Medical Treatment of **Infertile Male**

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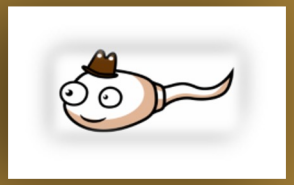

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School of Medicine

Feb 3rd 2021

Disclosures

Drs. Sadri, Howards and Velet have *no financial disclosures or conflicts of interest* to report relevant to this presentation.

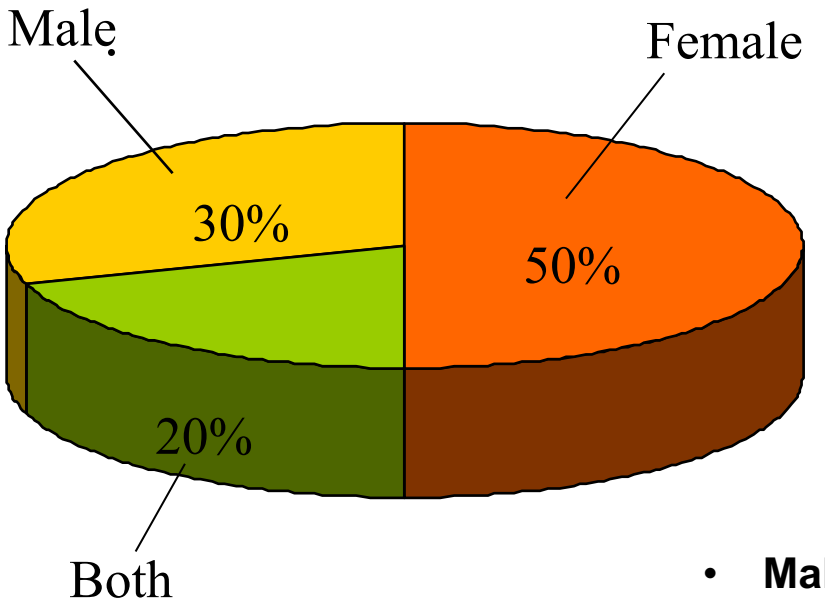
Learning objectives

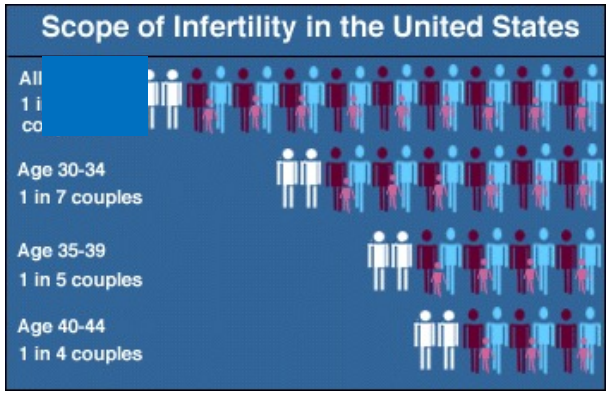
After this presentation, the learner should be able to :

- **Perform the appropriate evaluation and medical treatment of the male in an infertile couple.**
- **Apply the latest recommendations of AUA/ASRM on medical management of the male in an infertile couple.**

Male and Female Infertility

- No conception after 1 yr of unprotected sexual intercourse is defined as possible infertility
- 85% of couples conceive with in 1 yr
- 50% of infertility involves male factor.





http://library.med.utah.edu/kw/human_reprod/seminars/seminar2A.html

- **Male infertility is a problem in 7% of all men**

New AUA/ASRM Guideline

Approved by the AUA Board of Directors

October 2020

Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline

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Best Practice Statement (16 Pages) → **Clinical Guideline (53 Pages)**

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AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm sub-stantial)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research is unlikely to change confi-dence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but bet-ter evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances and future research is unlikely to change confi-dence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate Applies to most patients in most circumstances but bet-ter evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/Burdens Best action depends on individual patient circum-stances Future research unlikely to change confidence	Benefits = Risks/Burdens Best action appears to depend on individual pa-tient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence
Clinical Principle	A statement about a component of clinical care that is widely agreed upon by urolo-gists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	A statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence		

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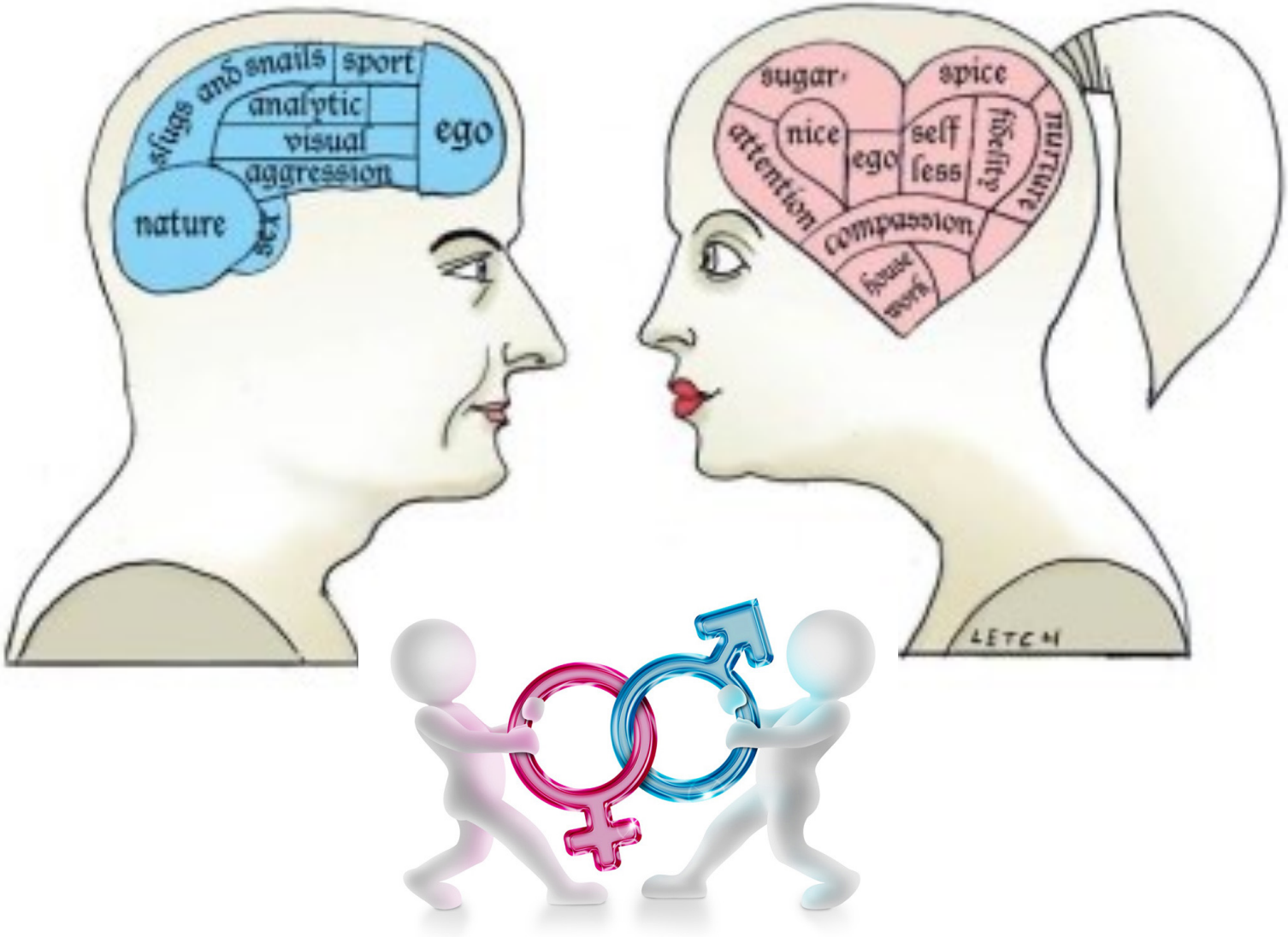
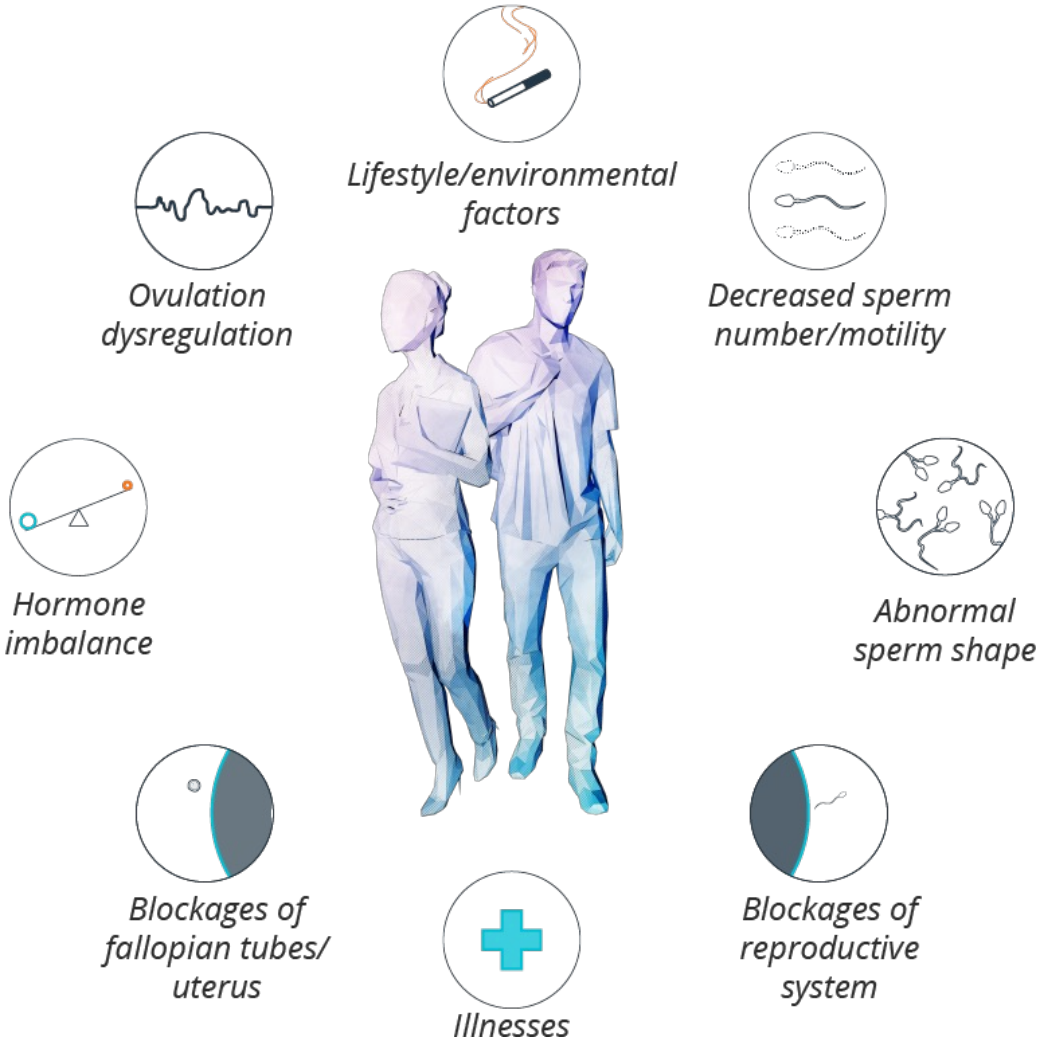
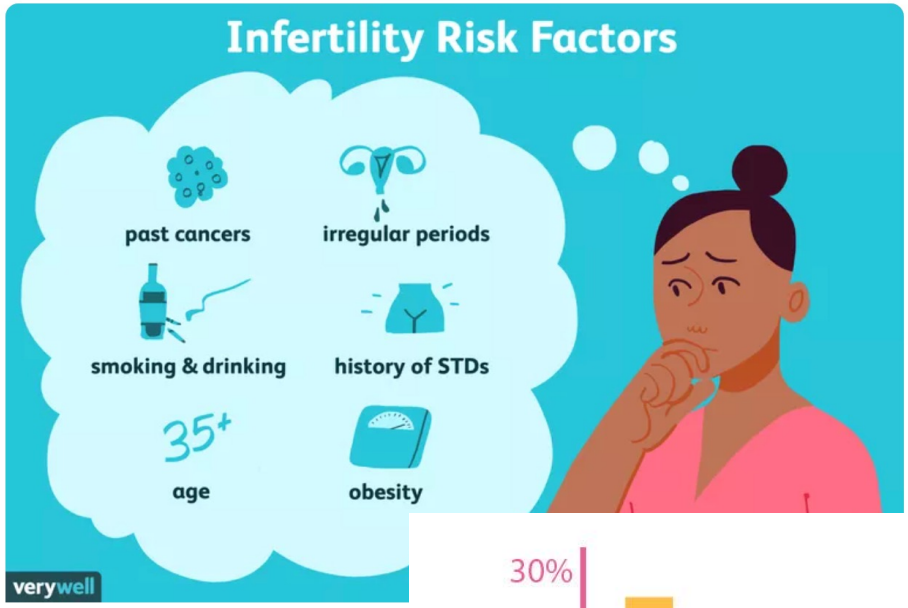
Couple! Not only Male!

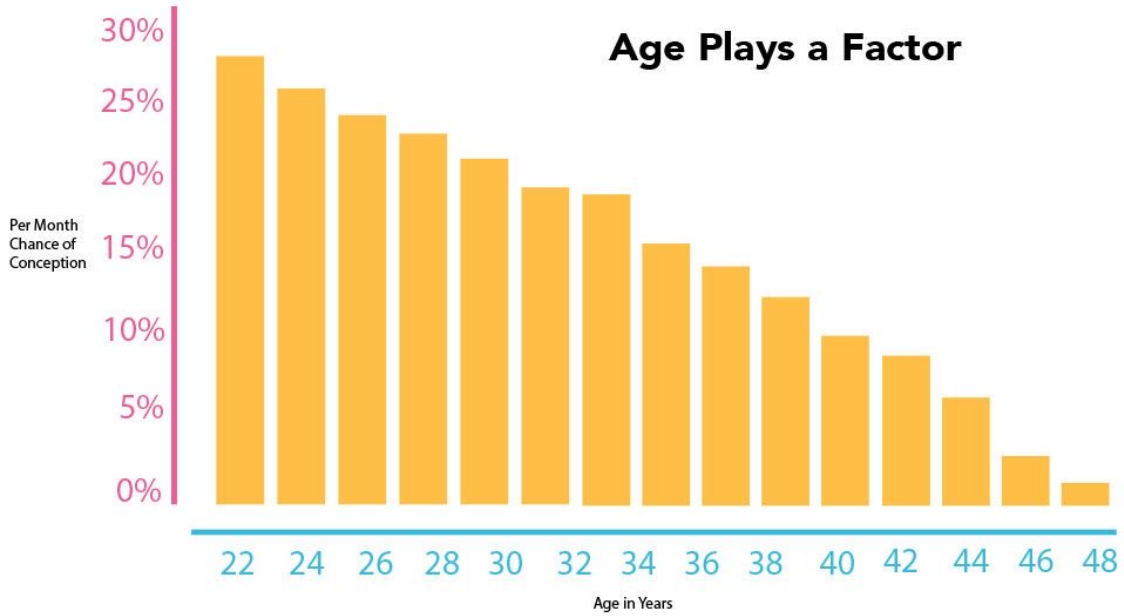


Comprehensive Approach



Female Factor





Female Factor

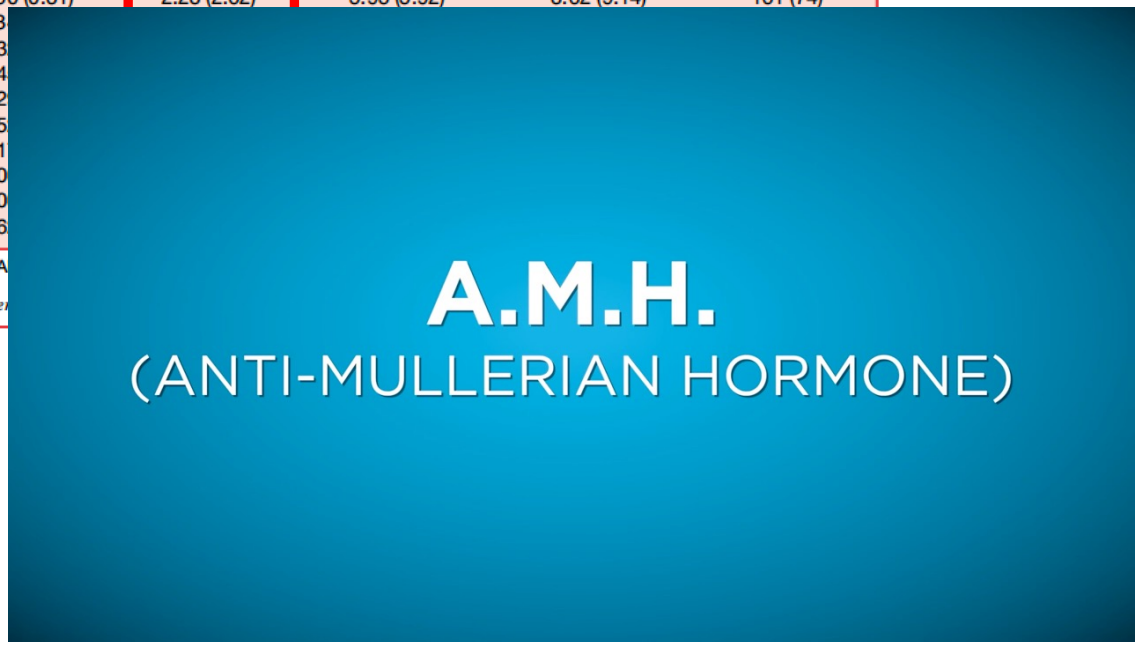
AMH or anti-mullerian hormone

Serum AMH level distribution (ng/mL) in all reviewed patients (presumably healthy cohort).

Age (y)	5th percentile	10th percentile	Median	90th percentile	95th percentile	n
<25	0.97 (1.13)	1.78 (1.78)	5.13 (3.59)	13.45 (8.87)	15.63 (10.40)	194 (65)
25	1.56 (0.81)	2.01 (1.56)	5.42 (3.91)	10.64 (7.29)	13.87 (8.20)	83 (33)
26	1.02 (1.00)	2.19 (1.98)	4.91 (4.23)	9.98 (8.53]	11.87 (9.08)	111 (48)
27	1.02 (1.44)	1.59 (1.77)	4.12 (3.33)	9.87 (7.52)	11.71 (8.38)	143 (60)
28	0.99 (1.02)	1.40 (1.34)	4.96 (4.24)	11.39 (9.39)	14.06 (10.73)	120 (58)
29	0.51 (0.51)	1.03 (0.79)	3.87 (3.87)	9.12 (7.97)	11.10 (9.12)	163 (69)
30	0.72 (1.10)	1.16 (1.42)	3.53 (3.51)	8.35 (6.36)	11.02 (6.75)	184 (76)
31	0.60 (0.55)	1.14 (1.15)	3.59 (3.23)	9.14 (6.59)	13.54 (8.68)	187 (73)
32	0.48 (0.81)	0.88 (1.01)	3.44 (3.50)	7.86 (6.03)	10.19 (8.80)	183 (70)
33	0.56 (0.92)	0.80 (1.09)	2.70 (2.80)	7.98 (5.36)	11.94 (7.88)	158 (64)
34	0.42 (0.69)	0.65 (0.92)	2.49 (2.54)	6.57 (6.60)	7.62 (7.00)	164 (64)
35	0.36 (1.14)	0.73 (1.26)	2.58 (3.10)	5.15 (5.99)	6.87 (7.17)	162 (64)
36	0.31 (0.37)	0.50 (0.81)	2.28 (2.62)	5.95 (5.92)	8.62 (9.14)	161 (74)
37	0.09 (0.05)	0.3				
38	0.15 (0.47)	0.3				
39	0.29 (0.41)	0.4				
40	0.09 (0.09)	0.2				
41	0.38 (0.43)	0.5				
42	0.07 (0.15)	0.1				
43	0.00 (0.12)	0.0				
>43	0.00 (0.00)	0.0				
All	0.30 (0.47)	0.6				

Note: Age-dependent analysis of basal serum A

Shebl. AMH in women of reproductive age. Fertil Ste



AMH can be measured at any point of menstrual cycle, not just on **day** 3

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Home > Guidelines > Clinical Guidelines > Male Infertility

Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline

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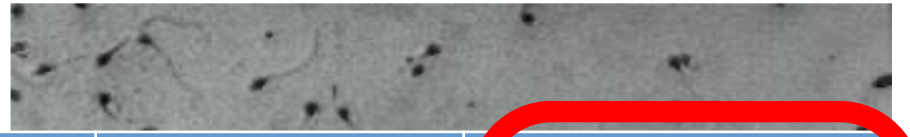
RECOMMENDATION

For initial infertility evaluation, both male and female partners should undergo concurrent assessment. (Expert Opinion)

Semen Analysis

- **WHO minimally acceptable criteria (2010)**



- Vol. > 1.5 ml

	WHO 1999	WHO 2010
Volume (mL)	2.0	1.5
Sperm Concentration (M/mL)	20	15
Total sperm count (M/ejaculate)	40	39
Total Motility (%)	50	40
Strict Morphology (% normal)	N/A	4

- [illegible]%
  - **< 1 million wbc/cc**

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RECOMMENDATION

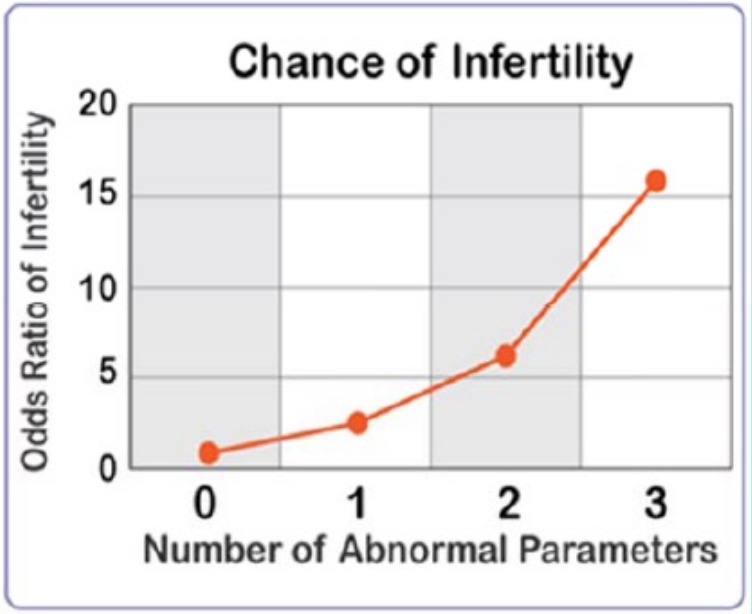
- In the interpretation of the semen analyse (S/A), the clinician should remember that semen parameters are highly variable biological measures and may vary substantially from test to test. Therefore, at least two S/As obtained a month apart are important to consider, especially if the first SA has abnormal parameters

- Men with **one or more abnormal semen** parameters or presumed male infertility should be evaluated by a male reproductive expert for complete history and physical examination as well as other directed tests when indicated.

(Expert Opinion)

The Chance of Infertility Increases With Increasing Number of Abnormal Semen Parameters

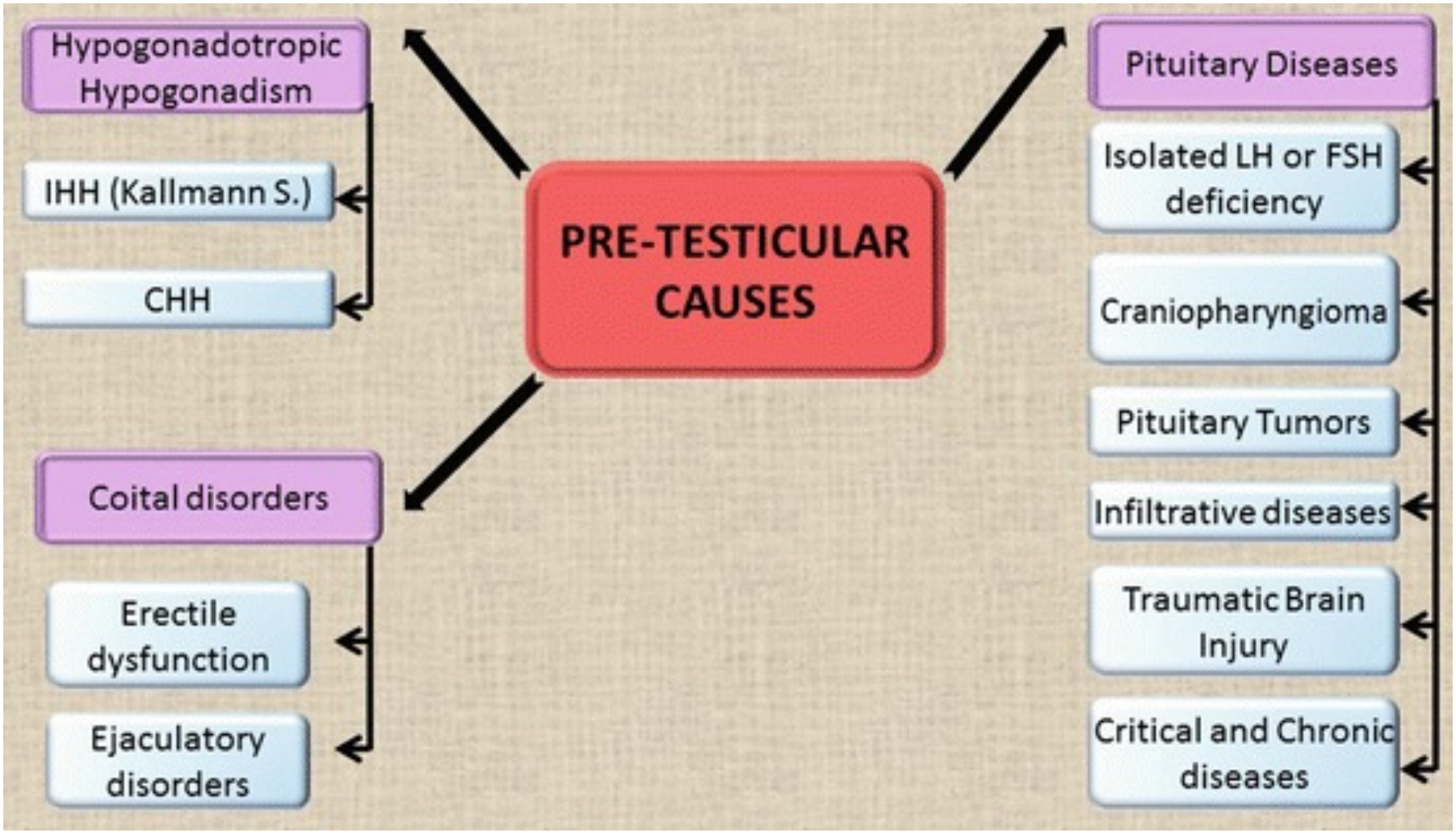
Semen Parameter	Lower Reference Limit (95% Confidence Intervals)	Patient 1	Patient 2
Semen Volume	1.5 mL (1.4-1.7)	1.6 mL	1.4 mL
Total Sperm Number	39 million per ejaculate (33-46)	8 million / ejaculate	43 million / ejaculate
Sperm Concentration	15 million / mL (12-16 million / mL)	5 million / mL	31 million / mL
Vitality	58% Live (55-63%)	60%	70%
Progressive Motility	32% (31-34%)	5%	45%
Total Motility Progressive + Non-Progressive	40% (38-42%)	6%	58%
Morphologically Normal Forms	4.0% (3.0-4.0)	1.4%	2.3%



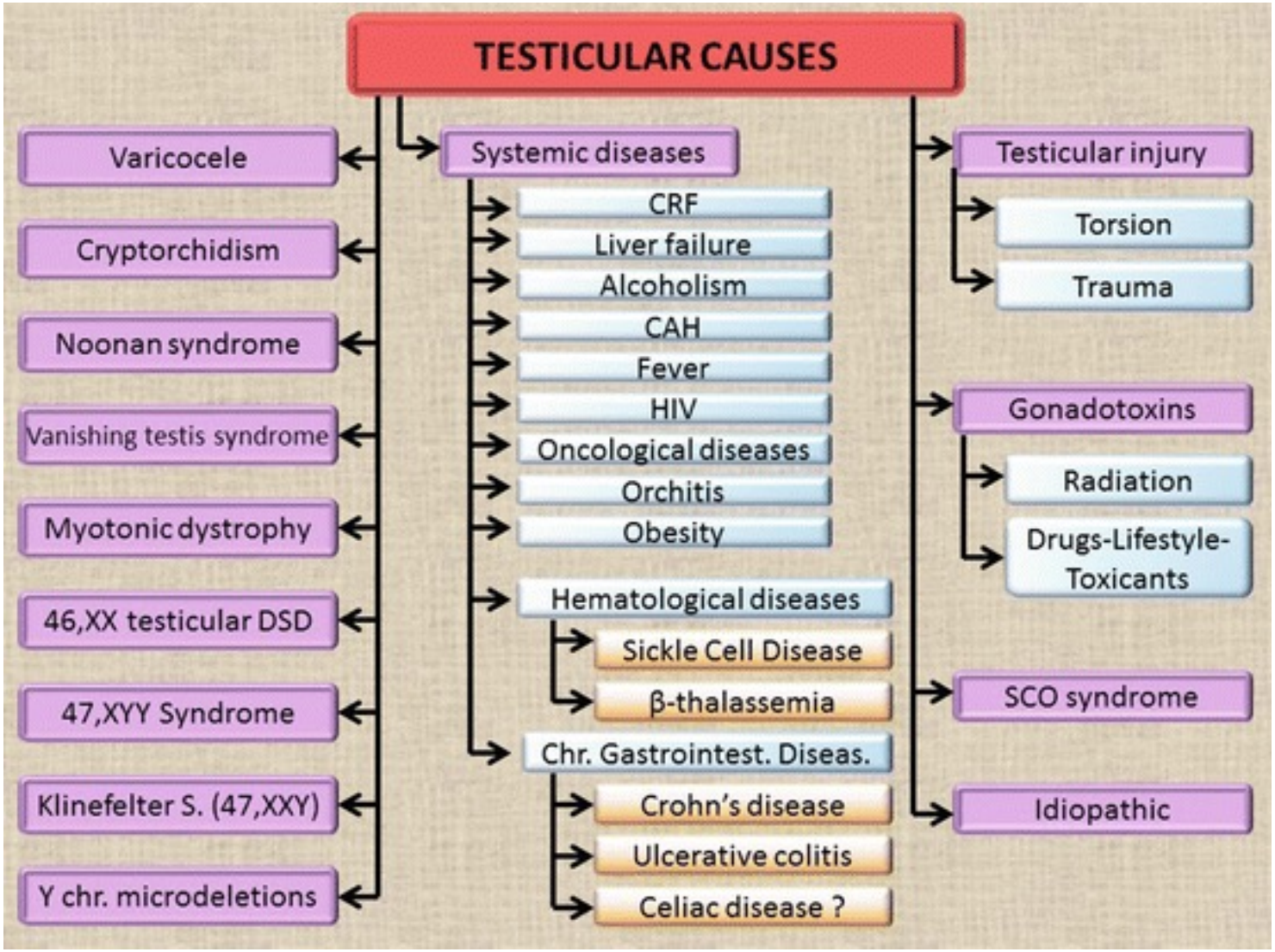
The Table on the left shows the lower limit of the reference range of values for normal fertile men (WHO5), as well as the semen analysis results for two men undergoing an evaluation for male infertility. Patient #1 has oligoasthenoteratozoospermia (OAT) and Patient #2 has abnormal morphology. According to Guzick, et al., 2001 Patient #1 has an increased chance of being infertile because of his higher OR (~15) of infertility with 3 abnormal semen parameters (motility, sperm concentration and morphology) than Patient #2 with abnormal morphology (1 abnormal semen parameter) with an OR of ~2.5.

Etiology of impaired sperm production

- Pre-testicular
- Testicular level
- Post-testicular



Dimitriadis et al 2017



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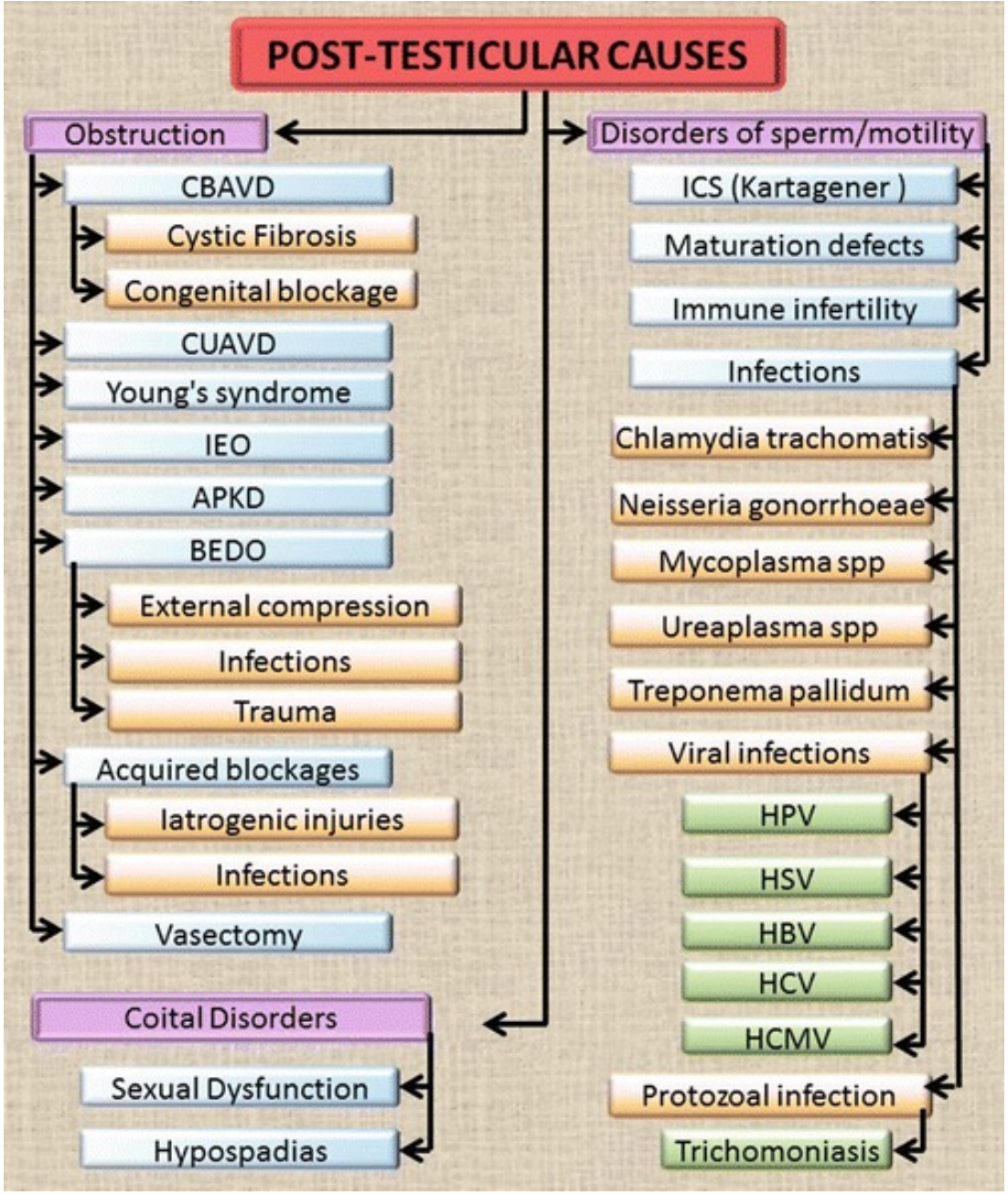


Dimitriadis et al 2017

Etiology of Male Infertility

Category	*N*	*Percentage (%)*
Varicocele	629	26.4
Infectious	72	3.0
Hormonal	54	2.3
Ejaculatory dysfunction	28	1.2
Systemic diseases	11	0.4
Idiopathic	289	12.1
Immunologic	54	2.3
Obstruction	359	15.1
Cancer	11	0.5
Cryptorchidism	342	14.3
Genetic	189	7.9
Testicular failure	345	14.5
TOTAL	2,383	100.0

Source: Androfert, Center for Male Reproduction, Campinas, Brazil

Goals of Medical Treatment

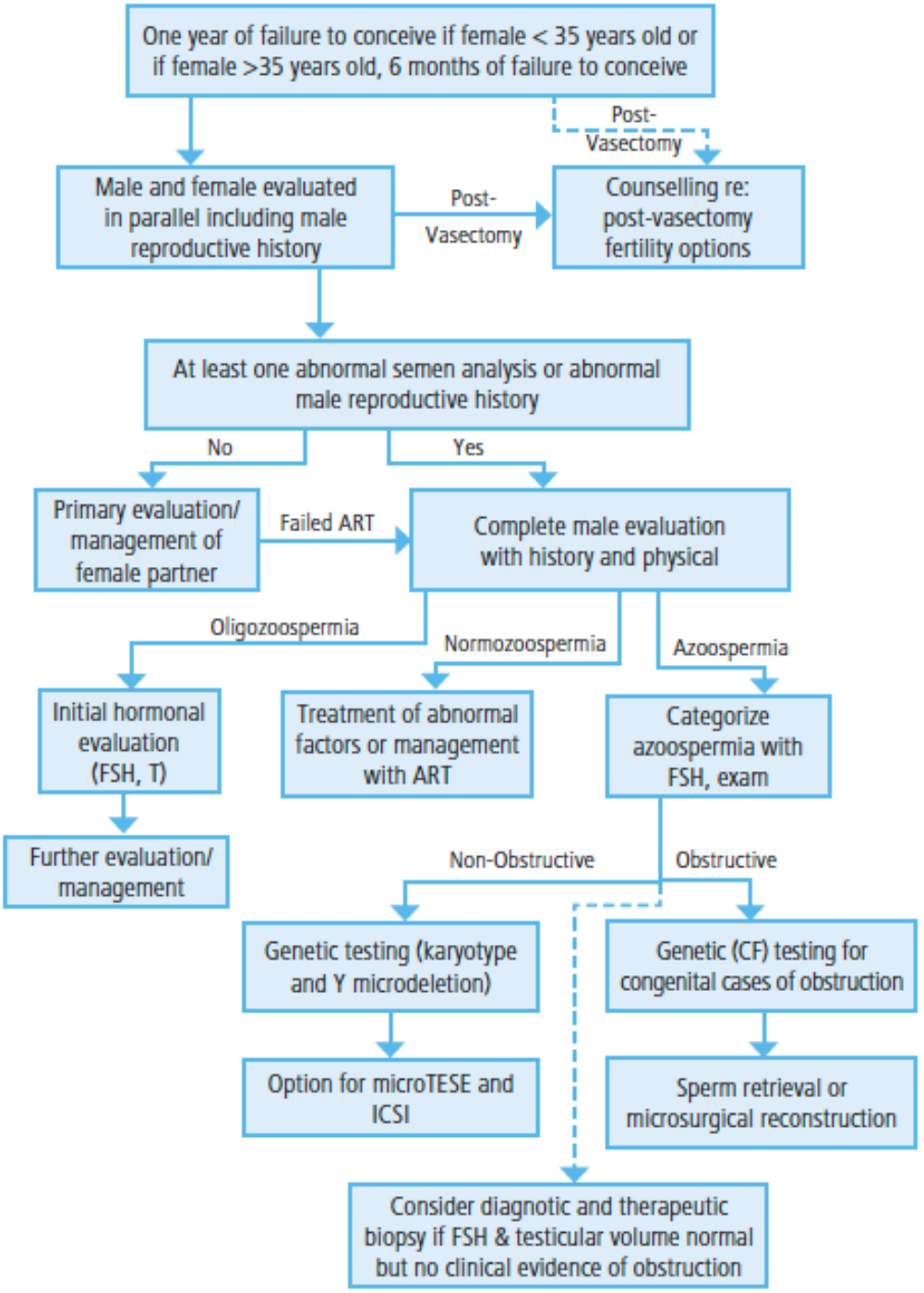
- **The goal of the therapeutic attempts to optimizing the male potential fertility can be one of following:**

1. **To help the couple to achieve a spontaneous pregnancy.**

2. **To use a less invasive method of assisted reproduction like conventional intrauterine insemination (IUI) or in-vitro fertilization (IVF) instead of intracytoplasmatic sperm injection (ICSI).**

3. **To improve the success rate from either method of assisted reproduction.**

Male Infertility Algorithm



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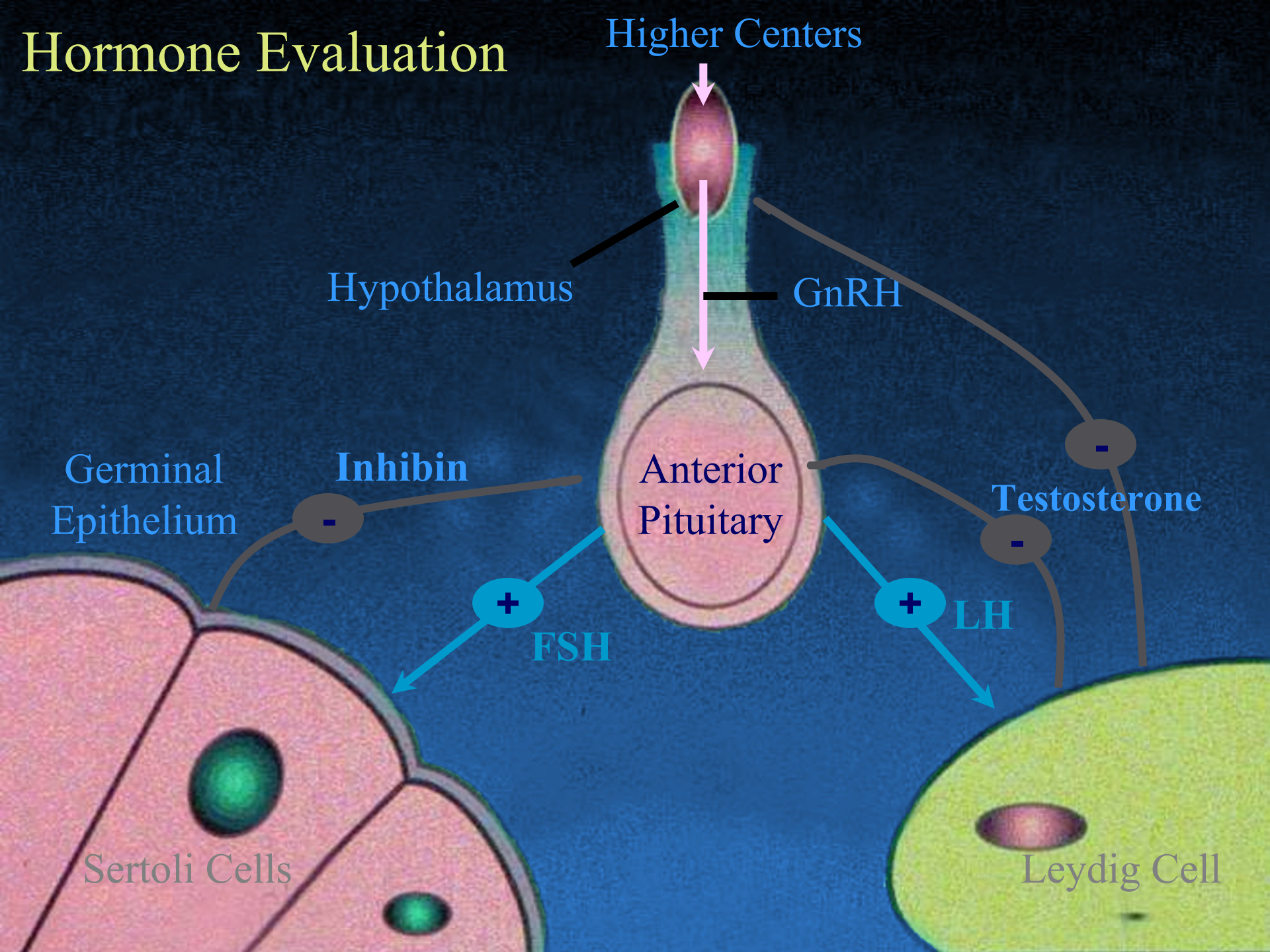
Hormone Evaluation
Higher Centers
Hypothalamus
GnRH
Germinal Epithelium
Inhibin
Anterior Pituitary
Testosterone
FSH
LH
Sertoli Cells
Leydig Cell

Clinical Male Infertility: When to Order Hormones?

- Sperm density <10 x 10^{6} sperm/mL
- Evidence of impaired sexual function (low libido, impotence)
- Findings of an endocrinopathy (thyroid)
- Before starting medical treatment

Sigman M, Jarow JP. Urology, 50: 659, 1997

Jarow JP et al. J. Urol. 167: 2138, 2002

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Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline

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RECOMMENDATION

- Clinicians should obtain hormonal evaluation including follicle-stimulating hormone (FSH) and testosterone for infertile men with impaired libido, erectile dysfunction, oligozoospermia or azoospermia, atrophic testes, or evidence of hormonal abnormality on physical evaluation. (Expert Opinion)

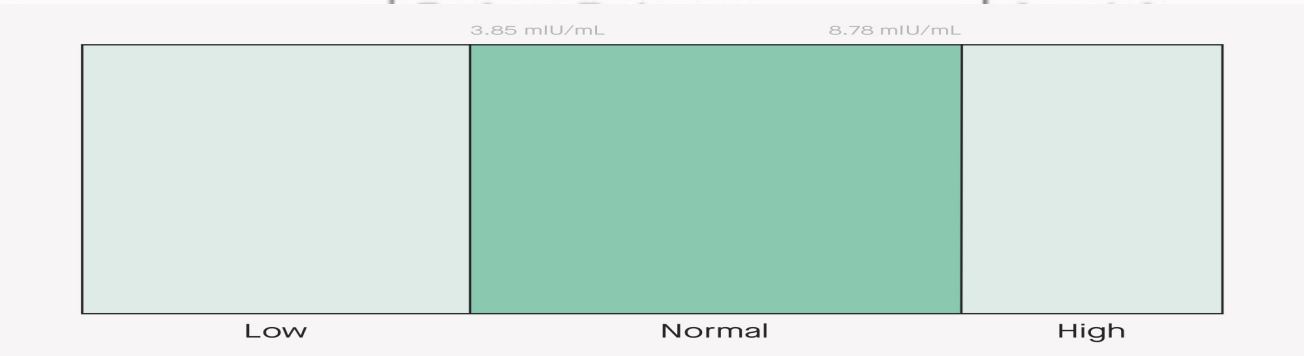
H-P-G Axis: Abnormal Patterns

Condition	Testosterone	FSH	LH	Prolactin
Normal	Normal	Normal	Normal	Normal
Primary testis failure	Low	High	High	Normal
Hypogonadotrophic hypogonadism	Low	Low	Low	Normal
Hyperprolactinemia	Low	Low	Low	High
Androgen resistance	High	Normal	High	Normal

Very important for your Board Exams

FSH (Follicle-Stimulating Hormone) Level

Sex	Time of life	Normal levels (mlu/ml)
Male	Before Puberty	0 - 5.0
Male	During Puberty	0.3 – 10.0
Male	Adult	1.5 – 12.4



- FSH level even in the upper range of this reported "normal" range (above approximately 7.6 mIU/mL) is indicative of an abnormality in spermatogenesis.

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Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline

RECOMMENDATION

- If the fasting morning total testosterone level is low (**<300 ng/dL**), a repeat measurement of total and free testosterone (or bioavailable testosterone) as well as determination of **serum LH, estradiol, and prolactin** levels should be obtained.
- The patient presenting with hypogonadotropic hypogonadism (HH) should be evaluated to determine the etiology of the disorder and treated based on diagnosis. (Clinical Principle)

Medical treatment of male infertility

Substance	Administration	Dosage and frequency	Current availability
GnRH	Subcutaneous infusion pump	25-200 ng/kg per pulse every 2 hours	Only in specialty centers or part of clinical trials
Human chorionic-gonadotropin (hCG)	Subcutaneous/ intramuscular	1,500-3,000 IU 2 times/week	Available, FDA approved for treatment of infertility due to gonadotropin deficiency
Human menopausal gonadotropin (hMG)	Subcutaneous/ intramuscular	75 IU 2-3 times/week	Available, FDA approved for treatment of infertility due to gonadotropin deficiency
Highly purified or recombinant human follicle-stimulating hormone (rhFSH)	Subcutaneous/ intramuscular	100-150 IU 2-3 times/week	Available, FDA approved for treatment of infertility due to gonadotropin deficiency
Dopamine agonist	Oral	Cabergoline (0.5-1 mg twice weekly), bromocriptine (2.5-5.0 mg twice weekly)	FDA approval for treatment of hyperprolactinaemia
Aromatase inhibitors	Oral	Anastrozole 1 mg/day	Off label use
		Letrozole 2.5 mg/day	Off label use
		Testolactone	Not available in the USA
Selective estrogen receptor modulators (SERMs)	Oral	Clomiphene citrate titrate to 50 mg/day	Off label use
		Tamoxifen 20 mg/day, toremifene 60 mg/day, raloxifene 60 mg/day	Off label use

Dabaja and Schlegel, Transl Androl Urol 2014

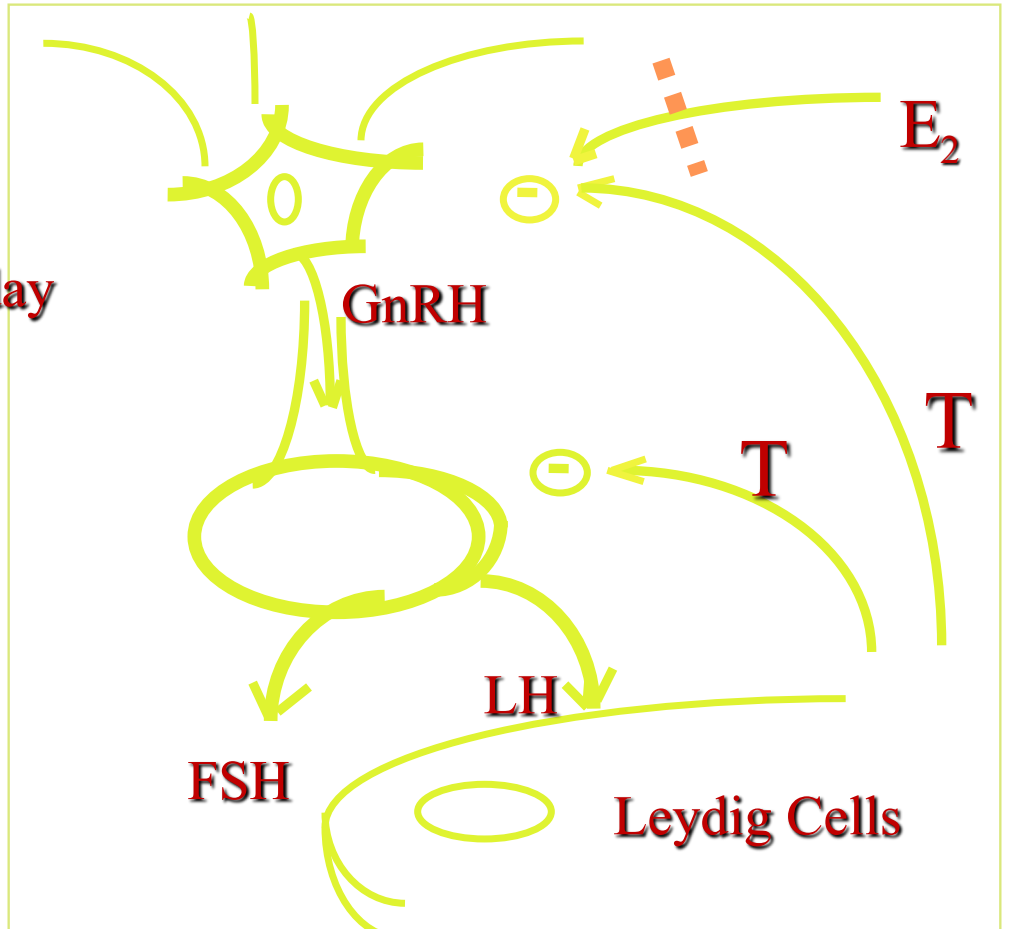
Clomiphene Citrate

Nonsteroidal hormone
An anti-estrogen (SERM)
Increases GnRH output:
Raises T and FSH

Rx 12.5-25 (Up to 100) mg/day
Check FSH, T in 4 weeks
Monitor semen q 3 mos

Good for 2ndary hypogonadism
due to diabetes, prolactinoma

Side Effects: gynecomastia,
weight gain, visuals, acne



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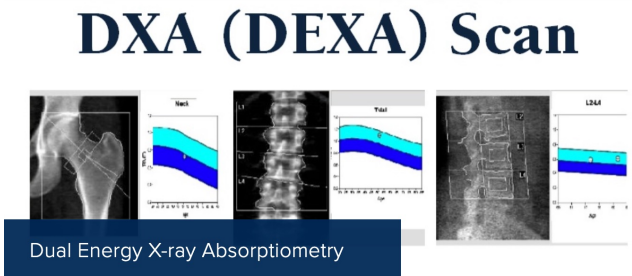
Selective estrogen receptor modulators (SERMs)	Oral	Clomiphene citrate titrate to 50 mg/day Tamoxifen 20 mg/day, toremifene 60 mg/day, raloxifene 60 mg/day	Off label use Off label use

Dabaja and Schlegel, Transl Androl Urol 2014

Aromatase Inhibitors

- **Off-label use for hypogonadism**
  - **Aromatase inhibitors block conversion T → E_2**
    - **↓ the negative feedback of E_2 → ↑ T**
    - **Arimidex: 0.5 mg 2-3x per week to 1 mg /day**
  - **May be useful in obese patients with impaired T/E_2 ratio (>10) or infertility subpopulations (Klinefelter's syndrome)[2]**
  - **No data on long-term use**
- **Side effects:**
  - **Bone density loss, blood clot, LFT elevation, HTN**



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Dabaja and Schlegel, Transl Androl Urol 2014

Gonadotropins (hCG, hMG, FSH)

Compounding pharmacies

Spermatogenesis depends on FSH and testosterone
If some is good, more is better
Works great in replacement therapy

R_x hCG, 1,500-2,500 IU I.M. 3x weekly (To Every other day)
hMG (FSH and LH) 75-150 IU I.M. 2x weekly (To Every other day)
Check serum testosterone levels after 4 weeks
Follow semen analyses q 3 months.

Side Effects: expensive, low compliance, mood and libido changes.
Efficacy: Semen improvement in uncontrolled trials
No controlled trials.

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Home > Guidelines > Clinical Guidelines > Male Infertility

Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline

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RECOMMENDATION

- Clinicians may use aromatase inhibitors (AIs), hCG, selective estrogen receptor modulators (SERMs), or a combination thereof for infertile men with low serum testosterone. (Conditional Recommendation; Evidence Level: Grade C)

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Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline

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RECOMMENDATION

- For men with idiopathic infertility, a clinician may consider treatment using an FSH analogue with the aim of improving sperm concentration, pregnancy rate, and live birth rate. (Conditional Recommendation; Evidence Level: Grade B)

* Baseline FSH in or slightly above he normal range

Male	Adult	1.5 – 12.4

Medical treatment of male infertility

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Highly purified or recombinant human follicle-stimulating hormone (rhFSH)	Subcutaneous/ intramuscular	100-150 IU 2-3 times/week	Available, FDA approved for treatment of infertility due to gonadotropin deficiency
Dopamine agonist	Oral	Cabergoline (0.5-1 mg twice weekly), bromocriptine (2.5-5.0 mg twice weekly)	FDA approval for treatment of hyperprolactinaemia
Aromatase inhibitors	Oral	Anastrozole 1 mg/day	Off label use
		Letrozole 2.5 mg/day	Off label use
		Testolactone	Not available in the USA
Selective estrogen receptor modulators (SERMs)	Oral	Clomiphene citrate titrate to 50 mg/day	Off label use
		Tamoxifen 20 mg/day, toremifene 60 mg/day, raloxifene 60 mg/day	Off label use

Dabaja and Schlegel, Transl Androl Urol 2014

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Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline

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- The infertile male with hyperprolactinemia should be evaluated for the etiology and treated accordingly. (Expert Opinion)

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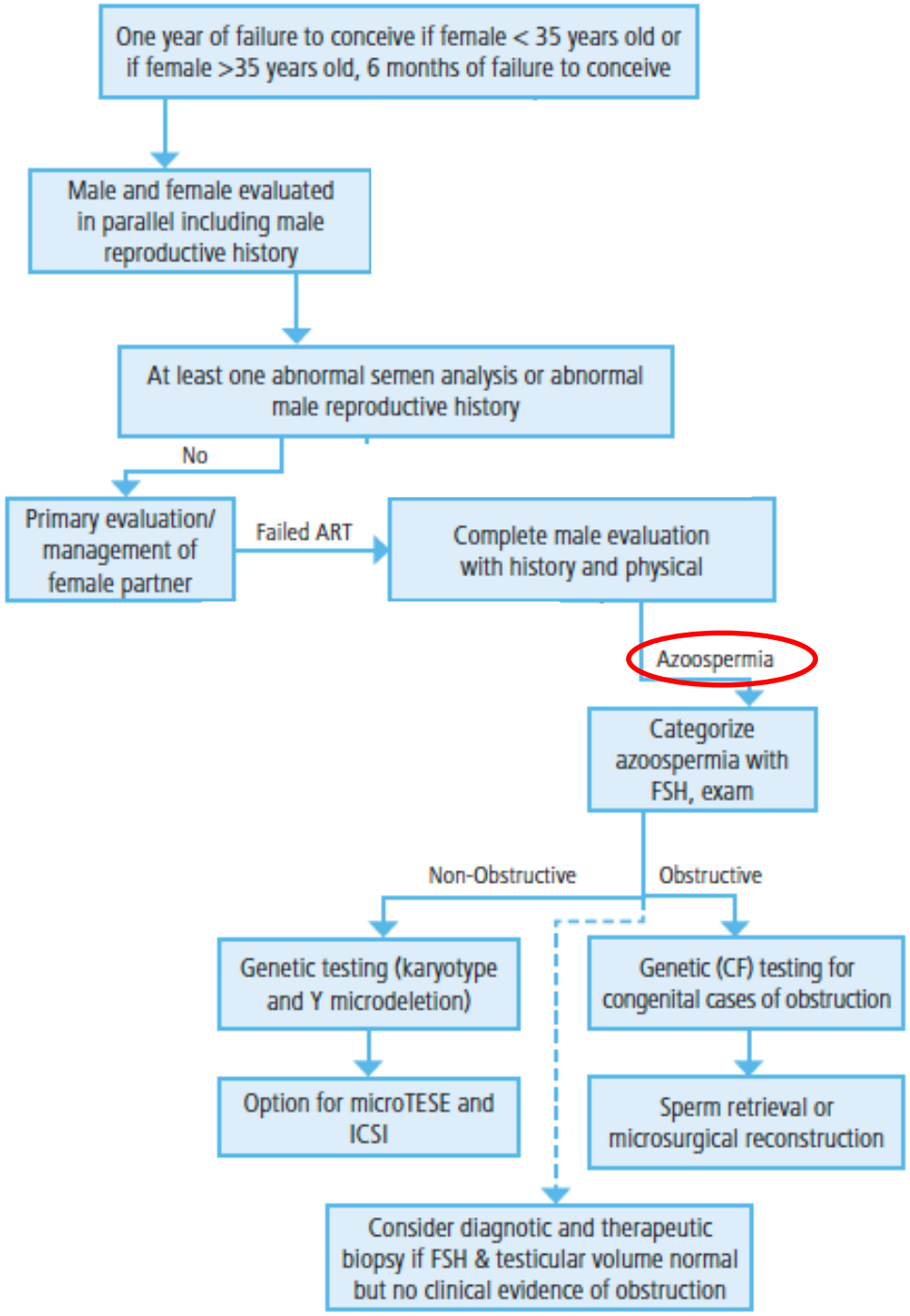
RECOMMENDATION

- Men with decreased libido and/or impotence and/or testosterone deficiency accompanied by a low/low normal LH level warrant measurement of serum prolactin to investigate for hyperprolactinemia.

- If prolactin is mildly elevated (≤1.5 times the upper limit of normal), a repeat fasting prolactin should be drawn to rule out a spurious elevation.

Male Infertility Algorithm



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RECOMMENDATION

- Patients with NOA should be informed of the limited data supporting pharmacologic manipulation with SERMs, AIs, and gonadotropins prior to surgical intervention. (Conditional Recommendation; Evidence Level Grade: C)

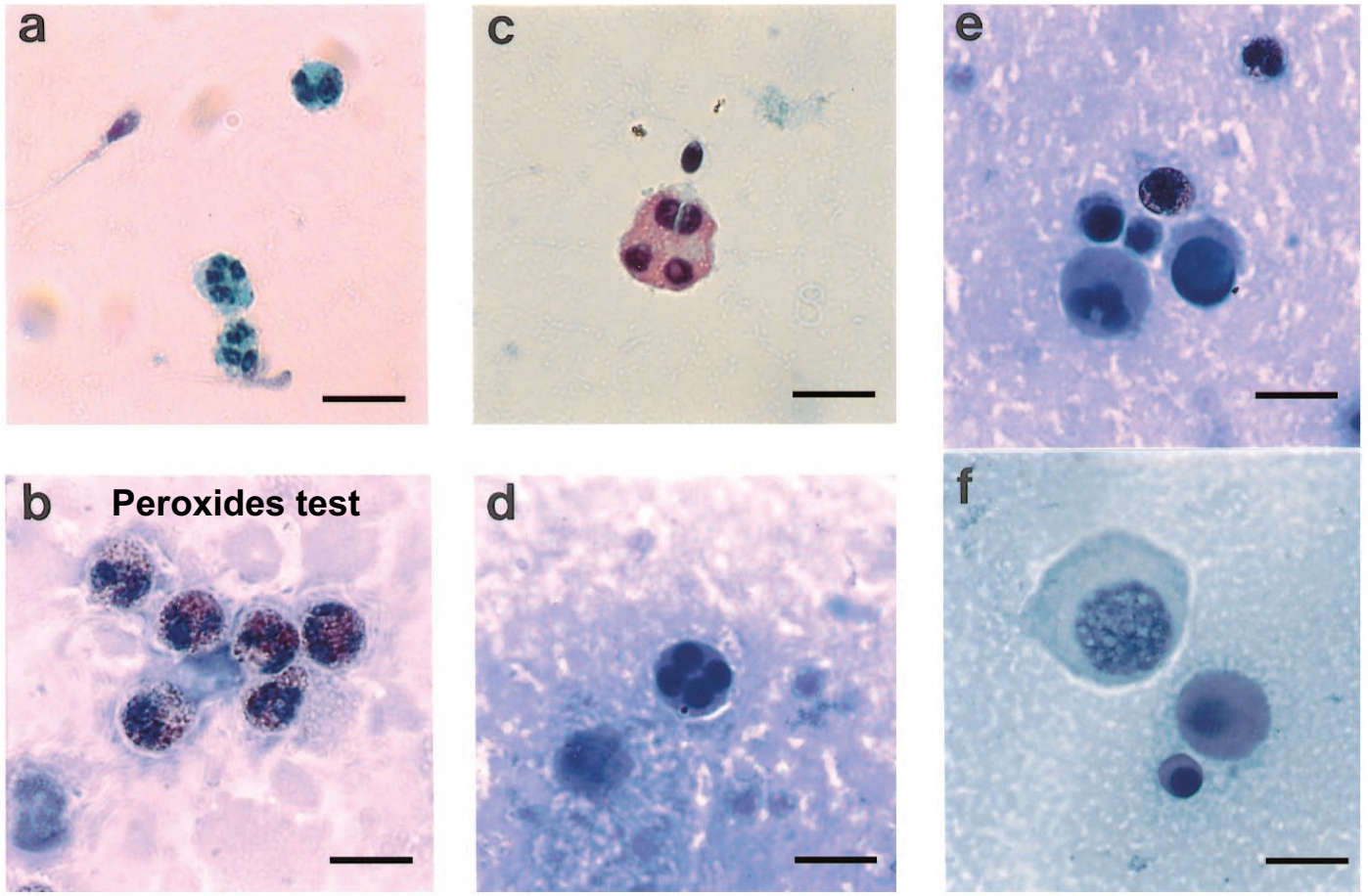
Synthroid®
(levothyroxine sodium tablets, USP)

- **Hypothyroidism associated with reduced sperm quality**
  - **Readily treatable**
- **Hyperprolactinemia**

Thyroid Function Test Interpretation			
TSH	Free T4	Free T3	Condition
High	Normal	Normal	• Subclinical hypothyroidism • Recovery from euthyroid sick syndrome
High	Low	Low	• **Primary hypothyroidism**
High	High	High	• TSH producing pituitary adenoma

1.

Round cells in the semen



(>1million/mL

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RECOMMENDATION

- Men with increased round cells on SA (>1million/mL) should be evaluated further to differentiate white blood cells (pyospermia) from germ cells. (Expert Opinion)

- Patients with pyospermia should be evaluated for the presence of infection. (Clinical Principle)

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RECOMMENDATION

- Clinicians may discuss risk factors (i.e., lifestyle, medication usage, environmental exposures) associated with male infertility, and patients should be counseled that the current data on the majority of risk factors are limited. (Conditional Recommendation; Evidence Level Grade: C)

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RECOMMENDATION

- Clinicians should inform patients undergoing chemotherapy and/or radiation therapy to avoid pregnancy for a period of at least 12 months after completion of treatment. (Expert Opinion)

The Main Mechanisms Involved in the Effects of Male Obesity/Overweight on Fertility

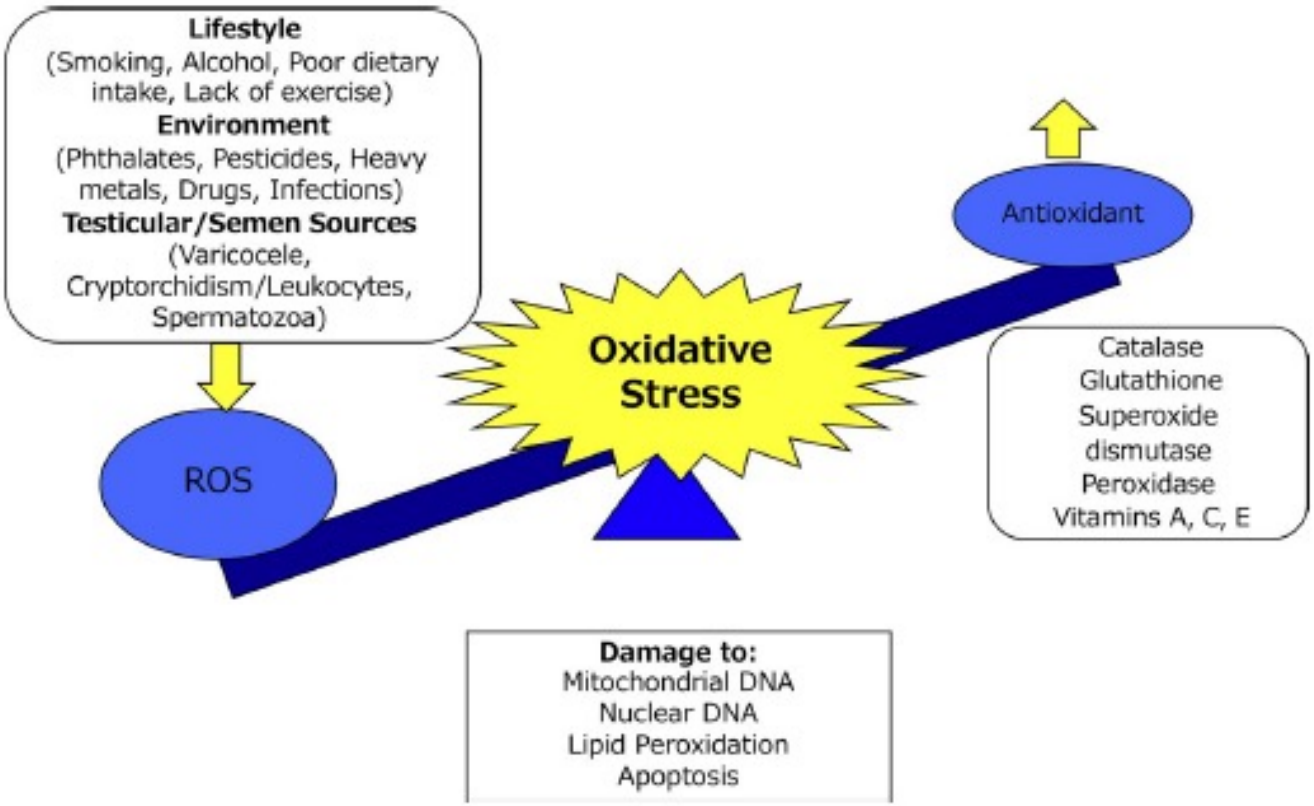
Effects of Male Obesity/Overweight on Fertility
1) Disturbances in the hypothalamus-pituitary-testis axis[a]
Normal or ↓ LH
↓ SHBG
↑ Aromatization of testosterone
↓ Testosterone
↑ Estrogen
2) Effect on sperm quality
Sperm DNA damage (leading to lower pregnancy and higher miscarriage rates)
↑ Testicular temperature (leading to reducing sperm quality and infertility)
Impairment of the physical and molecular structure of sperm during both spermatogenesis in the testis and sperm maturation in the epididymis
↓ Sperm concentration, sperm motility, and acrosome reaction decline
3) Indirect effects
Chronic inflammation in the reproductive tract and an increase in scrotal temperature due to high-fat content in the scrotum area
Abnormal levels of adipokines (leading to hypogonadism, severe inflammation, and oxidative stress in the male reproductive tract, which can damage testicular and epididymis tissues)
Erectile dysfunction due to peripheral vascular disease

Abbreviations: LH, luteinizing hormone; SHBG, sex hormone-binding globulin; ↑, increase; ↓, decrease.
[a]All these hormonal disturbances can lead to spermatogenesis impairment.

Amiri & Ramezani Tehrani

Int J Endocrinol Metab. 2020

Oxidative stress and male infertility



Takeshima et al,
Reprod Med Biol. 2021

Origins of Oxidative Stress

- Lifestyle
  - Smoking
  - Insufficient diet
  - Obesity
  - Alcohol
  - Age
- Environmental
  - Pollution
  - Heavy metals
  - Heat
  - Phthalate
  - Mobile phone radiation
- Infection
  - Genitourinary tract infection
- Testicular
  - Clinical varicocele
- Iatrogenic
  - Cryopreservation
  - Centrifugation
  - Drugs

Direct and indirect semen assays of ROS

Direct assays	Indirect assays
Chemiluminescence	Myeloperoxidase (Endz) test
Nitroblue tetrazolium test	8-OHdG
Oxidation-reduction potential	Thiobarbituric acid reaction (TBAR) test
Flow cytometry	Total antioxidant capacity (TAC) assay

Takeshima et al,
Reprod Med Biol. 2021

Various antioxidant therapies and outcomes

Antioxidants	Outcomes
Vitamin C	low vitamin C intake: DFI increased high vitamin C intake: DFI decreased
Vitamin E	LPO decreased sperm motility increased
	zona binding rate increased
Vitamin C + Vitamin E	DFI decreased
	DFI decreased
L-Carnitine	sperm density, motility increased DFI decreased
Coenzyme Q10	sperm density, motility, TAC increased ROS level, DFI decreased
Vitamin C + Vitamin E + Coenzyme Q10	sperm density, motility increased
Vitamin C + Vitamin E + Zinc +Selenium + L-Carnitine + Coenzyme Q10 + N-acetyl L-cysteine and other components	sperm density, motility increased DFI, ORP decreased
Vitamin C + Vitamin E + Zinc +Coenzyme Q10 + L-Carnitine + Astaxanthin	total motile sperm count increased sperm density, motility no change

DNA fragmentation index (DFI), Lipid peroxidation (LPO)

Takeshima et al,
Reprod Med Biol. 2021

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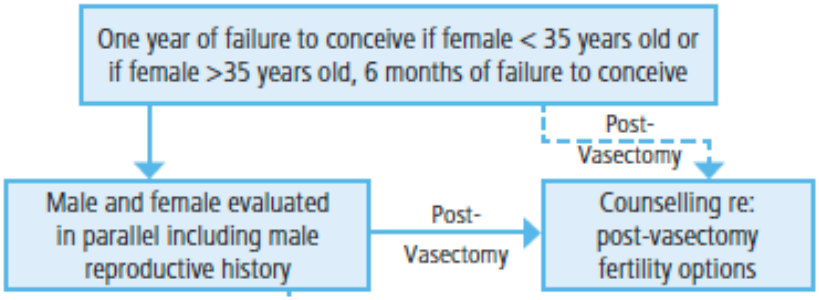
RECOMMENDATION

- Clinicians should counsel patients that the benefits of supplements (e.g., antioxidants, vitamins) are of questionable clinical utility in treating male infertility. Existing data are inadequate to provide recommendation for specific agents to use for this purpose. (Conditional Recommendation; Evidence Level Grade: B)

Male Infertility Algorithm



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FUTURE SESSIONS

- Session One: Clinical investigation of the infertile male
- Session Two: Genetic causes of male infertility and their impact on future generations
- Session Three: Medical Treatments for Male Infertility
- **Session Four: Surgical Treatments and Assisted Reproductive Technology (ART) for Male Infertility**
- **Session Five: Ejaculatory disorders**
- **Session Six: Clinical investigation and laboratory analyses in male hypogonadism**
- **Session Seven: Testosterone deficiency syndrome, , Androgen replacement—indications and principles**
- **Session Eight: Female-to-Male Transsexualism**

THE THREE W'S

WASH YOUR HANDS

WATCH YOUR DISTANCE

WEAR A MASK