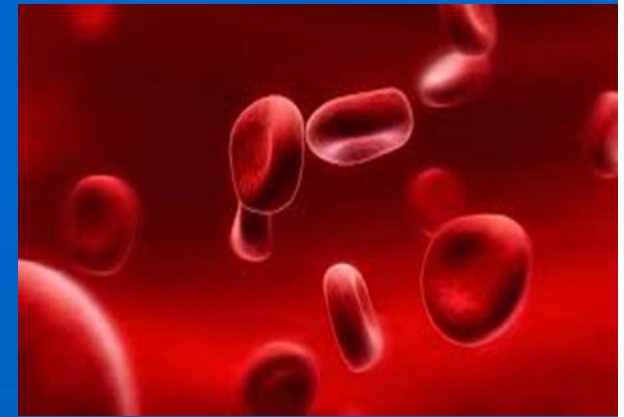




Anaemia in Pregnancy and Maternity

S Patni

Consultant Obstetrics and fetomaternal
Medicine

Birmingham Heartlands hospital

19th May 2014

Overview



- Background
- Physiology
- Etiology/Causes
- Management options
- Current Evidence/literature review
- Conclusion

Background

- Globally, anaemia affects 1.62 billion people about 25 % of the population.
- Highest prevalence is in preschool-age children (up to 47.4 %), and next is pregnant women, 41.8% and the lowest prevalence is in men about 12.7%. (WHO 2008)
- A precise definition of anaemia in pregnant women is not straightforward
 - given the pregnancy associated changes in plasma volume and RBC mass,
 - ethnic variation between white and black women,
 - and the frequent use of iron supplementation in pregnancy.

NICE	BCSH	WHO	CDC
11 g/dL: first contact	<11g/dL : 1 st trimester	<110 g/L (11 g/dL)	<11 g/dL:1 st and 3 rd trimesters
10.5 g/dL: at 28 weeks	<10.5 g/dL :2 nd &3 rd	or	< 10.5 g/dL: 2 nd trimester.
	<10 g/dL in postpartum period	hematocrit < 33 %	

- Severe anaemia in pregnancy is defined as hemoglobin <70 g/L (7 g/dL). Very severe anaemia is defined as hemoglobin <40 g/L (4 g/dL).

Physiologic changes in pregnancy

- **Physiologic (Dilutional) anemia**

- **Plasma volume**

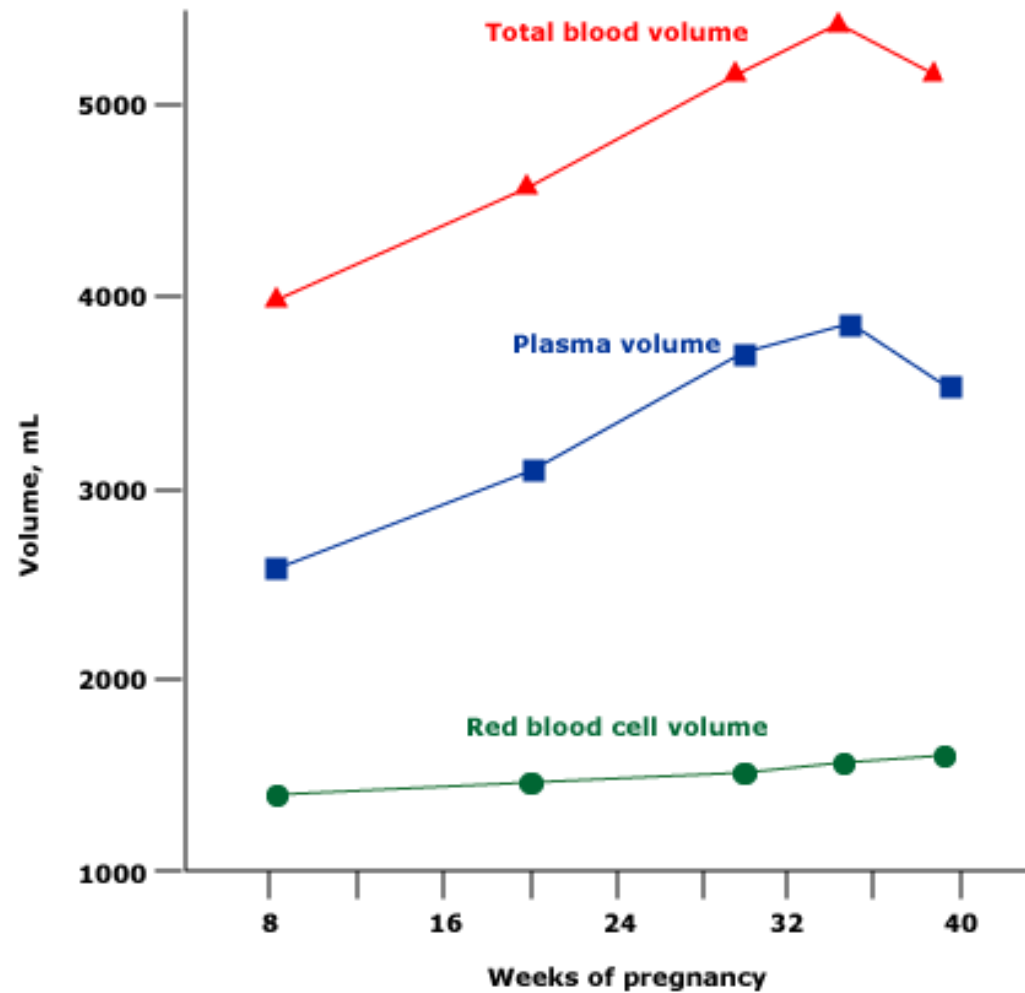
- Increases by 10 to 15 % at 6 to 12 weeks
- Expands rapidly until 30 to 34 weeks
- Plateaus thereafter
- Total gain at term : 1100 to 1600 mL
- Plasma volume at term: 4700 to 5200 mL, 30 to 50 % above non-pregnant
- Decreases postpartum and non-pregnant levels at six weeks after

- **Red blood cell mass**

- Increase at 8 to 10 weeks of gestation
- Steadily rises by 20 to 30 % (250 to 450 mL) above nonpregnant levels by term in women on iron supplements
- Versus an increase by 15 to 20 % (200-250 mL) in those not on iron supplements

- The greatest disproportion occurs during the late second to early third trimester (lowest hemoglobin is typically measured at 28 to 32 weeks).

Total blood volume, plasma volume and red cell volume in normal pregnancy



Data from Shnider SM, Levinson G. *Anesthesia for Obstetrics*, 3rd ed, Williams & Wilkins, Baltimore, p. 8.

UpToDate®

Etiology

- There are two general approaches one can use to help identify the cause of anaemia:
 - A kinetic approach, addressing the mechanism(s) responsible for the fall in hemoglobin concentration.
 - 3 subtypes:
 - Decreased RBC production
 - Increased RBC destruction
 - Blood loss
 - A morphologic approach categorizing anemias via alterations in RBC size ie, mean corpuscular volume (MCV) and the reticulocyte response.
- 3 subtypes:
 - Microcytic
 - Macrocytic
 - Normocytic
- The normal RBC:
 - Volume of 80 to 96 femtoliters (fL, 10^{-15} liter)
 - Diameter of approximately 7 to 8 microns
 - MCV decreases during pregnancy and averages 80 to 84 fL in the 3rd trimester

Etiology : Kinetic-1

Decreased RBC production:
Rate of RBC production is less than that of RBC destruction

Lack of nutrients: Iron, B12, or folate:

- Nutritional /Dietary lack
- Malabsorption, eg, IBD, pernicious anaemia, celiac disease, sprue,

Bone marrow disorders

- Aplastic anemia,
- Myelodysplastic syndromes,
- Tumor infiltration

Bone marrow suppression

- Drugs, chemotherapy, irradiation

Low levels of trophic hormones, which stimulate RBC production, such as EPO

- chronic renal failure
- hypothyroidism

The anemia of inflammation, associated with infectious, inflammatory, or malignant disorders

Increased RBC destruction
RBC life span < 100 days: definition of hemolysis
Anaemia when bone marrow unable to replace >5 % of the RBC mass / day, (RBC survival of 20 days)

■ **Inherited haemolytic anaemias**

- Sickle cell disease
- Thalassemia major
- Hereditary spherocytosis

■ **●Acquired haemolytic anaemias**

- Coombs'-positive autoimmune hemolytic anemia
- Thrombotic thrombocytopenic purpura
- Malaria
- Paroxysmal nocturnal hemoglobinuria

Etiology-Kinetic-2

Blood Loss

- Iron deficiency usually occurs
 - In males after losses of ≥ 1200 mL
 - In females after losses ≥ 600 mL.
- But this may occur with much lesser losses if females have absent iron stores:
 - 25 % of menstruating women,
 - Rapid successive childbirth
 - Prolonged breast feeding

Causes

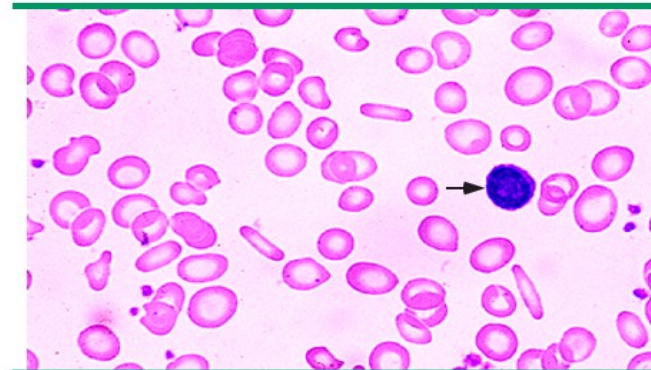
- Obvious bleeding :
 - **Childbirth** (up to 1000ml with no significant drop on Hb)
 - Trauma, melena, hematemesis, severe menometrorrhagia
- ●Occult bleeding
 - slowly bleeding ulcer or carcinoma
 - ●Induced bleeding: repeated diagnostic testing , hemodialysis losses, excessive blood donation)

Etiology: Morphologic-1

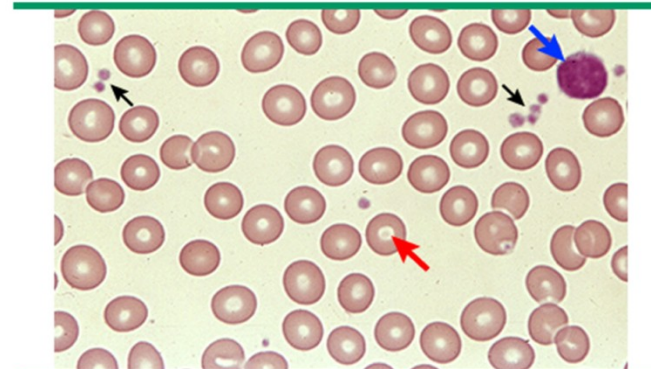
Microcytic Anaemia

- $MCV < 80$ fl
- Usually accompanied by a
 - ↓ Hb content within the RBC (mean corpuscular haemoglobin, MCH)
- 3 most common causes of microcytosis :
 - Iron deficiency
 - Alpha or beta thalassemia minor,
 - Anaemia of inflammation (anaemia of chronic disease).

Microcytic hypochromic red cells in iron deficiency anemia



Normal peripheral blood smear

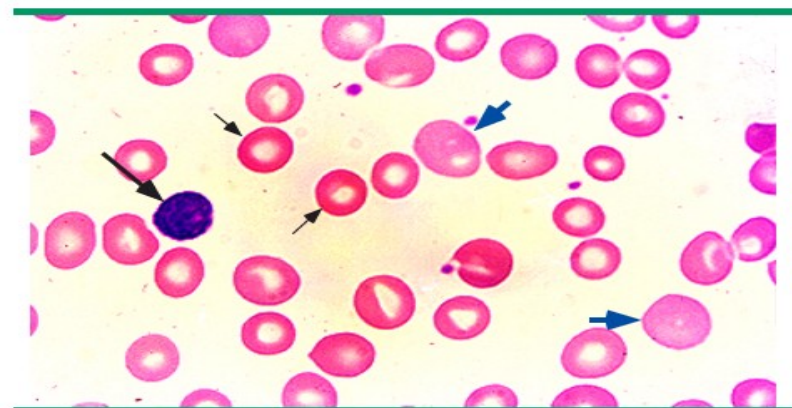


Etiology: Morphologic-2

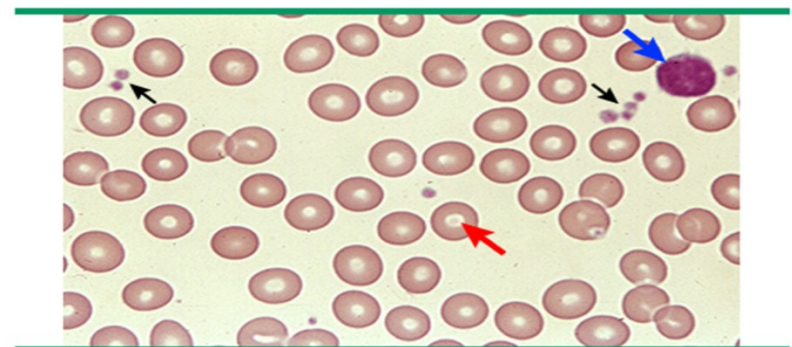
Macrocytic Anaemia

- MCV : >100 fl
- Common causes are:
 - Anemia of chronic renal disease
 - Cardiorenal anemia syndrome
 - Cancer-associated anemia
 - Acquired anemia in hospitalized patients

Polychromatophilia due to increased reticulocytes

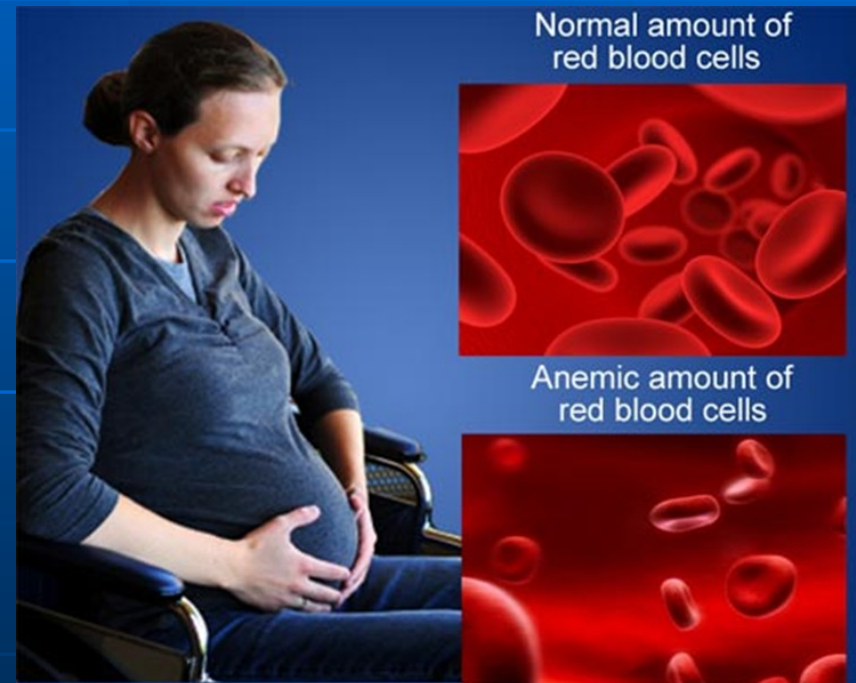


Normal peripheral blood smear



Common causes of Anaemia in pregnancy

- Anaemia in pregnancy usually related to
 - Iron Deficiency due to Inadequate iron stores secondary to nutritional /dietary factors: >90%
 - Folate deficiency due to inadequate intake,
 - Intestinal helminthic infections
 - Chronic hemolytic states, such as malaria.
 - Other



Case-1

- 26 years
- P5 + 0,
- Ethnic origin: Bangla Desh
- Tiredness, headaches and generally unwell.
- Pregnant 28 weeks
- Hb 8.5g/dl, MCV: 77, Ferritin: 5
- Likely diagnosis?

Iron Deficiency Anaemia

- Most common deficiency state in the world (20%) including during pregnancy (50%).
- Natural course:
 - *Iron depletion*: absent or decreased iron stores
 - *Iron deficiency*: depletion of stores + biochemical evidence
 - *Iron deficiency anemia*: Anaemia developing in an iron deficient patient
- Maternal iron requirements average close to 1000 mg over the course of pregnancy.
 - approximately 300 mg for the fetus and placenta
 - approximately 500 mg, if available, for the expansion of the maternal hemoglobin mass.
- Most women neither have adequate iron stores to handle the enhanced demands of pregnancy nor adequate dietary intake.

Why IDA is important: Effects on mum and baby-1

■ Maternal morbidity and mortality :

- Effects on immune function with increased susceptibility or severity of infections
- Poor work capacity and performance
- Disturbances of postpartum cognition and emotions
- There is little information regarding the Hb thresholds below which mortality increases, although this may be as high as 8.9g/dl.



Why IDA is important: Effects on mum and baby-1

■ Effects on the fetus and infant

- The fetus is relatively protected from the effects of iron deficiency by upregulation of placental iron transport proteins.
- Low birth weight
- Impaired psychomotor and/ or mental development are well described (co-enzyme function)
- May also negatively contribute to infants social emotional behaviour
- Have an association with adult onset diseases, although controversial (placentofetal ratio)



Why IDA is important: Effects on mum and baby-1

Effects on pregnancy outcome

- Spontaneous miscarriage
- Preterm delivery
- Possibly placental abruption
- Increased peripartum blood loss
- Area needing further research.



Signs and symptoms

- Varying degrees of fatigue and exercise intolerance
 - Weakness
 - Headache
 - Irritability
 - Palpitations, dizziness, dyspnoea and
 - Pica(craving for non-food items such as ice and dirt.)
 - Impair temperature regulation and cause pregnant women to feel colder than normal.
-
- Most patients are asymptomatic
 - The same symptoms may also be present in those with iron depletion but not anaemic.
 - fatigue,
 - irritability,
 - poor concentration and
 - hair loss.

Symptoms and signs like: Chlorosis, Glossitis, Angular stomatitis
nail changes are rarely seen in pregnancy



RUNNING OUT OF STEAM?

Diagnosis of Iron Deficiency Anaemia

Findings	Normal	Prelatent period	Latent period	Iron def. anaemia	
				Early	Late
Hb g/dl	N	N	N	8-11	<8
MCV fl	N	N	N	N, ↓	↓
S. Ferr.	N	↓	<30	<15	<15
T. Sat.	N	N	<15	<15	<15
BM iron	N	↓	-	-	-
Symptoms	-	-	-	+	+

Diagnosis of Iron Deficiency Anaemia

- Total iron binding capacity (TIBC, transferrin)(45-72 $\mu\text{mol/l}$):
 - Increased
 - Unreliable, fluctuate with iron ingestion

- Serum iron concentration (13-27 $\mu\text{mol/l}$):
 - Low, and as above.

- Other:
 - Red cell zinc protoporphyrin level ,
 - *Soluble transferrin receptor (sTfR) (tissue iron, most reliable)*
 - TfR-ferritin index,
 - Bone marrow iron

Pitfall: Differential Diagnosis

- Microcytic picture can be due to Thalassemia.

Variable	Iron deficiency anaemia	Thalassemia
Family History	Not-contributory	Positive
S Ferritin	Low	Normal / ↑
HbA2	↓	↑

- Other causes: Rare in pregnancy
 - Sideroblastic anaemia
 - Lead poisoning
 - Anaemia of chronic disease

Management -1

- **Dietary Advice: Universal (Grade1A)**



Recommended daily intake (RDA) of iron is 4mg/daily(2.5-6.6 mg)

Average daily iron intake from food for women in UK is 10-15 mg, pregnant 30mg.

Approximately 15% of dietary iron is absorbed.

Haem iron is absorbed 2-3 fold more readily than non-haem iron.

Vitamin C significantly enhances iron absorption from non-haem foods

Germination and fermentation of cereals and legumes improve the bioavailability of non-haem iron by reducing the content of phytate, a food substance that inhibits iron absorption.

Tannins in tea and coffee inhibit iron absorption when consumed with a meal or shortly after

Management-2



■ Oral Iron

- Dietary changes alone are insufficient and iron supplements are necessary.
- Ferrous iron salts are the preparation of choice.
- The oral dose for iron deficiency anaemia should be 100-200mg of elemental iron daily (1A).
- Advise on an empty stomach, 1 hour before meals, with a source of vitamin C (ascorbic acid) such as orange juice to maximise absorption.
- Other medications or antacids should not be taken at the same time (1A).
- For nausea and epigastric discomfort, preparations with lower iron content should be tried.
- Slow release and enteric coated forms should be avoided.
- Once Hb is in the normal range supplementation should continue for three months and at least until 6 weeks postpartum to replenish iron stores

Management -3



■ Parenteral iron therapy: IV Iron therapy

- Indications:
 - Absolute non-compliance with oral iron
 - Intolerance to oral iron therapy
 - Proven malabsorption (RCOG, 2007).
 - Stable postpartum women
- Mandatory to have prior serum ferritin levels.
- Plenty evidence that there is faster increases in Hb and better replenishment of iron stores in comparison with oral therapy,
- Free iron may lead to the production of hydroxyl radicals with potential toxicity to tissues and anaphylaxis (4.7%)
- Facilities and staff trained in management of anaphylaxis should be available.
- Contraindications;
 - History of anaphylaxis or reactions to parenteral iron therapy,
 - first trimester of pregnancy,
 - active acute or chronic infection
 - and chronic liver disease
- Paucity of good quality trials that assess clinical outcomes and safety of these preparations.

Summary of intravenous iron preparations available in the UK

	Cosmofer	Venofer	Ferinject	Monofer
	iron (III) hydroxide dextran complex	iron (III) hydroxide sucrose complex	Iron(III) carboxymaltose	Iron (III) isomaltoside
Dose of elemental iron	50mg/ml	20mg/ml	50mg/ml	100mg/ml
Test dose required as per manufacturer	Yes, before every intravenous dose, once before intramuscular treatment	First dose new patients only	No	No
Routes of administration	Slow intravenous injection Intravenous infusion of total dose Intramuscular injection total dose	Slow intravenous injection Intravenous infusion	Slow intravenous injection Intravenous infusion	Slow intravenous injection Intravenous infusion
Able to administer total dose	Yes (up to 20mg/kg body weight over 4-6 hours)	No	Yes (up to 20mg/kg body weight maximum of 1000mg/week over 15mins)	Yes (up to 20mg/Kg body weight over 1 hour)

Management -4

- **Parenteral iron therapy-*Intramuscular preparations***

- Low molecular weight iron dextran.
- Compared with oral iron, IM iron dextran has been shown in a randomised controlled trial to reduce the proportion of women with anaemia.
- However injections tend to be painful and there is significant risk of permanent skin staining.
- Can be administered in primary care, although facilities for resuscitation should be available.

Management -5



- **Blood transfusion: Packed RBC and components**
- Blood transfusion should be reserved for
 - Risk of further bleeding
 - Imminent cardiac compromise
 - symptoms requiring immediate attention.
- Provision of intra-operative cell salvage where appropriate to reduce the use of donor blood.
- Women receiving red cell transfusion should be given full information regarding the indication for transfusion and alternatives available.
- Consent should be sought and documented in the clinical notes (1A).

Management-6

■ Labour and Delivery

- Anaemic women may require additional precautions for delivery
- Delivery in a hospital setting
 - Intravenous access
 - Group and-save
 - Active management of the third stage of labour.
 - Plan in event of excess bleeding.
- Suggested Hb cut-offs are:
 - <10g/dL for delivery in hospital
 - <9.5g/dL for delivery in an obstetrician-led unit

Management -7

- **Other : : Recombinant Erythropoietin: EPO**
- Safe, as molecules large size, does not appear to cross the placenta.
- No fetal morbidity or mortality was noted.
- Use of EPO may be especially important for women who decline blood products.
- Further investigation is needed to establish a standard dosage and dosing interval.

Obstet Gynecol Surv. 2013 Aug;68(8):594-602, Sienas L¹, Wong T, Collins R, Smith J.

Iron supplement: Role

- To prevent iron deficiency anaemia in the mother.
- To allow for increase in the physiologic iron expansion.

Evidence :



Favour

- WHO, DOH- UK, International Anaemia consultative group, UN children's fund: Recommends routine iron supplement **unless enough stores at the beginning of pregnancy.**
- AJOG- 2007-Grade-A
- Prophylactic iron supplementation that is begun early in pregnancy **among low income women** may have benefits beyond the reduction of iron deficiency anaemia during pregnancy.

Against

- Iron has a negative effect on absorption of other divalent metals- Zn, Cu, Cr, Mg, Mn, Mo etc-.
- Iron supplements tend to augment the oxidative stress in pregnancy.
- Iron tablets induce a high concentration of free radicals in intestine, which may damage intestinal epithelium.
- BJOG-2007-Grade-A
Healthy women who take iron supplements in pregnancy are more likely to suffer from high blood pressure and have smaller babies!-increased blood viscosity.

What is the best way forward

- Follow '**Individual prophylaxis**' rather than '**General prophylaxis** approach' especially in Western countries like UK.
- Women at risk for iron deficiency only should be advised to take iron supplement.
- To keep the prophylactic iron dose as low as possible to prevent iron deficiency anaemia.
- All women should be given dietary information to maximise iron intake and absorption
- Intermittent oral iron supplementation during pregnancy.

How to find this?

Full blood count at booking for
Haemoglobin
and RBC indices-

*a women may be iron deficient despite
normal haemoglobin and MCV!*

Other parameters like
• Ferritin at booking



When should iron prophylaxis start

- Considering iron is essential for the development of CNS and birth weight, should be started at conception or early in pregnancy.
- No later than 20 weeks.

BMJ. 2013 Jun 21;346:f3443. doi: 10.1136/bmj.f3443.
Anaemia, prenatal iron use, and risk

Other Anaemias



Case-2

- 28 years
- P2+0
- Ethnic origin: Pakistani
- Pale, headaches, no energy.
- Pregnant 22 weeks
- Hb 7.6 g/dl, MCV:62, Ferritin: 264
- Likely diagnosis?

Haemoglobinopathies-1

- **Alpha Thalassemia**
- **BetaThalassemia major and Intermedia.**

- Basic defect is reduced globin chain synthesis and haemoglobin
- Ineffective erythropoiesis
- Enhanced extravascular haemolysis

- Alpha : rare. Bart's Hb, hydrops and stillbirth

- Beta: more common
 - More than 70 000 babies are born worldwide every year
 - There are approximately 1000 individuals affected by thalassaemia major or intermedia syndromes in the UK
 - New Guideline by RCOG, March 2014.
 - Severe transfusion-dependent anaemia.

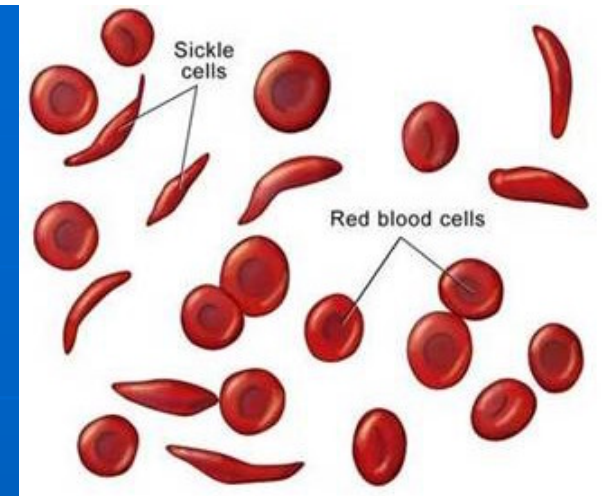
- Coexisting iron deficiency anaemia common.
- Women with known haemoglobinopathy should have serum ferritin checked and offered oral supplements if their ferritin level is <30 ug/l

Case-3

- 36 years
- P0+0
- Ethnic origin: African (Ghana)
- Asymptomatic.
- Pregnant 12 weeks
- Hb 9.4g/dl, MCV:93, Retics: 316, Ferritin: 50.
- Likely diagnosis

Haemoglobinopathies-2

■ Sickle cell disease



- Inherited single-gene autosomal recessive disorders caused by the 'sickle' gene.
- Affects haemoglobin structure
- Most common inherited condition worldwide, prevalent in Sub-Saharan Africa and the Middle East
- About 300 000 children with SCD are born each year., In the UK, over 300 infants born with SCD in the UK each year
- On-going pregnancy and neonatal screening programme.
- Multifaceted implications both to mother and fetus, including high morbidity and mortality
- Needs care within multidisciplinary setting at regional level with experienced haematologist alongside obstetrician.

Case-4

- 32 years
- P0+0
- Ethnic origin: Caucasian.
- Poor diet, processed foods
- Fatigue, and generally unwell.
- Pregnant 32 weeks
- Hb 8.5g/dl, MCV:115, Ferritin: 38
- Likely diagnosis

Megaloblastic Anaemia: folate and B12



- **Folate requirements:**

- In non pregnant individuals, the daily folic acid requirement is 50 to 100 mcg.
- 10-20 fold increase in pregnancy, more than met by the increased daily intake
- Routine prophylaxis recommended (400 mcg)
- Usually associated with iron deficiency due to poor intake

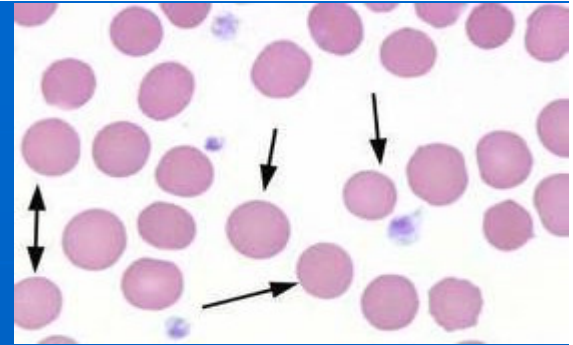
- **B12 requirements:**

- 2mcg non pregnant and 3 mcg pregnant
 - Serum B12 concentrations commonly fall during pregnancy (130ng/ml).
 - B12 deficiency rarely causes anaemia in pregnancy (vegans, processed foods).
 - Pernicious anaemia , rare as associated with infertility
-
- Tricky to diagnose as majority of patients with B12 or folate deficiency have no or only mild anaemia, and macrocytosis may be masked by a concurrent disorder (eg, iron deficiency, thalassemia).
-
- In the "classic" **advanced** case of vitamin B12 or folate deficiency:
 - Patient presents with severe anemia and macrocytic red cells (MCV >100 fL) with or without varying neurologic disturbances.

Case-5

- 19 years
- P0 + 0
- Ethnic origin: Romanian
- Mild fatigue
- Splenomegaly
- Hb 9.5g/dl, MCV:88, Ferritin: 55
- Likely diagnosis

Haemolytic Anaemia



- Hereditary spherocytosis (HS) is the most common hemolytic anemia
- Red cell membrane defect.
- Autosomal dominant inheritance in approximately 75 % of patients,
- Common clinical features are:
 - Anemia
 - Jaundice
 - Splenomegaly
- The degree of anaemia is extremely variable and may be absent, mild, moderate, or severe to the point of threatening life.
- Cord blood at delivery

Aplastic anaemia

- Rare: 2-4 per million population per year
- Characterized by diminished or absent hematopoietic precursors in the bone marrow.
- Most often due to injury to the pluripotent stem cell.
- Misnomer because the disorder is defined as pancytopenia rather than anemia .

Conclusions:

- Pregnant women should be offered screening for anaemia.
- Screening should take place early in pregnancy (at the booking appointment) and at 28 weeks when other blood screening tests are being performed.
- Offer screening for haemoglobinopathies, and red-cell alloantibodies alongside anaemia at first visit.
- 28 weeks: offer a second screening for anaemia and atypical red-cell alloantibodies
- Investigate a haemoglobin level below 10.5-11 g/100 ml and consider iron supplementation, as indicated.
- Remember Iron deficiency anaemia is commonest anaemia in pregnancy.

References

- Antenatal care - NICE guidance nice.org.uk/CG62. 2008
- UK Guidelines on the management of iron deficiency. www.bcshguidelines.com. 2011
- Iron prophylaxis in pregnancy—general or individual and in which dose?
N Milman. Ann Hematol (2006) 85: 821–828.
- A randomised placebo-controlled trial to determine the effect of iron supplementation on pregnancy outcome in pregnant women with haemoglobin > or = 13.2 g/dl. Ziaei S, Norrozi M, Faghihzadeh S, Jafarbegloo E. BJOG. 2007Jun;114(6):684-8.
- The effects of prophylactic iron given in prenatal supplements on iron status and birth outcomes: a randomized controlled trial. Siega-Riz AM, Hartzema AG, Turnbull C, Thorp J, McDonald T, Cogswell ME. Am J Obstet Gynecol. 2006 Feb;194(2):512-9.

