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Dear SOMI Members,

Greetings from Hyderabad. This issue of e newsletter focusses on a few common hematological problems encountered in pregnancy like anemia, thrombocytopenia, hemoglobinopathies and also an article on 'hemolytic anemia of pregnancy', a rare condition specific to pregnancy.

Anemia is seen in half of the pregnant women in developing countries. Fernandez Hospital protocol for screening and management of anemia in pregnancy and algorithm used for managing iron deficiency anemia are included in this issue. Hope you find them useful! Thrombocytopenia is a common problem in pregnancy and obstetricians need a pragmatic approach to find the etiology and management algorithm.

Hemoglobinopathies are common in our country and undiagnosed in majority. Universal screening of pregnant women can help detecting minor thalassemias. Partner screening, and if partner is positive for hemoglobinopathy, prenatal screening of fetus for major thalassemia can be offered before 20 weeks of gestational age. Both iron deficiency anemia and many hemoglobinopathies have microcytosis and can be mistaken for each other. Many pregnant women receive parenteral iron if anaemia does not respond to oral iron supplementation (with presumptive diagnosis of iron deficiency anaemia) and some of them could be having a hemoglobinopathy. For these reasons, universal screening for hemoglobinopathy of pregnant women needs to be considered.

I thank the authors on behalf of the SOMI Editorial Board for their valid contribution and request members to send in articles for our next issue. You can send original articles, case reports, review articles and comments on articles from previous issue to obsmedindia@gmail.com with a cc to drharikishan@gmail.com. There is no word limit as it is in electronic format and articles will be published after the Editorial Board's approval.

Regards,
Dr. Hari Kishan Boorugu
Editor

Anaemia in Pregnancy

– Dr Padmaja Lokireddy
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Introduction

Anaemia in pregnancy is a very common problem accounting to 50% pregnancies in developing countries. WHO defines Anaemia in pregnancy as Haemoglobin <11 g/dl in antenatal period and <10 g/dl in postnatal period. Anaemia has major implications on maternal and neonatal outcomes. Early recognition and effective management will help to reduce adverse maternal and fetal outcomes.

It is a challenge to have good follow-up for patients after identifying the cause. Most common cause being iron deficiency. Given the magnitude of the problem it is cost effective to treat every pregnant lady with Iron supplementation along with dietary advice. Universal Haemoglobin check and haemoglobinopathy screening is recommended in the first visit.

Causes of anaemia in pregnancy include nutritional deficiency, Haemoglobinopathies, Haemolytic anaemias, infections, Microangiopathy and rarely haematological malignancies during pregnancy.

All patients should have booking bloods which includes CBC and haemoglobinopathy screen and partner testing in patients with Thalassemia carriers in predicting risk of major thalassemsias and adopting informed management options.

Generally, iron deficiency is treated with oral iron supplementation. If the anaemia is severe with Hb<6 in third trimester, it should be treated as high risk with parenteral iron preparations.

Various iron preparations available include ferrous sulphate, ferrous fumarate. If patient is intolerant to one preparation, we can swap to different preparations before considering intravenous preparations.

Intravenous Iron preparations include older version Iron Dextran which are cheaper but has higher reaction rates compared to Ferrous Carboxymaltose (FCM) preparations and newer version of iron sucrose preparation which are expensive but with less reactions and enables higher doses to be delivered.

Response to treatment with Iron preparation should be assessed in 1wk. If severe iron deficiency diagnosed closer to delivery we can give erythropoietin injection along with intravenous iron to hasten the response. Every effort should be made to avoid blood transfusion for a correctable cause.

If there is no expected response, patient should be referred to haematologist for further investigations to look for alternative causes.

Detection

1. Hb variant analysis prenatal screening at booking
2. CBC at 28w
3. Third trimester
4. Any time when symptoms exist

Whom to screen in particular

1. Previous anemia
2. Multiparity
3. Consecutive pregnancy <1 y of delivery
4. Vegetarians
5. Pregnant teenagers
6. Women at high risk of bleeding or recent bleeding disorder
7. Jehovah's Witnesses

Education

1. Information leaflet
 - a. Diet
 - b. Iron rich food sources
 - c. Factors that inhibit or promote iron absorption

Classification of Typing of Anaemia

1. Microcytic or normochromic anaemia
 - a. R/o Haemoglobinopathy
 - b. Trial oral iron therapy

Sequence of changes during correction of Iron deficiency: Response

1. Clinical improvement
2. Initial bone marrow response
3. Increased reticulocyte count (0.5-1.5%)
4. Haemoglobin levels increase by 1 to 2 gm% in 2-4 weeks
5. Body iron stores return to normal (ferritin levels)

No Response

1. No Haemoglobin increment in response to trial of oral iron therapy conducted correctly
 - a. Serum ferritin measurement
2. Anaemia with haemoglobinopathy
 - a. Only if serum ferritin <30 ng/ml: Offer iron therapy

Diagnosis of Iron deficiency Anaemia

1. Hb less than 11gm% or PCV less than 33% PLUS
2. Ferritin < 40 ng/ml PLUS
3. Evaluation of other known major causes of anaemia
 - Blood loss
 - Haemolysis

- Bone marrow disease
- Medications that suppress bone marrow function
- Kidney disease
- Malignancy
- Vit B12 and folate deficiency

Oral Iron Therapy

- Areas of high prevalence {India tops the list in Asia: Global nutrition report 2016}
- Daily Iron 30-60 mg and folic acid 400mcg
- Mild to moderate IDA
- Ferrous iron : 80-100 mg/d elemental iron and folic acid 400 mcg
- Once corrected, continue supplementation for three more months

Parenteral Iron Therapy

- Fail to respond to oral iron (Hb conc increase < 10 or 20 g/l in 2 or 4 weeks)
- Intolerant to oral iron or noncompliant and GA>14 w
- Severe advanced or progressive IDA (Hb <80g/l)
- Newly diagnosed IDA beyond 34 w

Total Dose Infusion

- $(15 - \text{Pts HB}\%) \times \text{Body wt in KG} \times 3 = \text{Iron in mg}$
Ganzoni Equation
- $\text{Wt (Kg)} \times \{ \text{Target Hb} - \text{Actual Hb} \% \} \times 2.4 + \text{Iron stores in mg}$
- 500 mg if Wt is > 35 kg
- 15mg/kg if Wt is < 35 kg

Formulations used

- Iron sucrose {Test dose required}
- Ferrous carboxymaltose
- Should not be given with oral iron or in presence of active infection.

Iron Sucrose

- 200 mg dose per sitting
- Administered thrice weekly
- Iv bolus undiluted push or iv push
- Test dose required at least for the first dose (should be given at a place with cardiopulmonary back-up)
- 50 mg over 2 min. wait for 2-3 min then another 50 mg
- 100-200 mg to be diluted with 100 ml NS infuse at least 15 min

Ferrous Carboxymaltose

- A maximum dose of 20mg/kg upto 1000 mg per day can be given as iv infusion
- A maximum dose of 15 mg/kg upto 1000 mg per day can be given as iv injection
- Do not administer 1000 mg of iron more than once per week(Pregnancy Category C)
- No test dose required

Erythropoiesis Stimulating Agent

- ESA not approved to treat anaemia in pregnant women without chronic kidney disease, myeloid disorders
- Administration in moderate to severe anaemia not responding to parenteral iron, in consultation with haematologist
- DOSE: 50-100 units /KG IV/SC three times weekly initially

Blood Transfusion

- Severe anaemia < 6 gm % { ACOG,NICE 2008}
- Recommend a single-unit transfusion followed by clinical reassessment and/or Hb measurement to determine the need for further transfusion
- One red cell concentrate : 240 mg of iron, which is insufficient to replace total ID and replenish iron reserves
- Concomitant IV iron to replete the iron reserves in order to minimise the number of transfusions may be considered

Antenatal Indications of Blood Transfusion

1. Pregnancy less than 36 w
 - Hb < 5 gm/dl clinical signs of CHF
 - Hb 5-7 gm/dl with CHF, hypoxia, infection, septicemia, heart disease not due to anaemia
2. Pregnancy 36 w or more
 - Hb < 6 gm/dl
 - Hb 6-8 gm/dl with CHF, hypoxia, infection, septicemia, heart disease not due to anaemia

Common Queries

- Maintain a gap of at least 2-4 hrs between levothyroxine and iron supplements
- Ask for serum folate and vitamin B 12 levels estimation in an vegetarian mother with anaemia not responding to iron therapy
- If peripheral smear is showing macrocytes with anaemia...check vitamin B12 levels and Folate levels
- In case of iron anaphylaxis... inj epinephrine should be ready

Newer Recommendations

- Obtaining ferritin levels in first prenatal visit
- If pregnant women is not anaemic, iron deficiency is present if ferritin is < 15 ng/ml
- Providing 60-120 mg iron on alternate days in single morning doses increases iron absorption and because of simplicity might increase compliance

Postpartum Anaemia

Definition

- Hb < 10 g/ dl within 24–48 h after delivery
- WHO 2011
- Hb < 11 g/ dl at 1 week post-partum
 - Hb < 12 g /dl at 8 weeks postpartum

Detection and Classification

- Pregnant women, especially those with antenatal anemia, should have an Hb determination prior to delivery
- Hb concentration be determined in all women after significant peri-partum bleeding
- Timing of haemoglobin estimation post PPH depending on clinical condition, else after 24 hrs .
- A complete blood count plus a serum ferritin level at 4–8 weeks post-partum are adequate to assess anaemia and iron status with antenatal anaemia or significant peri-partum bleeding

Prevention of Postpartum Anaemia

- Correct moderate to severe anaemia prior to delivery
- Hospital delivery
- AMTSL
- Cell salvage in CS
- Strict Protocol for PPH management

Treatment of Postpartum Anaemia Oral Iron Therapy

- Haemodynamically stable, asymptomatic or mildly symptomatic
- Mild to moderate PPA (Hb 9-11 g/dl)
- 80–100 mg elemental iron daily for 3 months
- Recheck CBC in 2-4 weeks
- Folic acid for 6-12w in areas endemic for gestational anaemia

Parenteral Iron Therapy

- Fail to respond to the correct administration of oral iron
 - Hb increase < 1 or 2 gm % 1 in 2 or 4 weeks, respectively)
 - are intolerant to oral iron be switched to IV iron

- The administration of IV iron to cover individually calculated total ID in women with moderate to severe post partum anaemia Hb<9 g/L
- Total dose infusion in a single setting to be considered only if patient is noncompliant with follow-up.

Erthyropoietin Stimulating Agent

- In severely anaemic patients with blunted erythropoiesis due to infection and/or inflammation and not responding adequately to IV iron treatment
- severely anaemic patients who refuse blood transfusion
- consultation with the haematologist

Blood Transfusion

- RBC transfusion not be dictated by Hb levels alone
- Transfusion be considered in non-bleeding patients with an Hb <6 g/ L taking clinical signs symptoms
 - risk of bleeding
 - cardiac compromise
- Single-unit transfusion followed by clinical reassessment and/or Hb measurement to determine the need for further transfusion

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POSTPARTUM ANAEMIA (PPA)

- **DEFINITION (WHO 2011)**
 - Hb < 11 g/dl @ 1 wk Postpartum
 - Hb < 12 g/dl @ 8 wk Postpartum

ORAL IRON THERAPY

- Mild to moderate PPA (Hb 9-11 g/dl)
- 80-100 mg elemental iron daily for 3 months
- Recheck CBC in 4 weeks
- Folic acid for 6-12w

PARENTERAL IRON THERAPY

- In those who fail to respond to the correct administration of oral iron
- The administration of IV iron to cover individually calculated total ID in women with moderate to severe post partum anaemia Hb < 9 g/L

Anaemia in Pregnancy

Definition

Mild	9-10.9 gm%
Moderate	7-8.9 gm%
Severe	4-6.9 gm%
Very severe	< 4 gm%

Diagnosis

1. Haemogram:

Investigation	Normal	Iron Deficiency Anaemia	Megaloblastic Anaemia	Haemoglobinopathies
Mean Corpuscular Volume (MCV)	85-90 fl	<80	>100	<75
Mean Corpuscular Haemoglobin (MCH)	28-32 pg	<27	Normal	Normal
Mean Corpuscular Haemoglobin Concentration (MCHC)	32-34%	<32	Normal	Normal
Peripheral Smear	Normocytic Normochromic	Microcytic Hypochromic. Target Cells. Anisopoikilocytosis	Macrocytes. Anisocytes, Poikilocytes, Ovalocytes, Howell-Jolly Bodies	Microcytes. Sickle Cells. Anisopoikilocytosis
Serum Iron	70-120 mcg/dl	<60	Normal	Normal
Total Iron Binding Capacity (TIBC)	300-350 mcg/dl	>350	Normal	Normal
Transferrin Saturation	16-30%	<16	Normal	Normal
Serum Ferritin	20-250 mcg/L	<15	Normal	Normal
Red Cell Distribution Width (RDW)	11-15%	>15	Normal	>15
Vit B12 Levels	200-900 pg/ml	Normal	<200	Normal

2. **Haemoglobin electrophoresis** -- To be asked for if haemogram suggestive of haemoglobinopathies – especially very low or high MCV, and in anaemias resistant to Fe therapy.

3. **S. Iron, S transferrin saturation, TIBC, S. Ferritin, Vit B12** : To confirm etiology

4. **Stool examination: In nutritional anaemia treatment**

Cap Autrin 2-3 daily (1 cap, 1 hr before breakfast & 1 cap 1 hr before dinner)

Tab Livogen 3-4 daily (2 tabs 1 hr before breakfast & 1 or 2 tabs 2 hrs after dinner)
Preferably with a glass of citrus juice

Injectable Iron

Indications:

Non compliance/ Intolerance to oral iron
Proven malabsorption

Contraindications:

History of anaphylaxis to parenteral iron
First trimester of pregnancy
Active acute/chronic infection
Chronic liver disease

Iron Sucrose :Inj Orofer S

(1 amp = 100mg Elemental Fe)

Ferric carboxy maltose

(1amp= 500 mg Elemental iron)

Referral Criteria

Resistant anaemias
Severe anaemia
Haemoglobinopathies
Advanced gestation (>34 wks)

Recheck Investigations

Repeat haemoglobin after 2 wks
Haemoglobin electrophoresis if compliance assured and suspicion of haemoglobinopathy

Prophylaxis

Tab Livogen 1 daily, 1 hr before breakfast
Cap Autrin 1 daily, 1 hr before breakfast
From 16-18 wks till delivery

Blood Transfusion

Severe anaemia near term
Severe anaemia peripartum

P.S : The brand names of the drugs are given just to cite examples. We do not wish to promote/support any particular brand.

Idiopathic Hemolytic Anemia of Pregnancy

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Abstract

“Idiopathic Hemolytic Anemia of Pregnancy” or “Pregnancy Induced Hemolytic Anemia” is a rare entity where gravid mothers acquire a sudden severe anemia with features of a hemolytic process but no obvious autoimmune or other etiology, in spite of extensive testing. Some do show evidence of autoimmune antibodies on more sensitive tests and these cases may be termed “Pregnancy Induced Warm Autoimmune Hemolytic Anemia”. There is heterogeneity in case presentations suggesting that this entity may not have a common pathogenetic pathway. It typically occurs in the third trimester and can occasionally be life threatening to mother and fetus. It can recur in subsequent pregnancies. The only known association is the pregnant state, the only effective treatment is delivery. Some cases respond to steroids or other measures.

Clinical Presentation

This is a rare disorder, estimated to occur less than once in 500,000 pregnancies and is very scantily reported in the literature. Presentations may vary but it seems to be characterized by the mother developing a sudden, severe (<8 gm% Hb) anemia, late in the pregnancy, usually in the third trimester. Typical clinical features of anemia will be present in the mother but fetal status is usually normal unless fetal anemia develops as well. This is more likely in IgG Warm Antibody associated maternal hemolysis, since these maternal auto-antibodies easily cross the placenta. Mild to moderate hepatosplenomegaly may be present.

Pathogenesis:

Pregnancy is the only known association and there is no known cause and this entity probably does not represent any single pathogenetic pathway. However, a recent hypothesis suggests that the pregnant state induces increased sensitivity of the maternal reticuloendothelial system which may then respond to even low levels of maternal autoantibodies by lysing RBCs.

Differential Diagnoses:

There are numerous causes for maternal anemia, especially in the third world, which have to be

systematically ruled out. Any anemia is the result either of low RBC production or high RBC loss.

Hypoproliferative Anemias in pregnancy (low RBC production):

- Iron deficiency, B12/Folate deficiencies account for the vast majority in any trimester.
- Hemoglobinopathies usually manifest way before or in early pregnancy.
- Alcohol & medications
- Infections (Parvovirus B19, HIV, CMV, EBV etc)
- Aplastic Anemia

Hyperproliferative Anemias in Pregnancy (high RBC destruction or bleeding loss):

Blood loss may occur with abruptio, placenta previa or at delivery.

RBC destruction causes in third trimester include

- Malaria
- HELLP (Hemolysis Elevated LFT Low Platelets Syndrome)
- AFLP (Acute Fatty Liver of Pregnancy syndrome)
- TTP (Thrombotic Thrombocytopenic Purpura)
- HUS (Hemolytic Uremic Syndrome)
- Frank Autoimmune Warm Antibody or Cold Agglutinin Hemolytic Anemia, especially those associated with other autoimmune disorders or neoplasms

Investigations:

Review of the RBC indices, peripheral blood smear, Reticulocyte Count (adjusted for the Hb) are a must as in any anemia. These invariably give the clues towards a diagnosis and for further work up. IHA of Pregnancy usually shows normal indices, spherocytes or a bland smear and a low Reticulocyte count. It is important to realize that the Reticulocyte count neither confirms nor refutes the presence of hemolysis, it merely indicates the bone marrow response. There may be severe reticulocytopenia with hemolysis.

Other evidence of hemolysis including elevated LDH and high Indirect Bilirubin may be present but are not specific.

All other causes of pregnancy associated anemia should be systematically ruled out, including malaria, HIV, Parvovirus and EBV IgM.

Direct (DAT) & Indirect Coombs' tests are negative. Serum Haptoglobin level is usually severely low and a Bone Marrow Biopsy & Aspiration are generally needed, which shows increased erythropoiesis without evidence for any other disease.

Even if DAT is negative, RBC Surface Ig G or other class Warm Autoantibodies are sometimes positive if tested for by more sensitive techniques (Flow Cytometry, column gel agglutination, SPRCA, etc).

Monitoring the fetal status is usually a challenge with no proper guidelines and with the inconsistent results of available routine tests. Doppler US study of fetal Middle Cerebral Artery Peak Systolic Velocity (MCA-PSV) has been reported as an effective non-invasive monitor for fetal anemia. Invasive techniques (amniocentesis, cordocentesis) are not routinely encouraged and may be best reserved for those fetuses with high MCA-PSV.

Management:

- PRBC transfusions are indicated only if the mother is severely symptomatic, clinically unstable or there is fetal distress. There is no recommended routine Hb 'trigger' for transfusion. Finding the most compatible packed cells may be a challenge.
- High Dose IV Steroids are warranted as a trial or if the presence of autoantibodies is demonstrated. The responses are inconsistent in the reported literature.
- Rituximab (anti-CD20 antibody therapy) is indicated with severe anemia and inability to deliver, especially if the presence of warm autoantibodies is demonstrated. Rituximab does cross the placenta and inhibits fetal B lymphocytes, but subsequent development seems to be normal and vaccination titers at 10 months are adequate. It is deemed safe in pregnancy.
- Campath-1h (anti-CD52 antibody therapy) has also been tried in some case reports.

- IV Immunoglobulins are considered only in life-threatening situations. They have the issues of cost, risk, low efficacy and inconsistent results.
- Other supportive care includes adequate oxygenation to improve plasma dissolved O₂ concentrations, folic acid supplements, intravascular volume repletion and bed rest.
- Delivery as soon as possible is the most effective solution and results in rapid improvement of the mother.
- Mothers should be counselled that subsequent pregnancies are at high risk of repeat hemolysis.
- Infants usually do well after delivery if adequately supported. If there is severe hemolytic anemia in the newborn, PRBC Exchange Transfusions are preferred over simple transfusions as they both improve the Hemoglobin and simultaneously wash out maternal Immunoglobulins.

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Haemoglobinopathies, Prevention – in the Context of Pregnancy

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Introduction

It is well acknowledged now that anaemia is highly prevalent world over and is especially so in Indian women. The widely quoted figures for anaemia say that over 80% of women in the reproductive age group have low haemoglobin levels. It is also true that the most common cause for anaemia in the Indian woman and child is diet deficiency in iron and vitamins. These are largely preventable and hence of great importance. This fact has influenced health policies that have led to nationwide advocacy of iron and folic acid supplementation for the antenatal woman.

Why it is necessary to look for haemoglobinopathies?

Given that nutritional deficiencies are the most common cause of anaemia among women in the reproductive age in our population, it is a common assumption that supplementation for iron deficiency, folate deficiency or vitamin B12 deficiency will correct the anaemia in routine clinical practice and the same is applicable to the pregnant woman. In this background it is important to understand and emphasise that there are other preventable forms of anaemia and that demand appropriate interventions.

The leading example worldwide for these are the debilitating haemoglobinopathies. Beta Thalassemia major and Sickle cell anaemia are the most severe forms of these disorders. Beta Thalassemia major/ Thalassemia major as it is commonly known is the single most common cause of inherited form of anaemia. An affected individual is typically an infant with pallor, splenomegaly and anaemia severe enough to warrant transfusion of red cells often at first presentation. This transfusion requirement becomes a lifelong need, thus crippling the affected child and the family for the rest of the child's life through adulthood. The only cure if possible at present is bone marrow transplantation; although recent advances suggest that gene therapy is a suitable therapy.

Factors associated with the occurrence of haemoglobinopathies in India:

- i) Given that India is expected to have 30 million carriers (about 3 .5% of the population), has an existing burden of Thalassemia major around 65000 to 67000 to which 8000 to 10000 are added every year to the already existing affected population is considered. The other significant forms of inherited form of anaemia which have serious clinical implications in our population is Sickle cell anaemia, the carrier frequency for which

is 1 to 35% of population varying from region to region. In addition India is home to a less severe yet clinically significant HbE disease, another haemoglobinopathy, also clinically significant are HbD and HbC.

- ii) Haemoglobins that lead to these conditions are inherited as autosomal recessive trait, from parents who do not manifest the disease and are hence termed as 'carriers' of the abnormal haemoglobin. Genetic passage is the only manner in which haemoglobinopathies occur in the community. Sociocultural practice of marriages happening within communities contributes to the larger number of affected individuals being born among certain population groups and in some ethnic groups. In the southern Indian states as also among pockets of tribes across the country, consanguineous marriages are accepted (including first degree consanguinity) thus concentrating the genetic pool further.
- iii) In the background of high prevalence of iron deficiency anaemia that can coexist and also mimic carrier status for Beta thalassemia, carriers for this abnormal haemoglobin remain undetected. Nearly all carriers in the population are detected retrospectively after they attain parenthood and have a child affected with Thalassemia major or Sickle cell disease.
Concomitant iron deficient state also contributes to possible missing the carriers among women.
- iv) Lack of awareness on carrier detection is a significant factor contributing to the addition of children with Thalassemia major and other haemoglobinopathies. Carrier detection is best done premarital or pre pregnancy or even during early antenatal period (within 10 weeks of pregnancy).

Why detect carriers?

Haemoglobinopathies show an autosomal recessive pattern of inheritance and are hence protected by the other allele, in the heterozygous state. The homozygous state in which both alleles are abnormal for the globin chain will manifest the disease. An individual who has inherited one abnormal gene does not manifest the disease and remains a potential carrier for the disease. Thus when two carriers procreate, the birth of a homozygous

child is real with a 25% chance of such inheritance in every pregnancy. When a carrier's partner is not a carrier, a homozygous child is not a possibility. This emphasises the need to detect carriers of haemoglobinopathies as a potential tool in the prevention of the birth of affected children. Knowing the carrier status has the potential to offer options for the future.

How to identify carriers?

Abnormal haemoglobins can be identified by several methods of testing for their presence in blood as well as by identifying the specific mutation on the DNA. Testing blood is a simple and affordable way to establish the Hb status of an individual. The methods generally employed are:

- i) High Performance Liquid Chromatography (HPLC): Simple, automated technique useful for large number of samples such as in community screening, laboratories serving as referral centres.
- ii) Capillary electrophoresis: Automated and simple technique can be used for smaller sample loads and largely comparable to HPLC.
- iii) Conventional agar gel electrophoresis: Suitable for few or occasional sample load and labor intensive
- iv) DNA mutation analysis: Specific specialised PCR technique used for confirmation of the nature of abnormal haemoglobin requiring familiarity of steps and expertise to interpret

Of these, HPLC is recommended for screening and specific DNA mutation analysis for confirmation.

Complete Blood Count (CBC) is widely used as a pre-screen in view of the wide use of automated blood cell counts even in developing countries, to broadly separate iron deficiency anaemia from probable Beta thalassemia trait (BTT). The rationale is that a combination of microcytosis, hypochromia with a normal range Red cell distribution width (RDW) indicates possible BTT while microcytosis with hypochromia and raised RDW is expected in iron deficiency anaemia. CBC can also help pick up carriers with normal haemoglobin; but with microcytosis and hypochromia. Most carriers are asymptomatic and the anaemia remains undetected until a CBC is done for an unrelated cause.

When, who, how to screen?

While it would be good to screen all who are potential parents, it will be more practical to have target populations from among whom carriers can be detected

for appropriate interventions. Several strategies are employed. Thus:

- i) Screening members of a family related to an affected child is a sensible approach in the prevention of the birth of yet another affected child. This is a rewarding exercise in preventive medicine and must be diligently followed. Similarly screening among populations known to have higher incidence of carriers among groups or communities in Gujarat, Punjab, Central India, Eastern states, Tribal communities across the country yields results.
- ii) Pre pregnancy screening is possible in planned pregnancy; this must be offered when a couple seek counsel for pregnancy in general. Among those from communities known to have higher incidence of haemoglobinopathies; when there is a known affected individual among the biologically related members of the families screening by HPLC must be done.
- iii) Premarital screening can be done any time and is effective when followed up by counsel. It will be pertinent here to inform the individual that the result is valid for lifetime and will not change with time or any treatment thus ensuring compliance with testing and effective recall at the appropriate time in the individual's life.

What is the significance of antenatal screening?

A pregnant woman at the first instance of presentation presents the best opportunity to detect a carrier thus providing scope for counsel and intervention if indicated. Carrier detection is an established practice in many developing and developed countries, especially in the antenatal period as during this period follow-up interventions are possible.

- The first antenatal check must include CBC as well as HPLC for this to be of value in case intervention is deemed necessary.
- Carrier status for any of the haemoglobinopathies must be immediately reviewed with the findings on screening by HPLC of the partner.
- Any intervention would be necessary only in the instance of the partner also being detected with a carrier status and not otherwise. This provides an opportunity to inform the couple of the relevance of prenatal testing and counsel further.
- In addition to detecting beta thalassemia carriers, other clinically significant abnormal haemoglobins

like Sickle Hb, HbD, HbE or suspicion of Alpha thalassemia trait can be picked up. Identifying Sickle haemoglobin will be important if anaesthesia is to be administered and Sickle carriers may go undetected leading to likely complications resulting from hypoxia that can precipitate sickling.

- Also if a carrier is detected during the antenatal screen it is an opportunity to detect other possible carriers among her siblings.
- In all antenatal women with history suspicious of haemoglobinopathy in the family, screening by HPLC must be done in case not already performed.

What role can Gynaecologist – Obstetrician play in the prevention of Haemoglobinopathies?

It will be an understatement to say that the most significant and effective role in carrier detection falls within the realm of clinical practice of a Gynaecologist – Obstetrician for these reasons:

- i) The most effective counsel is possible in the circumstances in which a couple or prospective parent takes counsel from the physician.
- ii) With the current trend of increasing need for assisted reproduction; it is imperative that preventable and identifiable disorders must be screened for, including among sperm donors.
- iii) Preconception screening must include screening for abnormal haemoglobins in both the partners, to avoid unfortunate happenings such as the birth of a child with Thalassemia major.
- iv) Sickle cell disease can pose a threat during pregnancy and labour if not detected.
- v) Counselling for these preventable disorders will create awareness, willingness and participation in screening.
- vi) As for other procedures and clinical situations, it is best to take informed consent prior to testing for these inherited disorders to ensure post testing interventions is indicated.

What are the achievable goals?:

The possibility of a future without homozygous abnormal haemoglobin related disorders such as Thalassemia major, Sickle cell disease and Double heterozygous can be realised with sensible and persistent initiatives. This is a reality in some parts of the world; the best example of which is Cyprus, a small island that brought down the

birth of a Thalassemia affected child from 18-10 cases per year to near zero in a span of two decades.

Is there a National policy? : The National Health Mission (NHM) 2017, Government of India has issued guidelines for the prevention of Thalassemia and haemoglobinopathies. This has clearly highlighted the urgency for detecting carriers as the definitive step. The emphasis in these guidelines are on:

- Awareness in the community; including schools, colleges
- Screening of pregnant women and the husband
- Establishing prenatal diagnostic facilities

In terms of cost of screening for carriers, NHM underscores the cost effectiveness of population screening as compared to the cost incurred in the support of children born with Thalassemia major.

Suggestions:

Workable strategies for our population, our communities will be any of these:

- i) Antenatal screening as a universal test for every primigravida at the first antenatal check with CBC and HPLC
- ii) Antenatal screen for every woman at the time of presentation
- iii) Pre pregnancy screening in all planned pregnancies
- iv) Pre-marital screen which may be timed with pre-employment/ pre-college admission
- v) Mandatory screening of members related to an affected child
- vi) Any time when a microcytic hypochromic anaemia is detected
- vii) Unexplained anaemia
- viii) Pre surgical testing
- ix) Blood donor screening

Summary:

In order to work towards a healthier future generation, WHO and NHM have recognised the need to pursue actively the prevention of Thalassemia, Sickle cell anaemia and related haemoglobinopathies in the Indian context. The essential steps for this are well laid out through guidelines for preventive measures by NHM. In this process, the importance of antenatal screening

Haemoglobinopathies, Prevention – in the Context of Pregnancy

is emphasised as a vital tool. The first presentation at the antenatal clinic is the best opportunity to perform carrier detection tests. A CBC as well as Hb- HPLC are simple investigations that permit detection of Beta Thalassemia carriers, Sickle Hb and other abnormal haemoglobinopathies such as HbE, HbD, HbC which are all clinically significant. The detection of a carrier woman must be accompanied by screening of the

partner. This provides an opportunity to intervene if the partner is also a carrier for an abnormal haemoglobin; which implies 25% probability of a child affected with haemoglobinopathy being born.

In this entire effort towards prevention of serious disabling haemoglobinopathies in the community, the partnership of the Gynaecologist-Obstetrician, Pathologist and the potential parent is vital.

Introduction

Thrombocytopenia (platelet count of < 1.5 lakhs/cumm) is the most common hematologic disorder in pregnancy after anaemia. It affects 5-10% of women in pregnancy and postpartum period.¹ Many times, it is diagnosed incidentally in pregnancy as a part of complete blood count. But it can be an important marker for many underlying conditions. As the gestational age increases, the platelet counts fall gradually.² The cause for the physiologic decrease in platelet count is multifactorial and is related to hemodilution, increased platelet consumption, and increased platelet aggregation driven by increased levels of thromboxane A₂.³ However, we should note that this definition of platelets < 1.5 lakhs/cumm is arbitrary and not clinically relevant. However, counts of < 1 lakh/cumm, which is the definition for thrombocytopenia adopted by an International Working Group, are observed in only 1% of pregnant women.⁴ Any platelet count of less than 1 lakh/cumm needs to be investigated. In this chapter, we will go through the etiology, work-up and management of common conditions of thrombocytopenia in pregnancy.

Diagnosis

In pregnancy, thrombocytopenia is usually diagnosed incidentally while doing blood counts. Although clinical

findings such as easy bruisability may be seen in other bleeding disorders, but in thrombocytopenia, the most common manifestations are petechiae, echymosis, epistaxis, bleeding gums, bleeding mucus membranes and menometrorrhagia. So, if women present with any of these symptoms, it should prompt clinicians to look to platelet counts. In routine examination, presence of any of the following such as fever, high blood pressure, splenomegaly, caput medusae, GI bleed, click/murmur of a valve in cardiovascular examination or presence of any infections such as HIV, Dengue or viral should be a trigger to look for thrombocytopenia.

Etiology

To arrive at an etiology of thrombocytopenia in pregnancy, only two questions need to be answered

Is this related to pregnancy? Is this isolated thrombocytopenia?

And if the answer to both the questions is a “yes”, it is gestational thrombocytopenia. If it is pregnancy specific and associated with systemic disorders, then preeclampsia, HELLP (Hemolysis, Elevated Liver Enzymes, Low platelets) syndrome and Acute fatty Liver of Pregnancy (AFLP) need consideration.

To look at pregnancy specific conditions and their frequency, please refer to table 1.4,5

Table 1.4,5

Pregnancy specific conditions			
Isolated thrombocytopenia		Associated with systemic disorders	
Gestational	70-80%	Preeclampsia	15-20%
		HELLP Syndrome	$< 1\%$
		AFLP	$< 1\%$
		DIC	$< 1\%$

To look at conditions unrelated to pregnancy, please refer to Table 2.4,5

Table 2.4,5

Conditions unrelated to pregnancy			
Isolated thrombocytopenia		Associated with systemic disorders	
Immune	1-4%	TTP / HUS	< 1%
Drug induced	< 1%	SLE	<1%
Type 2 Von Willebrand	< 1%	APLA	< 1%
Congenital	< 1%	Viral Infections	< 1%
		Bone marrow related	< 1%
		Nutritional	< 1%
		Splenic sequestration	< 1%
		DIC	< 1%

TTP = Thrombotic Thrombocytopenic Purpura HUS = Hemolytic Uraemic Syndrome
 SLE = Systemic Lupus Erythematosus APLA = Antiphospholipid Antibody Syndrome
 DIC = Disseminated Intravascular Coagulation

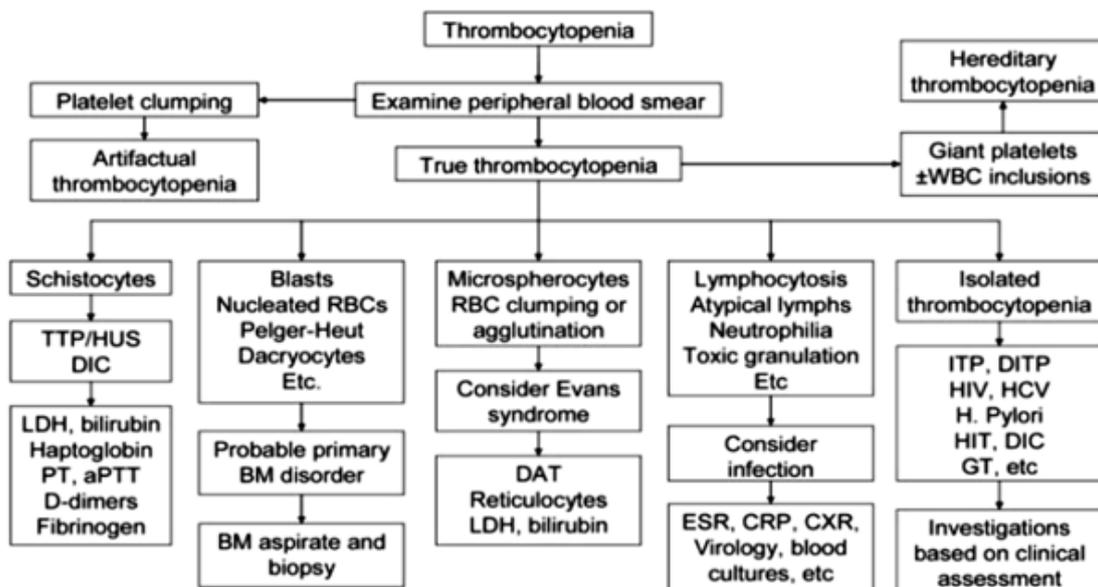
Work-up

The work-up of a woman presenting with thrombocytopenia depends on the history, clinical signs and symptoms. History taking involves enquiring about the onset, whether new onset or chronic, presence of mucosal bleeds, menorrhagic cycles, fever, medication use (Frusemide, Ranitidine, Heparin) or presence of any co-existing malignant conditions or infections such as HIV (Human Immunodeficiency Virus) and Hepatitis C Virus (HCV). History of travel to endemic areas for infections such as Dengue must be elicited. Presence of symptoms for imminent eclampsia must be looked for.

General examination to look for presence of fever, high blood pressure, lymphadenopathy and mucosal / conjunctival hemorrhages must be done. Systemic examination to look for any pointing signs such as splenomegaly, murmur of cardiac valves, any signs of thrombosis should be looked for.

Initial laboratory investigations include a complete blood count with peripheral smear, liver function tests and viral screening for HIV, Hepatitis B and HCV.^{4,5} A good peripheral smear may most often guide towards diagnosis.

The algorithm for peripheral smear is given in figure 1.4



The other tests such as tests for APLA, SLE, direct antiglobulin test, quantitative immunoglobulin measurement, Type 2 von Willebrand's and other viral markers, bone marrow biopsy and ultrasound of abdomen should be done as clinically indicated in consultation with relevant specialists.

Gestational Thrombocytopenia

This is the most common cause of thrombocytopenia in pregnancy. It occurs in 4.4-11.6% of all pregnancies.¹ The onset is usually in mid-second or third trimester. Postulated etiologies are hemodilution and increased clearance.⁵ Usually, platelet count in this condition is between 1.2-1.49 lakhs/cumm.¹ Around 1% of women may have counts from 50,000 – 99,000/cumm.¹ It is extremely rare to have platelet count below 50,000/cumm in this condition.¹ These women are asymptomatic and have no clinical signs and symptoms. The diagnosis is the one of exclusion. Here, thrombocytopenia does not exist outside of pregnancy. The recurrence risk in subsequent pregnancy is unknown. The risk for neonatal thrombocytopenia is very low 0.1-1.7%, and that is why there is low risk of fetal haemorrhage.⁵ There is no recommendation of frequency of repeating platelet count, although, monthly counts are recommended empirically.^{4,5} These women can be allowed to go in spontaneous labour at term and there is no recommendation for induction of labour because of this condition. Caesarean section should be reserved for obstetric conditions. Epidural for labour analgesia may be given at counts > 80,000/cumm. These women should be managed in a tertiary centre. Documentation of normal counts after six weeks postpartum should be done.

Pre-eclampsia/HELLP Syndrome

New onset of hypertension beyond 20 weeks of gestation with proteinuria and low platelet counts amounts to preeclampsia with severe features. The cause of thrombocytopenia in these conditions is microangiopathy and increased consumption. Bleeding from any site is not seen unless there is associated disseminated intravascular coagulation. Delivery is decided in consideration of other factors such as gestational age and other organ involvement. In most cases, it may warrant immediate delivery after maternal stabilization. This condition is also a reversible one. The improvement in counts is seen after delivery. The risk of neonatal thrombocytopenia is 1.8%, and neonatal intracranial haemorrhage is rare.⁵

Acute Fatty Liver of Pregnancy

This is a pregnancy specific condition, where jaundice, liver enzyme derangement and hypoglycaemia are the hallmarks. Thrombocytopenia may be seen due to either microangiopathy or as a part of DIC. This condition warrants delivery after maternal stabilization and the counts are known to improve after delivery.

Immune Thrombocytopenia (ITP)

ITP is the most common cause of platelets < 50,000/cumm in pregnancy during first or second trimesters.¹ Thrombocytopenia further aggravates in third trimester due to physiologic changes. Many times, the woman comes to obstetrician with a prior diagnosis. Pregnancy, per se is not a contraindication in this condition, unless, the woman is on teratogenic drugs such as Mycophenolate or Cyclophosphamide. Sometimes, this condition is diagnosed de-novo in pregnancy. It is characterised by isolated thrombocytopenia in absence of other etiologies. The diagnosis is that of exclusion. There are no tests to confirm ITP. Antiplatelet antibody test is not recommended, and bone marrow biopsy is done in resistant cases in pregnancy.⁴ The diagnosis and management of ITP should be done in consultation with a haematologist.

In pregnancy, usually, there is no need of any treatment if the counts remain > 30,000/cumm and there are no bleeding manifestations.⁴ However, if the woman is taking treatment and the drugs are not contraindicated, she can continue those in pregnancy. If the counts are < 30,000/cumm or there are bleeding manifestations, the first line therapy is oral corticosteroids or IV immunoglobulin.⁴ The second-line treatment is combined oral steroids and immunoglobulin. Splenectomy is also a recommended second-line treatment and can be done in second trimester, when warranted. The third-line drugs such as Cyclosporin, Azathioprine, Dapsone and Rituximab may be given. The other third-line drugs such as Danazol, Mycophenolate, Cyclophosphamide and Vinca Alkaloids are contraindicated in pregnancy.⁴

Pregnancy in these women can be allowed to go till term. There is no recommendation of repeating maternal platelet count, but empirically, monthly counts are advised. Also, there is no recommendation for ultrasound in antenatal period to look for fetal intracranial haemorrhage. Interventions such as induction of labour and caesarean section are reserved for obstetric indications.^{1,4,5} Epidural for labour analgesia may be given depending on platelet counts. If the counts are low, other

labour analgesia options such as Entonox or intravenous opioids can be offered. Fetal invasive procedures such as fetal scalp blood sampling and application of fetal scalp electrode are contraindicated. During delivery, counts should be more than 50,000/cumm for vaginal delivery and more than 100,000/cumm for caesarean section.^{1,4,5}

Platelet transfusion should be reserved for indications such as obvious bleeding, counts less than 10,000/cumm or any operative interventions with counts less than 50,000/cumm.^{4,5}

Neonatal thrombocytopenia in maternal ITP cannot be predicted, but in 52% of cases, it can be detected in antenatal ultrasound.⁵ There is no correlation of maternal counts to neonatal thrombocytopenia. The risk of neonatal thrombocytopenia is 10% if maternal platelet count is < 50,000/cumm and 5% if the counts are < 20,000/cumm. However, the risk of intracranial haemorrhage is < 1.5% of all ITP.⁴ The only predictor of neonatal thrombocytopenia and intracranial bleed is its occurrence in older sibling.⁴

In neonatal period, counts reach nadir in 2-5 days and start rising from 7th day onwards.⁴ The neonatologist should do platelet counts at birth (avoid heel prick-sample for fear of spurious thrombocytopenia) and if counts are normal, no further investigations are recommended. Although a close watch for any bleeding episodes should be done. If the counts are < 50,000/cumm, a neurosonogram should be done to look for intracranial haemorrhage. Intramuscular injections should be avoided. If the counts are < 30,000/cumm or there are bleeding episodes, then intravenous immunoglobulin at 1gm/kg and platelet transfusion are recommended. The counts are known to rise after 7th day.⁴

Other Causes

The other causes of thrombocytopenia are rare. The treatment of primary underlying condition is the dictum. All these conditions require consultations with respective specialists.

Conclusion:

It is important to do full blood counts at booking and diagnose a potential underlying ITP. Thorough history, examination and peripheral smear may usually lead to the diagnosis. The other tests can be done considering the clinical picture. The commonest causes of thrombocytopenia in pregnancy are gestational, preeclampsia, HELLP and ITP. The other causes are rare and all of them require joint consultation with a haematologist.

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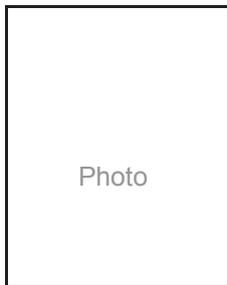
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