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THE MUMBAI OBSTETRIC & GYNECOLOGICAL SOCIETY

MOGS MEDIA

VOL 8 | SPECIAL SITUATIONS IN OBS GYN

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President's Message

Dear Colleagues,
It gives me great pleasure to bring to you the eighth and final edition of the **'MOGS MEDIA'** newsletter.. In this series of focussed newsletters through the year, we have brought to you important subjects discussed in detail with all the latest updates. This edition is focussed on the important issue of **'Special Situations in Obs Gyn'.** Though his pandemic has totally changed our lives and the way we practise, obstetric problems continue the same way as before and it is important for us to remain updated. The editor Dr Pratik Tambe and all the contributors have made a lot of effort to bring you the latest information on the subject and we are thankful to them.

This year has been unique, eventful and we have had to innovate at every step. We have worked really hard to bring you the latest academic updates in different creative ways like webinars, Pearls of Wisdom, digital newsletters and of course blended it with fun contests, MOGS Masti and 'Fit is It' activities. We have had very attended CMEs on contraception, Fetal medicine, vaccines, infertility, endocrinology and much more. The huge conference along with ICOG on NCDs was a big success.

Our digital PG training programmes which have hundreds of young doctors tuning in and the intensive Post graduate training course have been much appreciated by exam going students.

MOGS V Care & share programme which was started by us in this COVID pandemic, to support our frontline workers and the women whose health we look after, is going very well. This time we celebrated Holi by sending colourful care packages along with gulal to ANC and PNC patients in BMC and government hospitals in Mumbai.

Our much awaited Annual Conference, Gynaecology Obstetrics Techniques, Technologies and Therapeutics-GOTTT is being held on a a digital platform from 9th to 11th April 2021. It will be an academically enriching event full of fun and surprises and prizes. The Final round of the MOGS personality of the year contest will be held on 9th April. So do join us for this mega event.

Do visit our website for updates **www.mogsonline.org**
Thank you once again for all your support over the years.
Stay safe, Stay healthy.

Best wishes.
Dr Rishma Dhillon Pai

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MOGS V Care & Share

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Editors' message

Dear MOGS members,

The MOGS Media series of news letters have been one of the highlights of the MOGS year so far. The newsletter is the med on areas of practical interest with individual topics having relevance in day-to-day practice for practising obstetricians and gynaecologists. The previous seven issues on **Preterm Birth, Anaemia and Nutrition in Pregnancy, Optimising IUI Results, Endometriosis, PCOS, Premature Ovarian Insufficiency** and **COVID-19** were well received and widely appreciated by readers throughout the country.

It is with great pride that we bring you the eighth issue **"Special Situations in Obs Gyn"**, which focuses on areas where modern therapeutics has been able to offer significant improvements. A galaxy of eminent senior stalwarts has authored the articles contained in this volume and we thank them for their contributions.

We thank the MOGS President Dr Rishma Dhillon Pai and the office bearers for giving us the opportunity to be part of such an innovative, important and immensely practical initiative. We hope you enjoy reading the articles and find them useful. We would welcome any comments or suggestions regarding the same and encourage you to reach out to us with feedback.

Wishing you, your families and staff good health and safety in these difficult times!

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Management of Rh Sensitised Pregnancy

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Introduction

The antigens which are present on the human red blood cells (RBCs) are mainly ABO antigens (A, B, AB), rhesus D antigen (Rh-D) and infrequently other atypical rhesus (Rh) antigens like Cc, Ee, Kell (K), Duffy (Fy^a), Kidd (Jk^a, JK^b), M and S. The presence of particular antigens on RBCs confers an individual a specific blood group status. Alloimmunisation refers to an immunologic reaction against foreign antigens that are distinct from antigens on an individual's cells. In this case, it refers to the maternal formation of antibodies against fetal Rh D. The important Rh antigen responsible for majority of cases of severe Rh alloimmunisation is Rhesus D antigen. The other atypical Rh antigens with a potential to cause severe alloimmunization are c, E and Kell antigens. Rest of the Rh antigens (Duffy, Kidd, M and S) rarely cause significant problems.[1,6]

The presence of red cell antibodies signifies alloimmunisation that has occurred as a result of previous pregnancy, transfusion or transplantation. Haemolytic disease of the fetus and newborn (HDFN) is a condition in which transplacental passage of maternal immunoglobulin G (IgG) antibodies results in immune haemolysis of fetal/neonatal red cells. Some antibodies (including anti-D, anti-K (-Kell) and anti-c) confer significant fetal and neonatal risks such as anaemia requiring intrauterine or neonatal transfusion, jaundice or perinatal loss.

Anti-D is the most commonly encountered antibody during pregnancy. Before routine antenatal anti-D prophylaxis, late immunisation during a first pregnancy was responsible for 18–27% of cases.[2]

Screening for Rh alloimmunisation

Blood grouping and cross matching is performed in all pregnant women at the first visit. If the woman is Rh-D positive no further testing for blood groups is required. When the expectant mother is Rh negative, the husband's blood is tested for ABO grouping and Rh typing. If the husband is Rh positive, virtually all guidelines recommend performing genotype of the father for Rh-D coding gene.[2,3,6]

A homozygous father will transmit Rh-D gene to all his offspring and all pregnancies will have potential for sensitisation. If the father is heterozygous, there is a 50% chance of the fetus being Rh-D positive. Most of the western guidelines recommend finding the fetal blood group from circulating cell free fetal DNA in maternal blood.[7]

When the fetus is Rh-D negative no further testing required. If fetus is Rh-D positive, further follow- up is done. However in India, facilities for testing the zygosity for Rh-D gene and fetal blood group from circulating cell-free fetal DNA in maternal circulation are available in only a few centres. Therefore, when the mother is Rh-D negative and father is Rh-D positive, the pregnancy is considered potentially at risk of immunisation.

A small amount of FMH (total of less than 15 mL) is inevitable during the course of pregnancy. To detect sensitisation of the mother, presence of anti-D antibodies in maternal circulation is usually detected by Indirect Coomb's Test (ICT). Usually, 1:16 or 1:32 is considered as the critical titre (potential to cause significant fetal anaemia) which may vary with the laboratory. When the ICT is negative the test is repeated every 4 weeks and if ICT is positive, mother is managed as sensitised pregnancy.

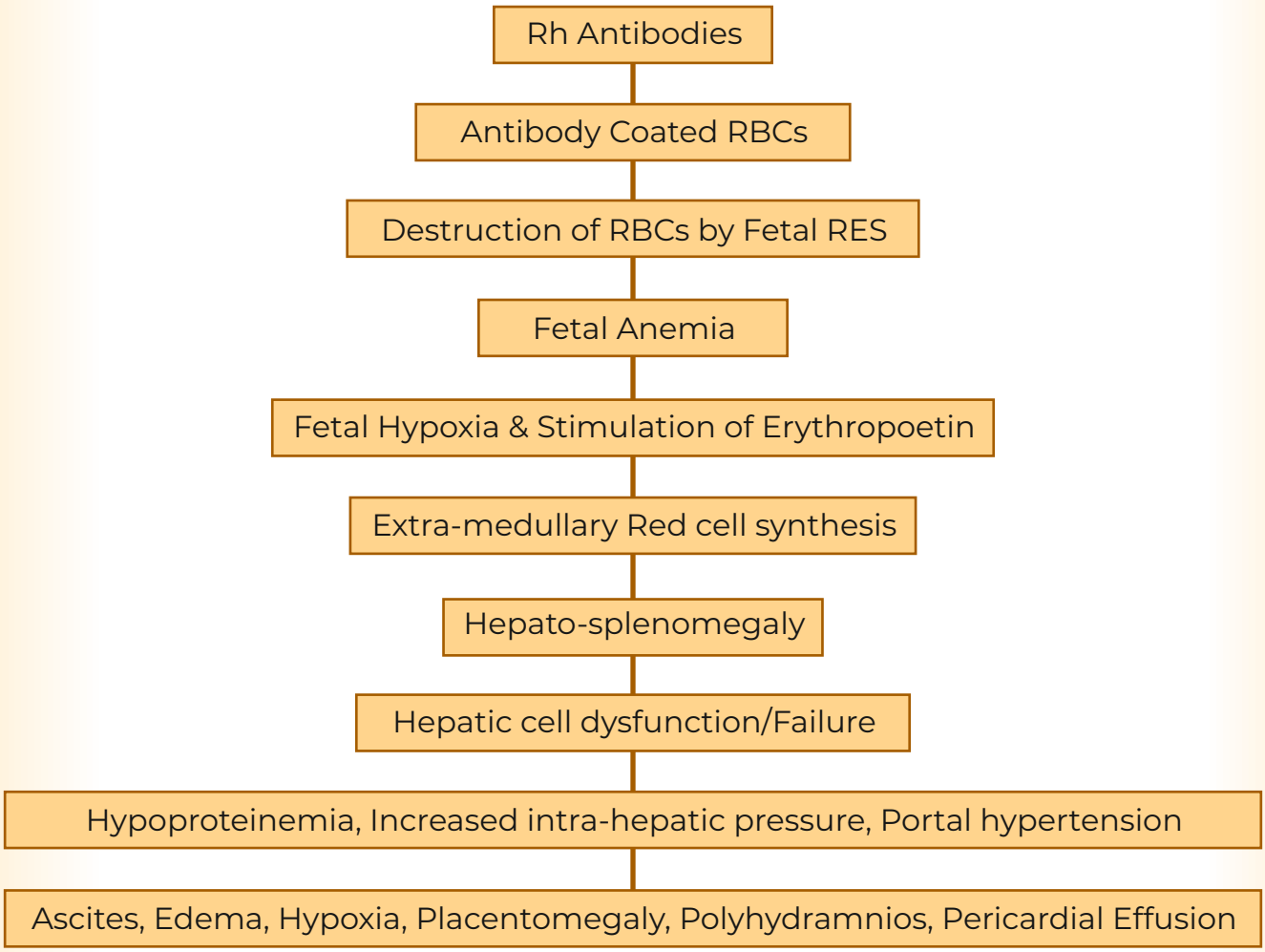


Fig 1 Pathophysiology

Primary prevention

For women who are not yet alloimmunised, the aim is to prevent sensitisation. It can be achieved by giving prophylactic dose of anti-D immunoglobulins to cover for the spontaneous feto maternal hemorrhages and also any antepartum event which has potential to cause additional FMH. If no prophylaxis is given, it is estimated that 1% of Rh-D negative women would develop antibodies by the end of first Rh-D positive pregnancy. Around 7–9% of additional women would be sensitised at the time of delivery. Another 7–9% would develop antibodies during 6 months following delivery. Therefore around 17% women would become sensitised by the second pregnancy.[3]

The most effective strategy to reduce the incidence has been the introduction of antenatal and at birth anti-D prophylaxis. The occurrence of Rh-D sensitisation in the last few weeks of an uncomplicated pregnancy has been stated to be the single most common reason for the remaining cases of alloimmunisation. It may be due to either the inability to cover the potential events causing FMH or inadequate dose of anti-D. Therefore, clear instructions regarding the event-specific doses and timing could almost eliminate this condition. Blood should be properly cross matched before transfusion so as to avoid possibility of alloimmunisation against other minor red cell antigens.

Causes of Rh-D alloimmunisation

This occurs when an Rh D negative woman is exposed to red cells expressing the Rh D antigen. Events such as miscarriage, ectopic pregnancy, antenatal bleeding, and delivery, as well as procedures such as chorionic villus sampling, amniocentesis, pregnancy-related uterine curettage, and surgical treatment of ectopic pregnancy can lead to maternal exposure to fetal red blood cells and, consequently, Rh D alloimmunisation. Between 3-11% of women with threatened abortion in the first trimester and approximately 45% giving birth in the third trimester, have a fetal–maternal haemorrhage. the volume of which can be as small as 0.1 mL or as large as 30 ml.[3]

Table 1 Potentially sensitising events during pregnancy

Amniocentesis, chorion villus biopsy and cordocentesis
Antepartum haemorrhage/ uterine (PV) bleeding in pregnancy
External cephalic version
Abdominal trauma (sharp/ blunt, open/ closed)
Ectopic pregnancy
Evacuation of molar pregnancy
Intrauterine death and stillbirth
In utero therapeutic interventions (transfusion, surgery, insertion of shunts, laser)
Miscarriage, threatened miscarriage
Therapeutic termination of pregnancy
Delivery – normal instrumental or Caesarean section
Intra-operative cell salvage

Antenatal prophylaxis

If ICT is negative at the first visit, it is repeated at four weekly intervals and if it remains negative on subsequent testing, prophylactic dose of anti-D immunoglobulin is given (300 µg deep intramuscularly) at 28–32 week of pregnancy. This will take care of the small amount of FMH and prevent alloimmunisation.[2,3,10]

One dose vs two doses

There are various thoughts regarding the one dose of 300 µg at 28 weeks versus two doses of 100–120 µg each at 28 and 34 weeks. But most guidelines prefer a single dose and have mentioned that the two dose schedule could be used as an alternative regimen.[4]

Potentially sensitising events <12 weeks gestation

In pregnancies <12 weeks gestation, anti-D Ig prophylaxis(minimum dose 250 IU) is only indicated following an ectopic pregnancy, molar pregnancy, therapeutic termination of pregnancy and in some cases of uterine bleeding where this is repeated, heavy or associated with abdominal pain. A test for FMH is not required.[3]

Potentially sensitising events 12-20 weeks gestation

For any potentially sensitising event listed in Table 1, confirmed D negative, previously non-sensitised women should receive a minimum dose of 250 IU anti-D Ig within 72 h of the event. D negative women presenting with continual uterine bleeding between 12-20 weeks gestation should be given at least 250 IU anti-D Ig, at a minimum of 6 weekly intervals.[3]

Potentially sensitising events 20 weeks gestation to term

An FMH test is required to detect fetal cells in the maternal circulation and, if present, to estimate the volume of FMH to allow calculation of additional anti-D doses required to clear the fetal cells. For any potentially sensitising event listed in Table 1, Rh-negative previously non-sensitised women should receive a minimum dose of 500 IU anti-D Ig within 72 h of the event. A minimum of 500 IU anti-D Ig should be administered within 72 h for any potentially sensitising events regardless of whether the woman has already received RAADP at 28 weeks.

Additional dose(s) of anti-D Ig will be necessary if the volume of FMH exceeds that covered by the standard anti-D Ig dose in use. A follow-up blood sample should be taken at 48 h following each IV dose of anti-Dand 72 h following each IM dose of anti-D to check if fetal cells have cleared.

Prophylaxis following birth of an Rh positive child or intrauterine death

Following birth, ABO and Rh D typing should be performed on the cord blood sample and if the baby is confirmed to be D positive; all D negative, previously non-sensitised women should receive at least 500 IU of anti-D Ig within 72 h following delivery. Maternal samples should be tested for FMH and additional dose (s) given as guided by FMH tests.[5]

If there is an intrauterine death (IUD) and hence no sample can be obtained from the baby, prophylactic anti-D Ig should be administered to D-negative, previously non-sensitised women.[8]

A minimum of 500 IU of anti-D Ig should be administered within 72 h following the diagnosis of IUD. Maternal samples should be tested for FMH and additional dose(s) given as guided by FMH tests. It should be noted that the diagnosis of IUD is the sensitising event rather than delivery and hence anti-D Ig should be administered within 72 h of diagnosis.

Management of sensitised pregnancy

In patients who do not have previous losses and are sensitised, Rh antibody titres are monitored monthly till they reach the critical titre for that laboratory. The critical titre for a laboratory is the titre below which no fetal death has been observed. At this juncture, traditionally, it was advised to intervene in the fetus to find out the degree of anemia by amniocentesis or cordocentesis.

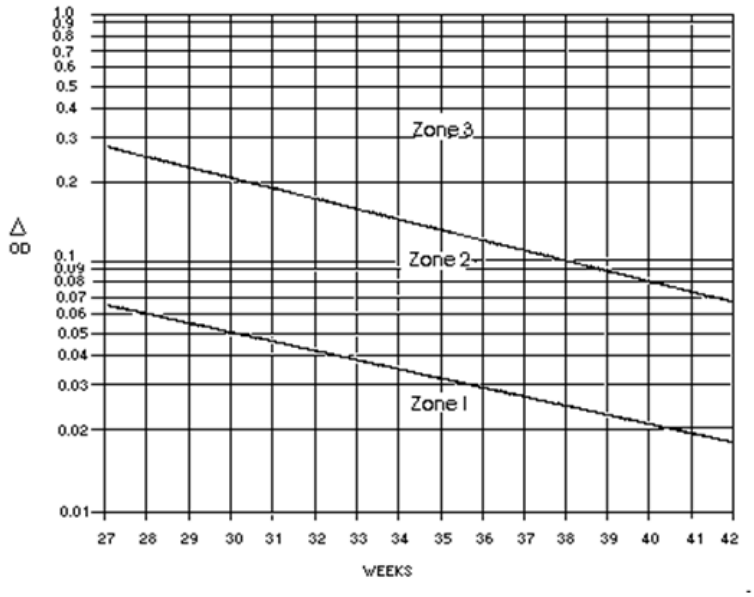


Fig 2 Liley's graph for plotting the ΔOD450 value

After amniocentesis, the amniotic fluid is subjected to spectrophotometry of the amniotic fluid done using a continuously reading spectrophotometer to estimate the change in absorption of light at a wavelength of 450 Angstrom (ΔOD450) which corresponds to the bilirubin level in the amniotic fluid. This reflects the degree of fetal anaemia. The ΔOD450 value is plotted on Liley's graph. If it lies in upper part of intermediate zone or higher, it corresponds to fetal anaemia requiring either delivery or intervention depending upon the gestational age.

With the wider availability of Color Doppler, the patient is monitored by serial Doppler and decision to intervene is taken when the MCA-PSV exceeds 1.5 MOM for the gestational age.

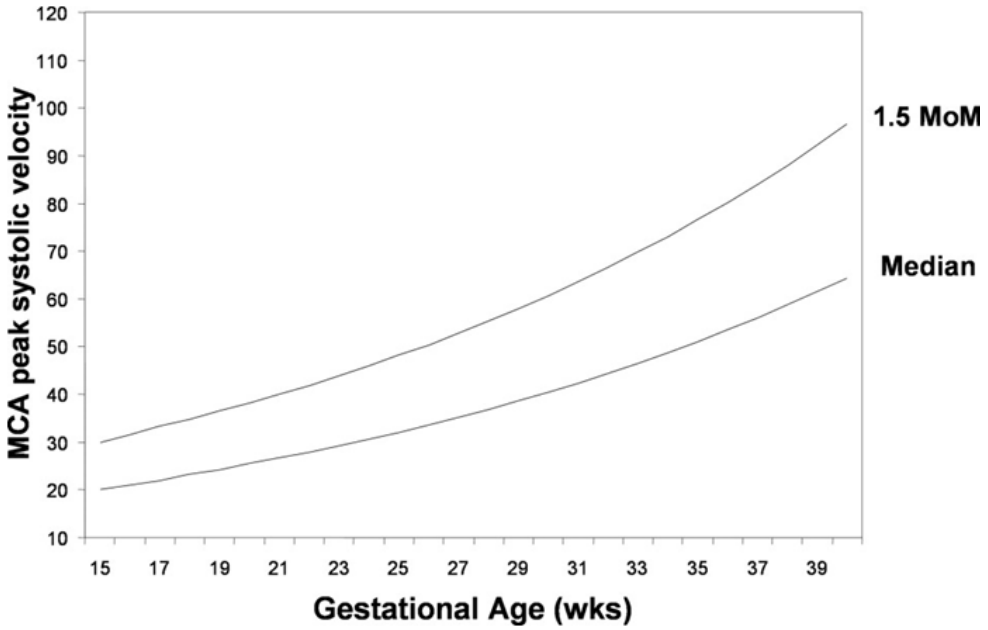


Fig 3 Graph of MCA PSV for gestational age in fetal anaemia (Mari et al)

At times the Rh antibody titers may not reflect the severity of the disease, hence if there is a history of previous losses, amniocentesis or cordocentesis is indicated at an appropriate time to diagnose anemia in the fetus. Cordocentesis will diagnose the blood group and hemoglobin level of the fetus and enable transfusion at the same or different sitting. In severely Rh isoimmunised cases during the early gestational period, percutaneous cord blood sampling can be done the earliest at 18-20 weeks. Conventionally cordocentesis is advised at least 10 weeks prior to the gestation at which the loss occurred in the previous pregnancy, but this may be done earlier if MCA PSV is abnormal.

Role of ultrasound and Doppler in monitoring

If the antibody levels/titres rise beyond the levels detailed above then the pregnancy should be monitored weekly by ultrasound, specifically assessing the fetal middle cerebral artery peak systolic velocities (MCA PSV).[2,6]

Referral to a fetal medicine specialist for consideration of invasive treatment should take place if the MCA PSV rises above the 1.5 multiples of the median (MoM) threshold or if there are other signs of fetal anaemia.

Table 2 Ultrasonographic features of hydrops

Ascites
Pericardial effusion
Hepatomegaly
Splenomegaly 3 to 4 times normal
Intrahepatic portal vein >5 mm
Scalp edema
Polyhydramnios
Placental Thickness >4 cm

If the MCA PSV rises beyond the interventional threshold then referral to a fetal medicine specialist with expertise in IUT should be made. MCA PSV monitoring is predictive of moderate or severe fetal anaemia with 100% sensitivity and a false positive rate of 12%.If monitoring of the MCA indicates anaemia (MCA PSV > 1.5 MoM), fetal blood sampling (FBS) and possibly IUT are indicated. Monitoring with MCA PSV should be used with caution after 36 weeks as its sensitivity for the detection of fetal anaemia decreases. If there are concerns beyond this gestation because of raised MCA PSV, further advice should be sought from a fetal medicine specialist experienced in managing fetal anaemia.

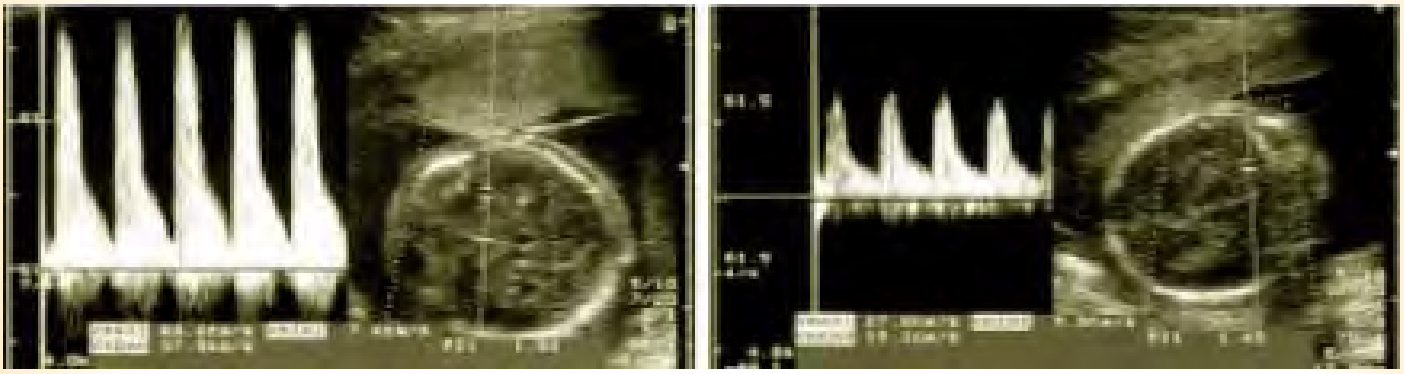
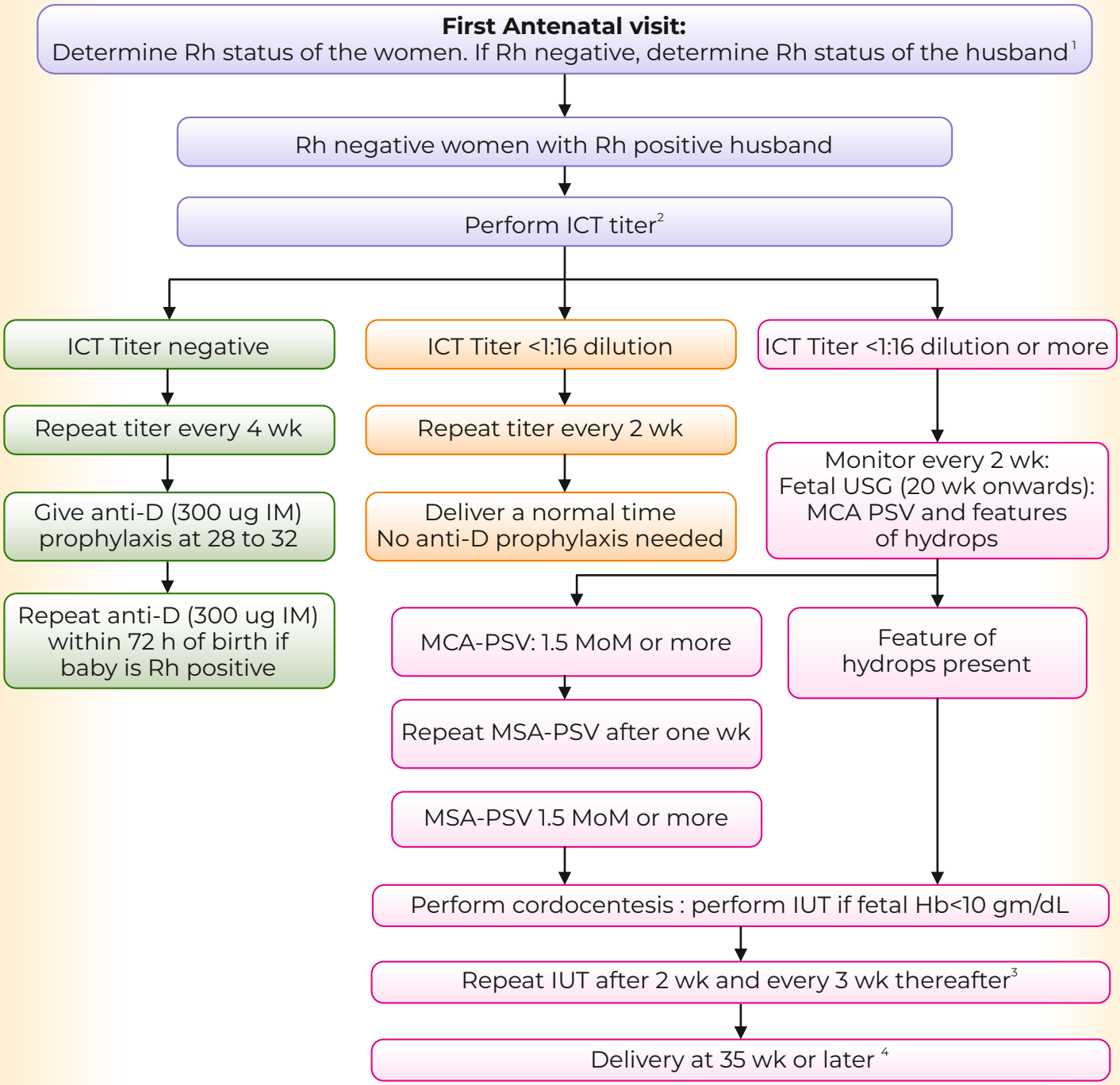


Fig 4 Peak systolic velocimetry in the middle cerebral artery

Intrauterine transfusion

The procedure is carried out under continuous ultrasound guidance with facilities for immediate analysis of the fetal blood haemoglobin and haematocrit. The risks and benefits of IUT should always be discussed with the woman who should be made aware of the consequences of untreated severe fetal anaemia (ie., hydrops, preterm birth, perinatal death, severe neonatal jaundice and kernicterus) as well as the risks of neonatal exchange transfusion.[2]

Red cell preparations for IUT should be group O (low titrehaemolysin) or ABO identical with the fetus (if known) and negative for the antigen(s) corresponding to maternal red cell antibodies. Blood should be IAT (indirect antiglobulin test) cross-match compatible with maternal plasma and negative for the relevant antigen(s) determined by maternal antibody status. K-negative blood is recommended to reduce additional maternal alloimmunisation risks. It should also be less than 5 days old and in citrate phosphate dextrose (CPD) anticoagulant, cytomegalovirus (CMV) seronegative, irradiated and transfused within 24 hours of irradiation. Blood packs should have a haematocrit (packed cell volume, PCV) of 0.70–0.85. Regular assessment of bilirubin and haemoglobin levels should be made and early discharge is not advisable.



1. Rh negative refers to absence of 'D' antigen
2. ICT Titer for anti-D antibodies. Management of isommnization due to non D-Rh antigen remains similar to that of D-Rh antigen (further explained in the text)
3. Once the feal bone marrow is suppressed by initial IUT, repeat IUT generally required every 3 Wk'
4. Give antenatal steroids if delivery is planned before 35 wk

Fig 5 Management algorithm

Postdelivery precautions

The mother should be encouraged to feed the baby regularly to guard against dehydration, since dehydration can increase the severity of jaundice. Clinicians should be aware that if bilirubin levels rise rapidly or above the interventional threshold, phototherapy and/or exchange transfusion may be required. Pregnancies complicated by red cell alloimmunisation with a minimal or no risk of fetal or neonatal anaemia

require no specific treatment. Exchange transfusion may be used to manage severe anaemia at birth and to treat severe hyperbilirubinaemia. Such a transfusion is undertaken with the aims of removing both the antibody-coated red cells and the excess bilirubin.

Future developments

In recent years, advancements infetal blood group genotyping using cell free fetal DNA (cffDNA) from maternal blood samples taken at 16–20 week gestation, have made it possible to determine fetal D type with a diagnostic accuracy of around 96%. Fetal blood group genotype can also be determined for Rh C, c, E and Kell (K)s tatus using cff DNA from maternal plasma.

Conclusion

Successful management requires a team approach with close coordination among the obstetrician, fetal medicine specialist or ultrasonologist and neonatologist as well as excellent laboratory, blood bank and NICU facilities**.**

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Hypothyroidism in Pregnancy

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Introduction

Hypothyroidism is one of the commonest endocrine disorders in women of reproductive age. Women with the severe form of the disease will fail to get pregnant, but women with the less severe form will face the impact of hypothyroidism during pregnancy. Uncontrolled hypothyroidism can adversely affect both maternal as well as fetal outcomes. Prompt diagnosis and treatment of hypothyroidism in pregnancy is important. Subclinical hypothyroidism also needs to be detected and treated to prevent adverse outcomes. Euthyroid women have higher rates of miscarriages when they are thyroid peroxidase antibody (TPO) positive.

Epidemiology

Data on prevalence rates of hypothyroidism in pregnancy is limited in India. Some reports state that it is between4.8-11 %.[1] One study reported 12.4% of thyroid auto immunity in Asian-Indian population. They reported significant association with miscarriages in the same population.[2]

Pathophysiology

During pregnancy, thyroid metabolism is working in three compartments simultaneously influencing the pregnancy outcome. The maternal thyroid, fetal thyroid and placenta have their own hormonal interplay. In addition, transportation of hormones across the placenta needs to be in order. The normal thyroid gland is able to cope up with the extra load and maintain euthyroid state during pregnancy but when thyroid function is compromised, hypothyroidism develops. Common causes of hypothyroidism are autoimmune thyroiditis and iodine deficiency, but very rarely hypothyroidism may result after radioiodine ablation of thyroid while treating hyperthyroidism or thyroid cancer, and after surgery of the thyroid tumors.

Effects of overt hypothyroidism on maternal health

- Infertility
- Higher risk of abortion
- Recurrent pregnancy loss
- Preterm birth
- IUGR
- Gestational hypertension
- Anaemia
- Abruptio placenta
- Postpartum hemorrhage
- Respiratory distress in neonates

The risk of these complications is greater in women with overt and untreated hypothyroidism rather than subclinical hypothyroidism. Subclinical hypothyroidism is associated with adverse outcomes in the presence of TPO antibodies.

Effects of hypothyroidism on the fetus, neonatal life and childhood

- Increased risk of impairment in IQ scores
- Mild defects in global intelligence
- Mild defects in neuropsychological developmental indices and learning abilities
- Women demonstrating Iodine deficiency have greater deficit in global IQ and attention deficit hyperactivity disorder
- Children born of untreated women, and of women with sub optimal supplementation are at higher risk of adverse consequences

The fetus is solely dependent on maternal thyroid hormones till 12 weeks of gestation. It starts producing its own thyroid hormone after 12 weeks and maternal thyroid hormone only partly supplies the fetus thereafter.

Clinical features

Women with subclinical hypothyroidism are usually asymptomatic, or may experience Inappropriate weight gain, cold intolerance dry skin, constipation, fatigue, somnolence. They may exhibit delayed relaxation of deep tendon reflexes. The symptoms are seen more often in overt hypothyroidism.

Diagnosis of hypothyroidism

Overt and subclinical hypothyroidism

It is based on levels of TSH titres. Subclinical hypothyroidism is diagnosed when serum TSH titres are between 2.5-10 mIU/L with normal FT4 concentration. Overt Hypothyroidism is diagnosed when serum TSH is between 2.5-10 mIU/L with low FT4 levels or TSH >10 mIU/L irrespective of FT4 levels.

When the thyroid physiology undergoes alteration in early pregnancy by way of increasing demand and increased secretion of thyroid hormone, the cut-offs used in non-pregnant women will not hold true in pregnancy. The diagnosis is based on the gestation specific reference ranges of TSH.

As per ATA 2011, the normal reference range recommended is 0.1-2.5 in first trimester, 0.2-3.0 in the second trimester and 0.3-3.0 in the third trimester.[3] The Endocrinology society guidelines, 2012 also suggested the same reference range.[4] However, ATA revised their recommendations in 2017.[5]

The larger analysis of more than 60,000 patients in ATA guidance 2017, demonstrated substantial population differences in the TSH upper reference limit and these differences were attributable to differences in the iodine status between populations as well as the TSH assays used for analysis. They recommended that the first trimester upper limit or cut-off for normal should be obtained by deducting. 5 mIU/L from pre-pregnancy TSH value. In case it is not known, then 4.0 mIU/L should be taken as upper limit of normal cut-off.

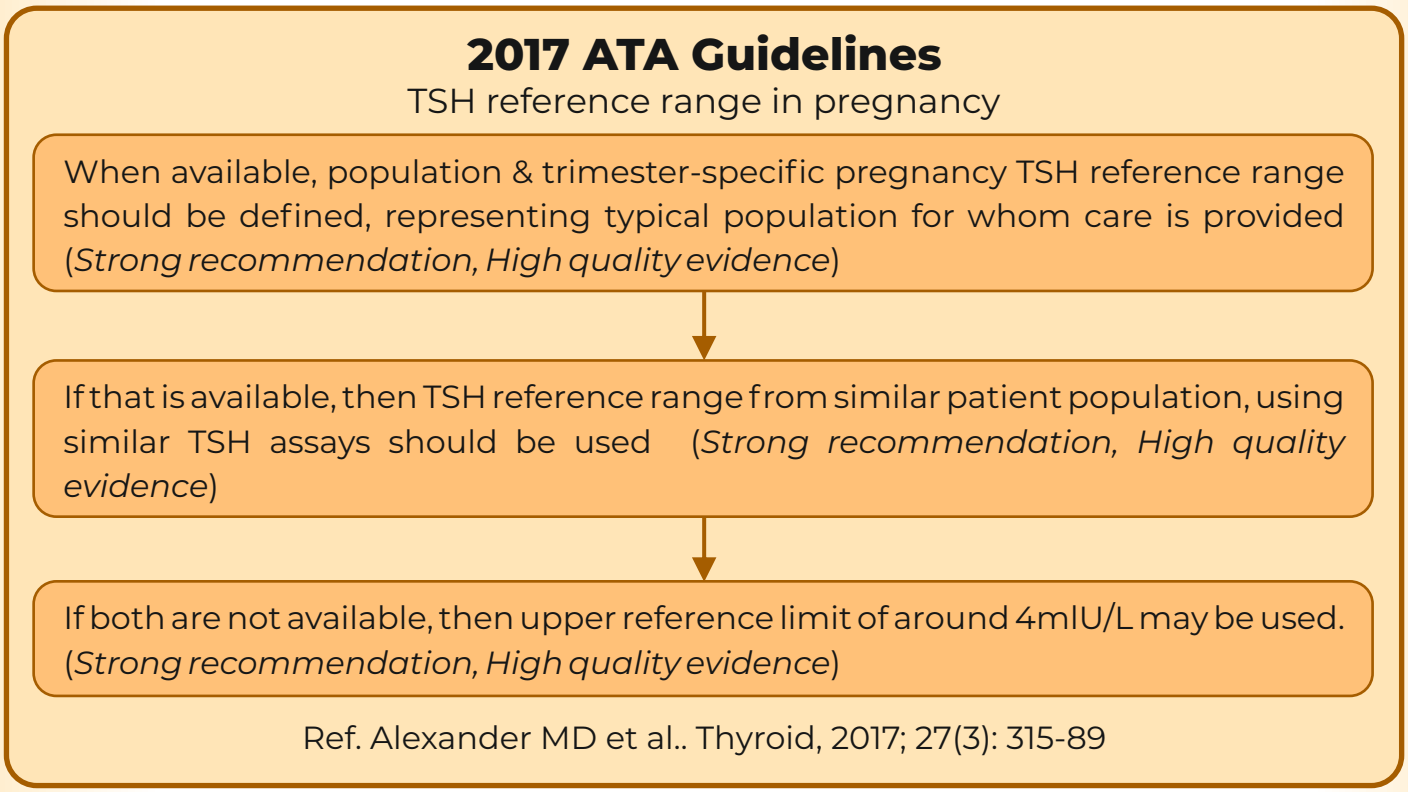

Fig 1 TSH reference ranges in pregnancy ATA Guidelines 2017

Women with subclinical hypothyroidism are more likely than euthyroid women to have TPO antibody positivity (31% compared to 5%).[5] Most guidelines recommend thyroxine replacement in women with subclinical hypothyroidism specially when have TPO antibody positive status. Treatment must begin for overt hypothyroidism as soon as diagnosis is established.

Auto immune thyroid disease

Thyroid peroxidase and thyroglobulin antibodies positive status denotes autoimmune thyroid disease. The risk of miscarriage in patients with autoimmune thyroid disease is higher. there is also increased perinatal mortality and large-for-gestational-age infants. Negro et al showed association between thyroid antibody positivity and preterm delivery in euthyroid women and a possible association with neonatal respiratory distress. They showed that LT4 administration in euthyroid pregnant women with higher titer of antibodies improves pregnancy outcome in women with TSH value >2.0 mIU/L hence treating with LT4 may be useful.[6]

Isolated maternal hypothyroxinemia

When a low FT4 is associated with normal TSH, it is diagnosed as isolated maternal hypothyroidism. Its incidence is 1-2% of pregnancies. It is associated with preterm labour, macrosomia and gestational diabetes when low FT4 levels are found in latter half of pregnancy. Treatment with LT4 has not shown any improvement in outcome.

High-risk Factors For Hypothyroidism

There are certain high-risk factors for hypothyroidism. When these are present, patients must be screened for hypothyroidism:

- 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

Universal screening vs. targeted case finding

This dispute is not yet completely resolved and remains controversial. But there are advantages and disadvantages of both the approaches of case finding. Targeted approach of screening only women at high risk, may miss upto 30 % of subclinical cases whereas universal screening will add to the costs and may not be cost effective.[8]

However, it is certainly recommended that all newborns should be screened for FT4 and/or TSH between day 2-5 of delivery.

General principles of treatment

The TSH and TPO antibody titres will guide the treatment. When TSH 0.1-2.5 mIU/L no further treatment is required, like wise when TSH is >10.0 mIU/L it is quite clearly an indication for starting the LT4 treatment. Pregnant women with TSH titers between 2.5-10.0 mIU/L should follow ATA 2017 guidance

- Levothyroxine (LT4) is the treatment of choice for maternal hypothyroidism
- Full replacement thyroxine dose is around 2–2.4 µg/kg/day
- Women who are already on thyroxine prior to pregnancy increase the dose by 30-50% above preconception dosage
- Repeat free T4 and TSH levels after 1 month after the initiation of treatment
- The thyroxine dose should be titrated to reach a serum TSH value <2.5 mIU/L, while maintaining free T4 levels in the high normal range.

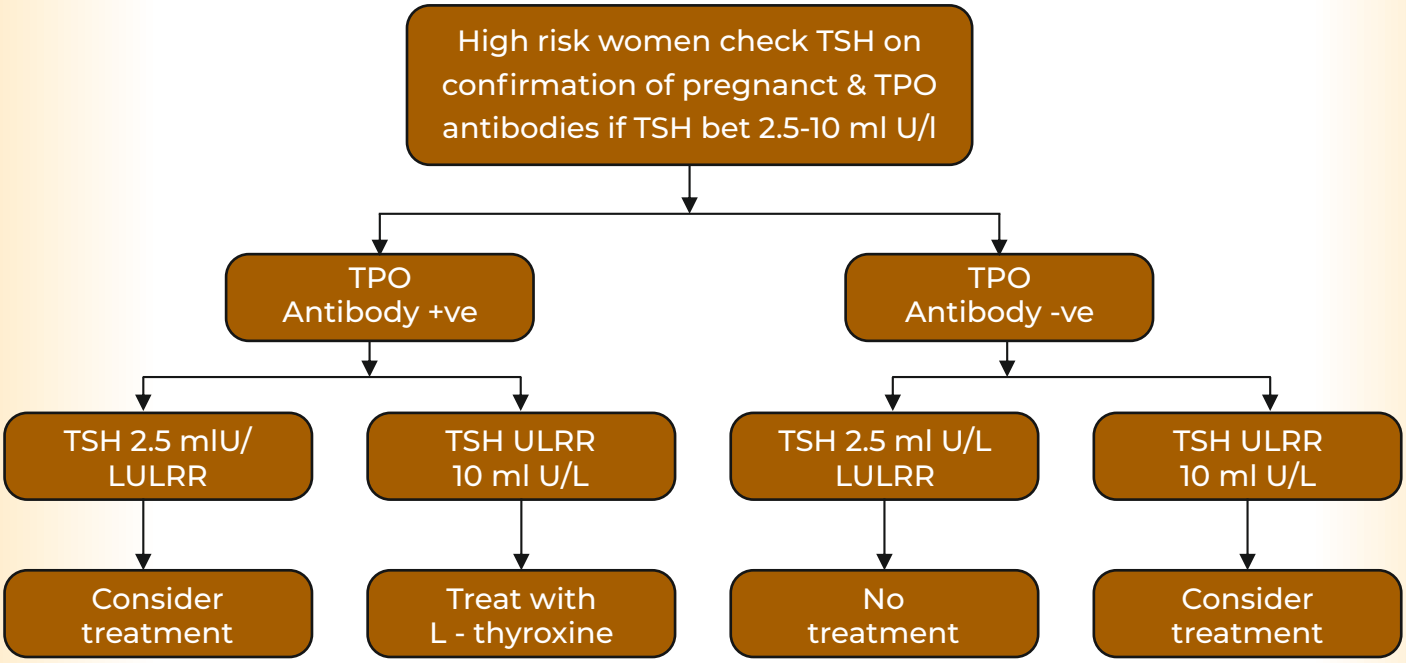

Fig 2 Algorithm for diagnosis and treatment of pregnant women (ATA 2017)

Postpartum follow-up

First follow-up should be generally after 6weeks unless early examination is warranted due to symptoms.In case women are thyroid antibodies positive, they are at increased risk of development of postpartum thyroid it is. In susceptible women, the immune system reverberates causing increased levels of thyroid antibodies.

Postpartum thyroid it is characterised by transient hyperthyroidism may result within 12 months of delivery. If severe, may be treated with beta-adrenergic antagonist drugs. A postpartum exacerbation of chronic Hashimoto's thyroid it is leading to transient or permanent hypothyroidism may occur which is treated with LT4.Further follow-up up to 6-12 months after delivery is usually recommended.

Conclusion

Thyroid hypofunctionis common endocrine disorder leading to adverse pregnancy outcome. The controversies in universal screening for thyroid function tests as well as TSH cutoffs continue but very effective and timely offered LT4 treatment will help improve the maternal andperinatal outcome.[8]

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Urinary Tract Infections

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Introduction

Acute and chronic urinary tract infections (UTIs) in women are one of the most common bacterial infections managed by obstetrician-gynecologists. Around 50% of a general Indian population experience UTIs.Spontaneous resolution is expected in around 50-70%, but recurrence is around 30%; approximately 2.5% develop into pyelonephritis when left unattended.[1,2,3]

Etiological agents

UTIs are commonly caused by bacteriological agents which include Escherichia coli (25-30%), Klebsiella (15-20%), Streptococcus (around 5-10%), Staphylococcus (around 5-10%), Enterococcus, Enterobacter, Proteus species, Acinetobacter species (less than 5%) and rarely Candida species.[4] The relative proportion of each pathogen varies sightly in different settings. Invariably, periurethral entry leads to ascent of the organisms into the urinary tract aided by various mechanisms, though differentially by different species. These mechanisms are briefly summarised in Figure 1.

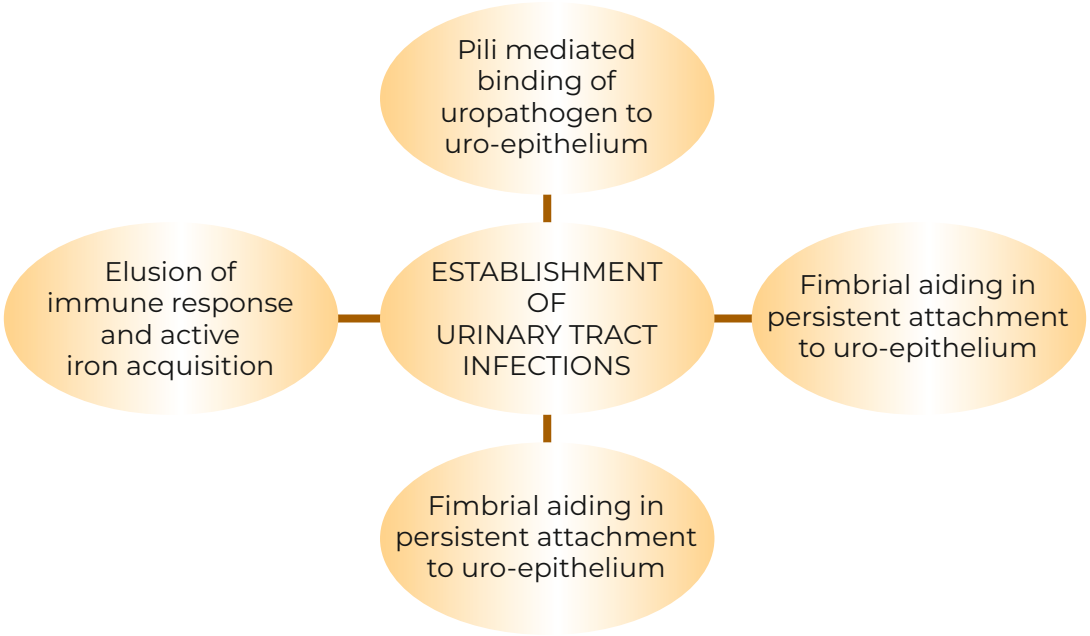

Fig 1 Pathogenetic mechanisms in establishment of UTI

Recent challenges include the development of multi-drug resistant E.coli (upto 45% in a recent study). Quinolone resistance and plasmid-mediated extended spectrum beta lactamase positivity are likely to cause further problems.[5]

Some new insights are emerging regarding uro-pathogens. While it was previously considered that urine is mostly "sterile", it is now being demonstrated almost 50% of individuals harbour "good microorganisms" in the urine, such as Lactobacillus, Gardnerella, Prevotella, and Ureaplasma, akin to vaginal microbiota.6On similar lines, depletion of certain Lactobacilli species and an imbalance in the relative proportions of various organisms, appears to be the common starting point for development of post-operative UTIs.[7] Recently, changes in the urinary tract microbiota corresponding to the menstrual cycle pattern has been observed just like vaginal microbiota.[8]

Risk factors [9-11]

The risk factors for UTIs are categorised and presented in Table 1. The reduction of the risk for uncomplicated UTIs can occur through behavioral and general health measures. However, optimal management of the specific disease state is the best preventive measure for complicated UTIs.

Table 1 Risk factors for UTIs

Risk factors for uncomplicated UTIs	Risk factors for complicated UTIs
• Prior UTI • Sexual activity • Vaginal infection • Diabetes • Obesity • Genetic susceptibility • Rural background • Inadequate water intake • Unsatisfactory toilet habits • Cesarean delivery (as compared to vaginal delivery)	• Urinary obstruction • Urinary retention caused by neurological disease • Use of spermicides/ diaphragm • Use of anticholinergic agents • Immunosuppression • Renal failure • Renal transplantation Pregnancy • Presence of foreign bodies (calculi, indwelling catheters or other drainage devices)

Eventually, these mechanisms lead to one of the following: reduction of urine flow, promotion of bacterial colonisation, or facilitation of ascent of microorganisms, which directly increase the occurrence of a UTI.

Clinical features

UTIs can be completely asymptomatic. Dysuria (painful micturition), pollakiuria (increased urinary frequency), lower abdominal pain, flank or groin pain and fever are the common symptoms. General debility, fever, suprapubic tenderness, flank tenderness, associated vaginal discharge are the common clinical signs that may be appreciated. In complicated UTIs, features of the specific condition may be seen. Some commonly used terminology are summarised in Table 2.

Table 2. Summary of commonly used terminology

Terminology	Definition
Uncomplicated urinary tract infection	A UTI where there are no relevant functional or anatomical abnormalities in the urinary tract, no relevant kidney function impairment, and no relevant concomitant diseases promoting the UTI or risk of developing serious complications
Acute uncomplicated cystitis	A lower UTI in which the acute symptoms involve only the lower urinary tract, for example, urgency, painful voiding (dysuria), pollakiuria, and pain above the symphysis
Acute uncomplicated pyelonephritis	An upper UTI with persistent symptoms including flank pain, flank tenderness, or fever (>38°C)
Asymptomatic bacteriuria	A positive urine culture (>10^5 colony-forming units/ml) in the absence of urinary symptoms
Recurrent uncomplicated UTIs	A recurrent UTI refers to the occurrence of ⩾2 symptomatic episodes within 6 months or ⩾3 symptomatic episodes within 12 months
Catheter-associated UTI (CAUTI)	It is defined as the presence of signs or symptoms of UTI in a patient with indwelling urethral, suprapubic, or even intermittent catheterization with a significant presence of bacteriuria

Diagnostic modalities

Midstream urine dipstick test Used mainly as a screening test.

There are two methods:

- Detection of presence of leucocyte esterase in the urine.
- Detection of presence of nitrites in the urine

Urinary microscopic analysis Urine analysis reliable only in a non- contaminated sample. (>10 squamous cells/high power field suggests contamination). Sensitivity 95%, specificity 70%. Most commonly relied upon test.

Urine culture Indicated when complicated or recurrent UTI is suspected. Performed if there are definite clinical signs of an infection and antibiotics have been ineffective. While midstream urine samples are pathological if there is a uropathogen growth of ≥105 cfu/mL, bladder catheterisation samples are pathological if a single uropathogen species grows ≥102 cfu/mL.

Imaging The features of cystitis on ultrasonography are non-specific. ≥2 pyelonephritis episodes per year is considered as an indication for kidney CT evaluation.

Cystoscopy Occurrence of ≥3 UTIs per year is considered as an indication for cystoscopy to identify any intravesical pathology.

Complications[12,13]

The identification of UTIs is critical because it can lead to complications such as pyelonephritis, renal failure, urinary incontinence and a spectrum urogenital problems. In the pregnant woman, UTI has also be identified as a risk factor for development of preeclampsia.

Treatment[14-16]

The management of UTIs can be classified into

- Antimicrobial therapy
- Non- Antimicrobial measures
- Behavioural modifications

A brief summary of the antimicrobial management of UTIs (culture not available/ negative) is presented in Table 3. The duration of therapy may be extended in complicated UTIs based on individual clinical circumstances.

Table 3 Antimicrobial therepy for UTI

Uncomplicated UTIs (1st line)		
Medication	Dosage	Duration
Nitrofurantoin	100 mg BD	5 days
Fosfomycin	3-gram single dose	Single dose
Trimethoprim/ sulphamethoxazole	800/160 mg BD	5 days
Uncomplicated UTIs (2ndline)		
Ciprofloxacin	500 mg BD	3 days
Amoxicillin (+/ - clavulanic acid)	500 mg BD or TDS	7 days

Complicated UTIs		
Amoxicillin/clavulanic acid (first choice)	625 mg TDS	7 days
Cefuroxime or other 2nd generation cephalosporin (second choice)	500 mg BD	3-5 days
Trimethoprim sulphamethoxazole (third choice)	800/160 mg BD	3-5 days
Fosfomycin (third choice)	3-gram OD every 2–3 days	3 cycles

However, antimicrobial therapy does not eradicate microorganisms and the possibility of emergence of resistant microbial strains always exists. Hence, some additional measures are taken to prevent recurrence.
Few of the non-antimicrobial measures are summarised below:

Urinary alkalinisation Though urinary alkalisation is used very commonly as an empirical agent, the evidence supporting the same is very limited. Commonly used alkalinising agents such as potassium citrate have not been conclusively demonstrated to show benefit in multiple trials.

Probiotics The improved understanding of urinary microbiota has suggested that Lactobacillus probiotics can help in preventing UTIs. Trials are in progress.

Cranberry Cranberry is a popular agent obtained from the shrubs of Oxycoccos and appears to have antioxidative properties and inhibitory action on fimbriae of uropathogens. However, evidence in divided with a 2012 Cochrane review showing no improvement of UTI with cranberry products.

Topical estrogens Topical estrogens improve the vaginal Lactobacillus and reduce the risk of uropathogenic colonisation. Recent analyses show a definite reduction of UTI with topical estrogen with no impact on cancers. It must be noted that systemic estrogens do not have any effect on the UTI rates.

Vaccines Urological vaccines are now available which rely on the concept of triggering a patient's innate immunity against urinary pathogens. Uro-Vaxom or OM-89, an oral vaccine containing different lyophilised strains of E coli is available. It is administered orally for 90 days followed by a 3 month gap and 10 days every month for 3 cycles. Vaginal vaccines are being studied.

Intravesical antibioitics The successful use of intravesical chemotherapy for bladder cancer has been attempted for extrapolation by administering antibiotics by intravesical instillation. Colistin and gentamycin have been attempted, mainly in patients who have indwelling catheters, have grown multidrug - resistant pathogens in the past.

Behavioural modifications

- Adequate fluid intake (a minimum of 2 litres/day)
- Check that urine is clear and report for treatment if turbid
- At least one passage of urine within an hour after a coital act
- Avoidance of contraceptive spermicides
- Correct anal and perineal hygiene – avoidance of cleaning from back to front
- Avoidance of intravaginal rinses or disinfectants

UTIs in pregnancy

After anaemia, UTI is the most prevalent pathology occurring in pregnancy. It is of importance because it can lead to serious complications such as miscarriage and prematurity. Approximately 10% of women develop UTI in pregnancy. Moreover, around 5% of all antenatal period admissions are attributable to UTIs. Suboptimal management of UTIs can lead to long standing renal damage such as pyelonephritis. When symptoms are present, the recognition is straightforward.

Asymptomatic Bacteriuria (ASB) can be defined as the presence of a positive urine culture without any clinical manifestation. Most women who have cystitis, likely had ASB in the preceding few months. The highest prevalence of ASB appears to be in the first trimester and lesser in the third trimester. In the general population, ASB does not require any treatment (treatment should be avoided to prevent antimicrobial resistance). However, in the pregnant women, treatment is always required.[17]

As in general UTI, in ASB also, E coli is the most common pathogen. However, the group B streptococcus (S. agalactiae) needs specific mention due to the 25-fold rise in risks of problems (PPROM, preterm, neonatal infection). Hence, screening is recommended in the first antenatal visit itself. However, there exists a large unmet need for a thorough antenatal screening for ASB in India and needs active action by all stakeholders.[18] Amoxicillin / clavulanic acid, Cefuroxime and Trimethoprim / sulfamethoxazole are the treatment options (in that order).

To conclude, UTIs cause a significant morbidity, albeit “silently” in many. The obstetrician-gynecologist should be vigilant towards the development of genito-urinary infections and be conversant with the optimal management of UTI.

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Nutrition Focus: Protein and DHA in Pregnancy

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Protein in pregnancy

Protein forms an essential component of a healthy diet in humans to support both growth and maintenance. Protein in the body plays structural (keratin, collagen) and functional (enzymes, transport proteins, hormones) roles. Most mammalian protein is composed of 20 different amino acids, and thus there is a need in our body for both an adequate supply of amino acids and total protein (nitrogen).[1,2]

The current definition of protein requirement is as follows: "the lowest level of dietary protein intake that will balance the losses of nitrogen from the body, and thus maintain the body protein mass, in persons at energy balance with modest levels of physical activity, plus, in children or in pregnant or lactating women, the needs associated with the deposition of tissues or secretion of milk at rates consistent with good health".[2]

Thus, during pregnancy, an exceptional stage of life defined by rapid growth and development and enormous maternal physiological changes from the time of conception to birth, adequate dietary protein is crucial to ensure a healthy outcome. Within several weeks of conception, adjustments in protein metabolism occur to support fetal growth and development while maintaining maternal homeostasis and preparing for lactation.[3]

Protein utilisation from foods and deposition as new tissues are energy dependent at stages of absorption, amino acid transport, protein synthesis and proteolysis. Thus, dietary intake during pregnancy must have sufficient energy and protein to ensure the full-term delivery of a healthy infant. The additional energy required during the full term of pregnancy has been estimated to be ~77,000 kcal, although the energy cost of pregnancy is not distributed equally throughout the gestational period.[4]

This is because the amount of protein deposited in maternal and fetal tissues varies during pregnancy, with non significant deposition during the first trimester, gradually increasing during the second trimester, and with most occurring in the third trimester. Thus, protein and amino acid intake recommendations during pregnancy should be gestational stage–specific, with adequate energy to ensure all needs are met.[5]

What is the role of protein during pregnancy?

Proteins are found in every cell of the body, making up skin, muscles, hair, fingernails, and all other tissues. They provide structure to cells and help them function properly, as well as helping cells repair themselves. Protein has a vital role during pregnancy because it helps the baby grow normally while contributing to other important areas of their development, including

- growth and repair of new and damaged tissues
- making antibodies for the immune system
- making hormones and enzymes
- helping muscles function properly
- transporting oxygen through their blood

Getting the recommended amount of protein may also help to promote a healthy birth weight. A baby with a healthy birth weight has a reduced risk for developing diabetes or becoming overweight later in life. All future growth and development then have a strong foundation to build upon, throughout infancy, childhood and beyond.

How much protein is required during pregnancy?

A slightly higher intake of protein is required during pregnancy to help with the various changes your body goes through to support your baby's growth.The Reference Nutrient Intake (RNI) of protein for adults is 0.75g per kg of body weight per day, plus an additional 6g per day for pregnant women.

For a woman weighing 60 kg, she will need: 60 x 0.75g/d = 45g of protein a day and 51g during pregnancy.

A good rule of thumb is to include a portion of protein at every meal so that you're getting 2-3 portions per day. A portion is generally equivalent to the size of your palm.

Good protein foods during pregnancy

It is not just the quantity of protein that matters. It's also important to eat a variety of protein sources because different proteins provide different amino acids. Eating a variety of protein sources will also provide you with a variety of vitamins and minerals. These include meat and poultry, fish, eggs, cheese and dairy, beans and pulses, seeds and nuts.

These foods are frequently eaten in the average diet, so unless a woman is a pure vegetarian or vegan, she probably doesn't need to adjust her intake to meet the increased needs. People who choose to avoid animal products can get many of the essential amino acids by eating a variety of fruits and vegetables.

Healthy protein snacks for pregnant women

Protein intake can be increased throughout the day with these healthy snack ideas.

- A small sandwich with grated cheese, lean ham, mashed tuna, salmon, or sardines, with a salad
- Hummus with carrots, cucumbers, or celery
- Vegetable and bean soup
- Baked beans on toast or a small baked potato
- Low-fat, lower-sugar fruit yoghurt, plain yoghurt with fruit.

DHA in pregnancy

Evidence suggests a strong association between nutrition during the first 1000 days (conception to 2 years of life) and cognitive development. Maternal docosahexaenoic acid (DHA) supplementation has been suggested to be linked with cognitive development of their offspring. DHA is a structural component of human brain and retina, and can be derived from marine algae, fatty fish and marine oils. Levels of maternal DHA decline during pregnancy and decrease even further when the lactation period is extended. Since Indian diets are largely devoid of such products, plasma DHA levels are low. It is currently recommended that diet of pregnant mothers contain 200–300 mg DHA/day.[6,7]

The brain develops rapidly through neurogenesis, axonal and dendritic growth, synaptogenesis, cell death, synaptic pruning, myelination, and gliogenesis. These ontogenetic events build on each other, such that even small perturbations can have long-term effects on the brain's structural and functional capacity. [8-11]

A mother's nutrition during this critical phase impacts both prenatal and postnatal growth and the development of offspring. Higher omega 3 long chain poly unsaturated fatty acid (n-3 LCPUFA) levels such as docosahexaenoic acid (DHA) have been associated with enhanced infant neuro development. [12,13,14]

Indians do consume sources of the precursor, alpha-linolenic acid (ALNA 18:3n-3; a short-chain omega-3 fatty acid) like mustard oil, soybean oil, flax seeds, walnuts. However, excess omega-6 fats in Indian diets inhibit the endogenous synthesis of DHA from ALNA. Thus, negligible DHA-rich products coupled with an excess of omega-6 sources result in low plasma DHA and a sub-optimal omega-3 to omega-6 ratio among Indian populations.[15,16,17]

DHA and neurodevelopment

Long chain polyunsaturated fatty acids, particularly DHA (22:6n-3) and arachidonic acid (20:4n-6), are integral to fetal, neural, and retinal development and accrete extensively in the last trimester of pregnancy. Despite the implications for child development, there have been few studies which have comprehensively tested interventions in humans.

Improvements in DHA levels in mother may confer some benefit for child neuro development. Further more, DHA appears to be safe, with no adverse birth outcomes related to DHA supplementation observed in low- risk pregnancy cases.

Importance of omega-3s

Omega-3 fatty acids are a family of polyunsaturated fatty acids, necessary for the development and proper functioning of the human body. DHA is a crucial omega-3 for the structure of the brain, the nervous system, and the transduction of visual signals. During gestation and lactation, the contribution of DHA in the mother's diet is essential for the development of the fetus. The brain and retina accumulate large amounts of DHA. This process begins at the time of conception and continues after birth until the age of 2.

Indeed, DHA intake during pregnancy is associated with a more extended gestation period, higher birth weight, larger head circumference, lower risk of preterm delivery and lower risk of hypertension (preeclampsia) and postpartum depression (WHO, 2011).

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Gestational diabetes

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Introduction

Gestational diabetes mellitus (GDM) is hyperglycaemia acquired by the mother during pregnancy. The White classification, named after Priscilla White, distinguished between gestational diabetes (type A) and diabetes that existed prior to pregnancy (pregestational diabetes).[1]

In patients who enter pregnancy with altered glucose tolerance, the insulin resistance caused by diabetogenic hormones secreted by the placenta accelerates hyperglycaemia in the mother. India is the diabetic capital of the world and more gestational diabetics are seen in younger population who later on convert to overt diabetics. The condition is result of a longstanding lifestyle disorder and is seen to be more common in Asian women with obesity. It is seen in all socioeconomic strata equally and is no longer a disease of the rich. Hence, universal screening is very important in the Indian population. Also, these gestational diabetics require closer follow up, more surveillance and are superimposed with complications like preeclampsia, macrosomia, caesarean births.

Women with GDM have increased risk of developing diabetes in the future along with recurrence of GDM in future pregnancies. According to Barker's hypothesis, GDM causes intrauterine programming of the baby for metabolic disorders in the future and is proposed to have a potential for transgenerational transmission through epigenetic mechanisms affecting the subsequent generations. When patients approach obstetricians for pregnancy, this offers a window of opportunity to diagnose insulin insufficiency, assess the future risk of diabetes and if well controlled prevent the intrauterine programming of the foetus and consequently the future generations.[2,4]

Aetiology and risk factors

Persistent maternal hyperglycaemia is the basic cause of the increased perinatal morbidity and mortality associated with GDM. Glucose crosses the placenta by active facilitated diffusion thus if the mother has hyperglycaemia there will be fetal hyperglycaemia. During the first trimester, maternal hyperglycaemia, whether known or not known to the mother is associated with increased risk for abnormal organogenesis. Glucose is a well-established teratogen and can lead to major fetal malformations to the tune of 25% in subjects with poorly controlled glycaemia.

In the later part of gestation chronic fetal hyperglycaemia causes hyperinsulinaemia which is associated with excessive fetal growth and delayed pulmonary maturation. Intrauterine fetal deaths are associated with uncontrolled hyperglycaemia. Risk of GDM is rising due to changed lifestyle and environmental factors and pregnancy is identified as a diabetogenic condition as it is associated with insulin resistance.

Placental secretion of diabetogenic hormones including growth hormone, corticotropin-releasing hormone, placental lactogen (chorionic somatomammotropin), prolactin and progesterone cause insulin resistance. This is a physiological arrangement to ensure that the fetus has an ample supply of nutrients. But when the balance of this metabolic adjustment topples, GDM develops or the pre-existing hyperglycaemia becomes exaggerated. GDM is a sign of pancreatic inadequacy to overcome insulin resistance.

Clinical presentation

Gestational diabetes is typically detected during routine screening of pregnant women for glucose intolerance. Any degree of glucose intolerance with onset or recognition during gestation places a patient in the category of gestational diabetes mellitus. All patients are universally screened but special attention should be paid to the ones at risk of diabetes as well as GDM. Excessive weight gain, recurrent genitourinary infections, accelerated fetal growth, presence of polyhydramnios, diabetic ketoacidosis, congenital abnormalities in the fetus, fetal demise are certain features where diabetes or hyperglycaemia should be investigated.

Work up

It has now been demonstrated that the early detection and treatment of GDM improves pregnancy outcome. Incidence of serious perinatal complications such as death, shoulder dystocia, nervepalsy and fracture was 4% amongst pregnant woman randomised to routine care compared with 1% among the intervention group. This is the most compelling immediate argument for screening of GDM given that the failure to identify a woman with GDM denies her the opportunity to have treatment for potentially preventable serious fetal complications.[3]

GDM is diagnosed by universal screening by OGCT (oral glucose challenge test) of all pregnant women. The typical time lines mentioned by the GOI guidelines are

1. During the first trimester
2. At 24-26 weeks
3. then at 34-36 weeks.

At the very first antenatal visit, the mother should be tested for GDM. The test recommended is the OGCT as proposed by the Diabetes in Pregnancy Society of India (DIPSI). The DIPSI-OGCT is a single step screening as well as diagnostic test for early and easy diagnosis of GDM. This test is advocated by WHO as well as Government of India.[12]

This involves taking 75 gm glucose over 10 mins, irrespective of the fasting status and a blood sugar test two hours later. Even a blood sugar with glucometer has been sanctioned by the Government of India for diagnosis of GDM to eliminate the need for laboratory in remote areas. The following are levels and diagnostic

2hr plasma glucose	
>200mg/dL	Overt Diabetes
>140 – 199mg/dL	Gestational Diabetes (GDM)
120 – 139mg/dL	Gestational glucose intolerance (GGI)
<120 mg/dL	Normal

However, the OGTT is time-consuming for both the women and the health care system as the women need to be fasting and wait for 2 h to complete the test, and an OGTT may induce or aggravate nausea and vomiting in pregnant women, ie., some fail to complete the test.

HbA1c is a marker representing the average of plasma glucose level in the last 8–12 weeks. Although HbA1c is not very good at diagnosing GDM, it may have a potential to predict adverse pregnancy outcomes. Pregestational DM is diagnosed if fasting blood sugar level is 126 mg/dL or more, HbA1c is 5.8% or more.[5]

Management

Once diagnosed, GDM can be treated bya combination oflife style changes, Medical Nutritional Therapy (MNT), drugs like metformin and/ or insulin. Fetal surveillance should include trimester wise growth scan for occurrence of accelerated growth, polyhydramnios, macrosomia and fetal cardiac hypertrophy, 22 weeks Uterine Artery Doppler(UAD) for prediction of preeclampsia and NST weekly 34 weeks onwards. There is a considerable rise in the occurrence of gestational diabetes in the past decade in India and this has been attributed to the Asian ethnicity.[5,6]

Diabetes in pregnancy has become a global emergency needing urgent attention as recommended by the FIGO. Women from India are 11 times more at risk of developing GDM as compared to women in other parts of the world.[7]

Indian diversity also is reflected in the variable prevalence of GDM across the country with 3.8% in Kashmir, Western India reporting 9.5%, 6.2% in Mysore and 22% in Tamil Nadu. [8-11]

The meal pattern should be a balanced diet and provide adequate calories sourced form large quantities of protein (@ 1g/kg body weight) and complex carbohydrates. Fibre, nutrients and correct portion size and food frequency has to be audited to meet the needs of pregnancy. The expected weight gain during pregnancy is 300–400 grams per week and total weight gain is 10–12 kg by term. After two weeks of initial treatment with MNT if the targeted control of FPG ~90 mg/dL and/or post-meal glucose ~120 mg/dl, not achieved then insulin may be initiated.

Metformin

Metformin is an insulin sensitiser and acts by reducing hepatic gluconeogenesis and enhances peripheral glucose uptake. This helps in lowering of blood glucose levels with minimal risk of hypoglycaemia and weight gain. Metformin helps to improve maternal glycaemic control with less maternal weight gain and a reduction in insulin dose requirement and this seems rational with the rising occurrence of Type 2 DM, older maternal age and obesity in pregnancy. Dose of metformin ranges from 500-2500 mg/day in divided doses or slow release formulations for treatment of GDM. Towards the third trimester larger doses are essential due to increased renal clearance and the impact of doses exceeding 2500 mg/day on maternal, foetal and neonatal safety has not been determined. Metformin is freely transferred through the placental barrier and the breast milk.[12,13]

Insulin therapy

Premix insulin 30/70 is started with a starting dose of 4 units before breakfast. Every 4th day 2 units are increased till 10 units. If fasting sugar levels remains > 90 mg/dL, 6 units are started before breakfast and 4 units before dinner. Review blood sugar test is done to adjust dose further. Total insulin dose per day can be divided as two-thirds in the morning and one-third in the evening.

If GDM is diagnosed in the third trimester; MNT is advised for a week and insulin is initiated. If 2-hour PG > 200 mg/dL at diagnosis, a starting dose of 8 units of premixed insulin could be administered straightaway before breakfast and the dose must be titrated on follow-up. Along with insulin therapy, MNT is also advised. The target for glycaemic control is maintaining a mean plasma glucose (MPG) level ~105–110 mg/dL. This is possible if fasting sugar and 2-hour postprandial peaks are ~90 mg/dL and ~120 mg/dL, respectively and ensures good fetal outcome.

Myoinositol

Myoinositol supplementation is known to reduce the rate of GDM in both overweight and obese women as well as in women with a family history of DM and thus have a preventive role. Given in the dose of 4 gm/day myoinositol is effective in reducing the dose of metformin as well as insulin. Glycaemic control can be achieved per hospital visit but it can be also done by the mother at home with a glucometer. Sugar levels are to be maintained as per the target mentioned above. Continuous glycaemic assessment is most ideal.

Other supportive measures

Correction of hypothyroidism, anaemia, screening for preeclampsia and regular blood pressure measurement and screening for urinary tract infection. Screening for dyslipidemia, fundoscopy and renal function with serum creatinine in mothers with overt diabetes. Regular exercise regimen to reduce insulin resistance and self-glucose monitoring with counselling about complications is essential. Fetal surveillance should

include trimester wise growth scan with a vigilance for occurrence of accelerated fetal growth, polyhydramnios, macrosomia and fetal cardiac hypertrophy (fetal 2D Echo), 22 weeks uterine artery doppler for prediction of preeclampsia and NST weekly 34 weeks onwards can be undertaken. Delivery before full term is not indicated unless there is evidence of macrosomia, polyhydramnios, poor metabolic control or other obstetric indications (eg. PPROM, pre-eclampsia or intrauterine growth retardation).

Delivery and postpartum care

It is preferable to terminate pregnancy around 38 gestational weeks to avoid still birth. During labour, it is essential to maintain good glycaemic control, while avoiding hypoglycaemia. Lower insulin requirements are common during labour (often no insulin is necessary). Maternal blood glucose level should be monitored after delivery, 24 hours postpartum and if found to be high, checked again on follow-up. A neonatologist's presence at the time of delivery is ideal, more so if significant neonatal morbidity is suspected.

Long term continued surveillance of the mother: It is a good practice to perform the OGCT at 6 weeks post-delivery and thereafter yearly and the patient is counselled about risks of overt diabetes, hypertension, obesity and its consequences. Avoidance of postpartum weigh retention and regaining optimum BMI goes a long way in reducing these morbid conditions.

Preconception counselling is very vital to high risk patients likely to develop gestational diabetes due to obesity, family history, or PCOS. They have to be made aware of the risks of congenital anomalies, perinatal mortality, diabetic complications for the mother, obstetric complications, neonatal risks and increased risk of diabetes in the offspring.

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Approach to a Patient with Vaginal Discharge

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Introduction

Excessive vaginal discharge is a common complaint amongst women coming to see a gynaecologist. Women may face this problem at any age.

A thorough history should be taken. History should include a sexual history. History of IUD use should be checked. History of immunocompromised status or diabetes should be noted.

The nature of the discharge is important. Thick,curdy white discharge accompanied by itching suggests a fungal infection. Greenish, foul smelling discharge suggests a trichomoniasis infection. Thin, watery discharge during the midcycle may be physiological. Cervical mucous tends to be copious, thin and watery during the midcycle at the time of ovulation.

Clinical examination

A speculum examination is done if possible. Important things to see are the nature of the discharge and the cervix. A Pap smear can be taken at the same time. Any abnormal area on the cervix like an erosion or ulcer or growth should be noted. A per vaginal examination can assess forniceal tenderness which may be a sign of pelvic inflammatory disease.In cases where recurrent leucorrhoea is a problem, a vaginal swab can be collected and sent for microbiology.

The three common causes of leucorrhoea are bacterial vaginosis, candidiasis and trichomoniasis. Chlamydial or gonococcal infection may also lead to vaginal discharge.

Treatment strategies

Usually, a syndromic approach is followed for treatment where patients are given a combination of antifungal and antibiotic treatment. Treatment may be oral and/or vaginal. In patients who are sexually active, the partner should be given simultaneous treatment.

Antifungal treatment

Oral Fluconazole can be given as 150 mg day 1,3,7 or 150 mg once a week for 4 weeks. Oral itraconazole is an alternative. Clotrimazole can be administered as a vaginal pessary or ointment for local application.

For bacterial vaginosis and/or trichomoniasis, metronidazoleor tinidazole or clindamycin can be given.

For patients who present with recurrent infection, they should be given treatment for a longer time. Oral Fluconazole can be given once a week for 6-8 weeks.

In pregnancy, vaginal pessaries containing a combination of clotrimazole and tinidazole are recommended.

Recurrent infections

Disturbed ecoflora of the vagina is the cause of recurrent vaginal infection.Lactobacilli present in the healthy vagina protect the host from infections by maintaining a low pH (<4.5). Thus, oral and vaginal lactobacilli given along with antibiotics and antifungals improve the cure rate. Pendharkar et al reported higher cure rates in women diagnosed with BV or VVC treated with antibiotics, antifungals and vaginal lactobacillus.

New research has identified new treatments that seek to restore the balance of vaginal microflora. Bioactive compounds such as probiotics and nutraceutical proteins (such as lactoferrin) deserve particular attention.It is known that healthy vaginal microbiota is disturbed by antibiotics.There is a risk that pathogenic microorganisms will develop resistance to antimicrobial drugs.Recurrent infections are also probably due to the elimination of commensal microorganisms.Hence, the use of lactobacillus spp to replenish the commensal microbes and reduce the risk of reinfection has been considered.

Lactoferrin is a major defense protein of the innate immune system. It is a food additive which protects the mucosa from infections and inflammations. Hence it is classified as a nutraceutical.The bacteriostatic and bactericidal effect of lactoferrin has been reported against a wide range of gram -positive and gram-negative bacteria.

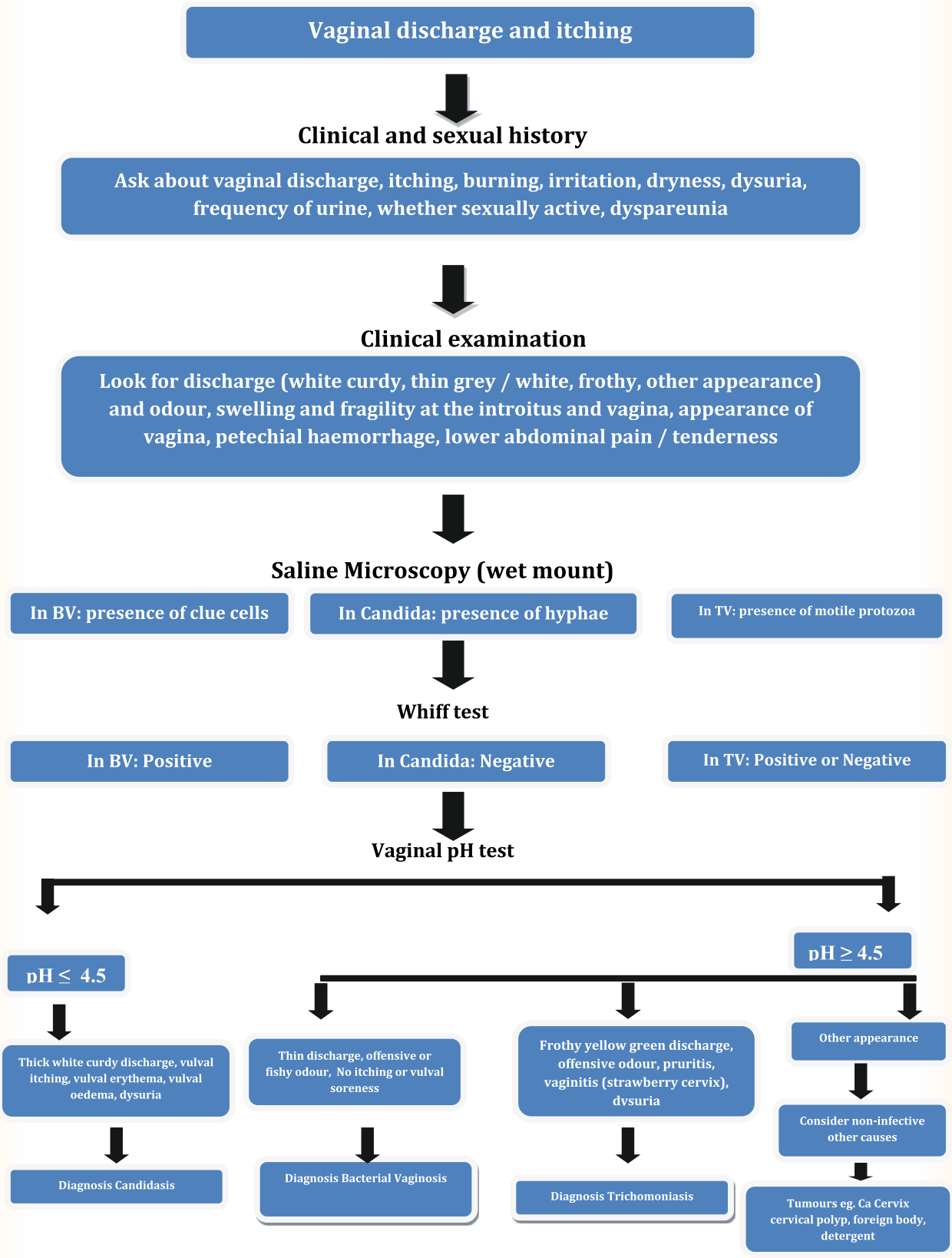
Thus, it is recommended that for vaginal infections patients should receive probiotic with azole and antibiotic. Use of lactoferrin and lactobacilli will promote the growth of beneficial bacteria and also balance local immunity.

Vaginal tablets are available which contain lactobacillus(1 million CFU). This is a probiotic vaginal tablet which maintains healthy vaginal flora. The recommended dose is 1 tablet daily to be inserted vaginally from the 8th day of the menstrual cycle for 8 days every month for 3 months.

Conclusion

The vagina of women is inhabited by a variety of microorganisms. Lactobacilli produce antimicrobial substances acting to counteract the growth of pathogenic microorganisms. Combining probiotics with antibiotics and antifungals is a new strategy for counteracting bacterial and fungal vaginal infections.

Diagnosis and management of vaginal discharge and itching



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Management of Severe Anaemia in Pregnancy

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Introduction

Anaemia is one of the most common medical disorders encountered during pregnancy, especially in the developing countries. It has many maternal and perinatal adverse effects, contributing to high maternal mortality.

Diagnosis of iron deficiency anaemia in pregnancy

History and clinical examination

A history of fatigue, alopecia, pica, restless leg syndrome, pagophagia should be asked for. Examine for pallor, koilonychia, atrophic tongue papillae, glossitis and stomatitis. Severe cases present with congestive cardiac failure such as orthopnea, edema, raised jugular venous pulse and pulmonary crepts and would require urgent treatment.

Investigations

Haemoglobin Hb and haematocrit should be done at first visit, 28–30 weeks and 36 weeks. Sahli's method is reliable for estimation of haemogloblin. The most commonly used method is complete blood count.

ICMR classification

Mild	10–11 gm/dL
Moderate	7–10 gm/dL
Severe	4–7 gm/dL
Very severe	<4 gm/dL

Peripheral blood smear

RBC indices and morphology are recommended as the first step in the evaluation of pregnancy associated anaemia and it helps to differentiate the type of anaemia. Normal smear—Normocytic (normal size RBC), normochromic (normal colour RBC)

Iron deficiency (Fig 1)—Microcytic (small RBC), hypochromic (pale RBC), anisocytosis (variation in size), poikilocytosis (variation in shape), with or without target cells. Malarial parasites can be seen. Aplastic anaemia shows low/no count. Sickle cells can be demonstrated. Target cells in thalassemia.

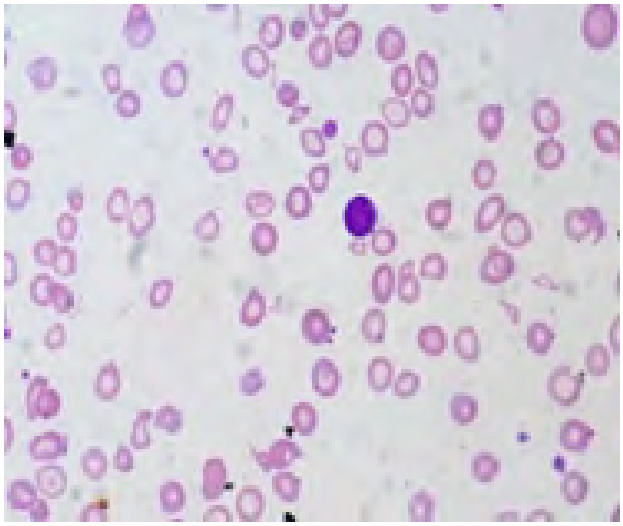


Fig 1 Peripheral blood smear: microcytic hypochromic red blood cells with anisocytosis in iron deficiency anaemia

RBC indices

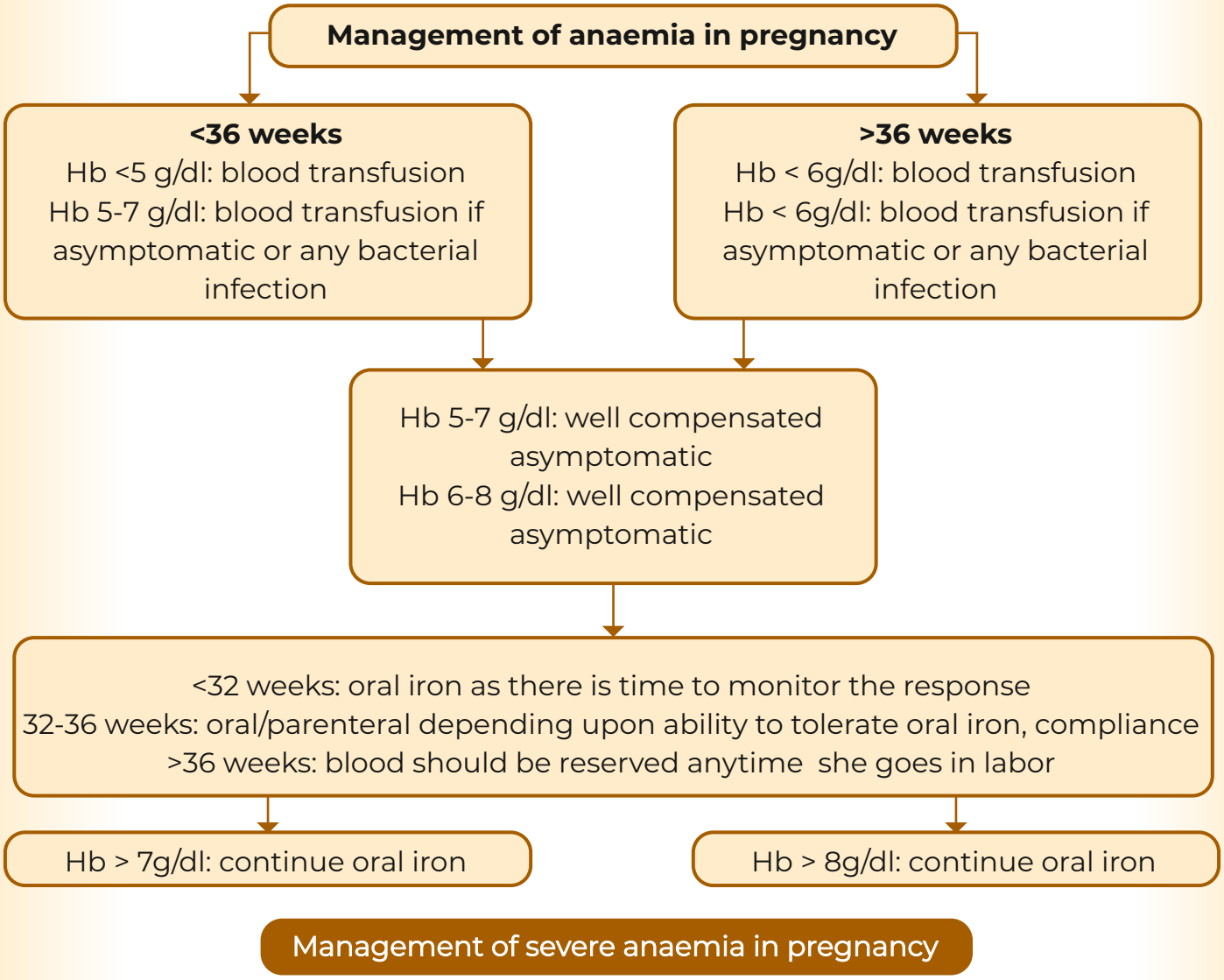
IDA is characterised by microcytosis, (low MCV < 80 fl) and hypochromia (Mean Corpuscular Hemoglobin {MCH} < 27 pg) and blood film may show presence of characteristic microcytic cells or pencil cells. A marked increase in RDW occurring early after the initiation of therapy can be used for confirmation of IDA.

RBC count—decreases in anaemia (N 3.2 million/c mm)
PCV—< 32%, (N37–47%)
MCH—decreases
MCHC—decreases, one of the most sensitive indices (N26–30%).
Blood indices help in differentiating microcytic anaemia on peripheral blood smear.

Serum ferritin

Serum ferritin is a more sensitive and specific marker for iron deficiency anaemia than serum iron, transferrin saturation. For confirming iron deficiency in pregnancy low serum ferritin values is regarded as the best test. Some studies suggests that serum ferritin cut off of 30 µg/dl to be used for diagnosis and management of iron deficiency anaemia in pregnancy.

Hb electrophoresis or chromatography is indicated to exclude genetic diseases such as - thalassemia. In cases of megaloblastic anaemia, vitamin B12 should be measured since vitamin B12 deficiency is a common condition. Folic acid deficiency anaemia, instead, is less frequent. Bone marrow activity—reticulocyte count (N 0.2–2%). Higher bone marrow activity is seen in haemolytic anaemia, following acute blood loss and iron deficiency anaemia on treatment.



Management of severe anaemia in pregnancy

Treatment of severe anaemia in pregnancy

The choice of the treatment of anaemia depends on the cause of anaemia and its severity, gestational age, risk factors and comorbidities.

Parenteral Iron

Indications for parenteral iron

- Poor compliance to oral iron therapy
- Intolerance to oral iron therapy
- Gastrointestinal side effect where oral iron is contraindicated
- Malabsorption syndrome
- Severe anaemia with chronic bleeding
- Women on haemodialysis
- Iron deficiency anaemia presenting late in pregnancy

Contraindications to parenteral iron

- Iron overload states like thalassemia
- Hypersensitivity to iron
- Anaemia not caused by iron deficiency like haemolytic anaemia
-

History of eczema, asthma, allergy

- Active renal disease
- Acute and chronic infection
- Disturbance in iron utilisation haemosiderosis haemochromatosis

Adverse effects of parenteral iron

- Acute anaphylaxis: collapse, fever, rigor, nausea, vomiting
- Delayed reactions: fever, arthralgia, myalgia, lymphadenopathy
- Local reactions: staining of skin, abscesses, thrombophlebitis
- Exacerbation of joint pain in rheumatoid arthritis

Parenteral iron dose calculation

Total dose in mg = 2.4* wt in kg* deficit (target Hb-actual Hb) +500

Iron sucrose

IV iron sucrose complex has a better a side effect profile than oral iron and is safe and efficacious in pregnancy. The maximum dose in a single administration should not exceed 200 mg. The infusion time should be at least 15 minutes for 100 mg and 30 minutes for 200 mg. Multiple doses may be required.

Ferric carboxymaltose

FCM is the first-choice IV iron preparation in cases in which parenteral iron therapy is recommended. FCM is a stable complex. FCM was found to be safe and effective IV iron product in pregnancy according to many randomized studies. It has lesser side effects compared to oral iron. FCM does not cross the placenta. The maximum daily dose is 1000 mg/20 mL. The administration rate should be 100–500 mg/min. Administration time is a minimum of 15 minutes for doses of 500–1000 mg. It can be given in the antenatal and postnatal period.

Role of Erythropoietin

Some studies have shown recombinant human erythropoietin (RhuEPO) to be safe and effective in severe anaemia in peripartum period. It should be used with IV iron. It is advised to patients with antepartum and postpartum hemorrhage. It can also be given to patients with rare blood groups. However currently there is insufficient evidence for routine use of EPO in pregnancy except in cases with renal disease.

Blood transfusion

Indications for blood transfusion in pregnancy with iron deficiency anaemia:

Antepartum Period	Intrapartum Period	Postpartum Period
1.Pregnancy < 36 weeks a. Hb < 5 g/dL with or without signs of cardiac failure or hypoxia b. 5–7 g/dL with presence of impending heart failure, hemodynamic instability or acute haemorrhage 2.Pregnancy > 36 weeks a. Hb < 7 g/dL even without signs of cardiac failure or hypoxia b. Severe anaemia with decompensation or acute haemorrhage with decompensation c. Haemoglobinopathy/ Bone marrow failure syndromes or malignancy	a. Hb < 7 g/dL [in labour] Decision of blood transfusion depends on medical history or symptoms. b. Severe anaemia with decompensation or acute haemorrhage with decompensation	a. Anaemia with signs of shock/ acute haemorrhage with signs of hemodynamic instability b.Hb < 7gm %: Decision of transfusion depends on medical history or symptoms

General principles of blood transfusion

Consent

A valid consent should be taken from the patient prior to administering a blood transfusion. In case of an emergency, if it is not possible to take consent, provide information on blood transfusion retrospectively. The indication of transfusion and consent should be documented in the patient's medical record.

- The initial administration of blood should be very slow as a life-threatening reaction may occur.
- Blood should be started within 30 minutes after removal from the refrigerator and completed within 4 hours of commencement of transfusion. Blood transfusion should not exceed 15-20 drops per minute.
- In case of fever, chills, breathlessness or any other feature of adverse transfusion reaction transfusion should be stopped immediately. Steroids should be given and patient should be monitored.

Management of labour in severe anaemia

First stage

- The patient should be propped up
- Oxygen should be given if required
- Intermittent chest auscultation
- Secure intravenous access with wide bore cannula
- Minimal vaginal examination
- Strict asepsis to be maintained
- Partograph to be maintained
- Fluid restriction
- Start antibiotic prophylaxis

Second stage

- Cut short the second stage. Assisted vaginal delivery -Ventouse or forceps to prevent maternal exhaustion and blood loss
- Avoid unnecessary episiotomies, tears if present to be repaired immediately
- Strict asepsis to be maintained
- Restrict intravenous fluids
- Oxygen if required should be given in concentrated form to avoid fluid overload

Third stage

- Active management of third stage
- Keep uterotonics ready. Injection methergine is contraindicated in patients with congestive heart failure. Hence tablet misoprostol 800 microgram is preferred. Oxytocin if required can be given as concentrated infusion – oxytocin 20 units in 500 ml of RL at a rate less than 125 ml/hr (Even a small amount of blood loss can cause decompensation)
- Look for genital trauma

Puerperium

- Watch meticulously at least for 6 hours postpartum for any signs of failure
- Prophylactic antibiotics can be given if episiotomy was given
- The mother should have adequate rest
- Urine output should be monitored and it should be more than 30ml/hour
- Iron and folate therapy should be continued for least 3 months to build up iron stores
- Any infection must be treated like urinary tract infection, respiratory tract infection
- Contraceptives should be advised
- Consider thromboprophylaxis in appropriate cases

Complications of severe anaemia

During pregnancy

- Poor weight gain
- Decrease immune response
- Preterm labour
- Congestive cardiac failure at 30-32 weeks
- Decreased work capacity

During labour

- Dysfunctional labour
- Congestive heart failure. Injection methergine is contraindicated in patients with congestive heart failure. Hence tablet misoprostol 800 microgram is preferred. Oxytocin if required can be given as concentrated infusion – oxytocin 20 units in 500 ml of RL at a rate less than 125ml/hr.
- Inability to stand even slight blood loss

Puerperium

- Puerperal sepsis
- Subinvolution
- Lactation failure

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From Preconception, Pregnancy to Lactation

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Calcium carbonate 1250 mg, Vitamin D_3 2000 IU, Methylcobalamin 1500 mcg,
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Mother's Horlicks: Mother's Horlicks is a nutritional beverage to be consumed as a part of daily diet. GI: Glycemic index # Added sugar refers to sucrose. Contains naturally occurring sugars.
* Based on in-vitro GIST method results (<55), data on file. ^ In the VD6B Protein and Nutrition Supplement Category by Gynecologist. Source: IQVIA Medical Audit July 2019

Protein Plus: *Based on in-vitro GIST method results (<55), data on file.GI is defined as the relation of the incremental area under the blood-glucose response curve (Incremental Area Under Curve, IAUC) of a tested meal containing 50 g of digestible carbohydrates and the average incremental area under blood-glucose response curve of a reference food.". ^ Blend of 3 good quality proteins (whey, soy, casein).

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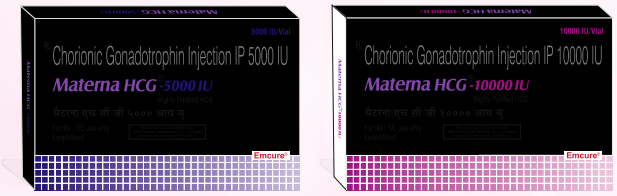

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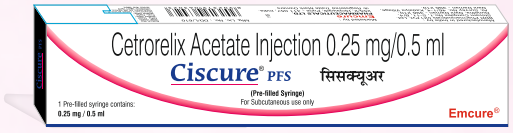

For successfully programming DAYS 28

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