Bones and Fertility in Thalassemia

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Objectives

- To discuss common bone diseases in thalassemia
- To discuss causes, investigation and management of osteoporosis in thalassemia
- To address fertility in men and women and induction of ovulation and spermatogenesis
- To review recent pregnancy outcomes in thalassemia major and intermedia patients

Introduction

- Historically, bone changes attributed to bone marrow expansion and cortical thinning caused by massive ineffective erythropoiesis.
- Treatment with transfusion programs and chelation has significantly improved survival.
- However, despite good transfusion practices, low bone mass is still seen in adults.
- Bone disease is a significant cause of morbidity and poor quality of life in thalassemia patients

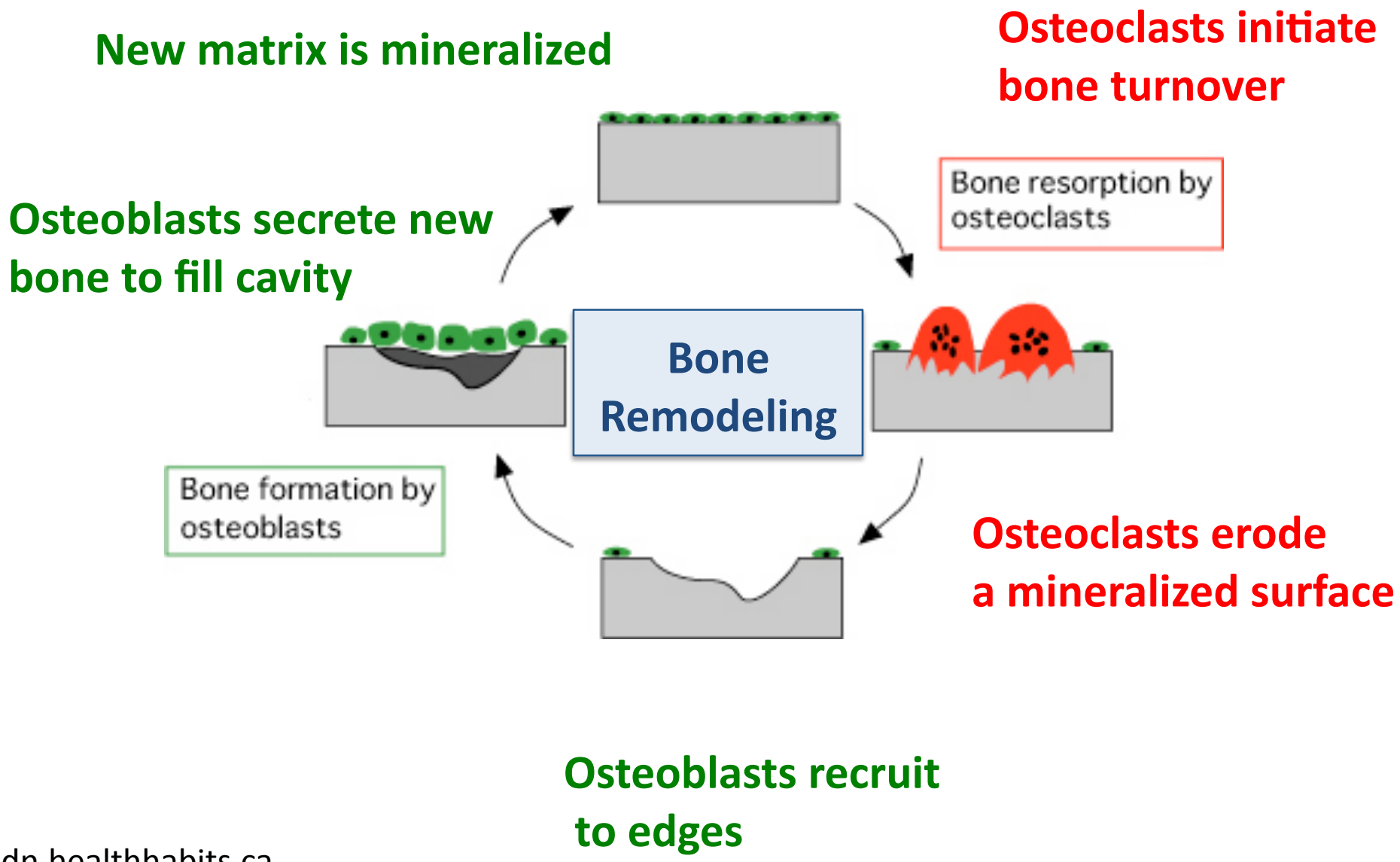
Bone Disease in Thalassemia

- Osteopenia/osteoporosis 46%
- Fractures 36%
- Pain 34%
- Intervertebral disc changes
- Spinal deformity – Scoliosis 67%

Medscape

Vogiatzi et al. 2009. J Bone Miner Res 2009;24:543-557

Bone is an active tissue



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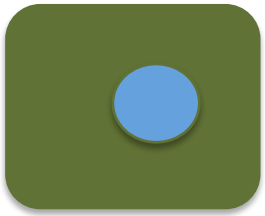
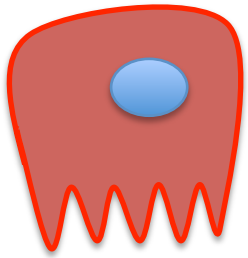
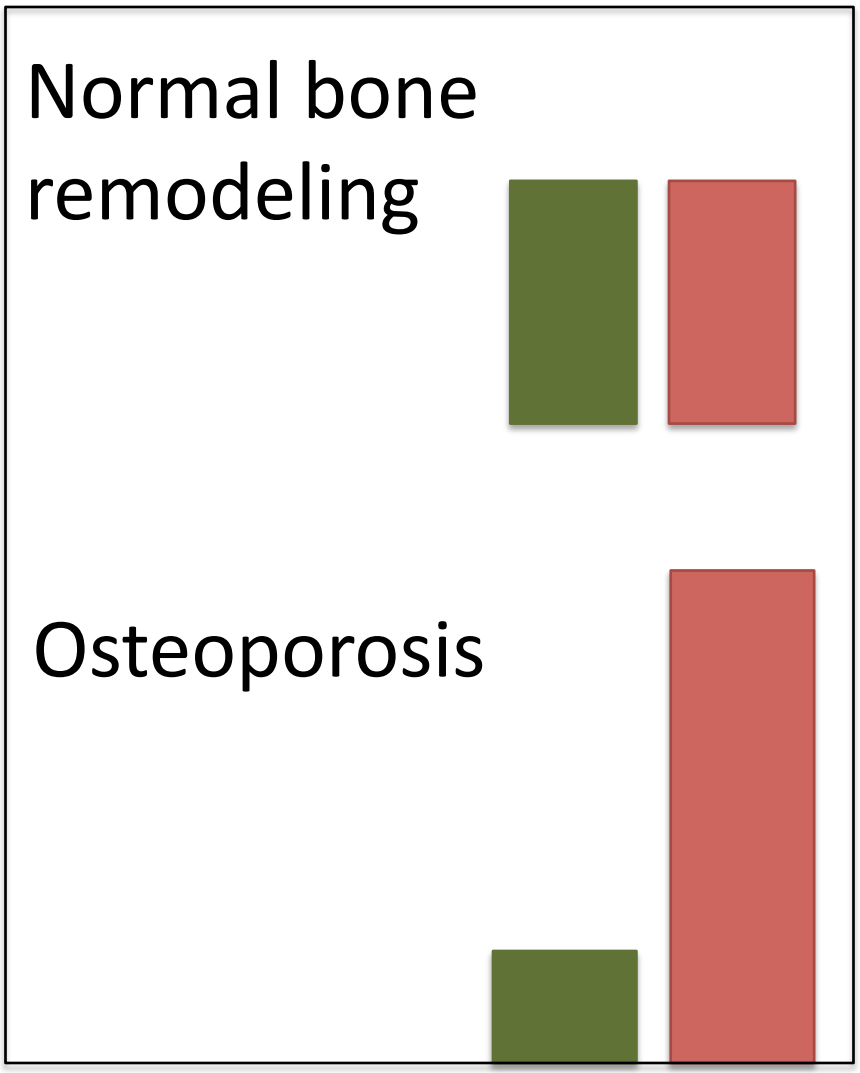
Bone Forming Unit: Osteoblast, Osteoclast



Osteoblast
bone formation



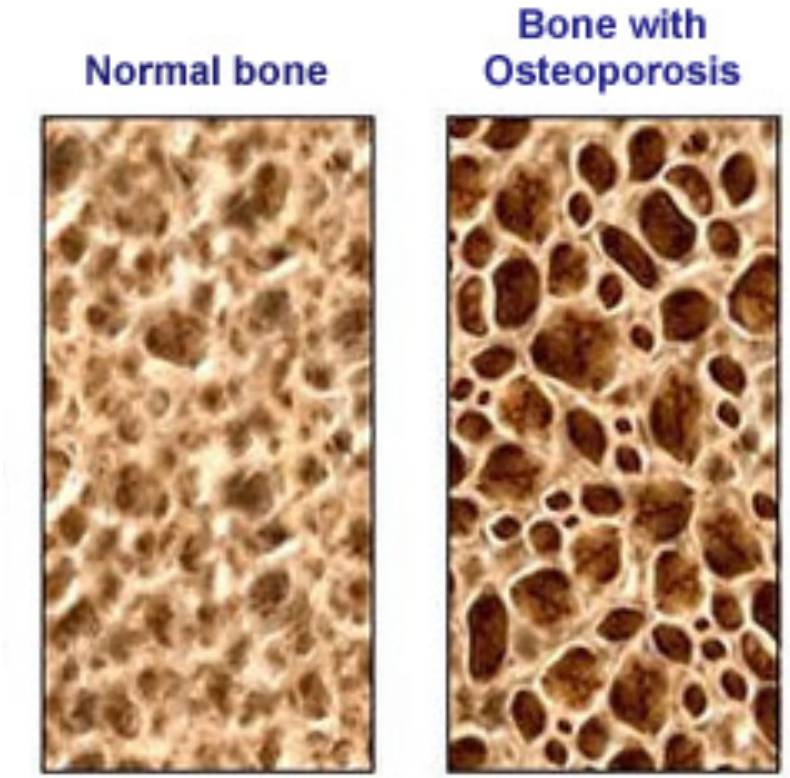
Osteoclast
bone resorption



Osteoporosis

Imbalance of bone remodeling

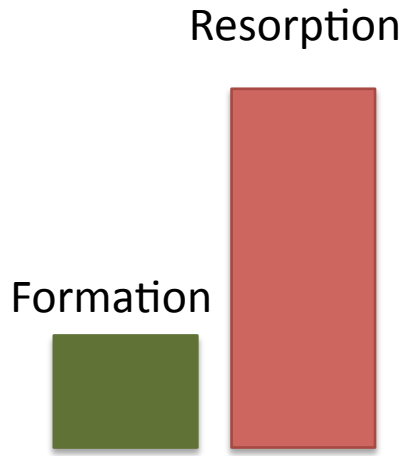
- Low bone mineral density (BMD)
- Microarchitectural deterioration
- Decreased bone strength
- Increased risk of fractures



In TM: peak bone mass is suboptimal

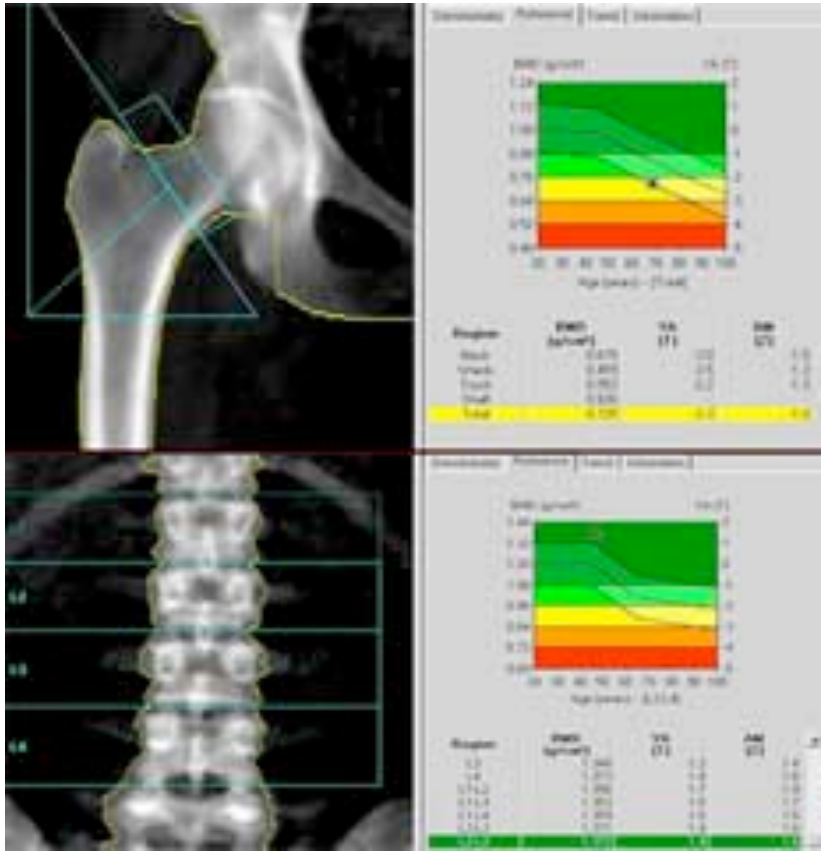
Causes of osteoporosis in TM

- **Acquired**
  - Bone marrow expansion
  - Hormonal deficiency
    - Hypogonadotrophic hypogonadism (70-80%)
    - Hypothyroidism
    - Hypoparathyroidism
    - Diabetes mellitus
  - Iron overload
  - Desferrioxamine toxicity
  - Calcium, zinc, vitamin D deficiencies
  - Inadequate physical activity
- **Genetic factors**



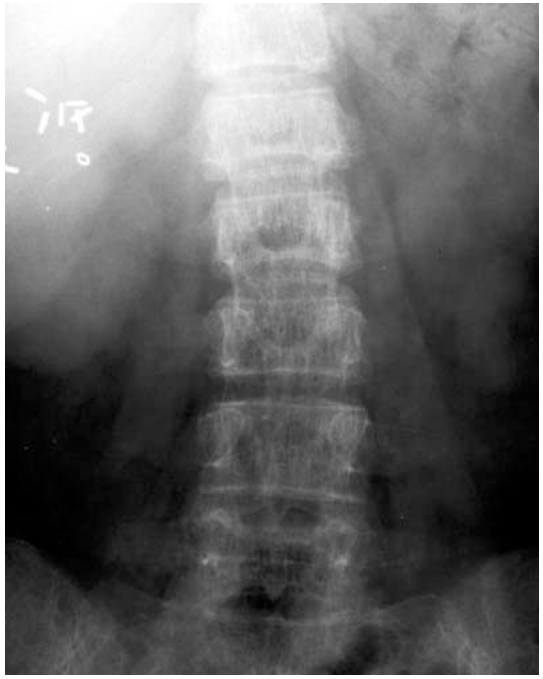
Investigations

- DEXA scan – bone mineral density
  - Spine, hip, forearm
  - WHO
  - Osteopenia
    - BMD > 1.5-2.5 SD below the young normal mean (T score)
  - Osteoporosis
    - BMD > 2.5 SD below the young normal mean (T score) or
    - BMD > 2.5 SD below in relation to patient's age (Z score)



Investigations

- Biochemical Tests
  - Endocrine profile
  - Bone profile
  - Liver function tests
- Spinal X-ray
- Spine MRI
  - Assess for degenerative disease, disc prolapse,
- Assessment of iron load



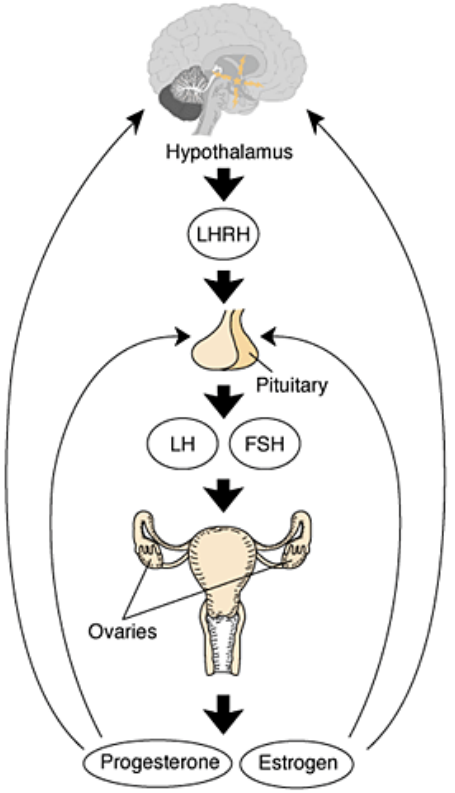
Management of Osteoporosis in TM

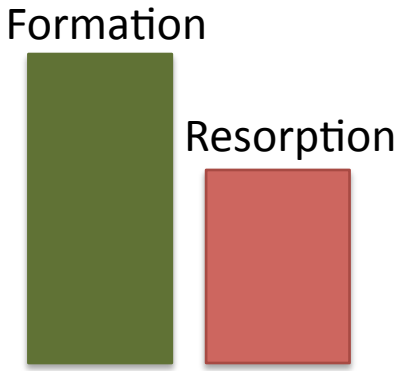
- PREVENTION
  - Correct anemia with regular transfusions
  - Reduce iron load with chelation therapy
  - Lifestyle
    - Increase physical activity
    - Quit smoking

  - Calcium, Vitamin D, and Zinc supplementation
  - Early recognition and management of endocrine complications eg. diabetes
  - Annual BMD assessment starting in adolescence

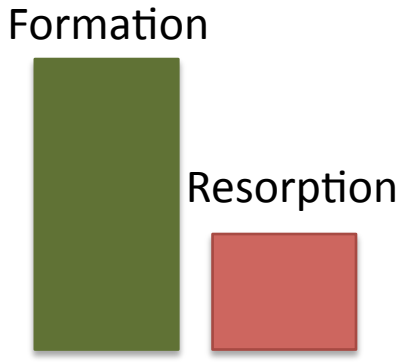
Treatment of Osteoporosis in TM

- Hypogonadotropic hypogonadism
  - No or decreased sex hormone production
  - Pituitary IRON OVERLOAD
  - Prevention of hypogonadism: IRON CHELATION
- Hormone replacement therapy
    - Estrogen and progesterone
    - Testosterone
    - promotes bone formation
    - improves BMD and reduces risk of fractures





Treatment of Osteoporosis in TM



- Bisphosphonates
  - Inhibit osteoclasts (bone resorption)
  - Oral: alendronate
  - Intravenous: pamidronate, zoledronic acid
  - Increase BMD in spine, Decreased pain
  - Which one? How long? What dose? Combination with HRT? Need further larger randomized studies.

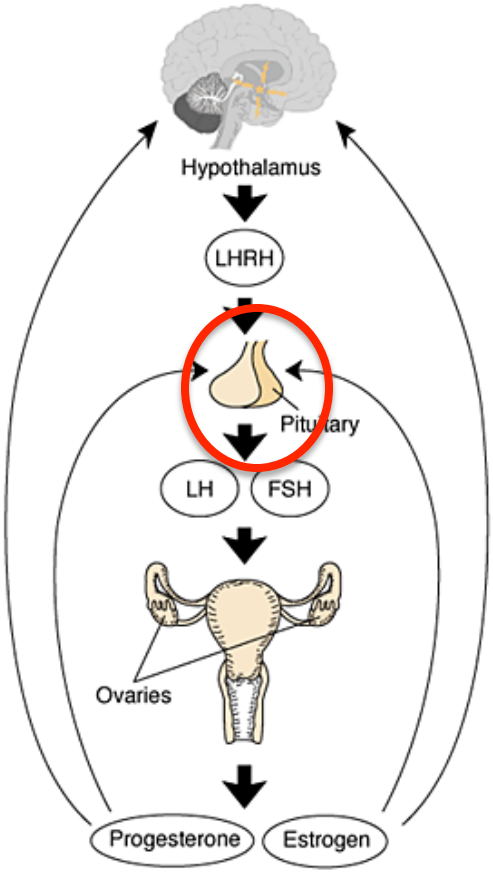
Summary

- Bone disease in thalassemia is common
- Thalassemia-induced osteoporosis is multifactorial
- Prevention is key
- Management includes effective transfusions, chelation, calcium and Vitamin D replacement, physical activity, and hormone replacement therapy
- The role of bisphosphonates is still not clear and further study is needed.

Fertility and Pregnancy in Thalassemia

Pituitary gland

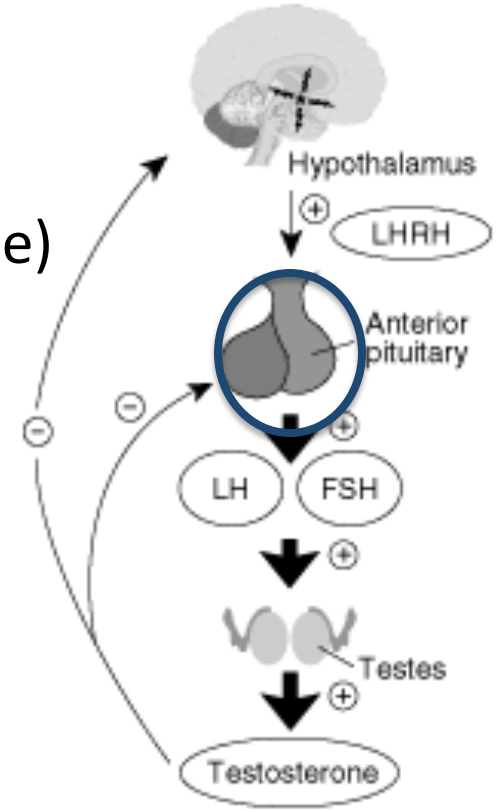
FEMALE



Controls the release of
FSH (follicle-stimulating hormone)
and LH (luteinizing hormone)

onset of puberty,
sexual development
reproductive function

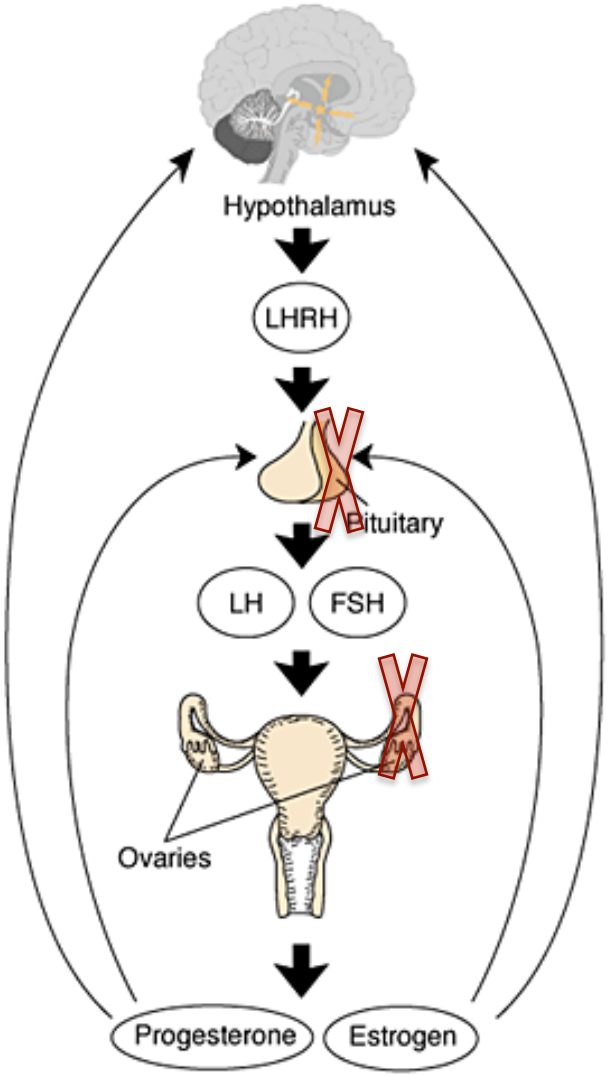
MALE



Fertility in TM

- Even though up to 90% of patients may have hypogonadotropic hypogonadism , the ovaries and testes are still intact.
- Ovulation and Spermatogenesis can be induced

Female infertility in Thalassemia



Pituitary Failure

Ovulation induction

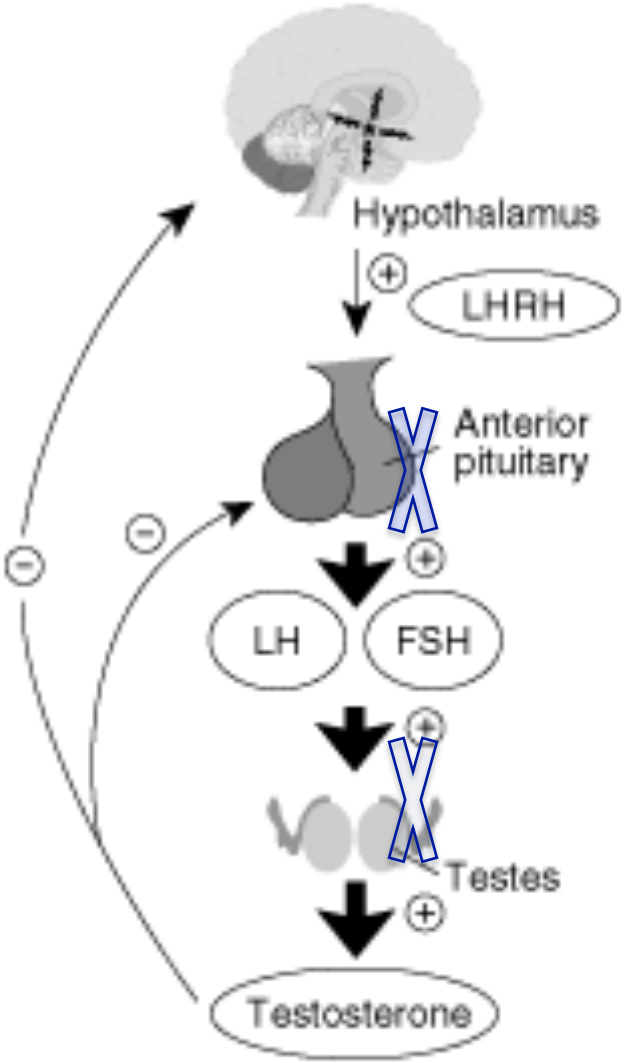
Primary Ovarian Failure

Donor Egg

Induction of Ovulation

- Pre-pregnancy counseling of couple
- Patient
  - Off HRT for 4-6 weeks
  - Check FSH, LH, E2 levels
  - Pelvic Ultrasound, Tubal patency
- Partner
  - Hemoglobin electrophoresis
  - Semen analysis
- Complications of Ovulation Induction

Male Infertility in Thalassemia



Pituitary Failure

Hormones

Gonaldal Failure

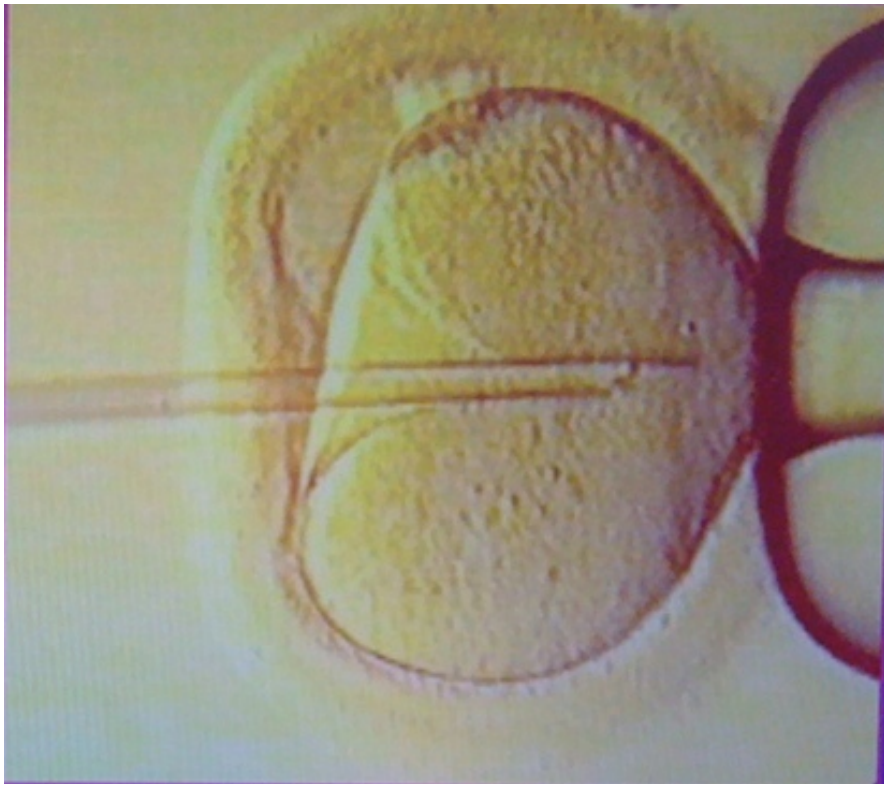
Donor Sperm

Induction of Spermatogenesis

- Pre-pregnancy counseling of couple
- Patient
  - Off TRT for 4-6 weeks
  - Check FSH, LH, testosterone levels
  - Semen analysis, Testes ultrasound
- Partner
  - Hemoglobin electrophoresis
  - Tubal test
  - Ovulation check

Induction of spermatogenesis

- Gonadotrophic hormones for upto 6 months
- If sperm production successful – cryopreserve
- Intracytoplasmic sperm injection



Fertility in Thalassemia

- **Induction of Ovulation**
  - Success rate 70-90%
- **Induction of Spermatogenesis**
  - Lower success rate ~ 15-30%

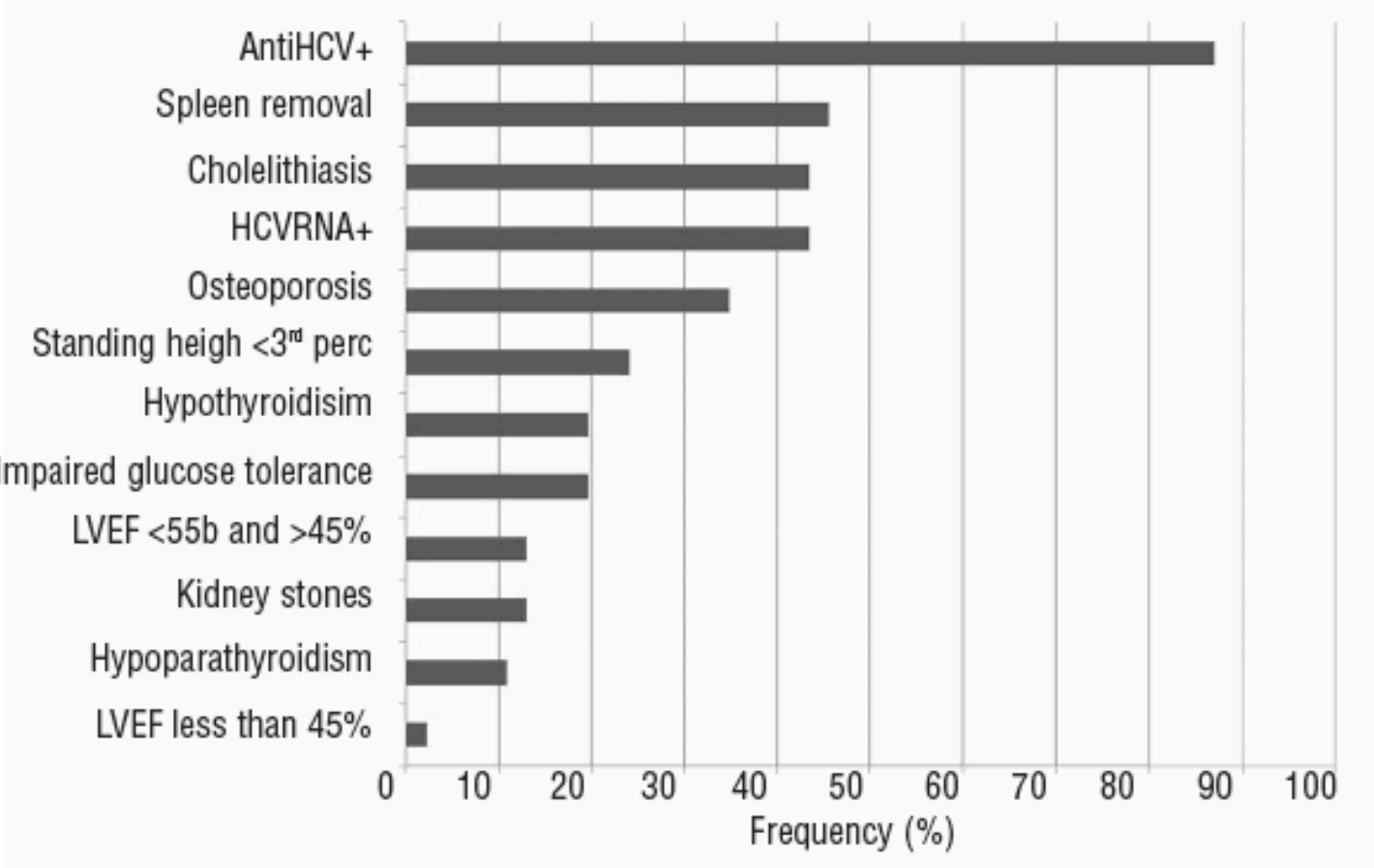
Pregnancy in Thalassemia

- Italian Multicentre Study
- 1997 – 2008
- Pre-pregnancy evaluations
  - Iron load assessment
  - Cardiac function
  - Women's fertility assessment, Endocrine optimization
  - Examination of partners for thalassemia status, sperm analysis
- Close cardiac, liver, endocrine, blood pressure assessment during pregnancy
- Multidisciplinary team approach

Origa et al. 2010. Haematological. 95:376-381

Pregnancy in Thalassemia

Pre-pregnancy medical histories in 46 women with TM



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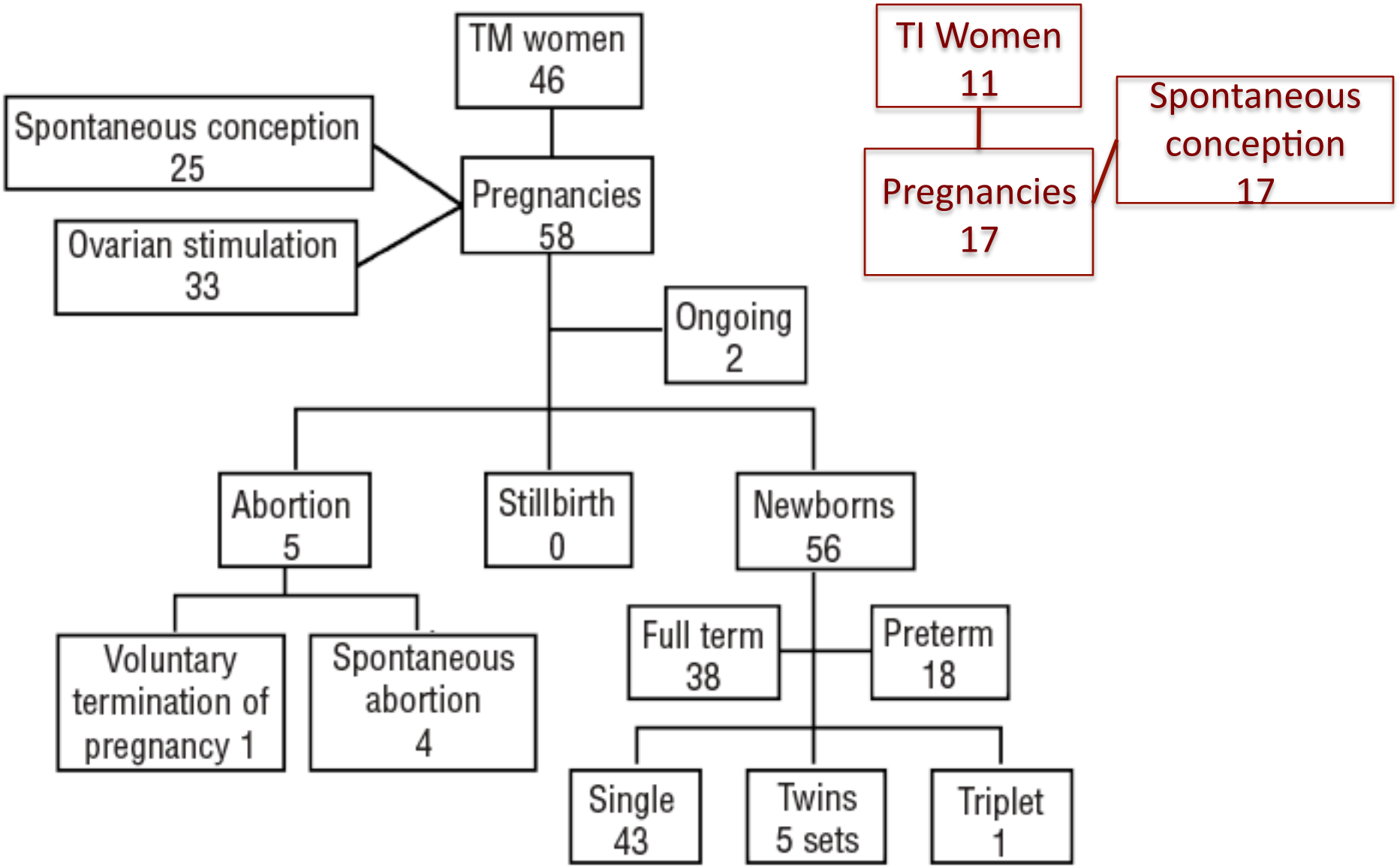

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Pregnancy outcomes

- Intrauterine growth restriction (4-8%)
- Increased preterm labor (17%)
- Increased twin pregnancies (2%)
- Increased rates of cesarean section (85%)

Summary

- In thalassemia patients, gonadal function is intact and ovulation and spermatogenesis are inducible.
- Pregnancy in TM and TI patients is possible, safe, and usually has a favorable outcome with comprehensive multidisciplinary care.
- No severe obstetrical complications
- Potential life threatening cardiac complications therefore optimization of cardiac function pre-pregnancy is crucial