HEMOGLOBINOPATHIES IN PREGNANCY
Hemoglobinopathies

• Most common single gene disorder

**Quantitative Variant**
• Alpha Thal
• Beta Thal

**Structural/Qualitative Variant**
• HbS, HbE, HbC
Quantitative Variant: THALASSEMIA

• Defects seen in the Beta and Alpha chains
• Essentially a childhood disease
• High incidence in the malaria endemic areas
• Now a worldwide disease - migration
Patho-physiology of Thalassemia

Inadequate globin production

1. Ineffective erythropoiesis
2. Hemolytic anemia

Accumulation of unpaired globins
EVOLUTION OF THALASSEMIA

• Historically a childhood disease; many didn’t survive past childhood
• Transfusion was introduced in 1960s
• Chelation therapy introduced in 1980s
• More adult patients seen now
LIFE EXPECTANCY OF THALASSEMIAS

Adapted from B. Modell and V. Berdoukas, 1984

MORE PRENGANT THALESSEMSICS
Case scenarios
Case 1

26 / Malay / G1P0 @ 8w POA
- Known case of Thalassemia Intermediate
- Not transfusion dependent
- 4 transfusions so far since childhood
What other history should we ask?
History & Physical Examination

- Transfusion History
- Chelation therapy and compliance
- Cardiac history
- Menstrual History
- Vaccination history

- CVS examination
- Hepato-spleenomegaly / post spleenectomy
- Presence of major bone deformity
O/E
- tinge of jaundice
- Short stature
- BP: 120/80
- PR: 80 bpm

CVS:
- DRMN

Abdomen:
- Hepatomegaly - 2 fb
- Spleenomegaly - 3 fb
FBC:

Hb: 10   WBC: 6   Plat: 200
Ferritin: 1500

Plan
See in 4/52 with repeat counts
T. Folate 5mg od
What supplements should be given?

a) Ferrous Fumarate / sulphate
b) Folate
c) Vit Bco
d) Vit C
e) Obumin
Supplements in Pregnancy

- Folate – at least 4mg od
- Iron – ONLY in iron deficiency
- Obumin + folate
- CaCO3
- Vit D – Rocaltriol
Review again at 18 w POA

c/o : mild reduced effort tolerance
No orthopnea / PND
No pedal edema

BP: 110/70
PR: 100 bpm
CVS : DRNM
Lungs: clear
FBC:
Hb : 8  Plat 320  WBC: 7

Imp: Symptomatic anemia

Admitted to the ward ; KIV for blood transfusion
Not Transfused
Discharged and KIV for transfusion if Hb < 7
PREGNANCY CHANGES

Hemodynamic changes:
• Maternal blood volume increases
• Volume overload – renin & aldosterone activity causing water retention
• *Dilutional anemia*
• Cardiac output increases – HR↑

Respiratory changes:
• Thoracic volume increases
• Total pulmonary resistance increases
• Mild respiratory alkalosis seen – placental gas exchange
4 weeks later

• Hb: 7.7 g/dl

• Well asymptomatic

• TCA in 2 weeks; KIV for transfusion if Hb < 7

• Patient eventually did not need any transfusion
Anemia

• More profound in pregnancy
• Transfusion requirement increases
• As frequent as 3-4 weekly sometimes
• Keep Hb > 10 ( > 7 may be sufficient in NTDT)
• If Hb too low
  - insufficient O2 to baby leading to IUGR
  - Pre term delivery
• Give Phenotype Matched & Leucodepleted Blood
When to transfuse?

- Hb<7 (NTDT)
- Increasing spleen size
- Evidence of IUGR
What should be done prior to blood transfusion??

- Red cell Phenotyping – esp in NTDT
- Coomb’s test
- GXM
- Serum ferritin
Case 2

24 G1PO @ 6w POA

- Transfusion Dependent Thalassemia; every 4-6 weekly
- Hb: 10 g/dl
- Sr Ferritin: 4500
- Spleenectomy done 2 yrs ago
- Hep B / pneumococal / hemophilus influenza vaccination given
- MRI T2*: moderate cardiac and liver iron overload
Current Medications:
- Folate 5mg od
- Deferiprone 1g tds
- S/C Desferral 4 vials od 5x/week
- T.Vit C 1/1 tds
- T Penicillin V 250 mg bd
- T Aspirin 75 mg od

Booked at KK and informed hematologist regarding pregnancy

- *Chelation therapy stopped – Deferiprone and Desferral*
Chelation Therapy

- usually stopped during pregnancy
- DFO is safe in pregnancy and breast feeding
- Oral chelating agents not safe
- DFO continued in myocardial iron overload with CCF after 1st trimester
- Ferritin levels usually stable during pregnancy

?? Placental iron binding
Other medication

- Stop OHA and ACE – inhibitors
- Change to Insulin
- Metformin - safe in pregnancy
- Continue thyroxine if hypothyroid
Other Investigations:

- **Cardiac**
  - Echo / ECG / MRI T2*

- **Endocrine**
  - FBS / HbA1C / OGTT
  - T3/T4/TSH
  - RP / UFEME

- **Liver**
  - LFT / Coagulation

**Infectious Screen**
- HbsAg / Anti HCV / Anti HIV
- Rubella / Syphilis
- Hepatitis B – vaccination/Ab
At 20 weeks POA

- **C/O:** reduced effort tolerance, pedal edema, orthopnea and PND

- **CVS:**
  - S1, S2 systolic murmur at LSE; apex beat at 6th intercostal space lateral to the mid clavicular line

- **Lungs:**
  - Bibasal crepitations

- **ECHO:** EF: 50%, hypokinetic LV

**IMP:**
- Heart Failure
- ? Sec to iron overload? Peripartum Cardiomyopathy
• Recommenced back on S/C Desferral 4 vials / day
• Started on anti failure drugs
• Referred to cardiologist

• Symptoms improved
• Continued on regular transfusion

• Delivered via SVD at 37 weeks POA
• Heart failure improved subsequently
Cardiac Function

- CCF worsens during pregnancy
- Early referral to cardiologist
- Impaired LV function & poor chelation status have high mortality
- Assisted delivery with shortened second stage of labour
- Return to baseline post-partum
Mode of Delivery

• Individualised mode of delivery
• Vaginal delivery preferred
• LSCS for CPD due to pelvis bony
• Assisted delivery if hemodynamically unstable
• LMWH peri-partum
Pre – pregnancy counselling

- Blood requirements will increase
- Optimise iron chelation before planning pregnancy
- MRI T2* before pregnancy
- Folic acid supplementation
- Genetic counselling

Post partum

- DFO safe during breastfeeding
- Small risk of HCV / HIV in breastfeeding
Qualitative Variant: SICKLE CELL DISEASE (HbS)

Sickle Cell Trait (HbSA)
• Normal life
• Renal hematuria & hyposthenuria
• Splenic infarct- reported

Sickle Cell Disease (HbSS)
• Usually suffer sickle crisis during stress
• Seldom reach reproductive age in the past
• Pregnancy avoided if ds complicated by pulmonary arterial hypt
Managing Pregnancy with Sickle Cell Disease

**Prenatal:**

- Folic Acid
- CBC
- Serum ferritin
- Iron Supplementation if need be
- Stop Hydroxyurea

- Tetratogenic; Stop 3-6 months before pregnancy
• Vaccination / Immunisation
• Antibiotic prophylaxis
• Contraception
• Inform how SCD affects pregnancy & how pregnancy affects SCD
Screening for chronic complications

- ECHO
- MRI T2*
- Screening for antibodies
- Retinal screening
- Renal / liver function
Information relevant for women planning to conceive

- Triggers of sickle cell crises
- Anaemia worsens in pregnancy
- Risk of crisis, ACS & UTI
- IUGR, fetal distress
- Baby being affected by SCD
Triggers of Sickle Crisis

- Infection - *UTI*
- Acidosis
- Dehydration – *nausea and vomiting in pregnancy*
- Cold Temperature
- Altitude
- Stress
- Fatigue
- Menstruation
Retinopathy

Cardiomegaly

Congestive heart failure

Cholelithiasis

Renal infarcts

Hematuria

Cerebral infarcts

Stroke

Mental retardation

Pulmonary infarcts

Pneumonia

Splenomegaly

Splenic atrophy (autosplenectomy)

Infarcts of the extremities

Bone marrow hyperplasia

Aseptic bone necrosis

Osteomyelitis

Vaso-occlusion

Ulcer
Intra- partum Management

- Infection Surveillance; *bacteriuria / pyelonephritis*
- Parvovirus B19 – *aplastic crisis*
- Avoid sick contacts
- Fetal Surveillance – *uteroplacental vascular stasis ; IUGR*
- Preterm labour risk – *up to 50% deliver before 36 weeks*
- Watch for Sickle Crisis
What medication should be given during pregnancy?

- Folic acid
- Antibiotics Prophylaxis
- Iron supplementation - iron deficiency.
- Low-dose aspirin (75 mg od) from 12 weeks of gestation - to reduce the risk of developing pre-eclampsia.
- Prophylactic LMWH during antenatal hospital admissions.
Role of blood transfusion during pregnancy

• Prophylactic transfusion not recommended - given in crisis

• Blood should be matched for an extended phenotype including full rhesus typing (C, D and E) as well as Kell typing

• Transfusion

- Hb < 6 g/dl or a fall of > 2 g/dl from baseline is often used as a guide to transfusion requirement
<table>
<thead>
<tr>
<th>Indication</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with previous serious medical, obstetric or fetal complications</td>
<td>Exchange or top-up transfusion may be indicated depending on clinical indications and should be decided in the multidisciplinary clinic setting</td>
</tr>
<tr>
<td>Women who are on a transfusion regimen before pregnancy for primary or secondary stroke prevention or for the prevention of severe disease complications</td>
<td>Transfusion should be continued during pregnancy</td>
</tr>
<tr>
<td>Twin pregnancies</td>
<td></td>
</tr>
<tr>
<td>Acute anaemia</td>
<td>Prophylactic transfusion should be considered owing to the high rate of complications in these women^{25}</td>
</tr>
<tr>
<td>Acute chest syndrome or acute stroke</td>
<td>Top-up transfusion</td>
</tr>
<tr>
<td></td>
<td>Exchange transfusion</td>
</tr>
</tbody>
</table>
Management Of Crisis

• Admission & Referral to a Hematologist/ O&G
• Hydration – 60 mls / kg /day
• Pain control
Avoid NSAIDs — oligohydramnions & premature closure of PDA
Avoid Pethidine - Seizures
• Septic workup & antibiotics
• Renal Disease – a/w pre-eclampsia
• Blood transfusion / exchange transfusion
  - significant anemia
  - antigen compatible and leucodepleted
Case Presentation

- 30 nigerian lady
- Known case of sickle cell ds
- Last crisis 20 yrs ago
- G1P0 @ 14 weeks
- Hb 7.0 in private
- GXM and transfused 2 pints
• 10 days later, presented with lower abdo pain, dyspnea and back pain
• Referred to Ampang
• GCS deteriorated
• Pale ++++ Jaundice +++ Haemoglobinuria
• Hb:2 Bil ID 400 LDH 2300
• Group O

• Red Cell Phenotyping: \( c\text{De}/C\text{de} = R_0R_0 \)

• Antibodies detected:
  Anti-E, Anti \( JK^b \) and anti Fy-a
• Delay getting matched blood
• Exchange transfusion performed after 24 hours
• Patient dies 8 hours later

Cause of death:
Delayed hemolytic transfusion reaction
Alloimmunisation

- Alloimmunisation (formation of Ab to red cell Ag)
- 18–36% of patients.
- Causes delayed haemolytic transfusion reactions or haemolytic disease of the newborn
- Common antibodies are to the C, E and Kell antigens.
- Significantly reduced by giving phenotype matched blood
Timing and Mode of Delivery

• Uncomplicated pregnancy induce after 38/52 of gestation.
• No contraindication to vaginal delivery
• Cross-match blood if atypical antibodies present, otherwise a ‘group and save’ will suffice.
During Labour

• Alert ‘team’ when active labour confirmed
• Mother kept warm and well hydrated
• Regional anaesthesia recommended
Postpartum care

- Test baby for SCD
- Maintain maternal spO2 > 94%
- Adequate hydration
- LMWH

*7 days post vaginal delivery or for 6/52 following c/s.*
Postpartum Contraceptive

• Progestogen-containing contraceptives such as the progesterone only pill, injectable contraceptives & the levenorgestrel intrauterine system - safe and effective in SCD.

• Estrogen-containing contraceptives - used as second-line agents.
## Tetrametric forms of hemoglobin

<table>
<thead>
<tr>
<th>Time</th>
<th>Region</th>
<th>Type of Globin Gene</th>
<th>Type of Hb</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 weeks of Gestation</td>
<td>Yolk Sac</td>
<td>ζ &amp; ε</td>
<td>Hb Gawer1 (ζ ε)₂</td>
</tr>
<tr>
<td>5 weeks of Gestation</td>
<td>Yolk Sac</td>
<td>γ&amp;α</td>
<td>Hb Portland (ζ γ)₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hb GawerI (αε)₂</td>
</tr>
<tr>
<td>6-30 weeks of Gestation</td>
<td>Liver &amp; spleen</td>
<td>α &amp; γ &amp; β</td>
<td>Hb F (α γ)₂</td>
</tr>
<tr>
<td>30 weeks of Gestation</td>
<td>Liver</td>
<td>δ</td>
<td>Hb A₂ (α δ)₂</td>
</tr>
<tr>
<td>At Birth</td>
<td>B.M</td>
<td>α &amp; β</td>
<td>HbA(α β)₂</td>
</tr>
</tbody>
</table>
Peripartum Evaluation

Anemia
- More profound during pregnancy
- Keep Hb at 10g/dL
- Phenotyped matched blood

Chelation Therapy
- usually stopped
- DFO is safe in pregnancy and breast feeding
- Oral chelating agents not safe
- DFO continued in myocardial iron overload with CCF
- Ferritin levels usually stable during pregnancy ?? Placental iron binding
INTRODUCTION

RED BLOOD CELLS
• Produced in the marrow
• Non nucleated
• 70% hemoglobin

HEMOGLOBIN
• Tetramer : 2 α and 2β with heme molecule
• Binds to O2
Pregnancy in Thalassemias

*Pre-conceptual Evaluation:*

- Transfusion needs
- Compliance to chelation therapy
- End organ damage assessment
- Endocrine & Hormonal function
- Evidence of bone disease
- Genetic counselling
- Viral screening
- Alloimmunisation screening
Beta Thalassemia
- Decrease in B globin chains
- Unmatched alpha globin chains will accumulate and aggregate

Beta Thal Trait
- Heterozygous beta globin mutation
- Mild or no anemia

Beta Thal Intermediate
- Have 2 beta thalassemia mutations ie Hb EB / Hb SB
Alpha Thalassemia
• Decrease in alpha globin chains
• 4 alpha globin genes

Silent carrier
• 1 gene defect
• Normal RBC parameters

Alpha Thal Trait
• 2 gene defect
• Heterozygous a thal 1
• Homozygous a thal 2

HbH Disease
• 3 gene defect
• Excess B globin chains froms tetramer = inclusion bodies

HbH Syndrome (Hydrops)
LIFE EXPECTANCY OF THALASSEMIAS

• Without regular transfusion < 10 years
• With regular transfusion and no/poor iron chelation < 25 years
• With regular transfusion and good iron chelation ??40 years, longer??

MORE PRENANT THALESSEMICS