Fertility and Pregnancy in Thalassemia

Sylvia Titi Singer, MD

UCSF Benioff Children's Hospital Oakland
Oakland, CA

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Adults and Young-Adults TDT Patients
Current concerns

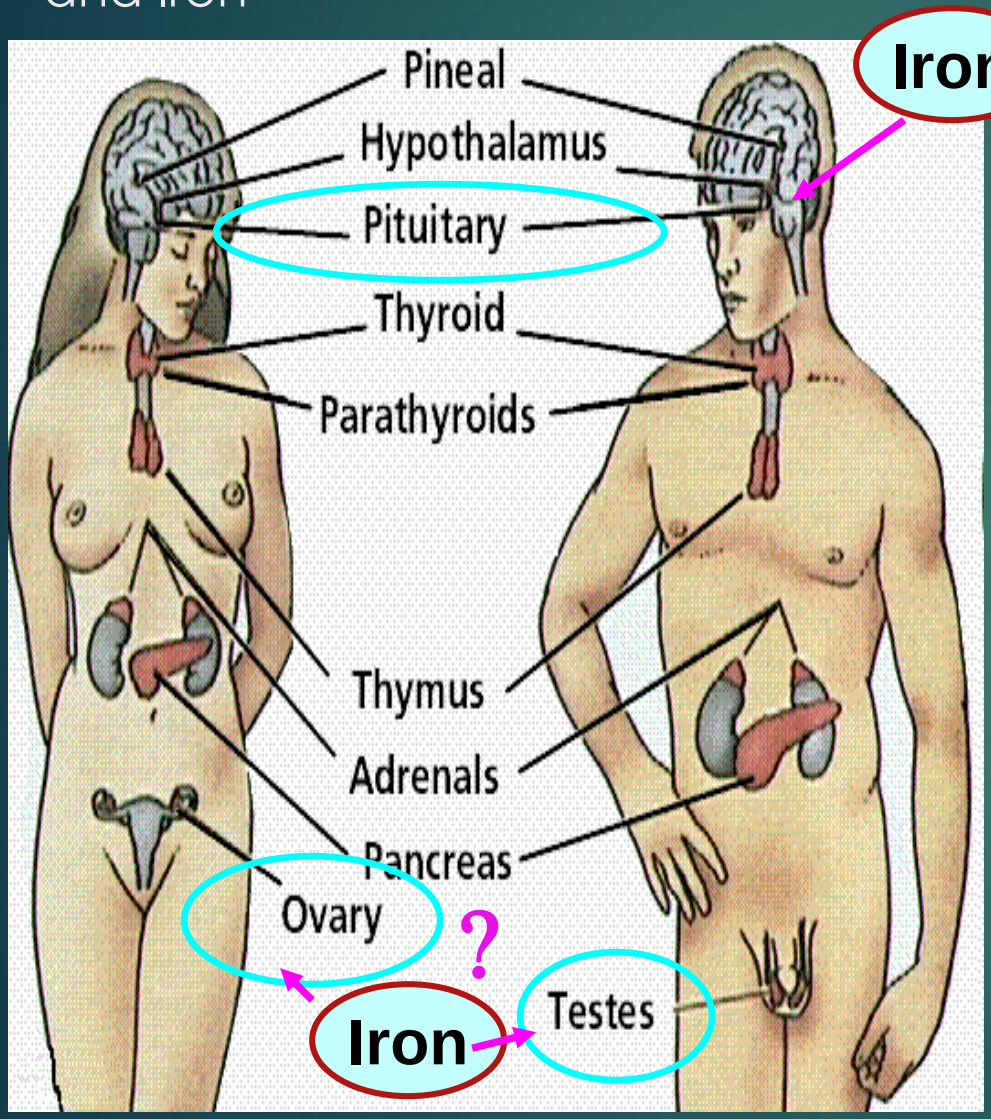
- Seeking better quality of life
  - Employment, form a family
- Asking about:
  - Reproductive potential
  - Options for fertility preservation
  - When to seek help for starting fertility treatment
- Insufficient information:
  - Delays treatment
  - Anxiety and disappointment

Iron and Fertility

PITUITARY GLAND

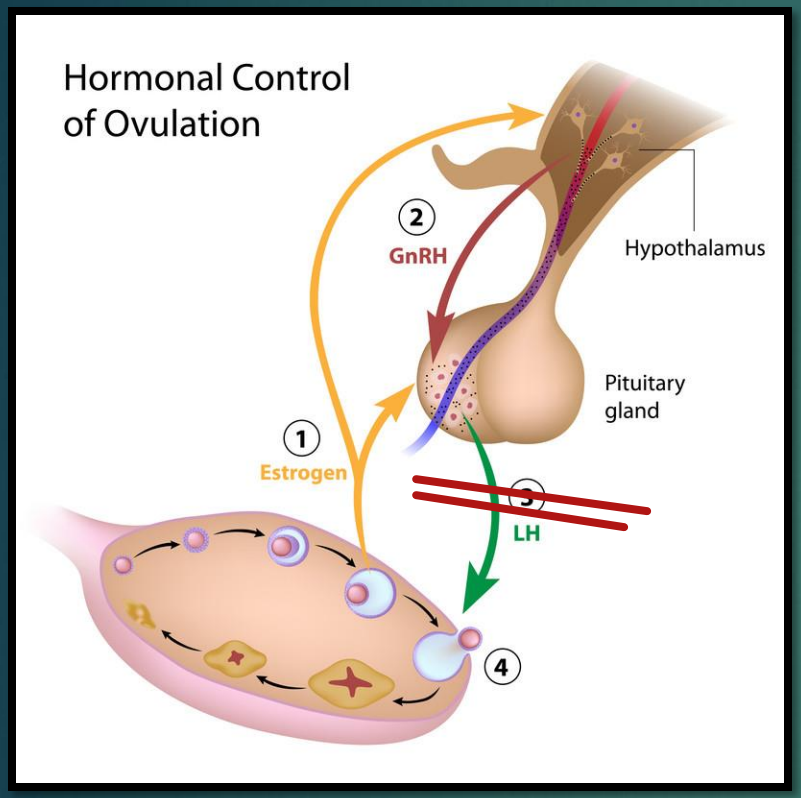
Hypogonadism

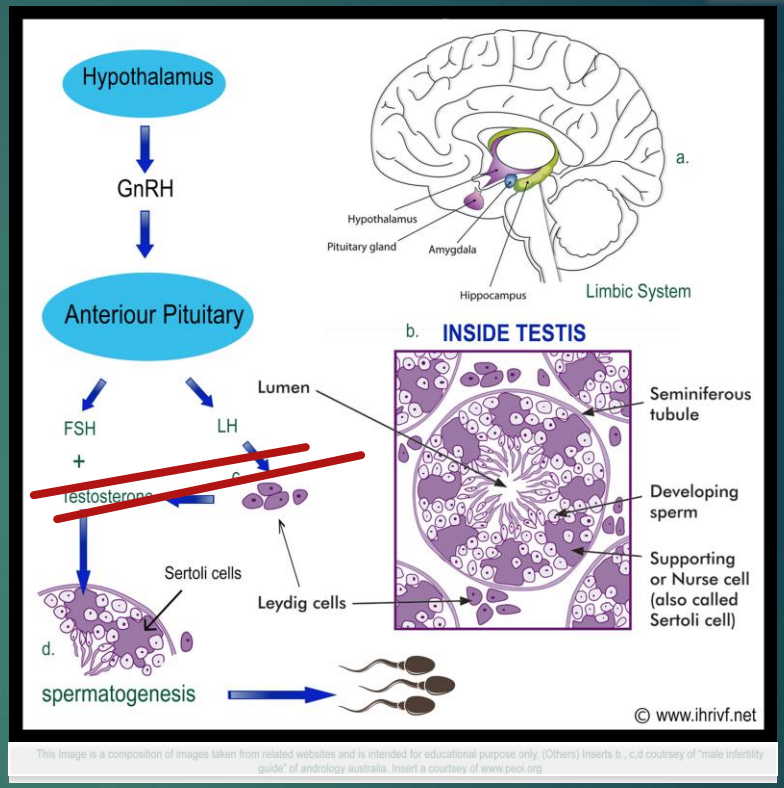
Hypothalamic-Pituitary-Gonadal Axis and Iron



- Anterior pituitary gland very sensitive to iron induced injury
- Iron penetrates cells→ cell death→ reduced hormone (LH/FSH) synthesis = Hypogonadism
- Low/no stimulation of gonads→ Low Estrogen/ testosterone
- Possible direct effect of iron/oxidative injury on ovaries and testes
  - Male > Female
  - Controversial

Hypogonadism and Infertility





- Reduced sex hormone (Testosterone/estrogen) synthesis and impaired ovarian follicles (eggs) or testicular sperm production
- Depending on severity, may result in partial or complete **infertility**

Hypogonadism and fertility

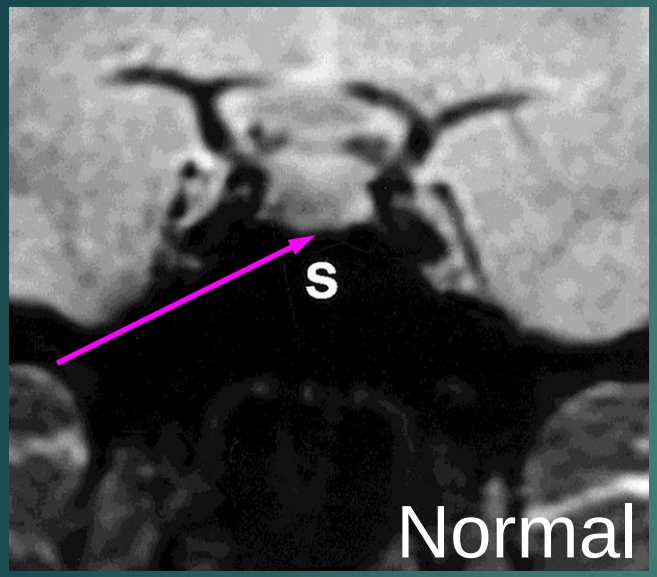
- Hypogonadism, the most common endocrinopathy in thalassemia: 25-55% in adult TDT patients (60-80% in less developed countries)
- Main cause of infertility
- Even with presumed adequate chelation (LIC 3-9 mg/gr dry wt) - disturbances in reproductive system are common
- The good news:
  - More intense chelation: lower frequency of hypogonadism/some reversal of malfunction

Casale, AJH 2014

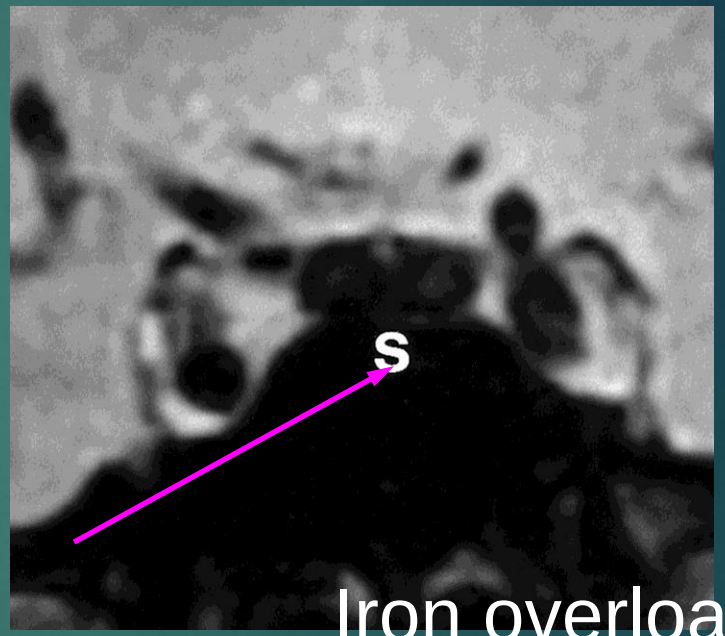
Farmaki BJH 2010

  - In women, ovarian function is typically preserved- Many successful pregnancies reported

Pituitary MRI imaging



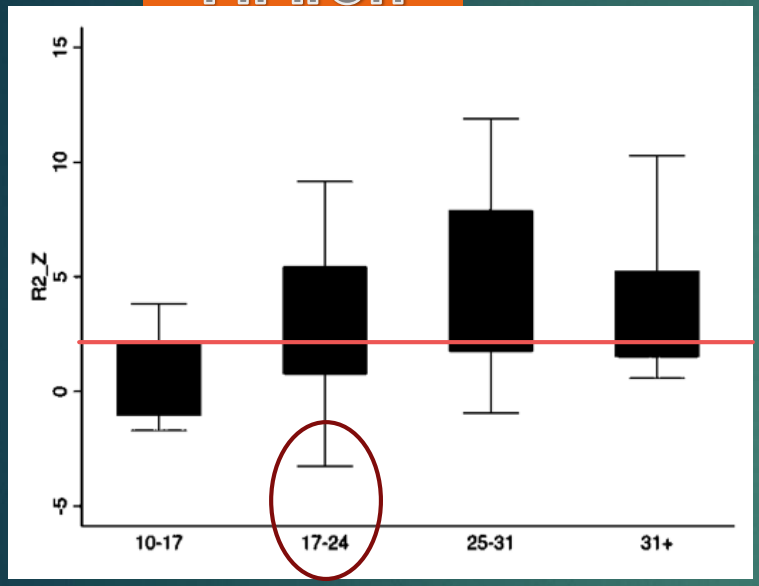
Pituitary MRI:
GRE T2*-weighted pituitary-to-fat signal intensity ratio



- Pituitary iron deposition: Difficult to reverse
- Toxic to cells causing pituitary volume loss

Change in pituitary iron and volume over time

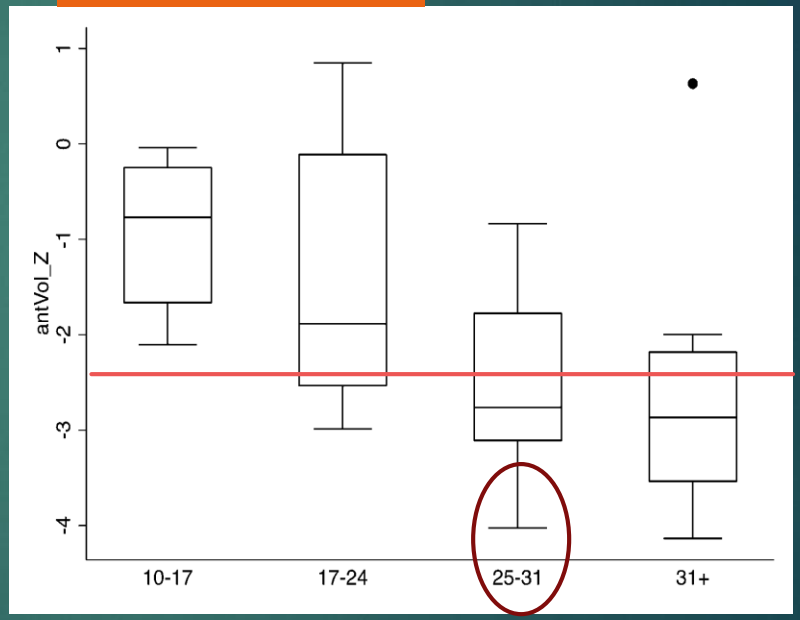
Pit Iron



Age (years)

n=53

Pit Volume

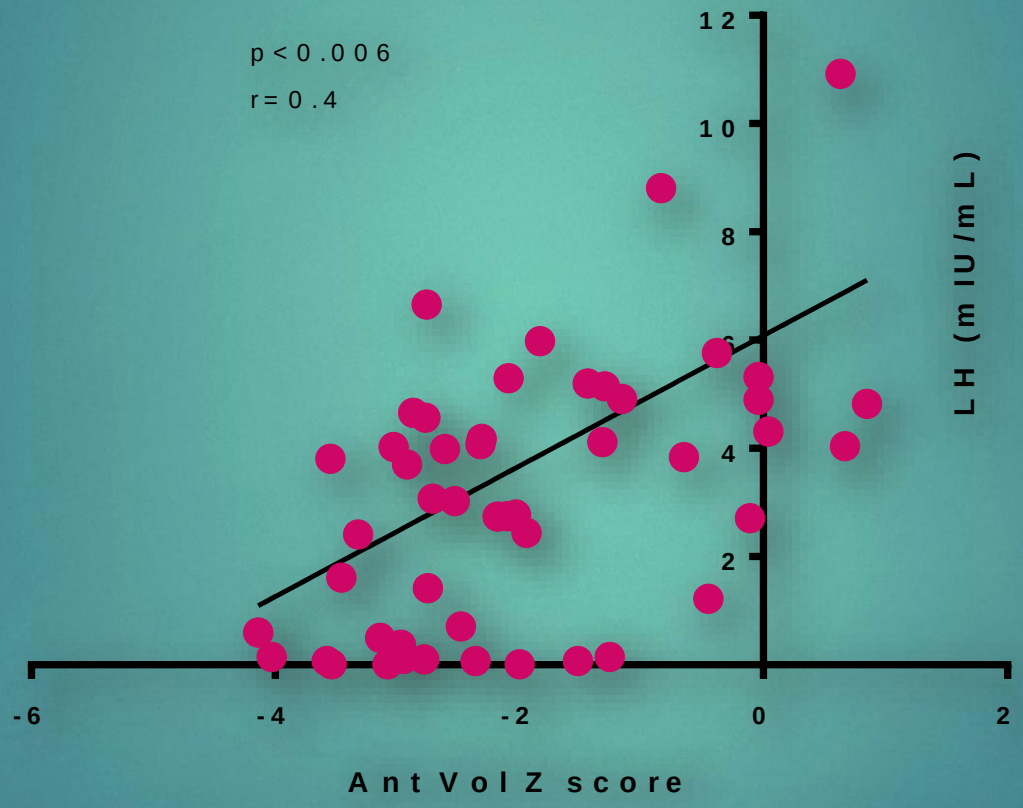


Age (years)

- Pituitary iron starting in 2nd decade
- Volume loss lags after iron accumulation.
- Window of opportunity for treatment intervention→ Intensify chelation, monitor closely

Singer ASH 2017
Noetzli AJH 2011

Decline in hormone secretion correlates with pituitary volume loss



n=50

Iron measures that will best tell us that fertility is declining

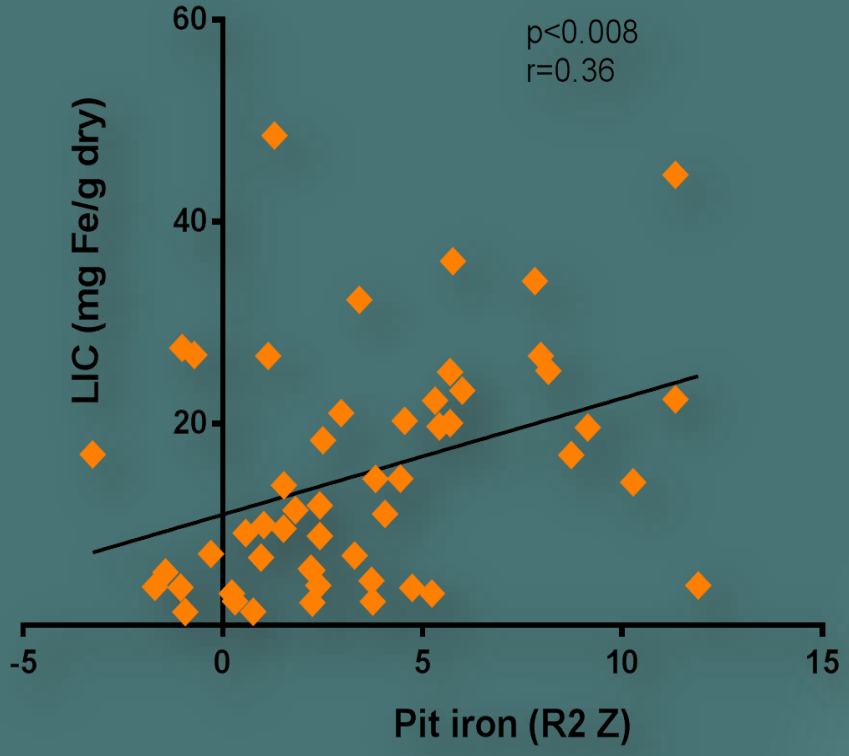
- Best correlation of pituitary iron is with Pancreatic iron (Noetzli 2011)
- Strong correlation with cardiac iron:

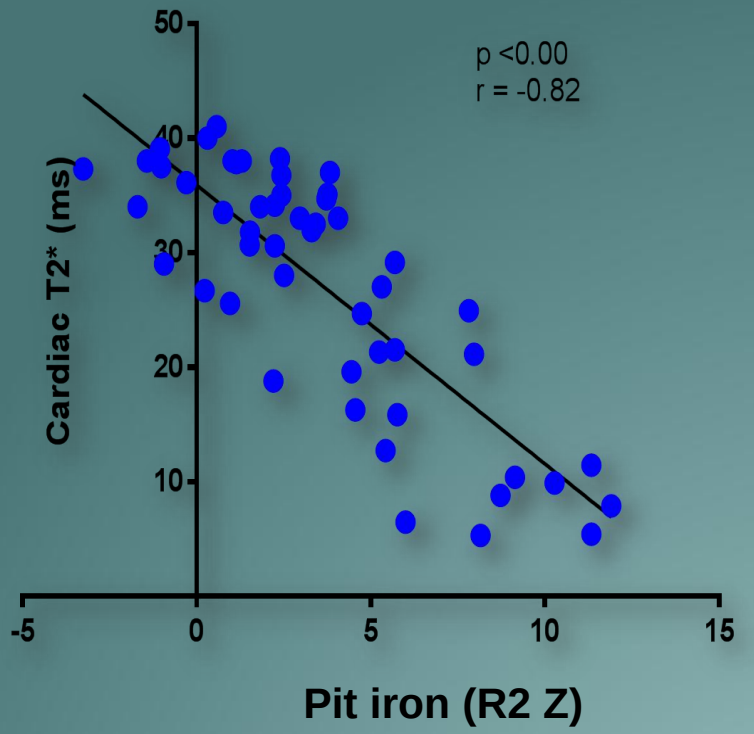
  T2* MRI of <20ms predicts significant pituitary iron (R2Z>4.0) AUC =0.84, which is associated with gland volume loss
- LIC >10mg/gdw also predictive for a high pituitary iron (R2Z>4.0) AUC of 0.74
- Consistent ferritin >1500ng/ml correlating with higher pituitary iron

Noetzli et al AJH 2011

Singer ASH 2017

Pituitary iron strongly correlates with cardiac iron and LIC





Assessment of Fertility Capacity

women, men

How to assess fertility potential?

Women

- Pituitary hormones (LH/FSH) and stimulation tests
- Ovarian Reserve Testing (ORT) various methods
  1. AFC (Antral Follicle Count) by U/S
  2. AMH (anti mullerian hormone) blood level
- AMH reflect the size of the remaining egg supply - ovarian reserve, correlates with AFC

  A low level of AMH suggests that the ovary may be depleted of eggs
- Not affected by LH/FSH as opposed to AFC- great advantage in thalassemia!

Ultrasound for Antral Follicle Count (AFC)

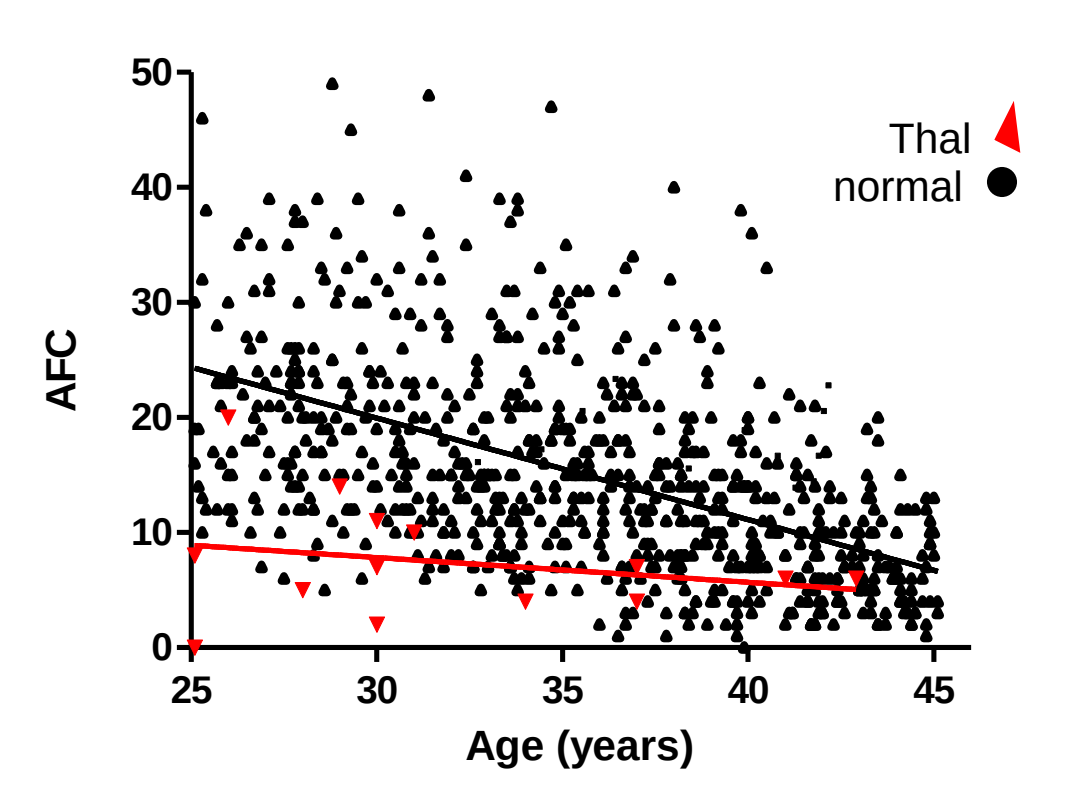
Normal

Low

Ovarian follicle count (AFC) in thalassemia and normal Controls

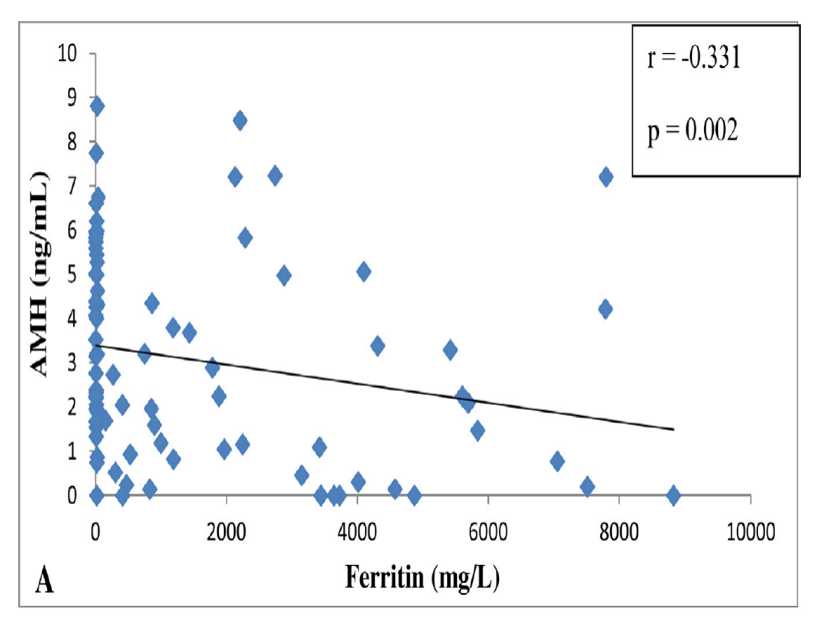
Good fertility potential: AFC>12-15.

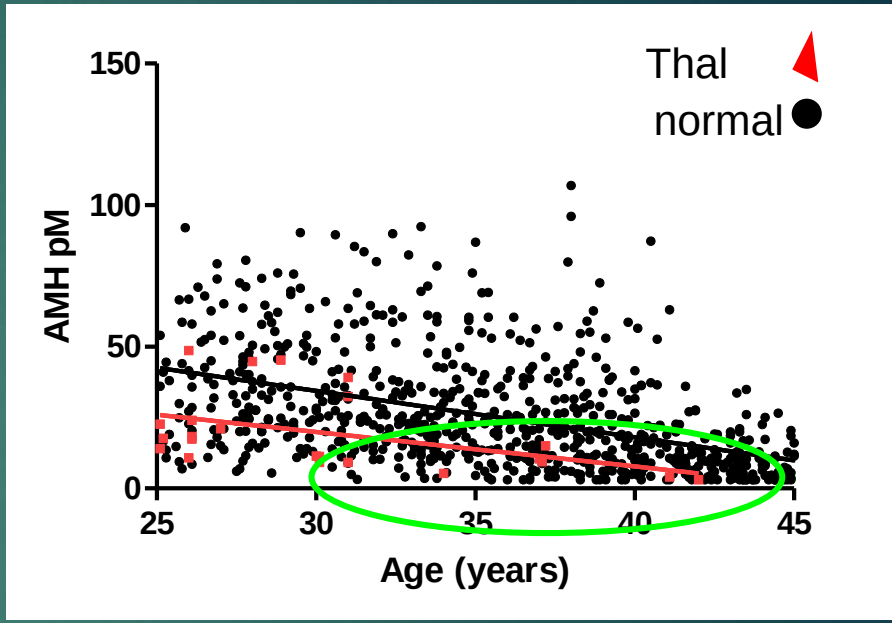
64% had AFC<8



- AFC is lower but **still present** in the majority of thalassemia women
- Probably represents low FSH/LH stimulation

AMH: A hormone that measures of Ovarian Reserve





- Most thalassemia women have preserved ovarian function
- Premature decline in women >33-35 y
- AMH declines with increased iron overload

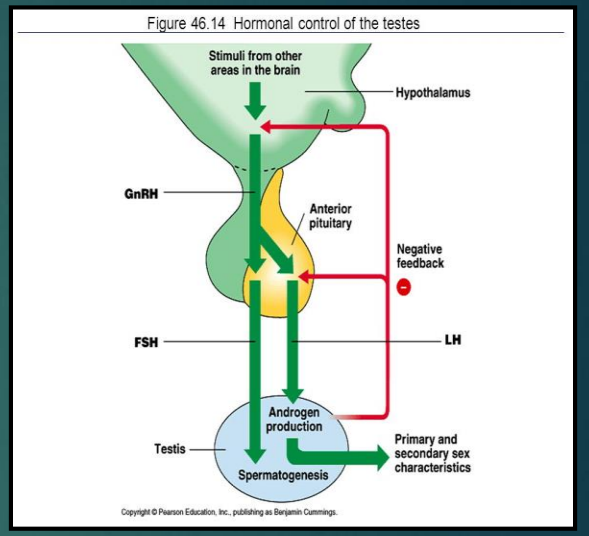
AMH 1pM=0.14ng/ml

Singer Blood 2011; Chang BJOG 2011;Uysal Ejorgb 2017

How to assess fertility potential ***Men***

- Pituitary hormones (LH/FSH)

  Less reliable when on testosterone treatment
- Inhibin B (blood level)
- Sperm analysis:
  1. Standard
  2. Sperm DNA fragmentation test



Semen analysis	2010 normal standards
Volume	> 1.5 ml
Sperm concentration	> 15 million / ml
Motility	> 40%
Morphology	> 4% Kruger Strict

Pregnancy in TDT

Pregnancy in Thalassemia

- A practical option with good prior care and monitoring during
- Well chelated TDT in their 20's- high rate of spontaneous pregnancy!
- Over 450 pregnancies reported (mostly TDT)
- 50-75% in females with amenorrhea
- Majority required hormonal treatment for ovulation induction.

  -Success rate 80% (Bajoria 2011)
- High success rate, suggests ovaries relative protection from iron damage

Planning for Pregnancy

- Multidisciplinary team: Hematology, Reproductive medicine, Obstetrician, Cardiologist, Psychologist
- Cardiac:
  1. Assure good T2*MRI (>20ms or more)
  2. ECHO, ECG, 24 hr Holter
  3. T2* <10ms or cardiac dysfunction→ delay plans
- Liver:
  1. Goal LIC<7 mg/gdw
  2. Complete hepatitis C (HCV) treatment, wait 6 month
- Bone health: DEXA scan, Vit D
- Recent goal: Delay pregnancy until Ferritin <1000, no cardiac iron (>30 T2*) and no/low liver iron load *(Cassinerio, Capellini 2017)*

Management during Pregnancy

- Transfusions

  Hb >10gr/dL or higher pre-Tx

- Chelation: Controversial…no studies

  1. Discontinue through pregnancy
  2. Restart in second/third trimester with Desferal (DFO)
  3. Early DFO treatment: Signs of decreased cardiac function, rapid increase in ferritin

- Cardiac: ECHO x3 during pregnancy (per TIF)
- Diabetes: Good glucose control, fructosamine
- Thrombotic risk (post splenectomy): Aspirin or LMWH recommended
- Higher Folic acid dose 5mg/day

Pregnancies in TDT Outcomes and Complications:

- Most report term delivery of normal babies
  - No increase rate of malformations
- High rate of C section (75-100%)
- High incidence of twins
- 7% spontaneous miscarriage
- 25-30% born premature (30-36 weeks)
- 8% Low birth weight

Pregnancies in TDT Maternal Issues/Complications:

- Mean Maternal Hb 11.2gr/dL
- Ferritin increased by ~ 10-50%
- LIC increase by 12.8- 65%
- Cardiac MRI

  stable in most reports

  Increase in 19% who had higher LIC
- Cardiac issues: increase RV volume, arrhythmias
- 90% of those with high glucose pre pregnancy developed gestational diabetes
- Maternal death 2 reported out of 417

(Meloni 2016; cassiniero 2017 others)

Thalassemia Male Fertility

- Infertility issues, diagnosis and treatment less well studied
- Only a few reports of TM males fathering children.
- Iron-induced sperm oxidative injury higher than ovarian follicle toxicity.
- Correlation of high iron/low zinc in semen with low sperm count
- Increased sperm DNA fragmentation

Perera Hum Rep 2002

Singer AJH 2015

Treatments and Fertility Preservation

Chelation type and timing

- Consistently well chelated→ Less findings of hypogonadism, better preserved fertility
- Ideally intensify chelation prior to irreversible decrease in pituitary volume
- Promising data on efficacy of deferasirox (Exjade/JadeNU):
  1. Poggi 2016: Less hypogonadism, 5 years (n=165)
  2. Casale 2014: Stable endocrinopathies, 3 years on Deferasirox
  3. Farmaki 2009: Intense chelation (DFO+Deferiprone) to normalization of LIC/ferritin→ Some reversal of hypogonadism

Treatment considerations

Women:

- Protocols for ovulation induction/hormonal stimulation (4-5 days)
- Hold chelation while treated until pregnancy test results? unknown

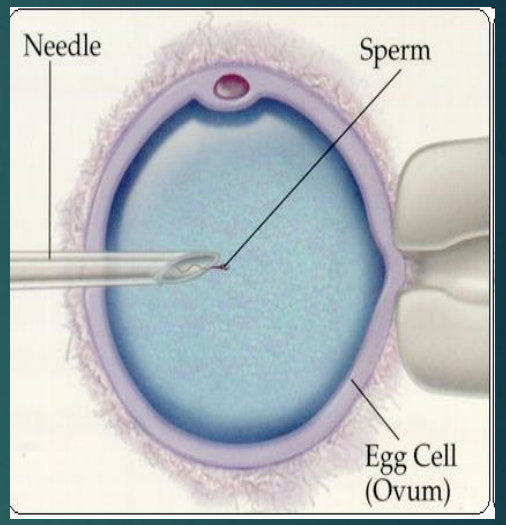
Men:

- Discontinue Testosterone treatment 3-6 months prior to plan having a child
- Start treatments to stimulate own testosterone and more sperm production,

  HCG: Human chorionic gonadotropin (+ FSH) – mimics LH or Clomid (Clomiphene)
- Minimizing oxidative damage, take Vitamins C, E, Zinc

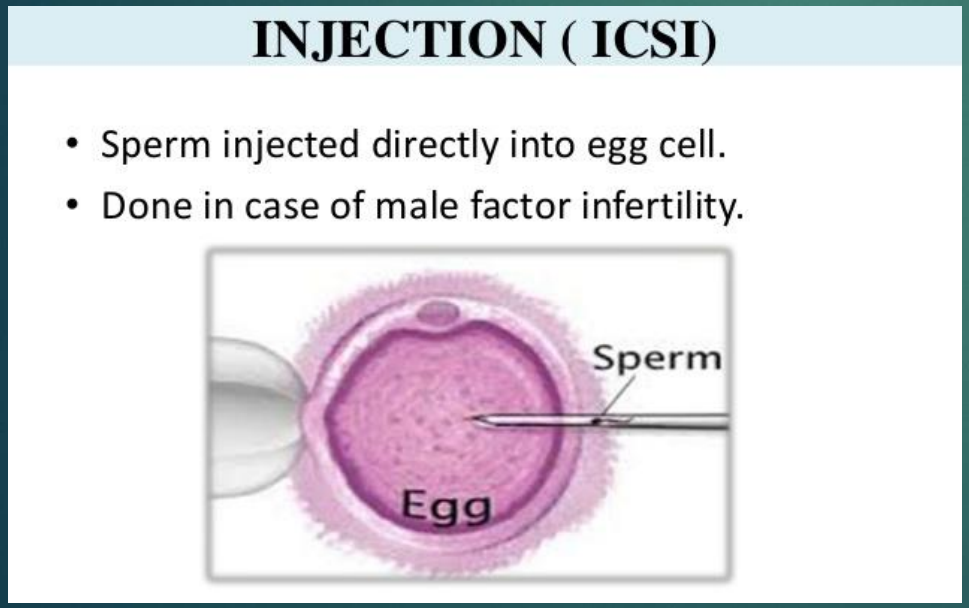
Assistant Reproductive Technology (ART) women and men

- Not all women able to become pregnant with ovulation induction
- Many men have zero/very low sperm count and motility
- ART: Fertility treatments in which both eggs and sperm are handled, examples:
  - In-vitro fertilization (IVF) –most common
  - Intracytoplasmic sperm injection (ICSI)
  - Gamete intrafallopian transfer (GIFT)
  - Preimplantation genetic diagnosis (PGD)

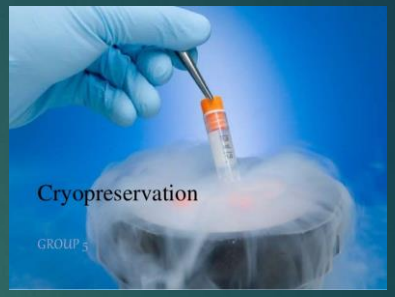


ART and thalassemia

- Women: IVF often indicated to overcome low follicle(egg) count
- Men: ICSI often indicated to overcome low sperm count



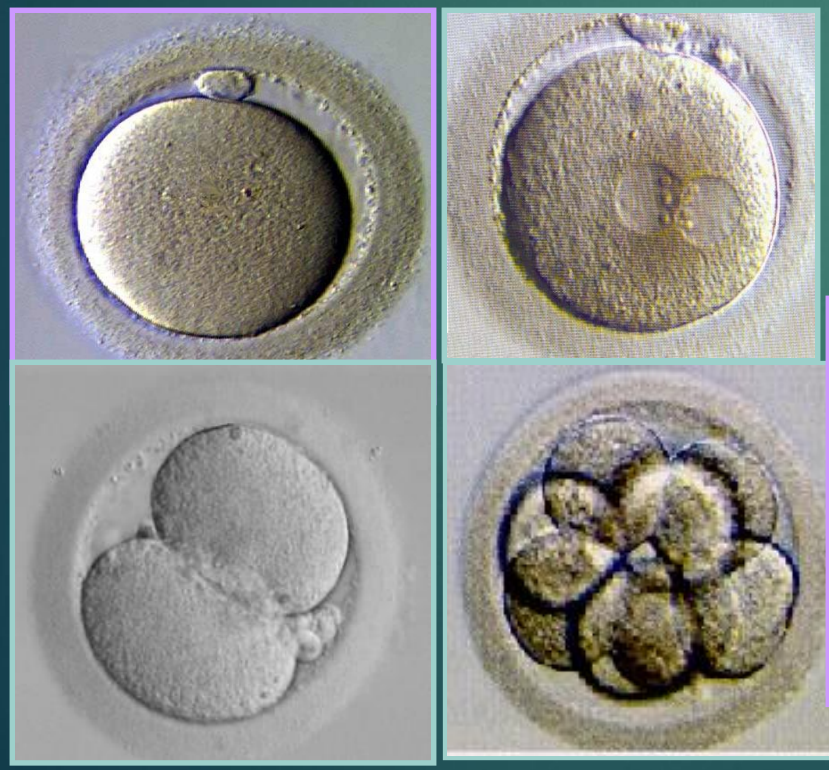
Fertility Preservation

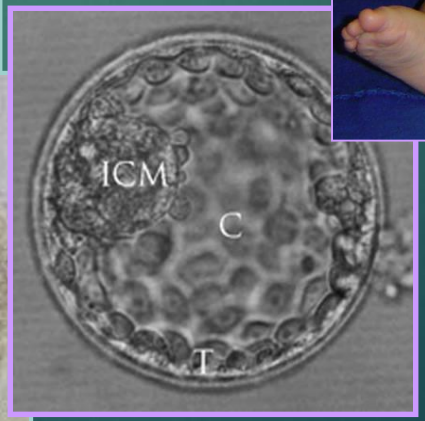


- Cryopreservation
  - Sperm, oocyte
  - Ovarian tissue
  - Embryo
- Relevant in thalassemia: Ovarian reserve and spermatogenesis decline faster…
- Should be offered to patients who are single, anyone concerned about their future reproduction ability
- Ethically and medically accepted in other conditions (young patients undergoing treatment for cancer)
- Thalassemia providers and patients need to gain understanding of the key components

Limitations of Cryopreservation:

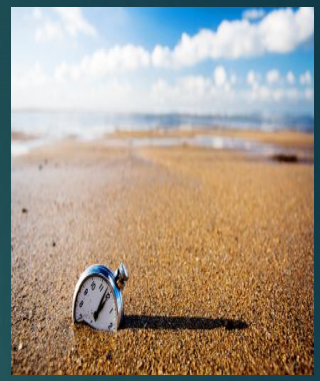
--Invasive procedure in women
--Sperm banking in men, easier
--Expensive
--Limited time of freezing
--Success rate varies





Summary

- Pituitary iron: common, peaks in third decade, can cause gland volume loss → fertility issues.
- Less severe with consistent chelation
- Intensified chelation (deferasirox) seems effective in stabilization (some reversal?)
- Cardiac iron (T2*<20) strong predictor for severe pituitary iron



- Women:
  - AMH: good marker for ovarian reserve
  - Overall preserved ovarian function- high success rate with ovulation induction
  - But…declines after ~mid 30's
  - Single women: Considerations for egg/ovarian tissue freezing

Summary-cont.

- Men:
  - Low sperm counts and motility-common with high iron
  - Fertility status: Sperm analysis, DNA fragmentation
  - Considerations for sperm banking

- Hematologist role:
  - Discuss fertility issues early
  - Make patients aware of fertility preservation options available for them

Needed:

- Guidelines for screening and intervention
- Make infertility treatment and preservation more acceptable and covered service as it is in the oncology setting for young adults/adolescents with cancer

Pediatric Clinical Research Center and thalassemia clinical team at BCHO

Jerry Wang PhD
Roland Fischer PhD
Elliott Vichinsky, MD
Ash Lal, MD

Reproductive Endocrinology, Urology
UCSF Medical Center

Novartis Pharmaceuticals Corporation

Cooley's Anemia Foundation

Patients and families