.
- Dosages : Dexamethasone/Betamethasone 12mg IM, two doses, 24 hours apart should be administered.[19]
- Do not routinely offer repeat courses of maternal corticosteroids, but take into account:
  - The interval since the end of last course
  - Gestational age
  - The likelihood of birth within 48 hours.

Antibiotics in preterm labour/PPROM

Should antibiotics be given?

Recommendation	Evidence Quality	Strength	Notes
Erythromycin should be given to 10 days following the diagnosis PPROM, or until the woman is in established labour (whichever is sooner)	1+	A	A Cochrane review found benefits when antibiotics administered: reduced chorioamnionitis, prolonged latency, and improved neonatal outcomes.[20]

- Ideal agent is penicillin if patient is allergic to erythromycin
- Co-amoxiclav is not recommended owing to its association with NEC

When do we plan delivery?

When is the appropriate time to deliver the baby?

Recommendation	Evidence Quality	Strength	Notes
Women in whom pregnancy is complicated by PPROM and who have no contraindications to continuing the pregnancy should be offered expectant management coma as this is associated with better outcomes compared with early birth	1+	A	A cochrane review found clear benefits from expectant management, rather than early delivery, following PPROM[21]
Early delivery may be preferable when PPROM occurs beyond 34+0 weeks of of gestation in women known to be colonized with group B streptococcus	4	D	RCOG Green-top Guideline No. 36.29[2]

RCOG: Royal College of Obstetricians and Gynaecologists; PPROM: Preterm premature rupture of the membranes.

Which is the preferred route of delivery?

- Discuss the general benefits and risks of caesarean section and vaginal birth with women in suspected, diagnosed or established preterm labour and women with P-PROM (and their family members or carers as appropriate).

What are the options if there is a malpresentation?

- Consider caesarean section for women presenting in suspected, diagnosed or established preterm labour between 26+0 and 36+6 weeks of pregnancy with breech presentation.

How do we monitor the fetus in labour?

Discuss with the woman

- The purpose of fetal monitoring and what it involves.
- The clinical decisions it informs at different gestational ages.
- Continuous FHR monitoring should ideally be performed.

Delivery considerations

- Aim for atraumatic delivery
- Avoid ventouse
- Obstetric forceps if indicated
- Neonatologist present
- Early transfer to NICU after stabilization

Are there any specific do's and don'ts for cord clamping?

If a preterm baby needs to be moved away from the mother for resuscitation, or there is significant maternal bleeding:

- Consider milking the cord.
- Clamp the cord as soon as possible.
- Wait at least 30 seconds, but no longer than 3 minutes, before clamping the cord of preterm babies, if the mother and baby are stable.
- Position the baby at or below the level of the placenta before clamping the cord.
- Keep the cord length long for subsequent access.

Conclusion

- Preterm labor is an improtant factor for neonatal morbidity and mortality.
- Early screening should be done to prevent preterm labour.
- Antenatal corticosteroids are recomended to reduce neonatal morbidity and mortality.
- Tocolytics have been found to be useful in delaying preterm labour.
- Only Isoxsuprine and Atosiban are approved by CDSCO in the management of pretem labour, however in Indian context isoxsuprine should be considered as it is economical and proven to be efficacious.
- Beta-adrenergic receptor agonists, isoxsuprine, has been approved by Drug Controller General of India (DCGI) for use in preterm labor in Indian women recent studies have shown its benefit in maintenance, however clinician should decide it based on the response of the patient.

- Magnesium sulphate should be used as neuroprotective.
- Erythromycin should be given for 10 days following the diagnosis PPROM, or until the woman is in established labour (whichever is sooner).

References

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