Female Athlete Triad/ Relative Energy Deficiency in Sport (RED-S)

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Financial Disclosures

- I have no disclosures.

Learning Objectives

- Define and review the epidemiology and prevalence of RED-S
- Discuss the clinical diagnosis of RED-S and how it fits under the umbrella of hypogonadotropic hypogonadism
- Discuss the management of RED-S related to fertility
- Discuss long-term health effects and management of patients with RED-S

Case

- 35 year old G1P1
- Levonogestrel IUD placed post partum, when removed to try for second child, menses did not return
- Presents with lifelong increasingly irregular menses, history of stress fracture as a teen
- Of note, BMI 18.5, and ran two marathons in the past year


W-101
John Hancock
BOSTON ATHLETIC ASSOCIATION
2015 BOSTON MARATHON
John Hancock

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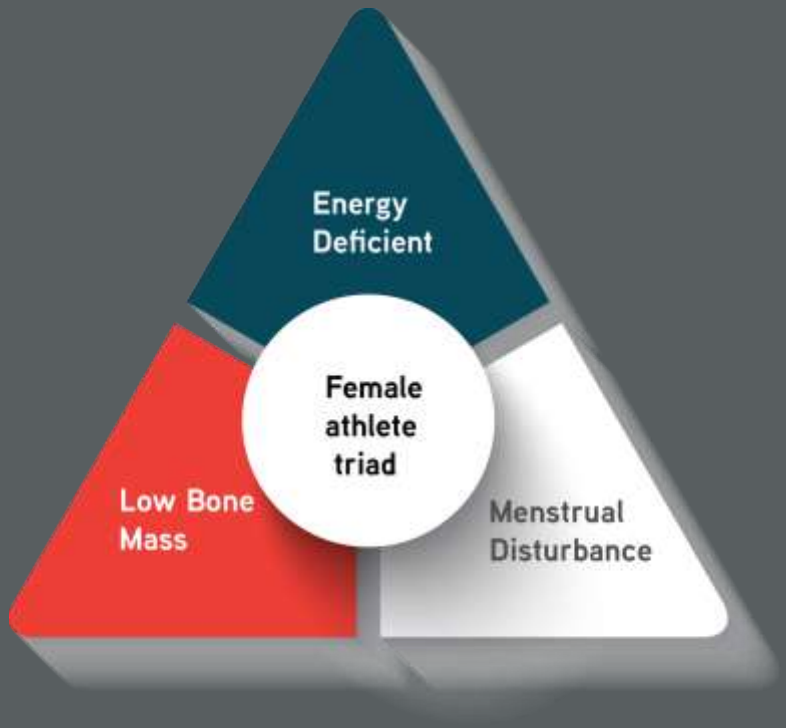
What is relative energy deficiency in sport (RED-S)?



https://www.pledgesports.org/wp-content/uploads/2018/05/femaleatheletetriad.png

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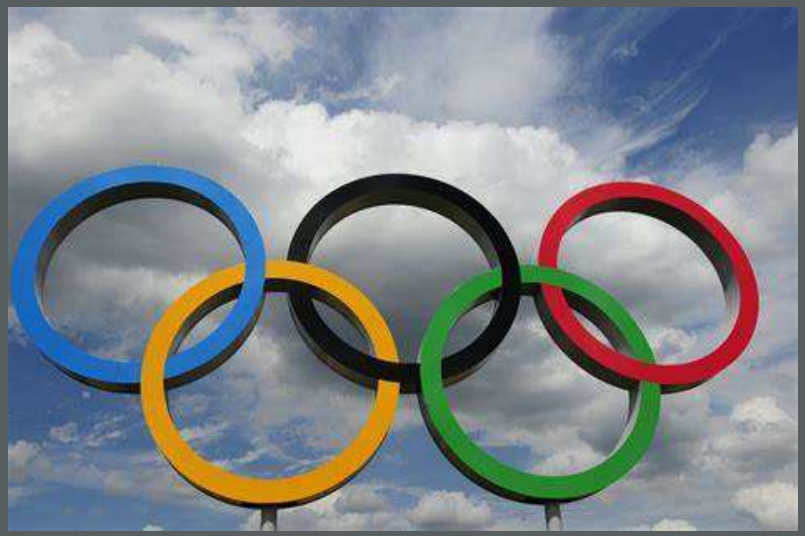
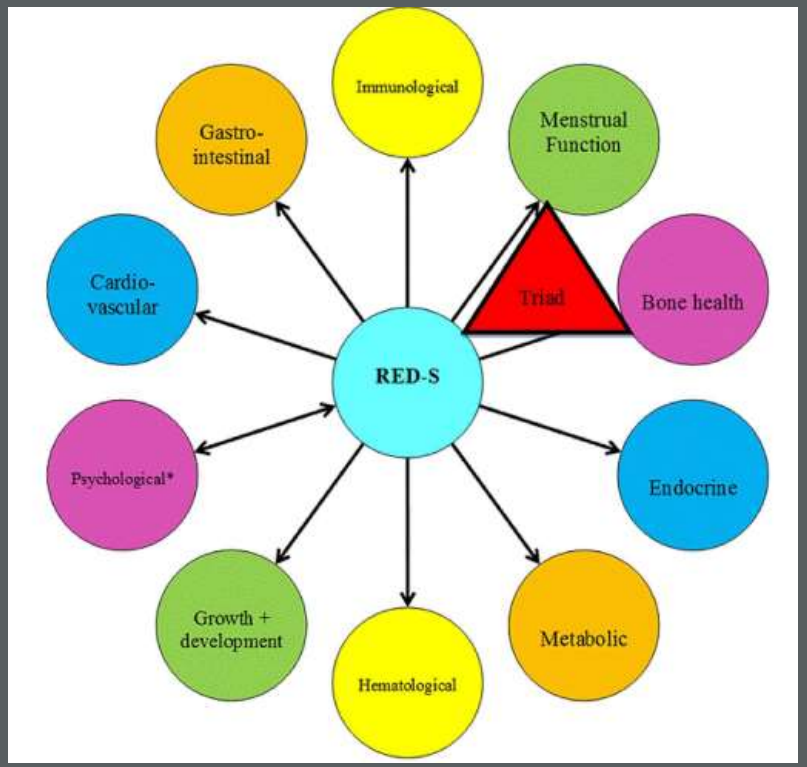
What is relative energy deficiency in sport (RED-S)?

The IOC consensus statement: beyond the Female Athlete Triad—Relative Energy Deficiency in Sport (RED-S)

Margo Mountjoy,[1] Jorunn Sundgot-Borgen,[2] Louise Burke,[3] Susan Carter,[4] Naama Constantini,[5] Constance Lebrun,[6] Nanna Meyer,[7] Roberta Sherman,[8] Kathrin Steffen,[2,9] Richard Budgett,[9] Arne Ljungqvist[9]





(Mountjoy 2014)

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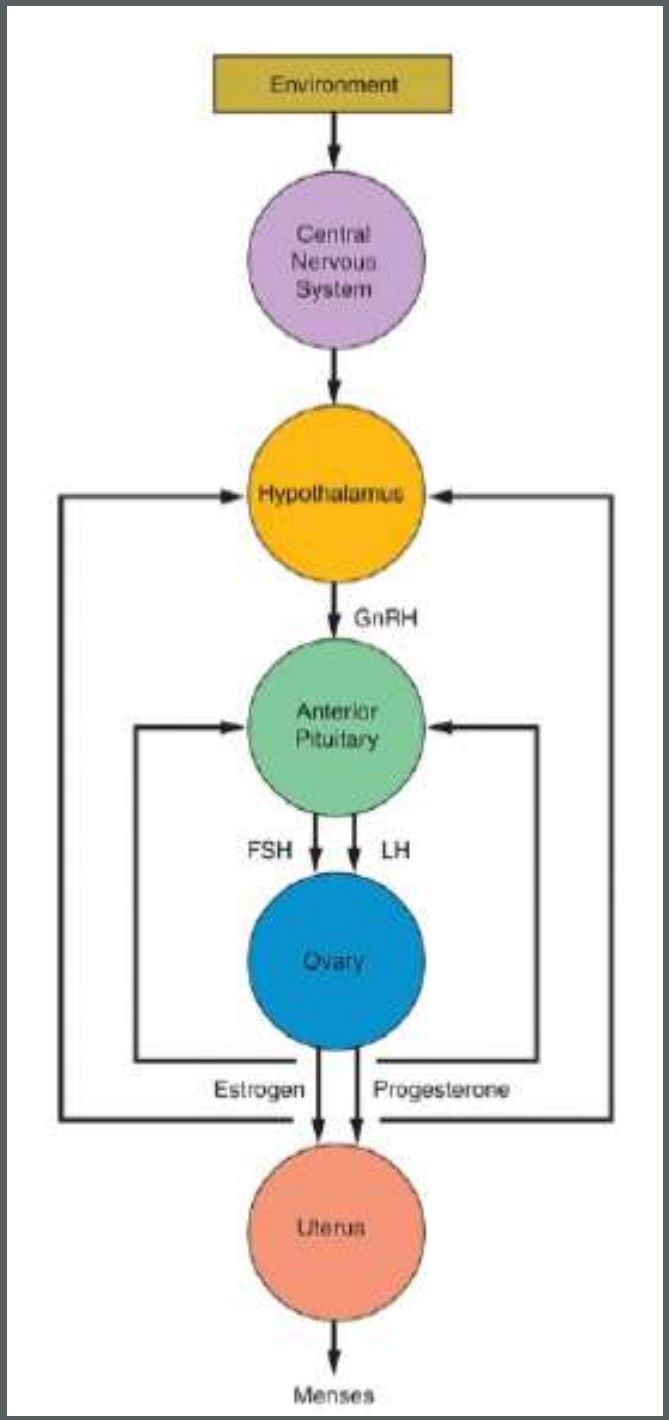
Hypogonadotropic hypogonadism



GnRH very low

LH and FSH low
or low-normal range

(Speroff 2020)

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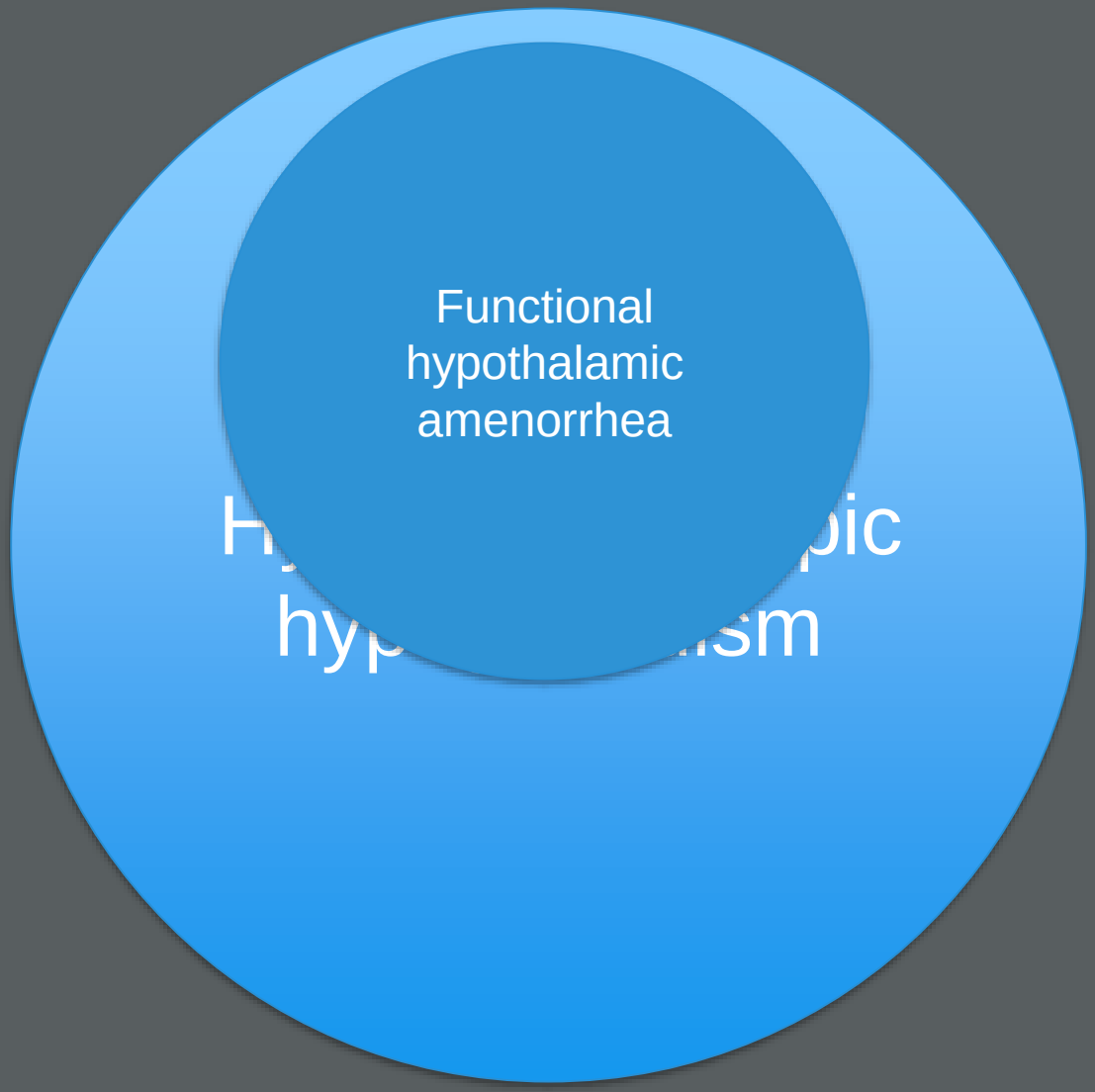

Amenorrhea with a precipitating factor: exercise, low weight, or stress

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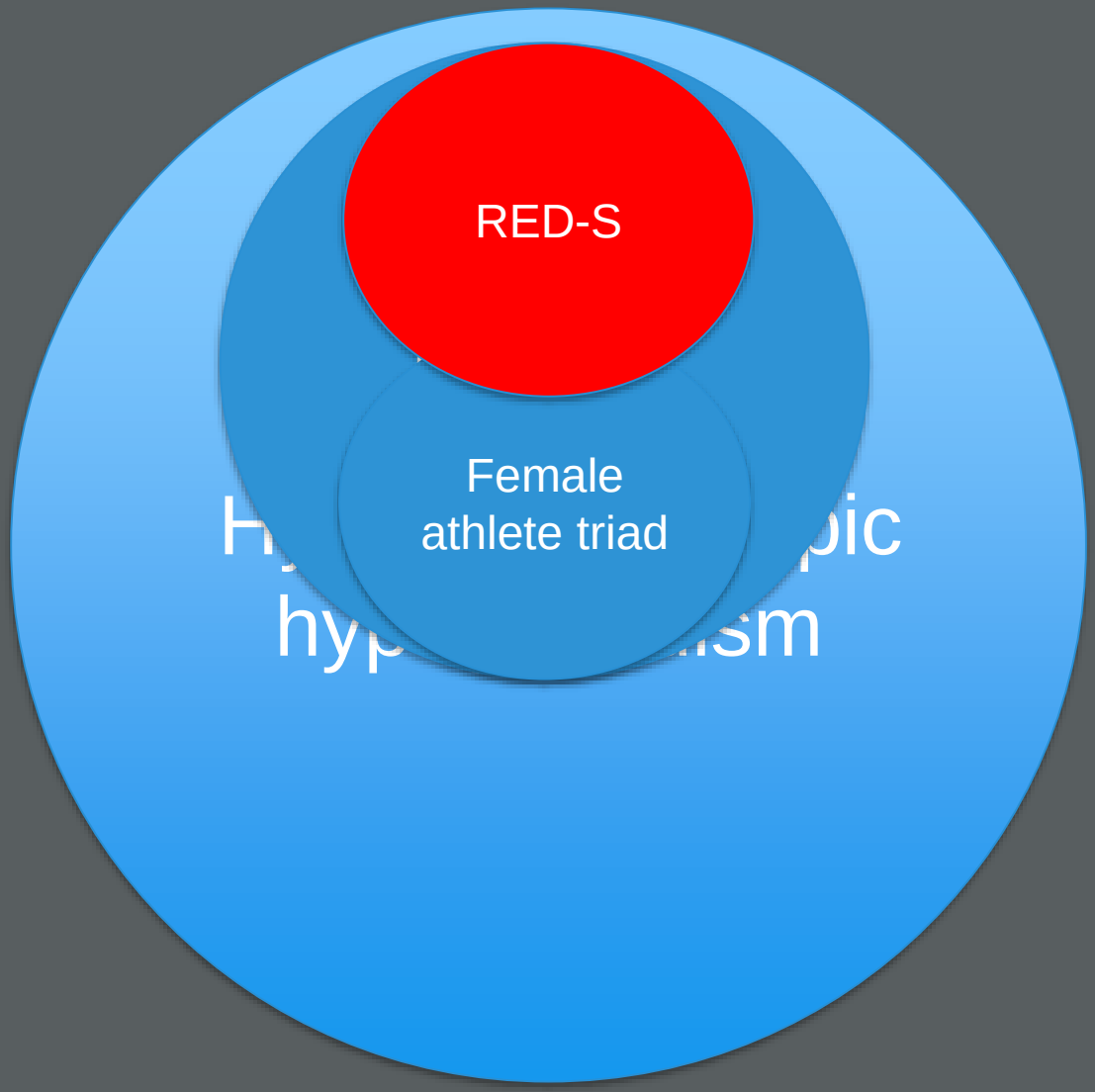
RED-S
Female
athlete triad

Bone health

- Lower (even subclinical) estrogen/progesterone can lead to poor bone health
  - Exacerbated by increased stress hormones
  - Less benefit from resistance training in low E environment
- High risk for stress fractures
  - Long term complications in adolescents

(Mountjoy 2014)

Long-term health impacts

- Nutrient deficiencies
- Chronic fatigue
- Increased risk for infection, illness
- May affect all organ systems
  - Increased cardiovascular risk- unfavorable lipid profile, endothelin dysfunction
- Psychological stress, depression
- Slowed metabolic rate

(Mountjoy 2014)

Evaluation: Labs

- Rule out other causes of amenorrhea or oligomenorrhea
- History: anxiety, depression, chronic diseases
- Review of systems including galactorrhea, headache, vision changes
- Physical and vital signs

(Mountjoy 2014; Gordon 2017)

Evaluation: Labs

- Rule out other causes of amenorrhea or oligomenorrhea

HCG
CBC
CMP

A1c
Prolactin
TSH
Free T4

Pelvic ultrasound
Progestin challenge

FSH
LH
Estradiol
AMH
Testosterone
Vitamin D
DHEA-S
17-OHP

(Mountjoy 2014)

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Evaluation: Imaging

- Baseline DXA
  - In athletes, low BMD is Z-score between -1 and -2 SD
  - <2 SD osteoporosis
  - Associated clinical risk factors
  - Repeat every 6 months in adolescents, 12 months in adults

(Mountjoy 2014)

Our patient

- Labs and pelvic ultrasound normal, including FSH and LH
- DXA with Z-score of -2, stable from 2 years prior
- Decreased exercise intensity
- Trial of letrozole, with no response

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Treatment

- Increase energy intake, reduce energy expenditure, or both
  - Add 300-600 kcal/day, a rest day
  - Dietician or nutritionist
  - Consider mental health consultation

(Mountjoy 2014)

Treatment

- Calcium (1500mg/day)
- Vitamin D (1500-2000 IU/day)
- Loading/resistance training can be helpful
- Bisphosphonates generally avoided in reproductive aged women due to risk of teratogenicity

(Mountjoy 2014)

Treatment: not desiring fertility

- Oral contraceptive pills
  - Benefit of contraception
  - Lack of benefit for bone health
    - May downregulate IGF-1
  - Can mask worsening symptoms, closely monitor
  - Use with more caution in adolescents with FHA
- Depot medroxyprogesterone acetate may be less preferred
  - Particularly in adolescents

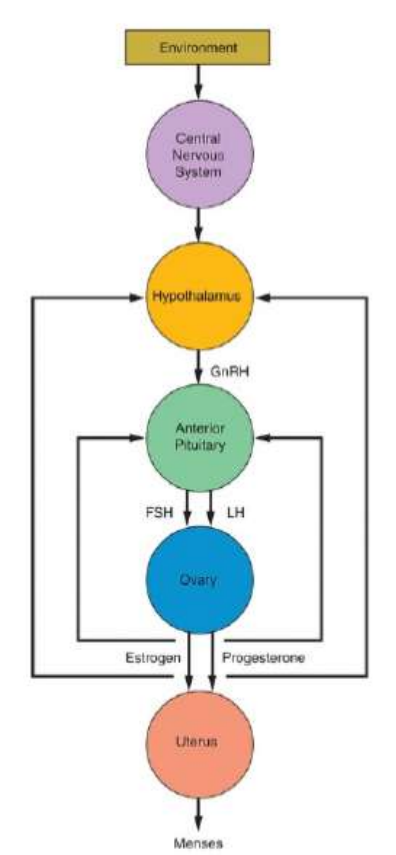
(Mountjoy 2014; Gordon 2017)

Treatment: what about hormone replacement therapy?

- Short-term use of transdermal estrogen and cyclic oral progestin if no return of menses with other interventions
- Studies showed increase in bone mineral density

(Gordon 2017)

Treatment: desiring fertility



- Lifestyle interventions first line to resume ovulation
- Weight gain, reduced energy expenditure, cognitive behavioral therapy

(Mountjoy 2014; Gordon 2017)

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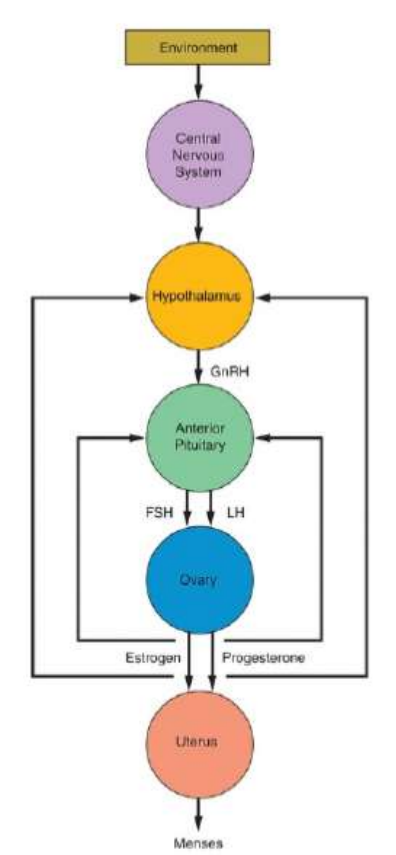
Treatment: desiring fertility



- Only recommend proceeding after above interventions and BMI ≥18.5
  - Increased risks fetal loss, small for gestational age, preterm labor, cesarean delivery

(Mountjoy 2014; Gordon 2017)

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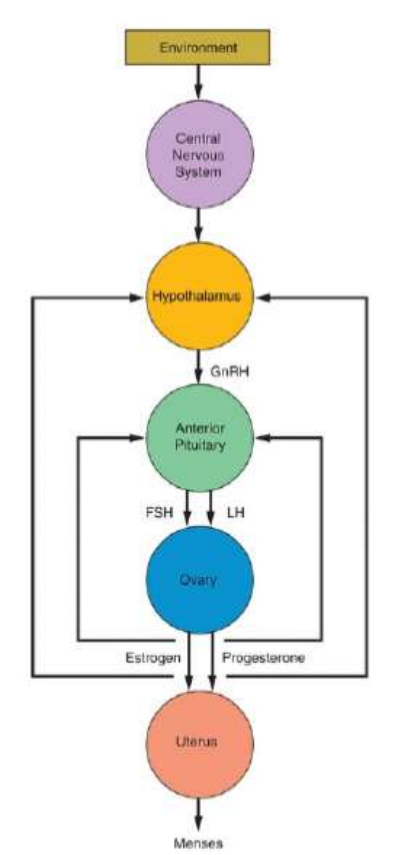
Treatment: desiring fertility



- Pulsatile GnRH first line- not available in US
- Gonadotropin ovulation induction or in vitro fertilization recommended

(Mountjoy 2014; Gordon 2017)

Gonadotropin ovulation induction

- Both LH and FSH required for patients with hypogonadotropic hypogonadism
- hMG (human menopausal gonadotropins) includes both FSH, LH
- Careful monitoring with ultrasound at 1-3 day intervals, assessment of uterine lining
- Recommend progesterone support for luteal insufficiency

(ASRM 2020)

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Gonadotropin ovulation induction

- High risk of multifollicular response, particularly in this patient population
- Multiple gestation risk as high as 36%
- Consider cancellation if ≥ 2 mature (≥ 16mm) follicles, or ≥ 3 immature follicles (≥ 10mm)

(ASRM 2020)

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Gonadotropin ovulation induction

- Expensive, time consuming, and invasive, with frequent monitoring
- Longer stimulations required with higher gonadotropin doses for their AMH/antral follicle count
- May be half the cost of an IVF cycle

(Cecchino 2019)

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In vitro fertilization

- Same stimulation medication at higher doses, with goal of multifollicular development
- Traditionally, do not use a GNRH-agonist trigger
  - risk of hyperstimulation syndrome
- Ability to transfer single embryo, freeze-all

(Gurbuz 2020)

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Our patient

- Declined IVF
- Underwent stimulation with gonadotropins over 13 days, then HCG trigger for intrauterine insemination
  - One mature follicle at trigger- conceived!

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Summary

- RED-S/female athlete triad are a form of functional hypothalamic amenorrhea
- Affects all aspects of health, beyond bone health and menstrual function/fertility
- Lifestyle measures first-line- involve a dietician and mental health provider
- Gonadotropins or IVF for fertility

For more information:

Functional Hypothalamic Amenorrhea: An Endocrine Society Clinical Practice Guideline

Catherine M. Gordon,[1] Kathryn E. Ackerman,[2,5] Sarah L. Berga,[3] Jay R. Kaplan,[3] George Mastorakos,[4] Madhusmita Misra,[5] M. Hassan Murad,[6] Nanette F. Santoro,[7] and Michelle P. Warren[8]

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Questions/Discussion

Travelportland.com/culture/4t-trail/