Endocrine Management of the Infertile Man

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Case #1

A 28-year old man and his 26-year old wife have been attempting to have a baby for a little over a year. Both are healthy and take no medications. He has a normal exam including normal-sized testes. She also has a normal exam and regular menses every 28-32 days.

Are they infertile?
Whose “fault” is it?
Definitions

Infertility

US: Failure to conceive after attempting for 1 year
Europe: Failure to conceive after 2 years

Why the difference?
15% of couples fail to conceive at 1 year
Half of those will conceive in the next year

Subfertility: Reduced fertility that might require treatment to conceive or to hasten conception

Lancet 2002; 360: 151–59
Epidemiology

- 15% of couples experience difficulties conceiving
- 50% isolated female factor
- 30% isolated male factor
- 20% combined factor

Note that a woman with normal fertility will generally conceive with a subfertile man!

- No “fault”!!
The couple want to conceive soon. For evaluation of the man, what is the most important aspect of the evaluation?

A. History: social and medical
B. Physical exam
C. Serum testosterone, LH and FSH
D. Seminal fluid analysis
E. Healthy bank account
Evaluation

Seminal fluid analysis is the key laboratory test

- Dictates the next steps in evaluation

Must have 2-3 seminal fluid analyses

- Significant daily variation
- Collected after 2-7 days of ejaculatory abstinence
- Lab that follows WHO standards

Hum Reprod Update. 2010;16:158-162
SFA normal values

- Volume should exceed 1.5 mL
- Normal concentration ≥ 15 million/mL
- Total sperm ≥ 39 million
- Motility and morphology (% of normal)
SFA interpretation

- Low volume: incomplete sample

- Low volume, azoospermia, pH < 7.4, low or absent seminal fluid fructose = distal obstruction

- Concentration = 0 (azoospermia) = endocrine eval
  - Check serum testosterone, LH, FSH
  - 10% azoospermic ♂ have Klinefelter syndrome

- Concentration < 5 million/ml
  Test for Y chromosome microdeletions
Case #2

A 29-year old man reports having difficulty conceiving after 16 months of attempting. His wife has regular menses every 28-32 days and has a 3-year old son (from a previous relationship). He has had 2 seminal fluid analyses revealing azoospermia. He is otherwise healthy and takes no medications.

Physical exam: 3 cm nontender gynecomastia; normal phallus; 4 cc (each) firm testes

Labs: Total testosterone 320 ng/dL (300-1000)  
FSH 55 (normal 1-7) LH 45 (normal 2-10)
Case #2

What is the most likely cause of his infertility?

A. Idiopathic spermatogenic failure
B. Karyotype abnormality
C. Y chromosome microdeletion
D. Gonadotropin-producing pituitary adenoma
E. Androgen resistance
Case #2a

You diagnose the man with Klinefelter syndrome. He and his wife want to know what are the chances of fertility.

You tell him that his chances are approximately

A. 0%
B. 20% with gonadotropin therapy
C. 40% with gonadotropin therapy
D. 20% with assisted reproductive technology
E. 40% with assisted reproductive technology
Case #2a

- Gonadotropin rx ineffective in 1° testicular failure

- 40-50% of XXY men have nests of sperm on testicular biopsy
  - 50% will conceive with harvested sperm & assisted reproductive techniques (ART)
  - Overall conception/live birth rate 20-25%

- No cases of Klinefelter transmission with ART!
A 28-year old ♂ with cystic fibrosis wants to have a child. His wife has no gene mutation associated with cystic fibrosis. They have been having trouble conceiving. She has no detectable reproductive abnormalities. His past medical history is otherwise normal except for well controlled diabetes mellitus. He has azoospermia documented twice. His physical examination reveals that he is short and has coarse ronchi. His testes are 15 cc bilaterally. Serum testosterone, LH and FSH levels are normal.
Case #3

Which of the following is the most likely cause of his infertility?

A. Idiopathic spermatogenic failure
B. Gonadotropin deficiency 2° to cystic fibrosis
C. Ejaculatory tract obstruction
D. Klinefelter syndrome
E. Primary ciliary dyskinesia (Kartagener syndrome)
Causes: categories

- Sexual disorders
- 1° testicular defect
- Endocrinopathies
- Defects in transportation
Spermatic duct

Spermatic cord

Testicular artery

Pampiniform plexus

Epididymis

Testis
Causes of male infertility

- Sexual disorders
  - Insufficient frequency, erectile dysfunction
- 1° testicular defect
  - Idiopathic, XXY
- Endocrinopathies
  - CAH, DM, obesity, Graves disease, etc
- Defects in transportation
  - Absence of the vas, retrograde ejaculation
Case #4

A 30-year old with a history of a resected pituitary macroadenoma wants to conceive. He has no sign of recurrent tumor, but he has persistent secondary hypogonadism. His pituitary function is otherwise normal. His wife has no detectable reproductive abnormalities. His past medical history is otherwise normal. His only medication is testosterone gel 1.62% 40 mg daily.

His physical examination is completely normal except that his testes measure 12 cc each. Off testosterone gel, his serum total T is 100 ng/dl, LH is 0.1 and FSH 0.2 (all very low)

Seminal fluid analysis: no sperm
Case #4

In addition to stopping the testosterone gel, which of the following is the best initial therapy?

A. GnRH
B. hCG
C. hCG plus rhFSH
D. Testicular biopsy with ICSI
Gonadotropin replacement therapy

GnRH
- Effective for hypothalamic, not pituitary disease
- Requires pump infusion every 2 hours
- Not widely available

Gonadotropin therapy
- Effective in hypothalamic or pituitary disease
- Start with hCG alone
- hCG alone often stimulates (or increases) spermatogenesis in patients with postpubertal gonadotropin deficiency
Gonadotropin (hCG + rhFSH) therapy

Start with hCG 1000-1500 IU SC three times weekly

- ↑ dosage with smaller testes (total volume < 8 cc)
- ↑ dosage every ~4 weeks until serum T increases to low to mid-normal range

√ [sperm] q 1-2 months 3 months after serum T at goal

If [sperm] < 10 million/mL & no pregnancy within 6 months of adequate hCG, then…

Add rhFSH 75 IU SC three times weekly

Double rhFSH in 6 months if [sperm] < 15 million/mL

Anawalt, J Clin Endocrinol Metab. 2013;98:3532-42
Effectiveness of gonadotropin therapy in ♂ with 2° hypogonadism

80-90% azoospermic ♂ with 2° hypogonadism will ↑ spermatogenesis with hCG +/- rhFSH


Average time to appearance of sperm = 6 months
Average time to conception = 28 months
Baseline testes (total volume ≥ 10 cc) respond quicker
[Sperm] ≥ 5 million predictive of pregnancy
Conception may occur at [sperm] < 5 million/mL (well below “normal” of > 13 million)

J Clin Endocrinol Metab. 2009;94:801-8
Gonadotropin therapy takes time to work!

N = 75 men
24/75 with pituitary disease

JCEM 2009;94:801-808
Case #5

A 29-year old man reports having difficulty conceiving after 16 months of attempting. His wife has regular menses every 28-32 days and has a 3-year old son (from a previous relationship). He is otherwise healthy and takes no medications.

Physical exam:
BMI 35
Normal phallus; 20 cc testes each
Labs: Total testosterone 370 ng/dL (300-1000)
FSH 10 (normal 1-11) LH 5 (normal 2-10)
2 seminal fluid analyses: [sperm] = 1 & 3 million/mL
Scrotal ultrasound is normal
Case 5

What is the best initial step in management if this couple wants to have their own biological child?

A. Initiate clomiphene
B. Initiate anastrazole
C. Initiate gonadotropin therapy
D. Referral to ART specialist for testicular biopsy
E. Anawalt snake oil with L-carnitine, vitamin E, gingko and green tea extract
Normal FSH levels in ♂

- In ♂ with normal reproductive function, the upper limit of normal for serum FSH levels is ~ 8.0 IU/L.
- Many labs report an upper limit of normal as high as 11 IU/L. This is wrong.
- ↑ FSH levels = primary spermatogenetic defect
- Gonadotropin therapy not indicated in this ♂ with an elevated FSH level
Success of sperm retrieval & ART

• 50-70% of men with primary spermatogenic failure and non-obstructive azoospermia may have sperm that can be surgically harvested

• There is no FSH threshold level that reliably predicts no sperm in the testes

• If sperm are retrievable, assisted reproductive techniques result in successful conception in about 40-45% of couples
Case #6

A 29-year old man reports have difficulty conceiving after 16 months of attempting. His wife has regular menses every 28-32 days and has a 3-year old son (from a previous relationship). He is otherwise healthy and takes no medications.

Physical exam:
BMI 35
Normal phallus; 15 cc testes each

Labs:  Total testosterone 370 ng/dL (300-1000)
FSH 3 (normal 1-11) LH 5 (normal 2-10)
2 seminal fluid analyses: [sperm] = 1 & 3 million/mL

Scrotal ultrasound is normal

Role for “empiric” medical therapy?
Empiric medical therapies

SERMs
Aromatase inhibitors*
Gonadotropin therapy**
Anti-oxidants

*Case reports of using aromatase inhibitor in infertile, obese ♂ with 2° hypogonadism (and high or high-normal [E₂])

** Rationale for FSH therapy in some infertile ♂️?
FSH therapy for idiopathic ♂ infertility?

Background:
2007 Cochrane review:
Insufficient data, but pregnancy rates 13.4% in FSH-treated group vs. 4.4% placebo (P = NS)

2011-13 publications:
Some infertile ♂ with polymorphisms of FSH promoter or receptor regions
2 small studies demonstrated ↑ spermatogenesis with rhFSH rx in these men

Cochrane Database Syst Rev. 2007;4:CD005071
Fertil Steril. 2011;96:1344-1349
Int J Androl. 2011;96:1344-1349
Adoption

Cost
   Varies from $5000 to > $50,000

Time
   Months to years

Convenience
Key points

1. ↑ uncommon causes of ♂ infertility in endo clinic

2. Scrotal exam important: testicular size and vas

3. Gonadotropin therapy only for ♂ with infertility due to hypogonadotropism;
   • Upper limit of normal for [FSH] = 8

4. ART, not empirical rx, for idiopathic infertility

5. Role for rhFSH rx in some ♂ with infertility?
Conclusions

Endocrinologists have an important role in the management of infertility

Endocrinologists should collaborate with ART specialists whenever possible