Fertility Issues in Sickle Cell Disease

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SCDAC Biennial Canadian Conference Nov 9-10, 2018
Disclosures

• None
Learning Objectives

• What is Sickle Cell Disease?
• How does Sickle Cell Disease affect fertility?
• Why is Fertility important in Sickle Cell Disease?
• Fertility Issues differ for
  • Males
  • Females
• Disease Modifying Therapies & Fertility
• Curative Therapies & Fertility
• Opportunities for fertility preservation
Molecular Pathology of Sickle Cell Disease

The $\beta^s$ Mutation

6th Codon of $\beta$-Globin Gene

| GAG | GTG |
| Glutamic acid | Valine |

The same mutation found in all $\beta^s$ genes around the world

HbS polymerizes in the deoxygenated state. This is the cause of red cell deformity. Thus, under low oxygen conditions, red blood cells that contain HbS become irreversibly rigid and sickle-shaped.

Consequence of Sickle-Shaped Red Cells

The sickle-shaped red blood cells have impaired ability to pass through narrow capillaries.

This leads to vascular occlusion, infarction, and associated symptoms including acute pain and progressive organ damage.

Sickled RBCs have a markedly shorter lifespan than normal RBCs (16-20 vs. 120 days), which leads to hemolytic anemia.
Complications of Sickle Cell Anemia

- **Brain**: Thrombosis or hemorrhage causing paralysis, sensory deficits, or death
- **Eye**: Hemorrhage, retinal detachment, blindness, retinopathy
- **Lung**: Acute chest syndrome, pulmonary hypertension, pneumonia
- **Kidney**: Hematuria, renal failure
- **Spleen**: Splenic atrophy (autosplenectomy)
- **Liver-gallbladder**: Hepatomegaly, gallstones
- **Skin**: Stasis ulcers of hands, ankles, and feet
- **Bones and joints**: Hand-foot syndrome, osteonecrosis
- **Heart**: Heart failure
- **Penis**: Priapism
Sickle Cell Survival Data
(Quinn et al 2010)
Advances in Sickle Cell Management
(Huang & Muneyyirci-Delale, 2017; Chartuvedi & DeBaun, 2016; Quinn et al, 2010)

- Newborn Screening
- Active screening for complications
- Penicillin prophylaxis
- Immunizations
- Aggressive fever management
- Hydroxyurea
- Transfusion support
- Quality of life and fertility are now very important issues
Sickle Cell Disease Therapeutic Options (Limited)
Sickle Cell Disease & Fertility

(Modebe & Ezeh, 1995; Chartuvedi & DeBaun, 2016; Smith-Whitley 2014; Huang & Muneyyirci 2017)

• Delayed sexual maturation
  • Males (Late Tanner stages)
  • Females (Delayed menarche)
• Testicular infarction
• Pituitary infarction
• Ovarian Infarction
• Erectile Dysfunction
Fertility Issues in Men
(Chartuvedi & DeBaun, 2016; Whitey, 2014)

• Hypogonadism

• Sperm abnormalities

• Erectile Dysfunction
Hypogonadism
(Huang & Muneyyirci 2017; Smith-Whitley 2014)

• Etiology unclear

• Primary hypogonadism
  • Vaso-occlusion
  • Recurrent testicular infarction
  • Hypothalamic pituitary infarction

• Associated with
  • Poor testosterone production
  • Poor libido
  • Erectile Dysfunction
  • Infertility
Sperm Abnormalities

(Osegbe et al 1981; Whitey, 2014)

• Rates as high as 91% reported vs. Controls
  • Low sperm density
  • Low counts
  • Poor motility
  • Abnormal morphology

• Sperm abnormalities persist even with normal testosterone levels
Erectile Dysfunction
(Osegbe et al. 1981; Whitey, 2014; Huang & Muneyyirci 2017)

- Etiology unclear
- Prevalence as high as 21-35%
  - Priapism
- Sexual Dissatisfaction
  - Fear of Priapism
- Hypogonadism
  - Low testosterone
  - Low libido
Fertility Issues in Females

(Ghafuri et al, 2017; Smith-Whitley 2014)

• Limited Studies
• Infertility
• Premature ovarian failure
  • Some studies have used rates of pregnancy
  • Lower rates of sexual activity
• Complications associated with pregnancy
• Use of NSAIDs
• Use of Opioids
Infertility
(Ghafuri et al, 2017; Smith-Whitley 2014)

• Limited Studies

• Failure to conceive after 12months
  – Regular sexual intercourse
  – Age < 35 years

• Lower rates of pregnancy vs Healthy controls
  – Other factors such lower rate of sexual activity
Premature Ovarian Failure

(Ghafuri et al, 2017; Smith-Whitley 2014)

• Primary Ovarian insufficiency
  • Ovarian Sickling
  • Pituitary-Hypothalamic Sickling

• Premature menopause
  • Amenorrhea for at least 4 months
  • Low estradiol, FSH > 40mIU/ml
  • Prior to expected age (Usually 40 years)
Pregnancy related complications

(Oteng-Ntim et al, 2015; Chartuvedi & DeBaun, 2016)

• Increased maternal mortality
• Pre-eclampsia
• Stillbirth
• Pre-term delivery
• Small for gestational age
Opioids

(Ghafuri et al, 2017)

• Main stay in pain management in SCD
• Chronic opioid use vs healthy controls
  – Suppresses hypothalamic-pituitary-gonadal axis
  – 48-57% reduction in Estradiol & Testosterone
  – 30% reduction in LH & FSH
• Limited studies on opioid use and fertility in SCD
NSAIDs

(Ghafuri et al, 2017; Mendonca et al, 2000)

- NSAIDs (Non steroidal anti-inflammatory drugs)
  - Ibuprofen, Naproxen etc.
- Inhibition of Cox 2
  - Reduction of prostaglandin synthesis
  - No follicular rupture & ovum release
  - Impaired ovulation
- Case series – 3 out of 4 women on chronic NSAIDs
  - Spontaneous conception post NSAID therapy
Sickle Cell Disease Therapeutic Options (Limited)
Hydroxyurea & Fertility in Males
(Berthaut et al, 2008; Whitley-Smith, 2014; Huang & Muneyyirci-Delale 2017)

• Documented effects on sperm
• 108 sperm specimens
  – 91% had abnormality at least in 1 area before treatment
    • Volume of ejaculate
    • Sperm concentration
    • Motility
    • Vitality & Morphology
  – All sperm parameters were affected post treatment
  – Recovery post-treatment
  – Unclear if fertility was affected
Hydroxyurea & Fertility in Females

(Chartuvedi & DeBaun, 2015; Ballas et al, 2009)

• Teratogenic in animal models
• No documented teratogenicity in pregnant women on Hydroxyurea (MSH)
• Live births occurred regardless of
  – Duration of Hydroxyurea
  – Stage of Pregnancy
    • Conception
    • Gestation
    • Throughout pregnancy
Curative Therapies & Fertility

(Ghafuri et al, 2017; Smith-Whitley 2014)

- Hematopoietic Stem Cell Transplantation
  - Myeloablative conditioning
  - Total body radiation
- Destruction of Oocytes (Eggs)
- Depletion of follicles
- Result – Infertility, Primary Ovarian insufficiency
- Non-myeloablative conditioning regimens less toxic
Gene Therapy & Fertility

(Ghafuri et al, 2017; Smith-Whitley 2014)

• Still in experimental stage
• Use of alkylating agents
• Results similar to myeloablative conditioning regimens
• No studies available
Fertility Preservation
(Ghafuri et al, 2017; Smith-Whitley 2014)

- Ovarian Transposition
- Oocyte & Embryo preservation
- Semen Cryopreservation
- Ovarian Cryopreservation
- In vitro maturation of Oocytes
Sickle Cell Disease Therapeutic Options (Limited)
Now what?

• Sickle Cell Patients are now living longer
• Quality of Life (QOL) is now the key issue
• Fertility has a profound impact on QOL
• More research is needed
• Studies are old, small, and limited in applicability
• Curative options for sickle cell disease can affect fertility
• Fertility preservation options need to be explored
• Berthaut at al (2008) Influence of Sickle Cell Disease & treatment with Hydroxyurea on sperm parameters and fertility of human males. Hematologica 93(7); 988-993
• Chartuvedi & DeBaun, (2016) Evolution of Sickle Cell Disease from a life threatening disease of children to a chronic disease of adults: The last 40 years. American Journal of Hematology, 91; 5-14