# FERTILITY AND PREGNANCY

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# Introduction

- Advances in the care of TM including transfusion and iron chelation improved patient survival
- Also patients' QOL has increased and the expectation of having a family became important
- Although spontaneous fertility can occur in well-transfused /chelated patients with spontaneous puberty , the majority are subfertile due to hypogonadotropic hypogonadism
- Those who fail to achieve pregnancy spontaneously require assisted reproductive techniques
- Pregnancy in TM is high risk for both the mother and the baby

# Introduction

- These risks can be minimized by counseling with hematologist, cardiologist, obstetrician, endocrinologist
- Management of patients with TI is similar to TM but:
- TM Patients usually have hypogonadotropic hypogonadism and are unlikely to conceive spontaneously, but patients with TI are potentially fertile with an intact hypothalamic-pituitary-gonadal axis
- Furthermore their management during pregnancy is different in that TI patients have an increased thrombotic risk, compared to TM and may need transfusion during pregnancy to decrease this risk
- In addition to complications of iron overload, TM patients also face the risk of thromboembolism; particularly after splenectomy and in those with auto-antibodies

# Introduction

- Women with TM appear to have premature ovarian aging and decreased ovarian reserve
- Ultrasound indirectly measures the size of residual ovarian follicle reserve
- Low gonadotropin in TM results in reduced ovarian follicle and volume
- Low ovarian reserve is considered predictive of low chances of spontaneous pregnancy and poor response to hormonal stimulation
- Fertility is preserved in majority of those < 30 to 35 years
- Spontaneous pregnancies in women with normal hypothalamic-pituitary-gonadal axis, and normal menstrual cycles, are common
- But women with primary or secondary amenorrhea are able to conceive following ovulation induction therapy
- Meanwhile other complications of TM must be considered before and during pregnancy

# Management of Subfertility in Females

- Although 80-90% of patients have hypogonadotropic hypogonadism , gonadal function is intact in majority of patients,
- So, ovulation and spermatogenesis can be induced by exogenous gonadotropins. However:
- Other endocrine disorders, namely hypothyroidism and DM, may influence the outcome of treatment
- Fertility assessment of patients with TM should also include evaluation of the partner

# Management of Subfertility in Females

- The fertility options are dependent on two factors:
- (a) her partner's carrier status and
- (b) the site of damage to the HPG axis
- If both partners are TM, use of donor gametes, preferably sperm, is the ideal option as sperm can be more easily available from banks,
- Whereas the use of donor eggs is more complicated with an unpredictable success rate
- If the partner is heterozygous, then pre- implantation genetic diagnosis (PGD) is another option, where diagnosis can be made prior to conception
- PGD may be more acceptable to communities with religious beliefs against abortion
- In patients with severe organ damage or both partners have TM, an alternative option may be adoption

# *Methods for induction of ovulation*

- Most of patients benefit from gonadotropin therapy (80% success)
- The drugs used, are powerful and can often induce growth of two or more follicles, with the risk of twin or triplet pregnancy
- Patients should be counseled about the risk of hyperstimulation syndrome, multiple pregnancy, ectopic pregnancy and miscarriage

# Methods for induction of ovulation

- Induction of ovulation may be indicated in:
  - Women with primary or Secondary amenorrhea
  - Those with normal menstrual function who fail to conceive, and
  - In planned pregnancy where both partners are thalassemics
- The induction of ovulation necessitates agents include FSH, LH, HCG and clomiphene citrate
- It is important to counsel the patient for egg collection before hemopoietic transplant or gene therapy

# *Male Fertility and Induction of Spermatogenesis*

- The induction of spermatogenesis in TM is more challenging
- with a success rate of only 10-15% in iron loaded patients and advanced aged patients
- Treatment is demanding and may take up to 2 yrs
- Sperm banking procedures, even in subjects with reduced sperm count and motility, are recommended

# Pre-Pregnancy Counselling

- Before fertility treatment, it is important to attend pre-pregnancy counseling for:

(a) Evaluation of eligibility,

(b) Review the medications involved

(c) Time for discussion between physician, patient and partner regarding the risks of induced fertility and pregnancy

# *Evaluation of eligibility*

- There are at least three important factors before encouraging women with TM to embark on pregnancy:
  - Degree of cardiac impairment,
  - Liver dysfunction and
  - The risk of vertical transmission of viruses

# Evaluation of eligibility

1. Cardiac function is the most important issue because it is the leading cause of death in TM

- The cardiac load is increased during pregnancy by 25-30% due to increased heart rate and stroke volume
- This, along with iron load, is a real risk for death from cardiac failure
- Therefore all patients should have cardiac assessment by echocardiography, and ECG
- In case of LV dysfunction or significant arrhythmias, It should be advised against pregnancy
- MRIT2* is very useful in this regard
- If cardiac iron load or complications are detected, it advised to intensify iron chelation
- Cardiac function can be restored by aggressive chelation, but may require several months and up to 2 years

# Evaluation of eligibility

2. Liver function should be evaluated by biochemical tests, and iron load assessed by MRI
   - In cases with positive hepatitis C, they should be given antiviral agents to attain hepatitis C negative status
   - Iron overload in the liver should be treated before pregnancy to achieve LIC < 7 mg/g
   - Liver/gall bladder and spleen ultrasound should be used
3. Performing BMD of hip and spine and correction of osteoporosis/ osteopenia before conception
   - In addition all women should have normal vitamin D level before pregnancy

# *Evaluation of eligibility*

4. All patients should be screened for HIV, hepatitis B/C ,and rubella

- If the patient is HIV positive, recieving antiviral agents, delivery by Caesarean section and the avoidance of breast feeding are recommended

5. Patients should be screened for hypothyroidism, DM, and RBC antibodies

6. Partner should be screened for Hb-pathies

# Review of medications

- This is a good opportunity to review drugs and to advise about dietary habits, smoking , and supplements of folic acid, calcium and vitamin D
- Patients on DFX or DFP should be switch to DFO, **prior to induction of ovulation/spermatogenesis**
- Hormone therapy should also be terminated at least 4-6 weeks prior to induction of gametogenesis
- Bisphosphonates are contraindicated during pregnancy and breast-feeding and should be stopped at least 6 months prior to conception

# Review of medications

- Ensure adequate calcium and vitamin D intake before and throughout pregnancy
- Interferon, ribavirin and hydroxyurea should be discontinued at least 6 months prior to treatment
- Hypothyroid patients receiving thyroid replacement therapy may need increased doses
- Hyperthyroidism is rare in patients with TM. But, if a patient is receiving anti-thyroid drugs such as carbimazole, they should be switched to PTU

**Table 5. Medication review for pregnancy focus points:**

- Emphasize folic acid supplementation even before conception.
- Oral iron chelating agents (DFP, DFX) should be discontinued 3 months before conception.
- Stop angiotensin-converting enzyme (ACE) inhibitors.
- Can safely continue metformin, but may need to change oral hypoglycaemic drugs to insulin.
- Stop bisphosphonates at least 6 months prior to planned pregnancy.
- Give calcium and vitamin D supplementation.

# Risks Associated with Pregnancy

- Note that pregnancy per se does not alter the natural history of TM
- There is a slight increased incidence of growth restriction in well managed pregnancy
- Pregnancy complications such as antepartum hemorrhage and pre-eclampsia in TM are similar to background population
- DFO is not required during pregnancy in patients who are not iron overloaded and have adequate cardiac function
- Ferritin is likely to increase by 10%,
- During pregnancy maintain pre-transfusion Hb > 10 g/dl
- The patient should be made aware that although pregnancy is high risk, the outcome is usually favorable

# Risks Associated with Pregnancy

- Bone deformities may affect pregnancy and labour management, especially in cephalo-pelvic disproportion
- Patients with osteoporosis usually have reduced height vertebral bodies
- So, it is important to correct osteoporosis prenatally using bisphosphonates,…
- Bisphosphonates have to be stopped at least 6 months prior to pregnancy due to their long half-life
- Most important risk to the mother is cardiac complication, which can be minimized by assessing cardiac function and good control of iron overload before the pregnancy

**Table 6. Potential risks associated with pregnancy include:**

- Pregnancy does not alter the natural history of the disease.
- Requires intense/vigilant monitoring.
- Cardiac complications.
- Risk of pregnancy-specific complications same as background population.
- Risk of miscarriage same as background population.
- Risk of fetal malformation: no increase.
- Risk of fetal growth restriction: two-fold increase.
- Preterm labour risk: two-fold increase.
- Risk of transmission to the fetus/baby of hepatitis B/C, HIV.
- Risk of iso-immunisation.
- Risk of prematurity and growth restriction is increased in multiple births.
- Thrombotic risk may be increased.

# Risks Associated with Pregnancy

***Monitoring the heart:***

- Evaluation of cardiac function by echo, and of LFT and TFT, in each trimester
- No significant cardiac complications were seen in patients with optimal iron load
- Ensuring about iron control, cardiac function and myocardial T2* before pregnancy

***Diabetes:***

- All patients should be screened for gestational diabetes at 16 weeks and, if normal,
- Screening should be repeated at 24-28 weeks

***Fetal growth:***

- Serial ultrasound scans from 24-26 weeks to monitor fetal growth
- Maintaining a pre-transfusion Hb at least 10g/dL is necessary

# Thromboprophylaxis:

- Pregnancy increases the risk of thrombosis by 3-4 fold
- TM is a hypercoagulable state especially after splenectomy
- But there is no reports of thrombosis in women receiving LMWH
- So, in splenectomized patients, particularly in those with TI:

- LMWH is required from mid-trimester
- Splenectomized women need ASA if the PLT>600,000

; these patients should also be given LMWH in addition

- Regular transfusion reduces erythropoiesis and decreasing abnormal RBC, especially in splenectomized patients, is also helpful

***Folic acid supplementation:***

- Folate demand in pregnancy is increased: specially in TM (due to BM overactivity) so:
- Folic acid is recommended in mothers with TM
- In addition, folic acid should start before conception to reduce the incidence of spina bifida

***Thyroid function:***

- Should be checked throughout pregnancy and
- In case of hypothyroidism the dose of thyroxine may need to be adjusted

# Iron chelation during pregnancy

- If cardiac function deteriorates, DFO may be used after 1st trimester
- This is because of equivocal data supporting teratogenicity of DFO
- DFO is used in higher risk pregnancies, particularly in 3rd trimester
- DFO increases risk of skeletal anomalies in animal models
- Although there are no reports regarding human fetal anomalies from this drug
- Therefore, in patients with myocardial iron load or cardiac dysfunction, DFO may be considered in the final trimester or in the peridelivery period
- Data on fetotoxicity of oral chelating agents are insufficient

# Managing delivery

- there is no consensus on the mode and timing of delivery
- About 80% of women with TM will require Caesarean section due to cephalopelvic disproportion, caused by maternal short stature and skeletal deformity combined with normal fetal growth
- Epidural anaesthesia is desirable , to avoid the risk of difficult intubation and trauma associated with anesthesia because of maxillofacial deformity
- If the mother has morbidities such as diabetes or cardiac disease then prolonged pregnancy should be avoided
- Low dose DFO may be used during prolonged labour in patients with cardiac disease

# Postpartum care

- After delivery, DFO can be used because concentrations are very low in breast milk and not absorbed by oral route
- Experience with breastfeeding in patients on DFO is scant,
- Breastfeeding should be encouraged except in
  - Those who are HIV positive
  - Hepatitis C RNA positive
  - HbsAg positive because of the risk of vertical transmission
- *Women with TM should be considered at high risk for VTE and should receive LMWH while in hospital*
- *LMWH should be used for 7 days post discharge following vaginal delivery or for 6 wks following C- section*

# Postpartum care

- In case of miscarriage or termination of pregnancy LMWH must be used during and following the loss for 7 days
- All patients should be offered counselling regarding contraception
- IUD should be avoided because of the risk of infection
- Taking estrogen containing OCP is not advisable because of the risk of thromboembolism
- In most cases, progesteron pill or barrier methods are appropriate
- Calcium and vitamin D supplements should be continued during breastfeeding, but
- Bisphosphonate therapy for osteoporosis should only be resumed after cessation of breastfeeding

**Table 7. Key points for pregnancy care include:**

- Check cardiac, liver and thyroid function once each trimester
- Screen for gestational diabetes.
- Increase frequency of blood transfusion to maintain pre-transfusion haemoglobin above 100 g/l.
- Serial ultrasound scans to monitor fetal growth.
- Higher incidence of caesarean section.
- Encourage breastfeeding unless HIV positive and/or HCV RNA and/or HBsAg positive.
- Resume DFO after delivery.
- Discuss contraception, where appropriate with either the progesterone-only pill (POP) or barrier method.
- Avoid intrauterine devices and oestrogen-containing preparations.
- Implement a multidisciplinary approach with all specialists involved in the medical care of thalassaemic women.

# Summary and Recommendations

- Iron overload in the pituitary is the main cause of infertility in females
- Successful pregnancy can be achieved in TM though ovulation induction because ovarian function is usually preserved
- Ovulation in females and spermatogenesis in males can be induced by gonadotropin therapy
- Several factors must be taken into consideration before embark on pregnancy :
  - The degree of pre-existing cardiac impairment and
  - Liver dysfunction
  - Possibility of vertical transmission of viruses

# Summary and Recommendations

- Pregnancy per se does not alter the natural history of TM
  - It is safe, if they have normal cardiac function
  - If cardiac function deteriorates, DFO may be used after 1st trimester
- Pre-transfusion Hb should be kept > 10 g/dl
- Fetal growth must be monitored since anemia may result in growth retardation
- Thrombosis is a major concern and so LMWH is recommemded from mid-trimester in all cases
  - Aspirin is provided when there is a high platelet count
- Monitoring of organ function, particularly heart is very important

# THANK YOU