Gonadotropin treatment

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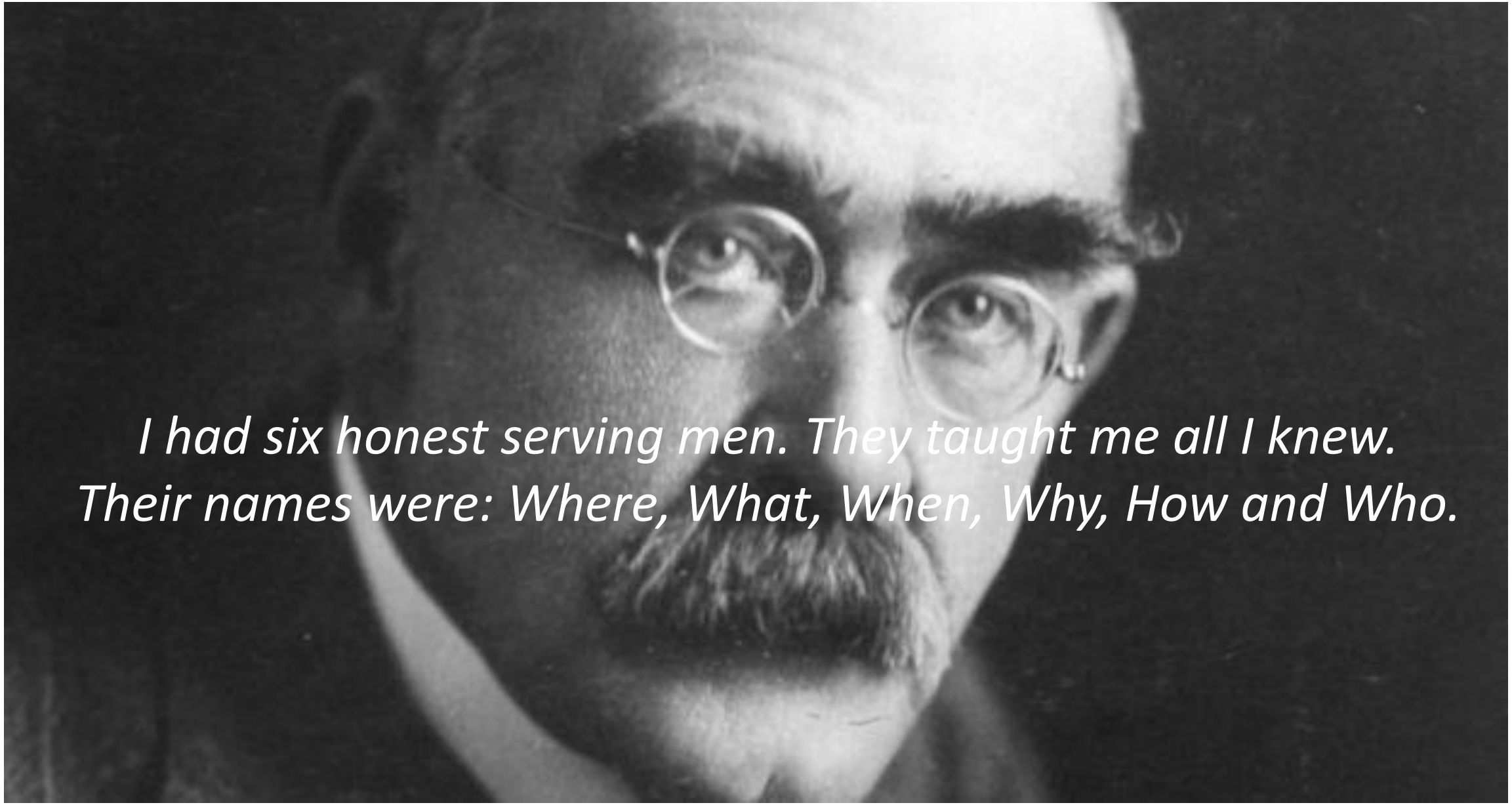
Conflicts of interest

- During the last three years, I have received research, educational and travel grants from scientific societies and pharmaceutical companies.
- I am currently or have been:
  - President, Hellenic Society of Andrology (2013 - 2017)
  - Secretary General, European Academy of Andrology (2014 - 2018)
  - Secretary General, European Menopause and Andropause Society (2017 - 2019)
  - Director, Training centre European Academy of Andrology (2013 - 2019)
  - Director, MSc in “Research Methodology in Medicine and Health Sciences” (2018 - 2021)
  - Member of the Executive Board, Hellenic Society of Endocrinology (2011 - 2013)
  - Member of the Executive Board, Hellenic Society of Climacteric and Menopause (2013 - 2019)
  - Associate Editor, Human Reproduction (2009 - 2013), Associate Editor, Hormones (2012 - 2019)
  - Member of the Editorial Board, Andrology (2012 - 2019), Member of the Editorial Board, Maturitas (2015 - 2019)
  - Member of the Editorial Board, Journal of Endocrinological Investigation (2014 - 2019)
  - Associate Editor, Human Reproduction Open (2017 - 2019)
  - Associate Editor, Human Andrology (2017 - 2019)
- None of these can be considered as a conflict of interest for today’s lecture.

Aims

- Gonadotropins for induction of spermatogenesis
- Gonadotropins for idiopathic infertility



Rudyard Kipling (1865 - 1936)

What?

What is hypogonadotropic hypogonadism?

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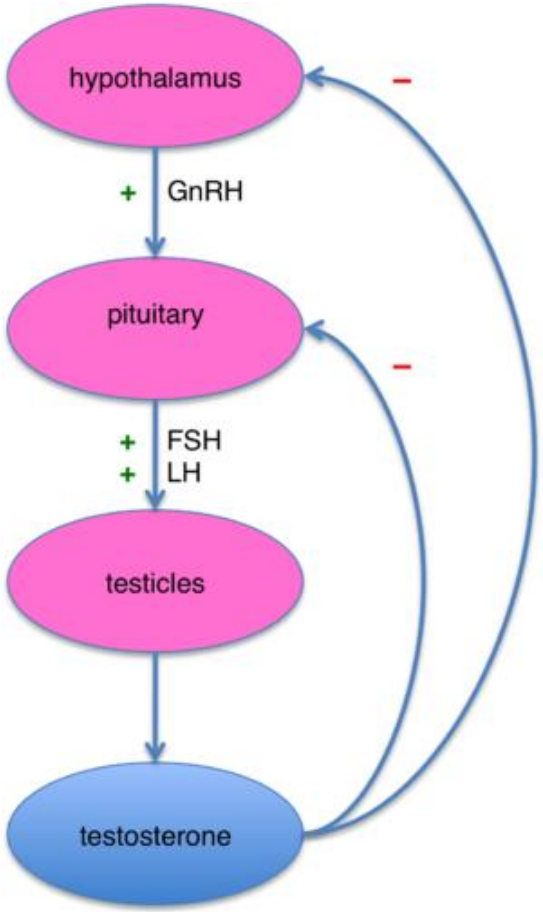
Hypogonadotropic hypogonadism



- Failure at the hypothalamus – pituitary level
- Kallmann's syndrome

Causes of hypogonadotropic (secondary) hypogonadism

Acquired
Tumors
Benign tumors and cysts
Craniopharyngiomas
Germinomas, meningiomas, gliomas, astrocytomas
Metastatic tumors (breast, lung, prostate)
"Functional" gonadotropin deficiency
Chronic systemic disease
Acute illness
Malnutrition
Hypothyroidism, hyperprolactinemia, diabetes mellitus, Cushing's disease
Anorexia nervosa, bulimia
Post-androgen abuse
Infiltrative diseases
Hemochromatosis
Granulomatous diseases
Histiocytosis
Head trauma
Pituitary apoplexy
Drugs - Marijuana
Congenital
Isolated GnRH deficiency
Without anosmia
Kallmann syndrome
Associated with adrenal hypoplasia congenita
GnRH deficiency associated with mental retardation/obesity
Laurence-Moon-Biedl syndrome
Prader-Willi syndrome
Idiopathic forms of multiple anterior pituitary hormone deficiencies
Congenital malformations often associated with craniofacial anomalies

GnRH: gonadotropin-releasing hormone.

Snyder PJ. UpToDate, 2019

Genotype and Phenotype

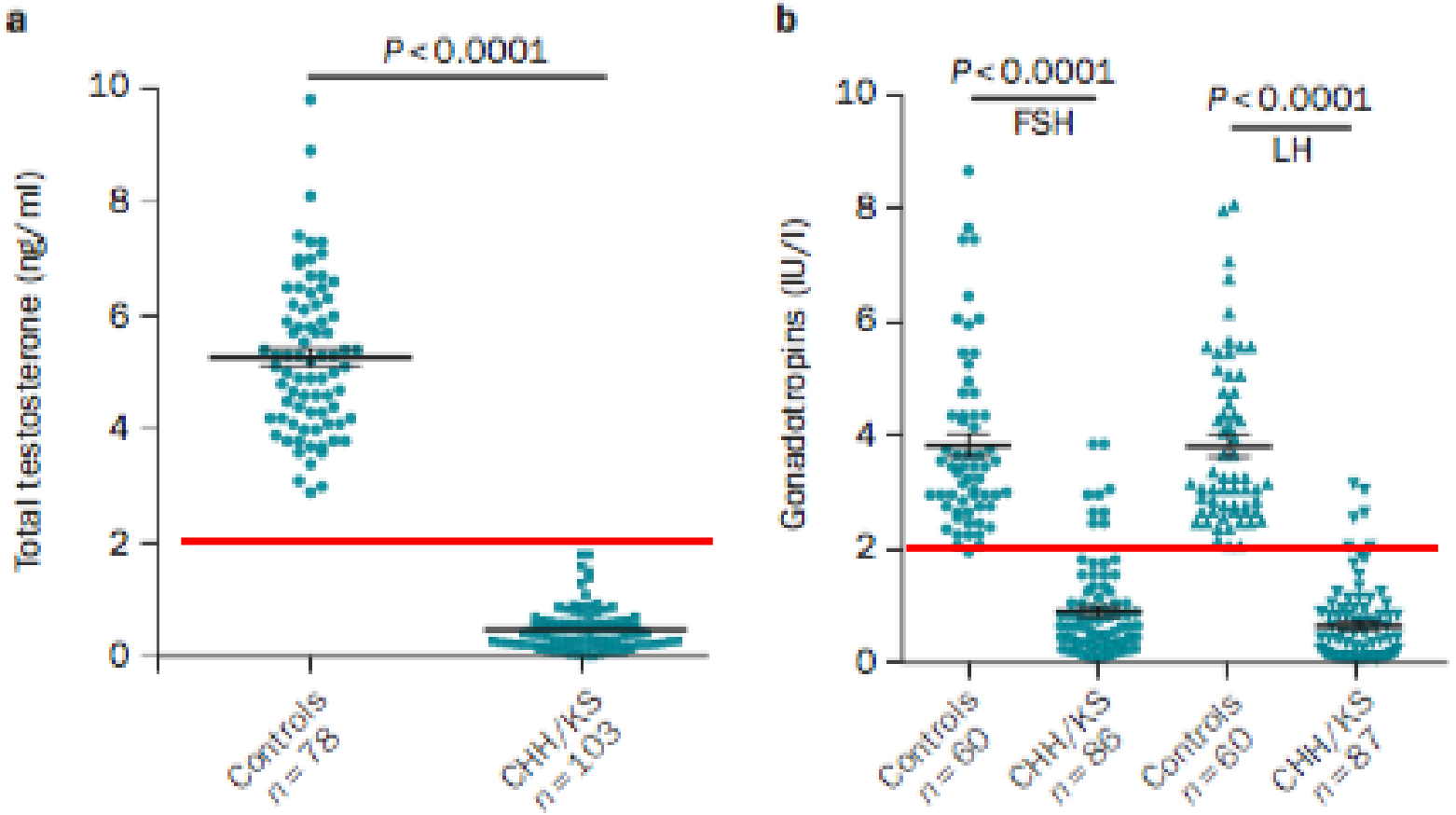
Table 1 | Genes implicated in CHH

Gene	OMIM	CTO	CHH phenotypes			Overlapping syndromes									
			KS	CHH	CHH reversal	CPHD	CPHD + SOD	WS	CHARGE	HS	SHFM	D-WS	MGS	PEPNS	GHS
KAL1 (ANOS1)	300836	✓	✓	×	✓	×	×	×	×	×	×	×	×	×	×
SEMA3A	614897	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×
SOX10	602229	×	✓	×	×	×	×	✓	×	×	×	×	×	×	×
OL14RD	606807	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×
HESX1	182230	×	✓	×	×	✓	✓	×	×	×	×	×	×	×	×
FEZF1	613301	×	✓	×	×	×	×	×	×	×	×	×	×	×	×
FGFR1	147950	✓	✓	✓	✓	✓	✓	×	×	✓	✓	×	×	×	×
FGF8	612702	✓	✓	✓	×	✓	×	×	×	×	×	×	×	×	×
CHD7	612370	×	✓	✓	✓	×	×	×	✓	×	×	×	×	×	×
FGF17	603725	✓	✓	✓	×	×	×	×	×	×	×	✓	×	×	×
HS6ST1	614880	✓	✓	✓	✓	×	×	×	×	×	×	×	×	×	×
PROK2	610628	✓	✓	✓	×	×	×	×	×	×	×	×	×	×	×
PROKR2	147950	✓	✓	✓	✓	✓	×	×	×	×	×	×	✓	×	×
SEMA7A	607961	✓	✓	✓	×	×	×	×	×	×	×	×	×	×	×
WDR11	614858	✓	✓	✓	×	✓	×	×	×	×	×	×	×	×	×
NSMF	614838	✓	✓	✓	✓	×	×	×	×	×	×	×	×	×	×
AXL	109135	×	✓	✓	×	×	×	×	×	×	×	×	×	×	×
GNRH1	614841	×	×	✓	×	×	×	×	×	×	×	×	×	×	×
GNRHR	146110	✓	×	✓	✓	×	×	×	×	×	×	×	×	×	×
KISS1	614842	×	×	✓	×	×	×	×	×	×	×	×	×	×	×
KISS1R	614837	✓	×	✓	×	×	×	×	×	×	×	×	×	×	×
TAC3	614839	✓	×	✓	✓	×	×	×	×	×	×	×	×	×	×
TACR3	614840	✓	×	✓	✓	×	×	×	×	×	×	×	×	×	×
LEP	614962	×	×	✓	×	×	×	×	×	×	×	×	×	×	×
LEPR	614963	×	×	✓	×	×	×	×	×	×	×	×	×	×	×
PCSK1	162150	×	×	✓	×	×	×	×	×	×	×	×	×	×	×
DMXL2	616113	×	×	✓	×	×	×	×	×	×	×	×	×	✓	×
RNF216	609948	×	×	✓	×	×	×	×	×	×	×	×	×	×	✓
OTUD4	611744	×	×	✓	×	×	×	×	×	×	×	×	×	×	✓
PNPLA6	603197	×	×	✓	×	×	×	×	×	×	×	×	×	×	✓
NR0B1	300200	×	×	✓	×	×	×	×	×	×	×	×	×	×	×

Abbreviations: CHH, congenital hypogonadotropic hypogonadism; CHARGE, coloboma, heart defects, atresia of choanae, retardation of growth and/or development, genital and/or urinary defects, ear anomalies or deafness; CPHD, combined pituitary hormone deficiency; CTO, contributes to oligogenicity; D-WS, Dandy-Walker syndrome; GHS, Gordon Holmes syndrome; HS, Hartsfield syndrome; KS, Kallmann syndrome; MGS, Morning Glory syndrome; OMIN, online Mendelian inheritance in man; PEPNS, polyendocrine deficiencies and polyneuropathies; SHFM, split-hand/foot malformation; SOD, septo-optic dysplasia; WS, Waardenburg syndrome.

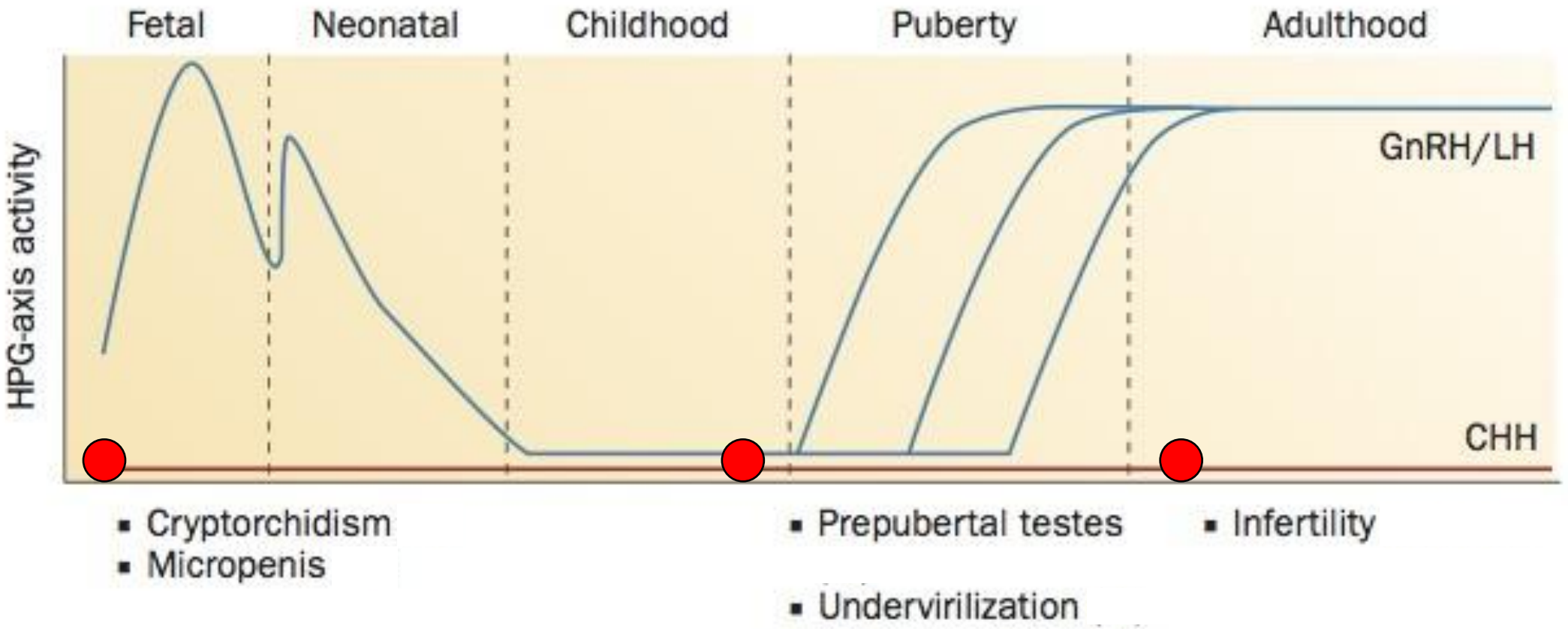
Boehm U et al. Nature Rev Endocrinol 2015;11:547

Hormonal profile



Trabado S et al. J Clin Endocrinol Metab 2014;99:E268
Young J. J Clin Endocrinol Metab 2012:97:707

Hypogonadism according to age



Boehm U et al. Nature Rev Endocrinol 2015;11:547

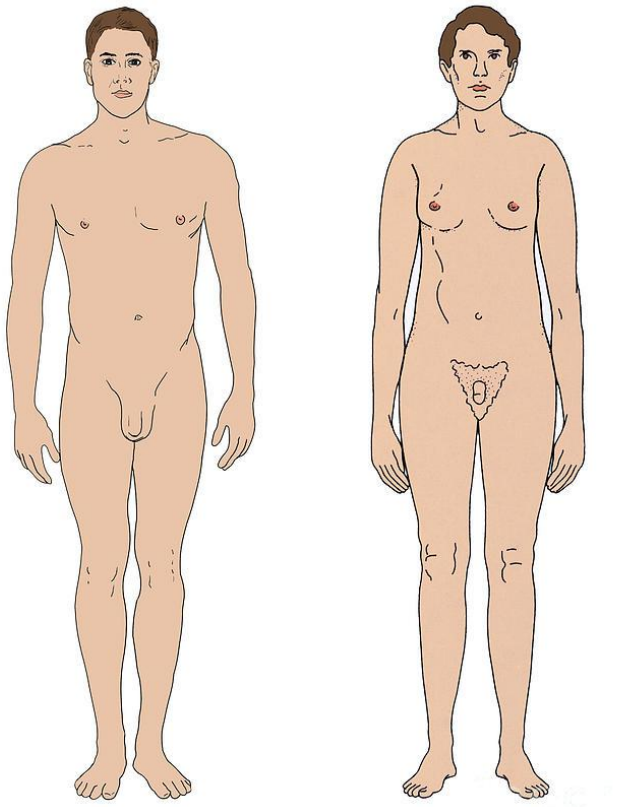
Clinical spectrum of Kallmann's syndrome

- Cryptorchidism ± micropenis
- Delayed puberty
- Hypogonadism
- Male infertility
- Anxiety and depression

- Hyposmia / anosmia
- Optic nerve hypoplasia
- Cleft lip and/or palate
- Dental agenesis
- Sensorineural deafness
- Congenital hearing impairment ± pigmentation defects
- Bimanual synkinesia (mirror movements)
- Unilateral renal agenesis

Boehm U et al. Nature Rev Endocrinol 2015;11:547

Hypogonadotropic hypogonadism



Healthy Male

Kallmann's syndrome

- Always

- Induce puberty
- Treat hypogonadism
- Treat co-morbidities
- Treat infertility

Which?

Which is the appropriate treatment for hypogonadotropic hypogonadism?

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What to give?

- **Hypothalamic disease**
  - Gonadotropins
  - Gonadotropin-releasing hormone (GnRH)

- **Pituitary disease**
  - Gonadotropins

Gonadotropin-releasing hormone

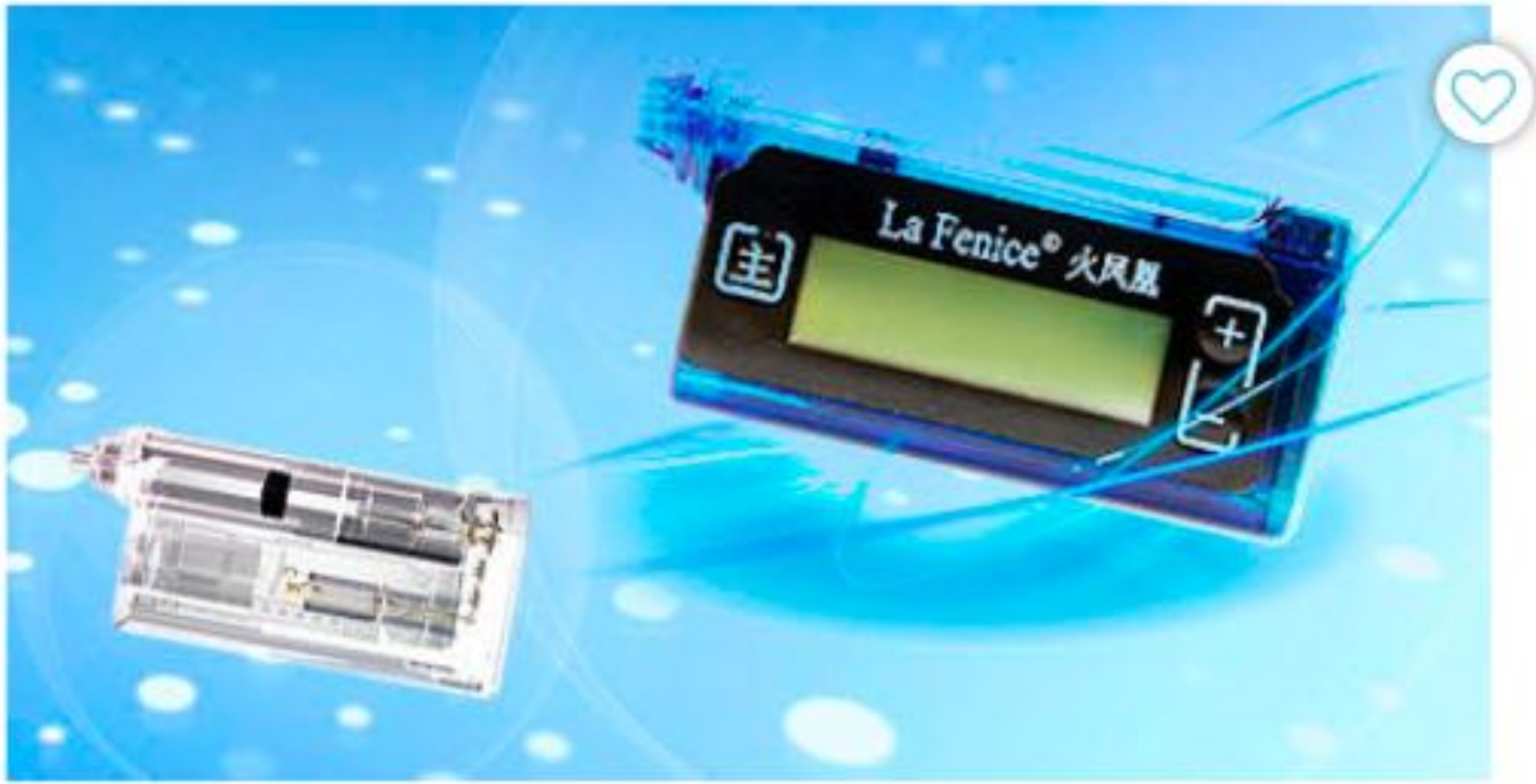
- **Gonadotropins vs. Pulsatile GnRH treatment**
  - Similar stimulation of spermatogenesis
  - Limitations
    - Subcutaneous infusion pump
    - Cost
    - Limited availability

Liu L, et al. J Clin Endocrinol Metab 1988;67:1140
Kliesch S, et al. Eur J Endocrinol 1994;131:347

1-CHANNEL INFUSION PUMP / AMBULATORY / ADULT

LA FENICE™

SHANGHAI MICROPORT ORTHOPEDICS




La Fenice

GnRH pump

• **GnRH frequency**	Every two hours
• **GnRH dose**	25 ng/kg (up to 600 ng/kg)
• **Target**	Normal serum T concentration
• **Sperm appearance**	12 – 36 months
• **Until when**	Pregnancy

Spratt DI, et al. Ann Intern Med 1986;105:848

With which?

With which substances to induce spermatogenesis?

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How to induce spermatogenesis?

- **LH** ~~hCG~~ / ~~recombinant hCG~~ / recombinant LH
- **FSH** hMG / highly purified FSH / recombinant FSH
- **Combinations**

Clinical gems

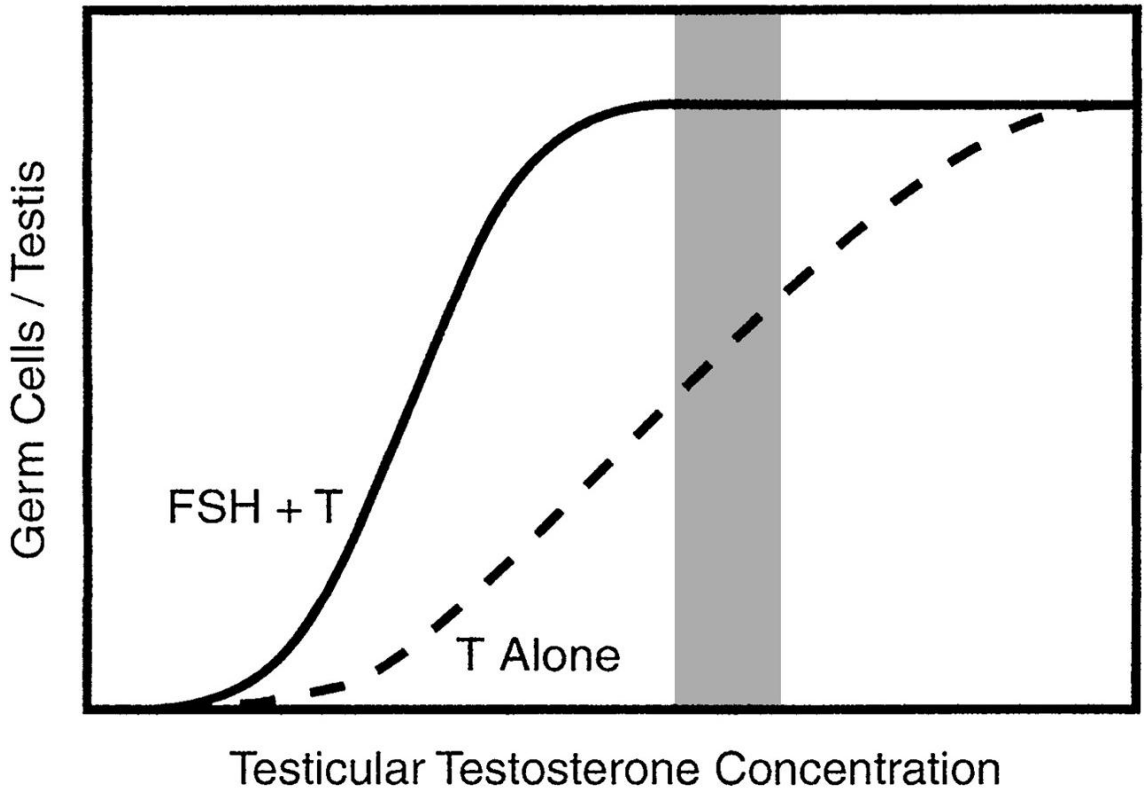
- **Biological activity** hCG = LH
- **Half-life** hCG > LH

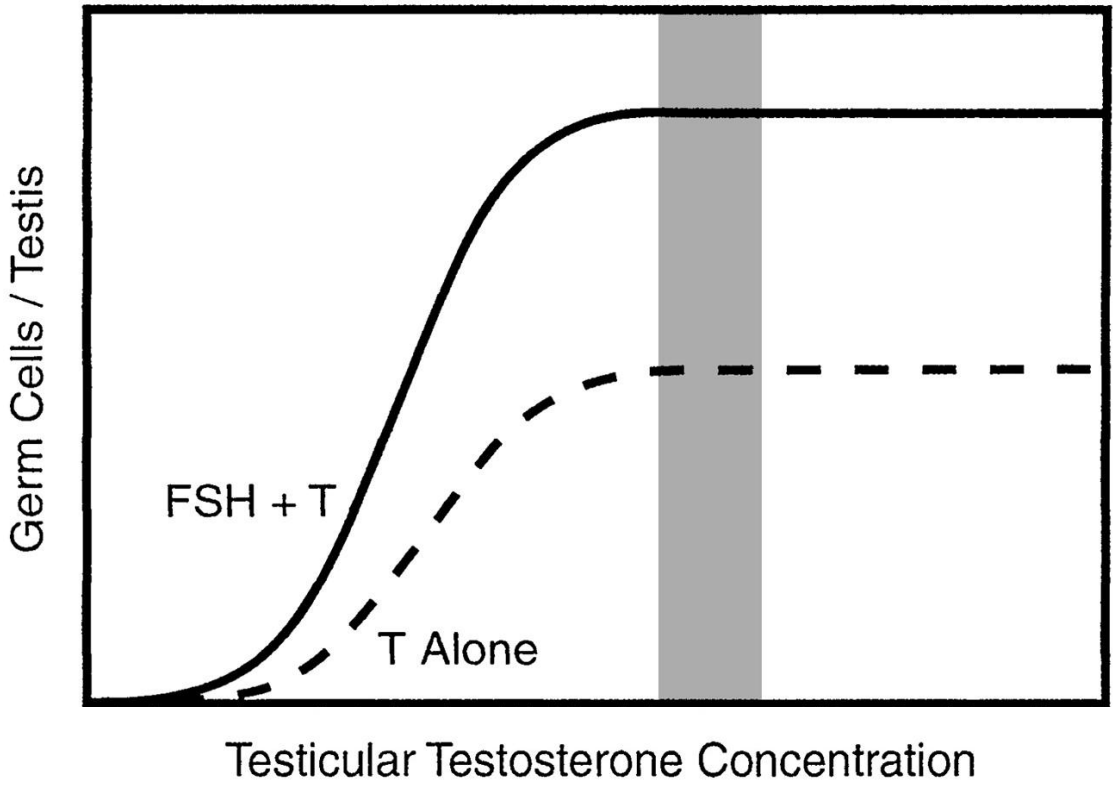
hCG before FSH

- hCG stimulates the Leydig cells to secrete T, which results in an **intratesticular** T concentration 100 times that in the peripheral circulation, a concentration essential to stimulate spermatogenesis
- hCG alone may be **sufficient for stimulation** of spermatogenesis; FSH alone is not effective.
- hCG preparations are considerably **less expensive** than exogenous FSH preparations, in particular, recombinant FSH

Finkel DM, et al. N Engl J Med 1985;313:651
Schaison G, et al. J Clin Endocrinol Metab 1993;77:1545

T or FSH?





Plant TM, et al. Endocr Rev 2001;22:764

What?

What doses are necessary to induce spermatogenesis?

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Gonadotropin administration

- **hCG**
  - Intramuscular injection
  - Self-administration
  - Initial dose: 2,000 UI, three times a week
  - Maximum dose: 10,000 units, three times a week
- **FSH**
  - Initial dose: 75 IU, three times a week
  - Increase: 150 IU, three times a week
  - Maximum dose: 300 IU, every other day

Timing

- **Time to respond**
  - 6 – 36 months (hCG)
  - 6 – 10 months (hCG + hMG)

- **Time to discontinue**
  - Pregnancy not achieved — 12 – 24 months (hCG)
Proceed to ART
  - Pregnancy achieved — Immediately, if no pregnancy is desired
Postpone, if another pregnancy is desired

Liu PY, et al. J Clin Endocrinol Metab 2009;94:801
Farhat R, et al. Pituitary 2010;13:105

Gonadotropin administration (GRE)

- **Recombinant LH**
  - Intramuscular injection
  - Initial dose: 75 IU, once a week

- **Recombinant FSH**
  - Initial dose: 75 IU, every other day
  - Increase: 150 IU, every other day
  - Maximum dose: 300 IU, every other day

Timing (GRE)

- **Time to respond**
  - 6 – 24 months (recLH + FSH)

- **Time to discontinue**
  - Pregnancy not achieved — 12 – 18 months
Proceed to ART
  - Pregnancy achieved — Continue, until the end of first trimester
Cryopreserve semen

Which?

Which patients are likely to respond to therapy?

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Which patients are likely to respond?

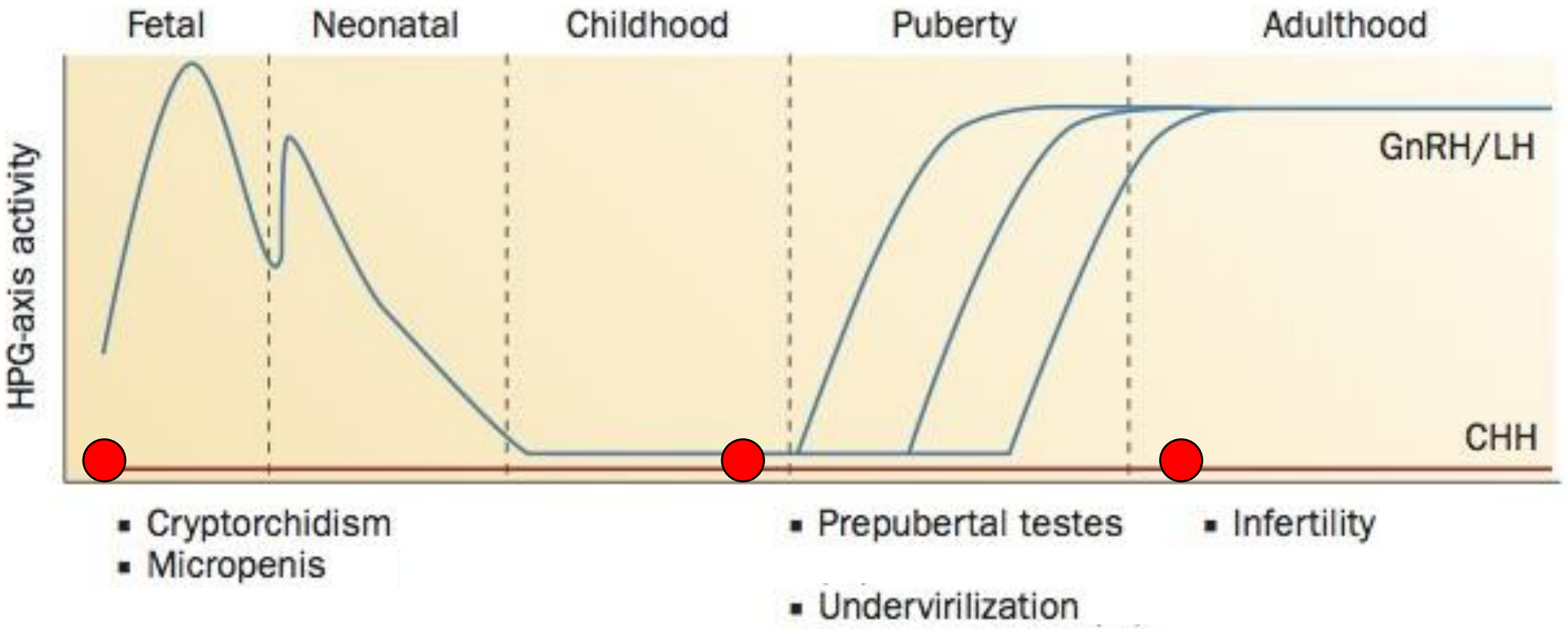
Good prognostic factor

- Development of hypogonadism after puberty

Bad prognostic factor

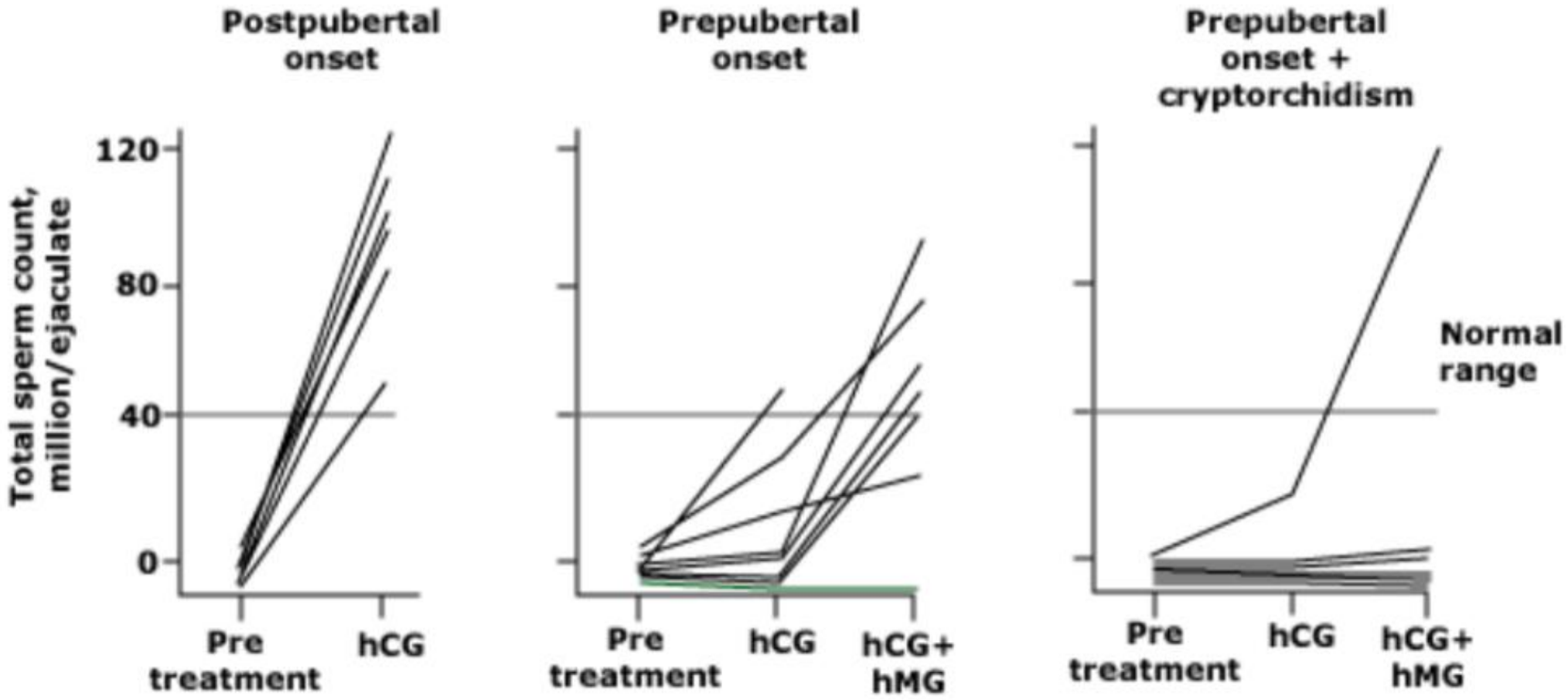
- Development of hypogonadism before puberty

Hypogonadism according to age



Boehm U et al. Nature Rev Endocrinol 2015;11:547

Time of hypogonadism onset



Finkel DM, et al. N Engl J Med 1985;313:651

Which patients are likely to respond?

Good prognostic factor

- Development of hypogonadism after puberty
- Partial hypogonadism

Bad prognostic factor

- Development of hypogonadism before puberty
- Complete hypogonadism

Partial vs complete hypogonadism

- Testicular volume
- Serum FSH
- Serum inhibin B
- Serum testosterone

Büchter D, et al. Eur J Endocrinol 1998;139:298
Liu PY, et al. J Clin Endocrinol Metab 2009;94:801

Which patients are likely to respond?

Good prognostic factor

- Development of hypogonadism after puberty
- Partial hypogonadism
- No cryptorchidism

Bad prognostic factor

- Development of hypogonadism before puberty
- Complete hypogonadism
- Unilateral or bilateral cryptorchidism

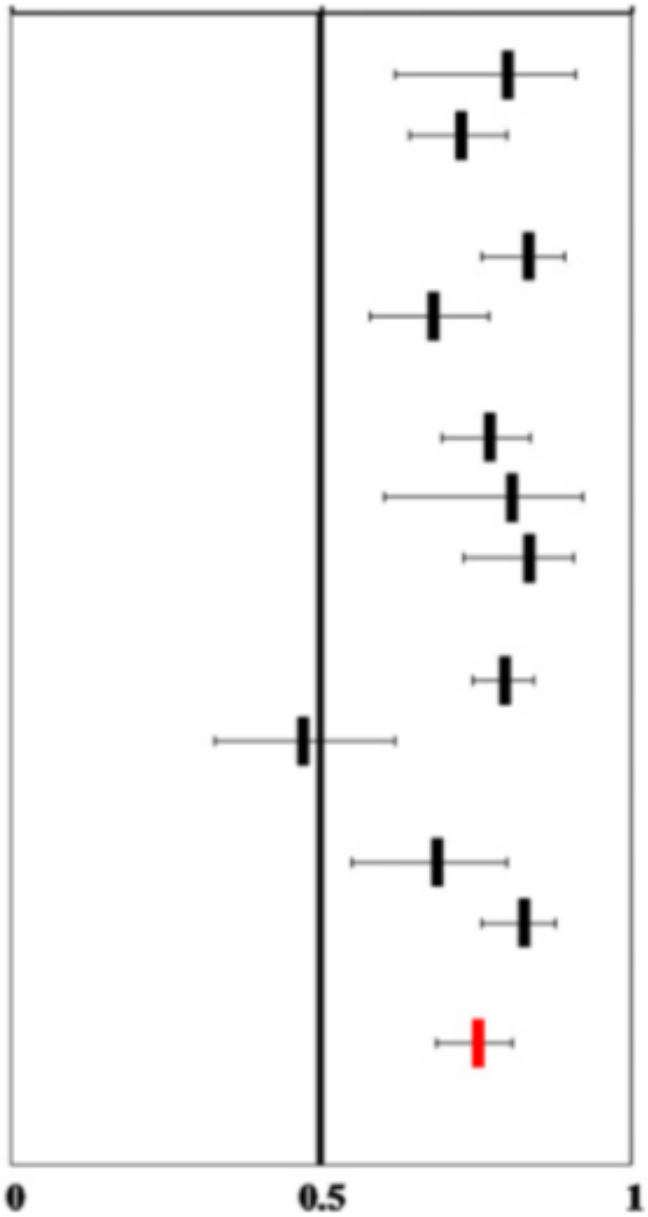
Which patients are likely to respond?

Good prognostic factor

- Development of hypogonadism after puberty
- Partial hypogonadism
- No cryptorchidism
- No prior treatment with testosterone

Bad prognostic factor

- Development of hypogonadism before puberty
- Complete hypogonadism
- Unilateral or bilateral cryptorchidism
- Prior treatment with testosterone



	# Studies	# Subjects	Event Rate	LL	UL	
Pituitary related HHG	9	39	0.80	0.62	0.91	Q = 0.680
Hypothalamic related HHG	29	501	0.73	0.64	0.80	p = 0.410
Mixed pre- and post -pubertal onset HHG	6	126	0.84	0.76	0.89	Q = 6.52
Only pre pubertal onset of HHG	26	445	0.68	0.58	0.77	p = 0.011
Urinary-derived FSH	20	366	0.77	0.69	0.84	
Purified FSH	5	108	0.81	0.60	0.92	Q = 1.127
Recombinant FSH	10	236	0.84	0.73	0.91	p = 0.569
hCG+FSH	36	723	0.80	0.74	0.84	Q = 18.623
Only hCG	10	151	0.47	0.33	0.62	P < 0.0001
No previous TRT (0% of previously treated subjects)	8	152	0.69	0.55	0.80	Q = 4.562
Previous TRT (at least 1 previously treated subject)	25	355	0.83	0.76	0.88	p = 0.051
OVERALL	**48**	**897**	**0.75**	**0.69**	**0.81**	

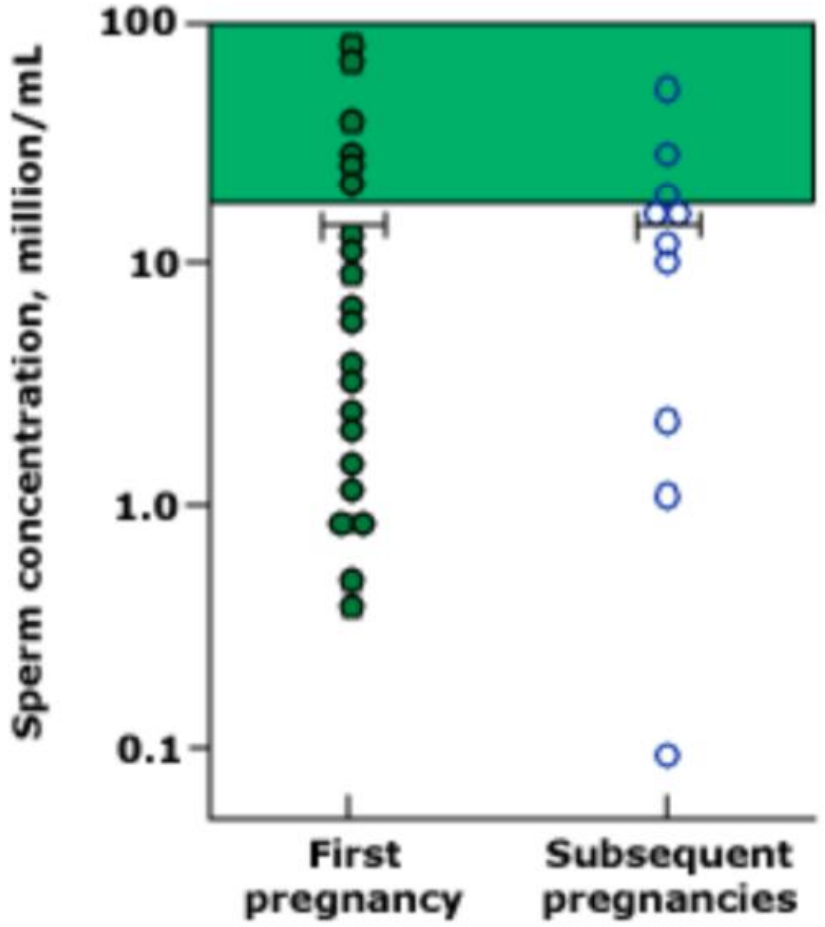
Rastrelli G, et al. Andrology 2014;2:794

Success rate

- Sperm in the ejaculate
  - 90%, often not within normal range

Büchter D, et al. Eur J Endocrinol 1998;139:298

Sperm count at conception



Burris AS, et al. Fertil Steril 1988;50:343

How?

How to induce spermatogenesis?

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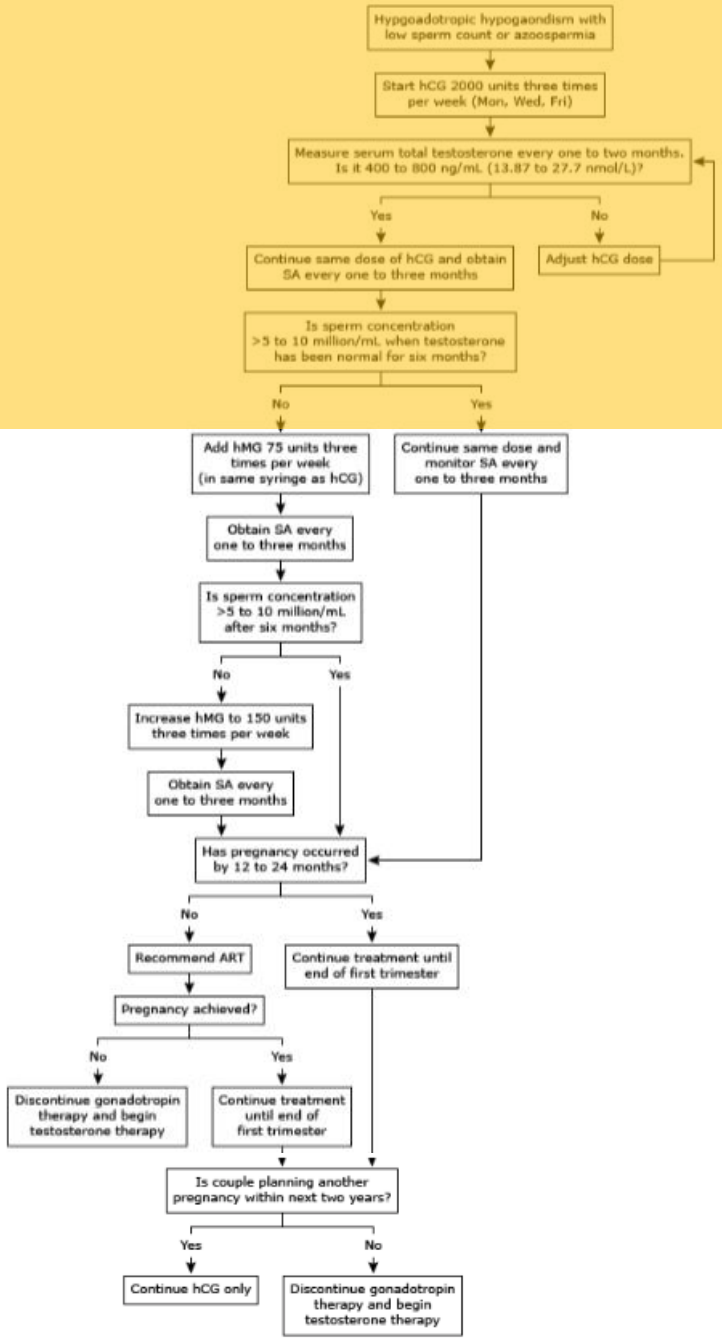
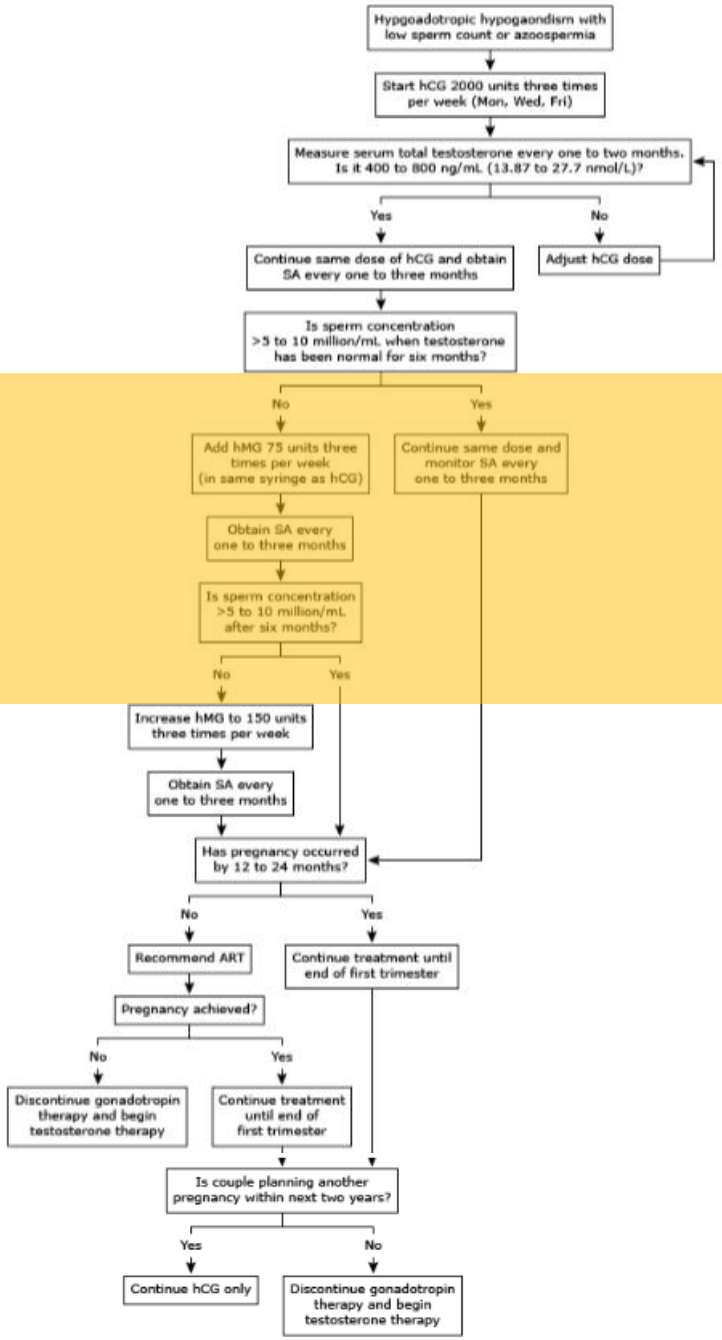
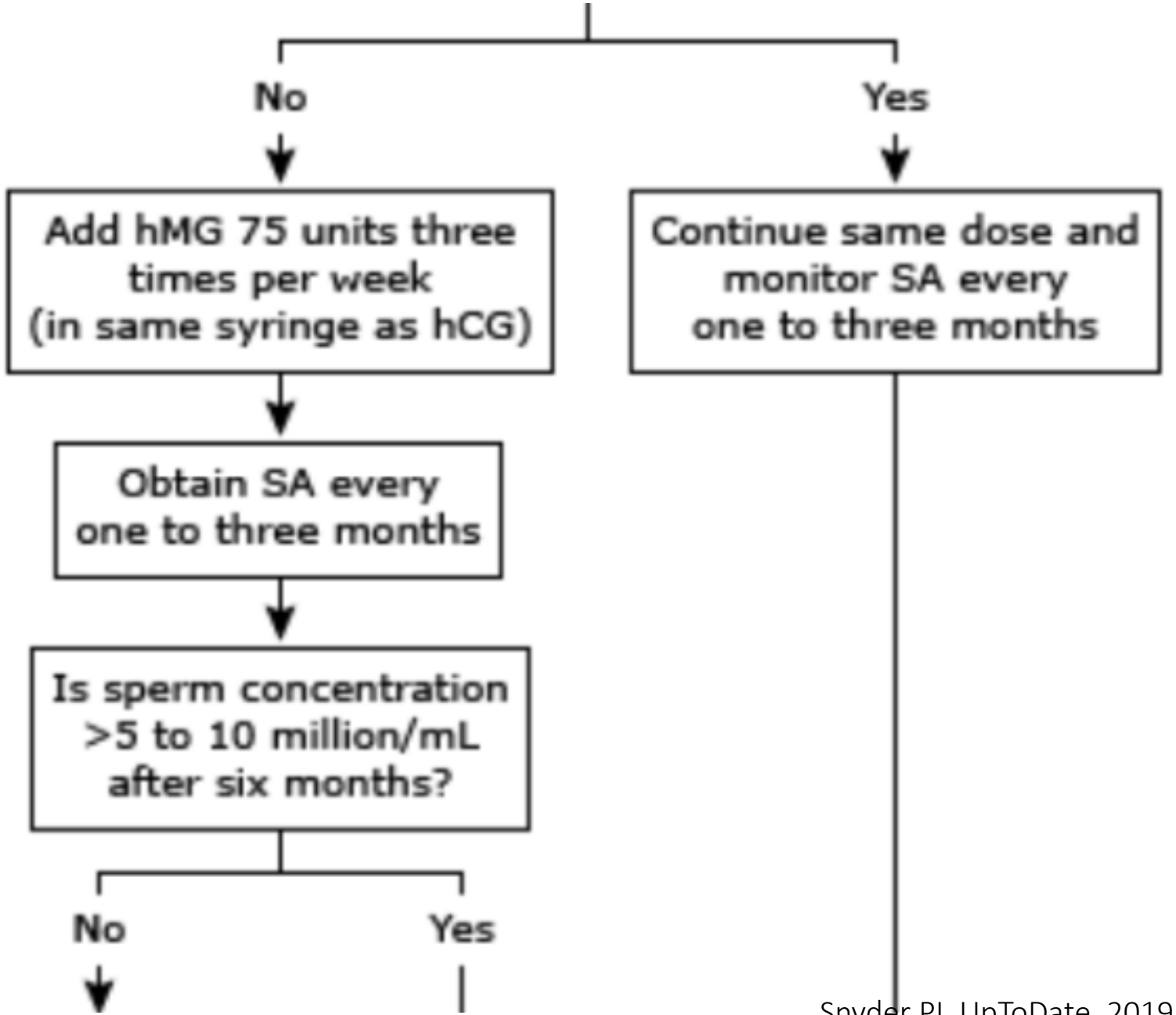
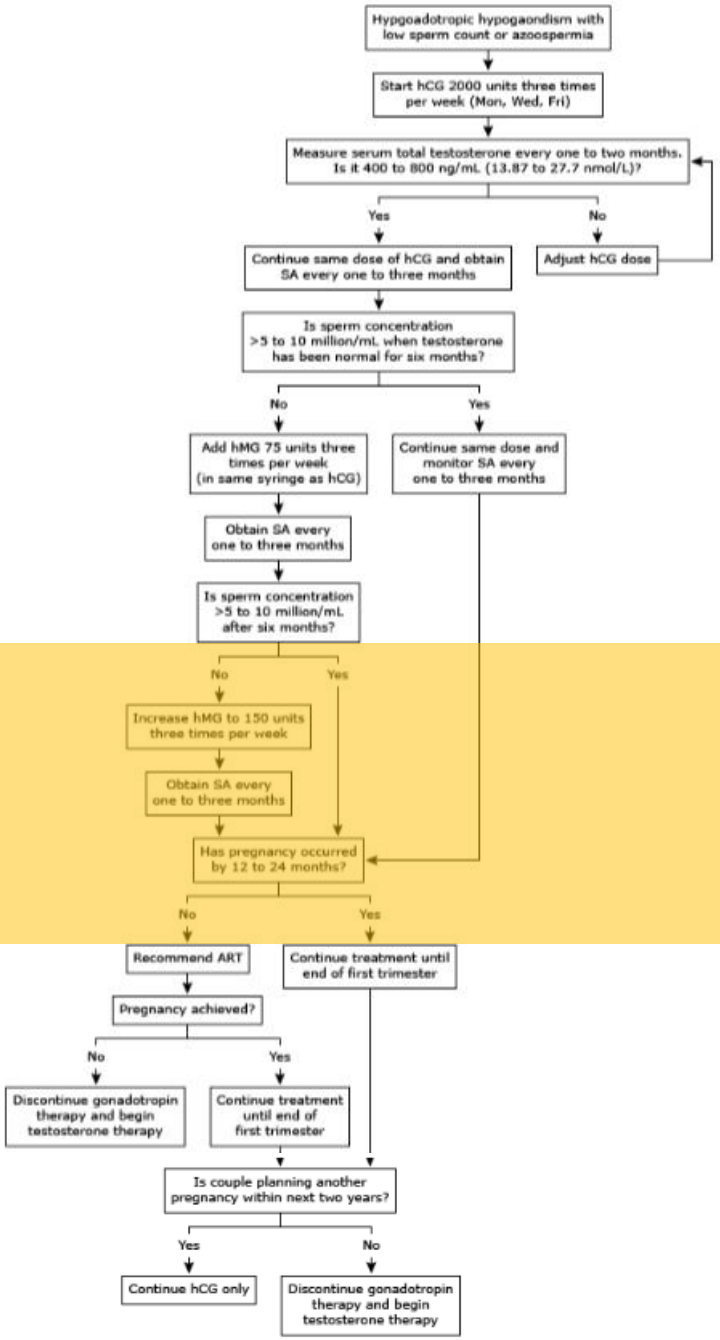


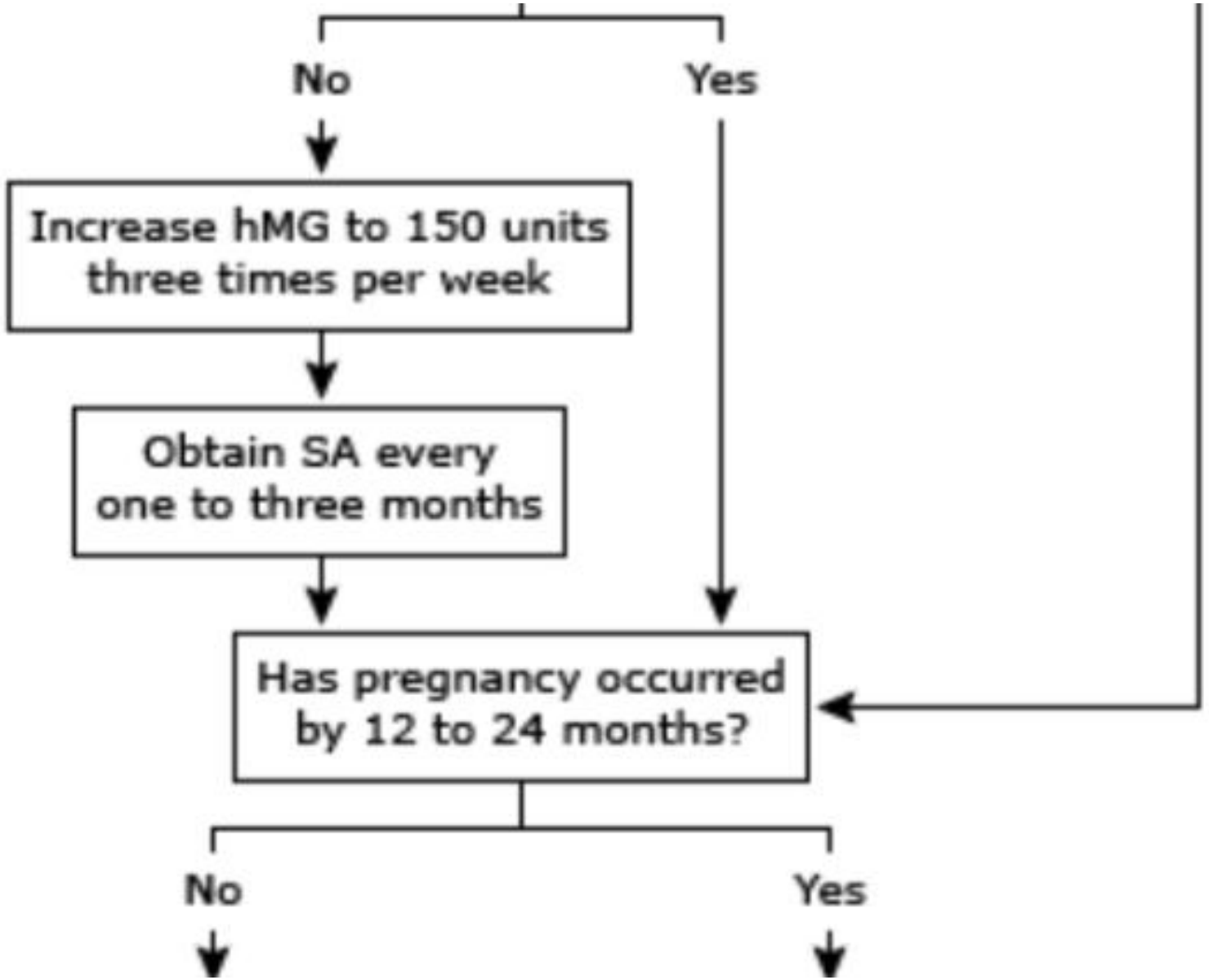
Snyder PJ. UpToDate, 2019



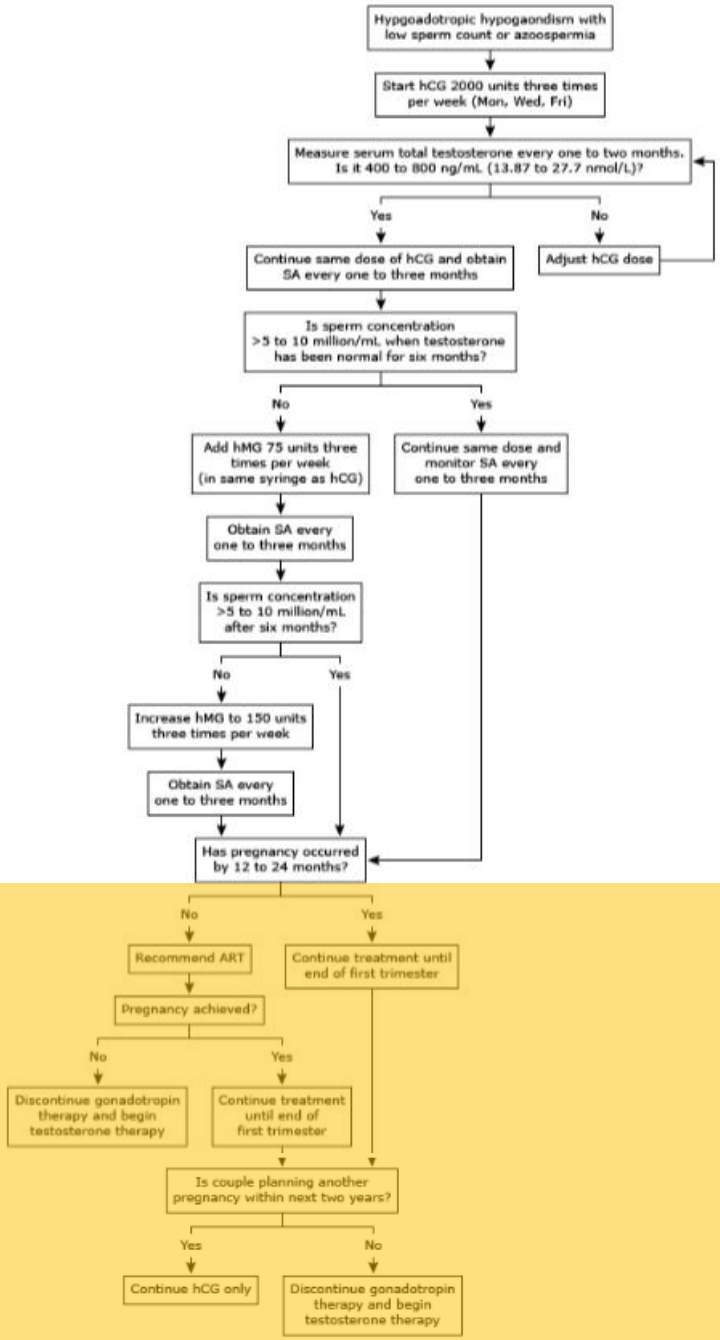


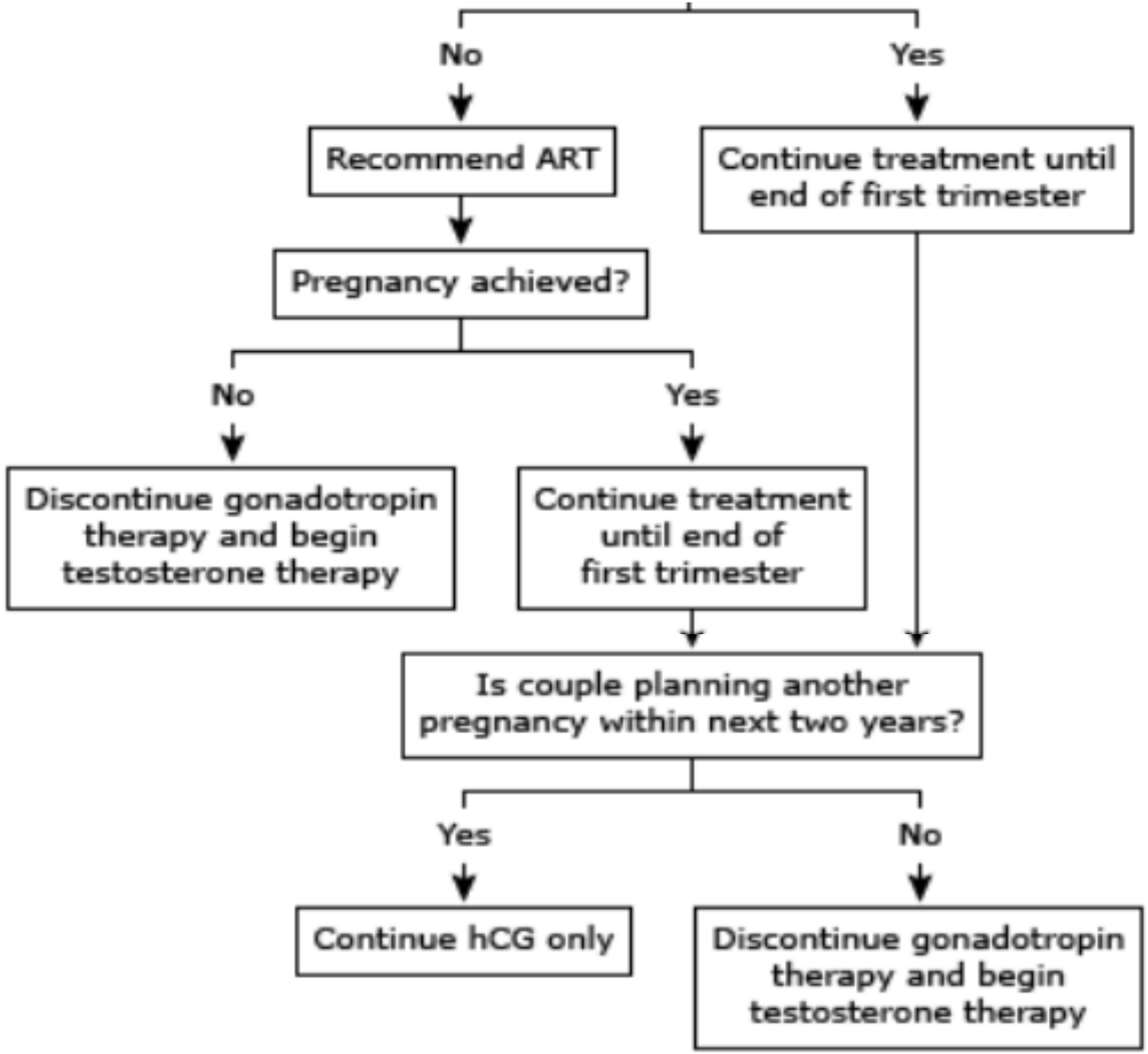
Snyder PJ. UpToDate, 2019





Snyder PJ. UpToDate, 2019


Hypgoadotropic hypogaondism with low sperm count or azoospermia
Start hCG 2000 units three times per week (Mon, Wed, Fri)
Measure serum total testosterone every one to two months. Is it 400 to 800 ng/mL (13.87 to 27.7 nmol/L)?
Yes
No
Continue same dose of hCG and obtain SA every one to three months
Adjust hCG dose
Is sperm concentration >5 to 10 million/mL when testosterone has been normal for six months?
No
Yes
Add hMG 75 units three times per week (in same syringe as hCG)
Continue same dose and monitor SA every one to three months
Obtain SA every one to three months
Is sperm concentration >5 to 10 million/mL after six months?
No
Yes
Increase hMG to 150 units three times per week
Obtain SA every one to three months
Has pregnancy occurred by 12 to 24 months?
No
Yes
Recommend ART
Continue treatment until end of first trimester
Pregnancy achieved?
No
Yes
Discontinue gonadotropin therapy and begin testosterone therapy
Continue treatment until end of first trimester
Is couple planning another pregnancy within next two years?
Yes
No
Continue hCG only
Discontinue gonadotropin therapy and begin testosterone therapy


No
Yes
Recommend ART
Continue treatment until end of first trimester
Pregnancy achieved?
No
Yes
Discontinue gonadotropin therapy and begin testosterone therapy
Continue treatment until end of first trimester
Is couple planning another pregnancy within next two years?
Yes
No
Continue hCG only
Discontinue gonadotropin therapy and begin testosterone therapy

What?

What about idiopathic infertility?

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Male idiopathic infertility

- 30% of male infertility
- Infertility
- Oligo-astheno-teratozoospermia / azoospermia
- No apparent cause

FSH protocols

- **Standard protocol**
  - 3 months
  - 75 IU every other day
  - Quantitative / qualitative improvement of seminal parameters
  - Increase the probability of both natural and ART conception

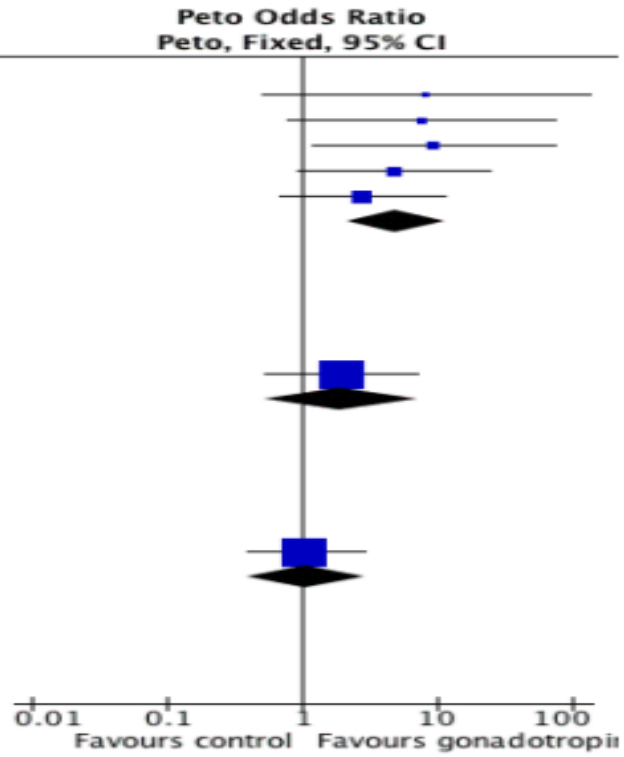
- **Short protocol**
  - 1 month
  - 75 IU every other day
  - Increase the proportion of functionally competent sperm prior ART

Pregnancy rate (all studies)

Figure 1. Forest plot of comparison: 1 Gonadotrophins versus placebo/no treatment for the treatment of idiopathic male subfertility, outcome: 1.2 Pregnancy rate per couple randomly assigned.

Study or Subgroup	Gonadotrophins Events	Total	Control Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.2.1 Spontaneous pregnancy rate per couple						
Knuth 1987	2	19	0	20	8.9%	8.23 [0.50, 136.74]
Kamischke 1998	3	34	0	33	13.4%	7.63 [0.77, 76.00]
Paradisi 2006	4	15	0	15	16.5%	9.31 [1.17, 73.75]
Matorras 1997	5	68	1	80	26.5%	4.75 [0.93, 24.34]
Foresta 2005	6	65	2	63	34.7%	2.79 [0.67, 11.61]
Subtotal (95% CI)		**201**		**211**	**100.0%**	**4.94 [2.13, 11.44]**
Total events	20		3			
Heterogeneity: $Chi^2 = 1.24$, df = 4 (P = 0.87); $I^2 = 0\%$						
Test for overall effect: Z = 3.72 (P = 0.0002)						
1.2.2 Pregnancy rate per couple after ICSI						
Baccetti 2004	8	24	4	20	100.0%	1.93 [0.52, 7.20]
Subtotal (95% CI)		**24**		**20**	**100.0%**	**1.93 [0.52, 7.20]**
Total events	8		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
1.2.3 Pregnancy rate per couple after IUI						
Matorras 1997	8	68	9	80	100.0%	1.05 [0.38, 2.89]
Subtotal (95% CI)		**68**		**80**	**100.0%**	**1.05 [0.38, 2.89]**
Total events	8		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						

Test for subgroup differences: $Chi^2 = 5.49$, df = 2 (P = 0.06), $I^2 = 63.5\%$



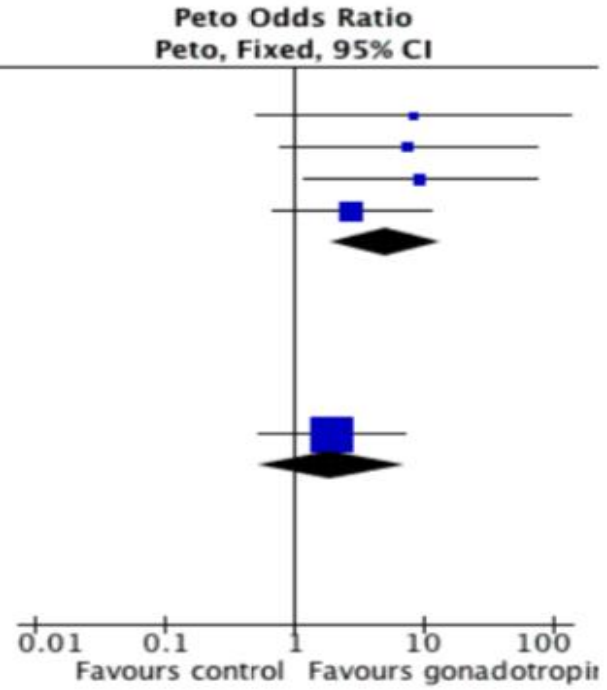
Attia AM, et al. Cochrane Database Syst Rev 2013;8:CD005071

Pregnancy rate (no female factor)

Figure 2. Forest plot of comparison: 1 Gonadotrophins versus placebo/no treatment for the treatment of idiopathic male subfertility, outcome: 1.3 Subgroup analysis: pregnancy rate per couple randomly assigned with no female factor.

Study or Subgroup	Gonadotrophins Events	Total	Control Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.3.1 Spontaneous pregnancy rate per couple with no female factor						
Knuth 1987	2	19	0	20	12.2%	8.23 [0.50, 136.74]
Kamischke 1998	3	34	0	33	18.2%	7.63 [0.77, 76.00]
Paradisi 2006	4	15	0	15	22.4%	9.31 [1.17, 73.75]
Foresta 2005	6	65	2	63	47.2%	2.79 [0.67, 11.61]
Subtotal (95% CI)		**133**		**131**	**100.0%**	**5.00 [1.88, 13.34]**
Total events	15		2			
Heterogeneity: $Chi^2 = 1.24$, df = 3 (P = 0.74); $I^2 = 0\%$						
Test for overall effect: Z = 3.22 (P = 0.001)						
1.3.2 Pregnancy rate per couple after ICSI with no female factor						
Baccetti 2004	8	24	4	20	100.0%	1.93 [0.52, 7.20]
Subtotal (95% CI)		**24**		**20**	**100.0%**	**1.93 [0.52, 7.20]**
Total events	8		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						

Test for subgroup differences: $Chi^2 = 1.30$, df = 1 (P = 0.26), $I^2 = 22.8\%$



Attia AM, et al. Cochrane Database Syst Rev 2013;8:CD005071

Live birth rate (all studies)

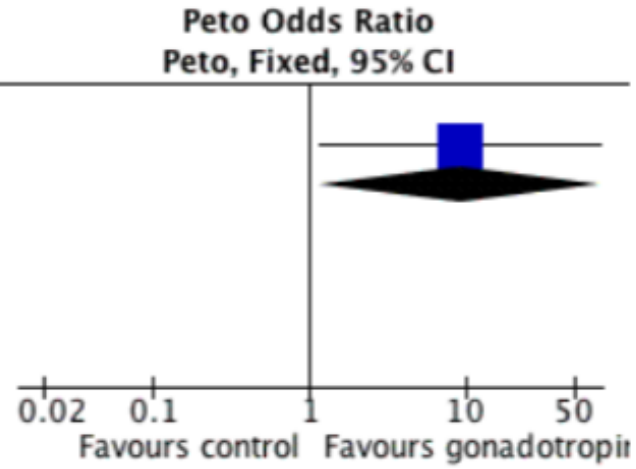
Figure 5. Forest plot of comparison: 1 Gonadotrophins versus placebo/no treatment for the treatment of idiopathic male subfertility, outcome: 1.1 live-birth rate per couple randomly assigned.

Study or Subgroup	Gonadotrophins Events	Total	Control Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.1.1 Live birth rate per couple						
Paradisi 2006	4	15	0	15	100.0%	9.31 [1.17, 73.75]
Subtotal (95% CI)		**15**		**15**	**100.0%**	**9.31 [1.17, 73.75]**
Total events	4		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.11 (P = 0.03)

Test for subgroup differences: Not applicable



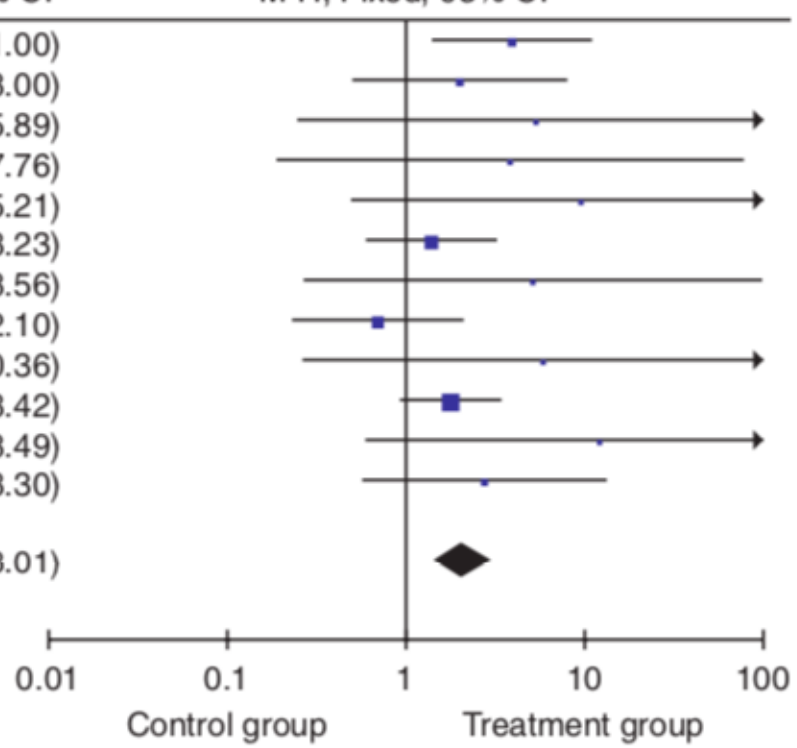
Attia AM, et al. Cochrane Database Syst Rev 2013;8:CD005071

Pregnancy rate (all studies)

A	FSH treatment		Control group			Odds ratio
Reference	Events	Total	Events	Total	Weight (%)	M-H, Fixed, 95% CI
(12)	18	39	7	39	9.0	3.92 (1.40, 11.00)
(14)	8	24	4	20	6.9	2.00 (0.50, 8.00)
(35)	2	31	0	31	1.1	5.34 (0.25, 115.89)
(36)	3	40	0	20	1.4	3.83 (0.19, 77.76)
(37)	7	23	0	10	1.1	9.55 (0.49, 185.21)
(39)	16	65	12	63	21.9	1.39 (0.60, 3.23)
(42)	4	57	0	30	1.4	5.13 (0.27, 98.56)
(13)	8	31	10	30	17.9	0.70 (0.23, 2.10)
(43)	2	19	0	20	1.0	5.86 (0.26, 130.36)
(44)	36	68	31	80	31.9	1.78 (0.92, 3.42)
(16)	4	15	0	15	0.9	12.13 (0.59, 248.49)
(45)	10	70	2	35	5.4	2.75 (0.57, 13.30)
Total (95% CI)		482		393	100.0	2.09 (1.46, 3.01)
Total events	118		66			

Heterogeneity: $\chi^2=10.09$, df=11 ($P=0.52$); $I^2=0\%$

Test for overall effect: $Z=3.99$ ($P<0.0001$)



Santi D, et al. Endocr Connect 2015;4:R46–R58

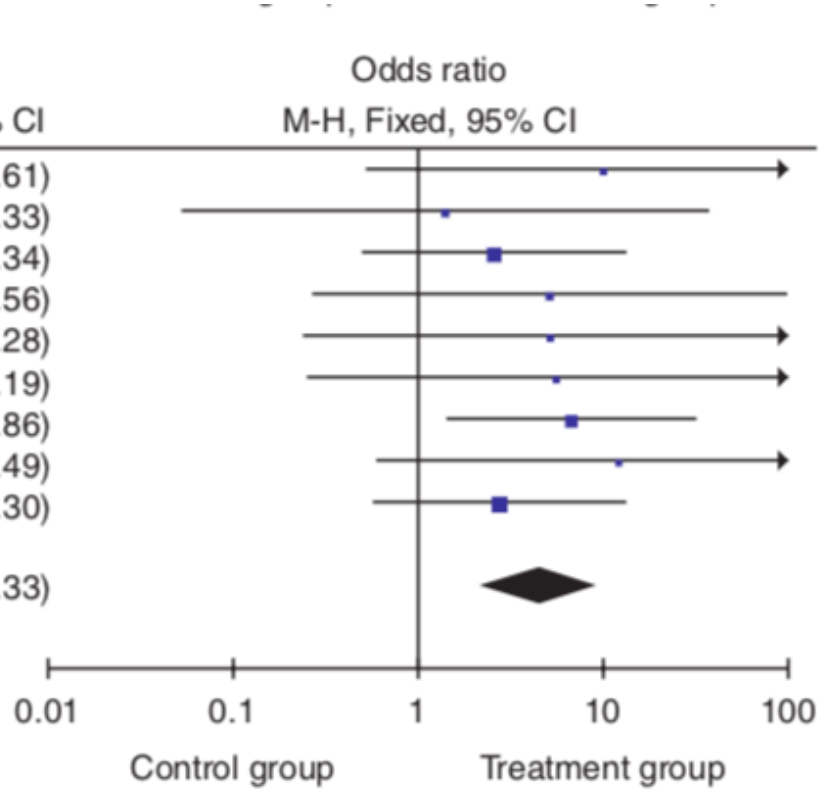
Pregnancy rate (spontaneous conceptions)

B

Reference	FSH treatment Events	Total	Control Events	Total	Weight (%)	Odds ratio M-H, Fixed, 95% CI
(12)	4	39	0	39	5.0	10.01 (0.52, 192.61)
(37)	1	23	0	10	7.3	1.40 (0.05, 37.33)
(39)	6	62	2	50	22.7	2.57 (0.50, 13.34)
(42)	4	57	0	30	6.8	5.13 (0.27, 98.56)
(13)	2	31	0	30	5.3	5.17 (0.24, 112.28)
(43)	2	19	0	19	5.0	5.57 0.25, 124.19)
(44)	10	68	2	80	17.8	6.72 (1.42, 31.86)
(16)	4	15	0	15	4.1	12.13 (0.59, 248.49)
(45)	10	70	2	35	26.0	2.75 (0.57, 13.30)
Total (95% CI)		384		308	100.0	4.50 (2.17, 9.33)
Total events	43		6			

Heterogeneity: $\chi^2=2.29$, df=8 ($P=0.97$); $I^2=0\%$

Test for overall effect: $Z=4.04$ ($P<0.0001$)



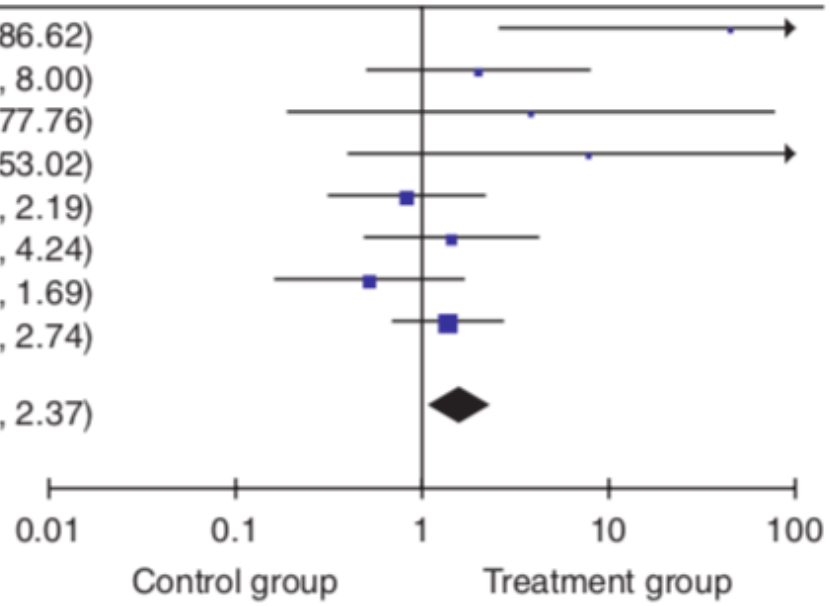
Santi D, et al. Endocr Connect 2015;4:R46–R58

Pregnancy rate (ART conceptions)

C	FSH treatment		Control			Odds ratio	Odds ratio
Reference	Events	Total	Events	Total	Weight (%)	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
(12)	14	39	0	39	0.8	44.92 (2.57, 786.62)	
(14)	8	24	4	20	7.2	2.00 (0.50, 8.00)	
(36)	3	40	0	20	1.5	3.83 (0.19, 77.76)	
(37)	6	23	0	10	1.2	7.80 (0.40, 153.02)	
(39)	10	56	10	48	22.0	0.83 (0.31, 2.19)	
(42)	14	53	6	30	14.0	1.44 (0.49, 4.24)	
(13)	6	29	10	30	19.4	0.52 (0.16, 1.69)	
(44)	26	58	29	78	33.9	1.37 (0.69, 2.74)	
Total (95% CI)		322		275	100.0	1.60 (1.08, 2.37)	
Total events	87		59				

Heterogeneity: $\chi^2=12.22$, df=7 ($P=0.09$); $I^2=43\%$

Test for overall effect: $Z=2.36$ ($P=0.02$)



Santi D, et al. Endocr Connect 2015;4:R46–R58

Which?

Which patients are likely to respond to therapy?

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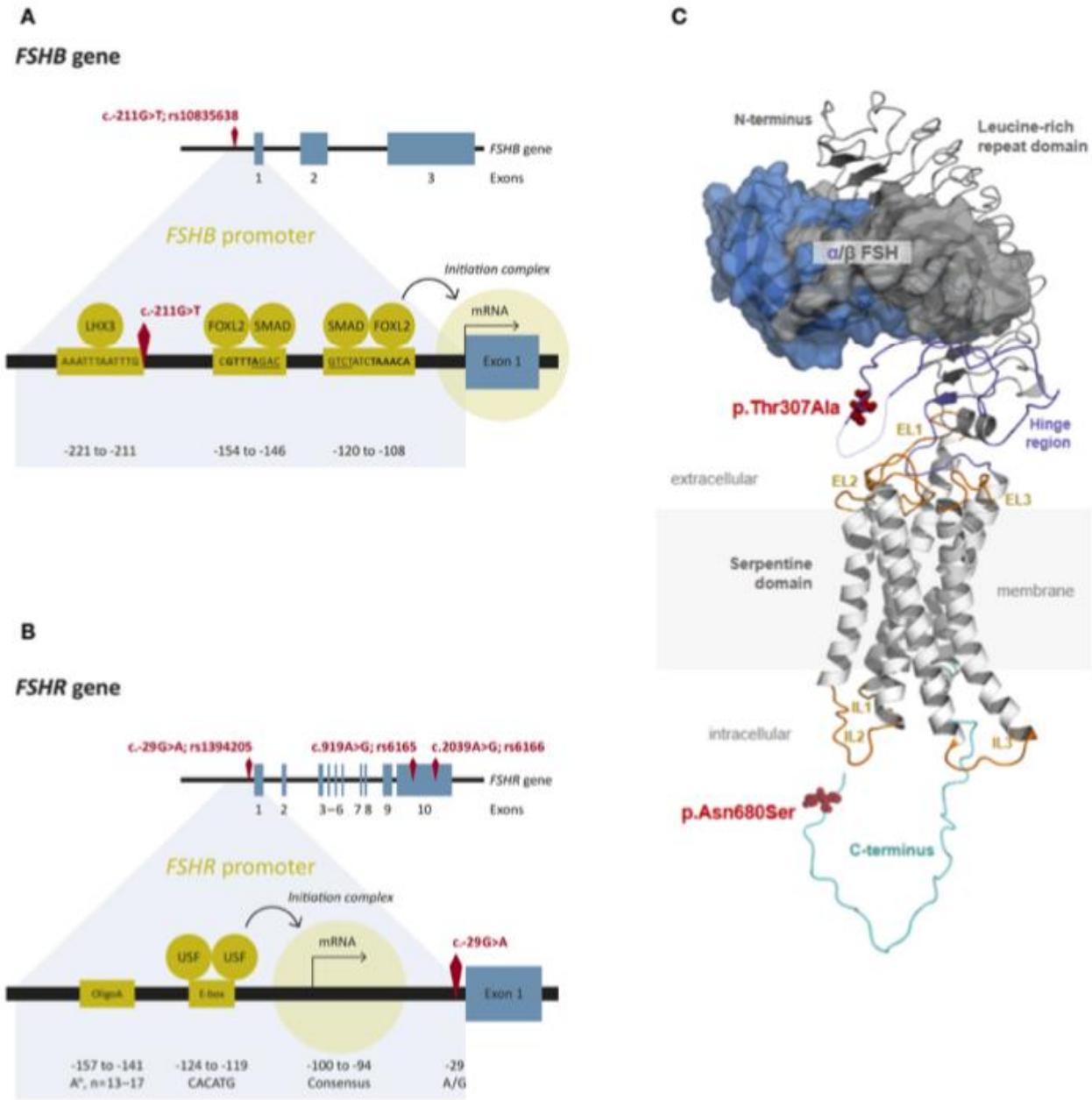
Aristotle University of Thessaloniki

Predictors of response to therapy

- Basal FSH concentrations
- DNA fragmentation
- Genes



Schubert M, et al. Front Endocrinol 2019;10:47

Single Nucleotide Polymorphisms (SNPs)

Gene	SNP ID	DNA nucleotide	Protein	Minor allele frequency (32)
FSHB	rs10835638	c.-211G>T	Promoter, non-coding	T = 0.0839
FSHR	rs1394205	c.-29G>A	Promoter, non-coding	T = 0.3450
FSHR	rs6165	c.919A>G	p.Thr307Ala	T = 0.4922
FSHR	rs6166	c.2039A>G	p.Asn680Ser	C = 0.4073

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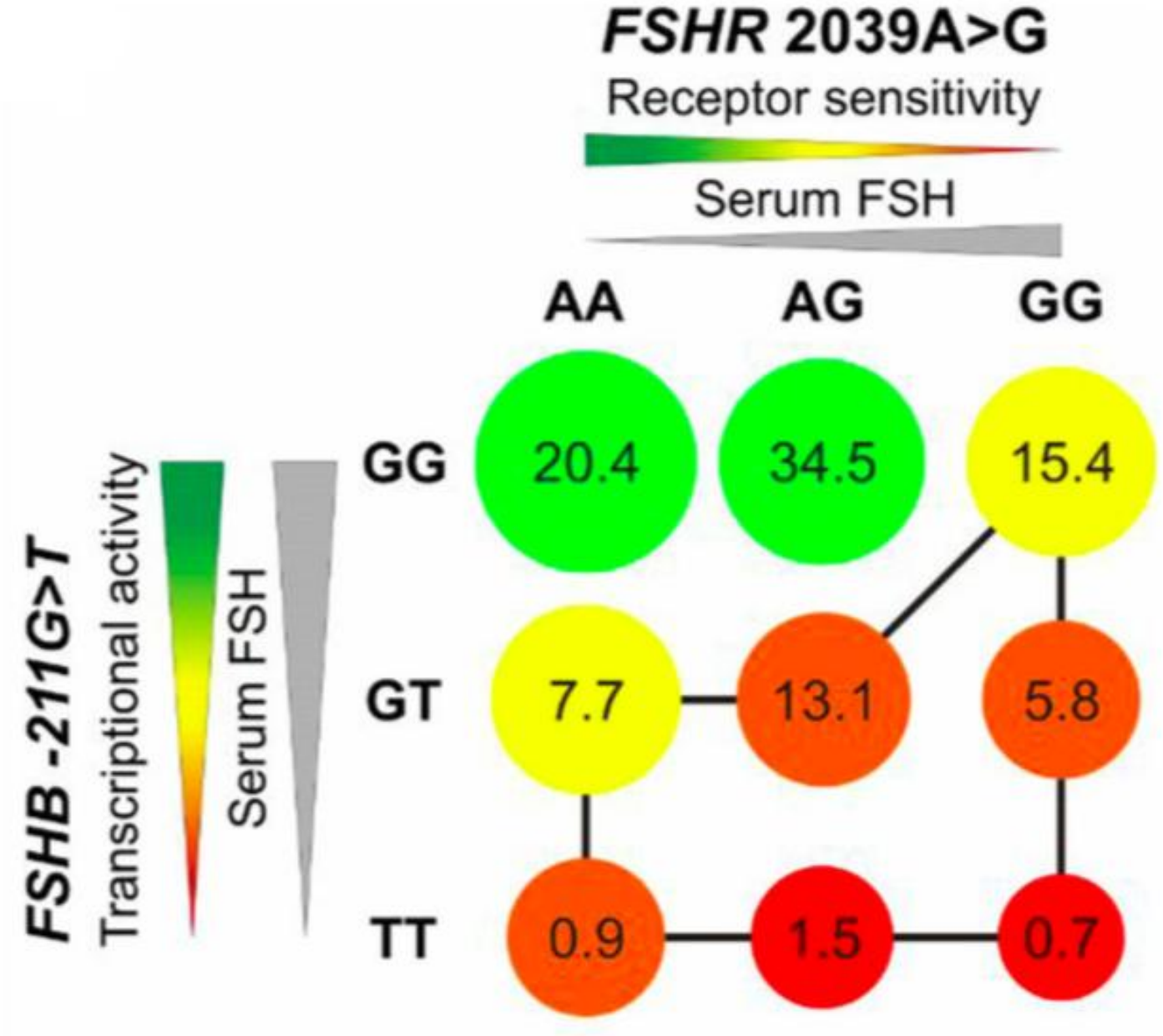

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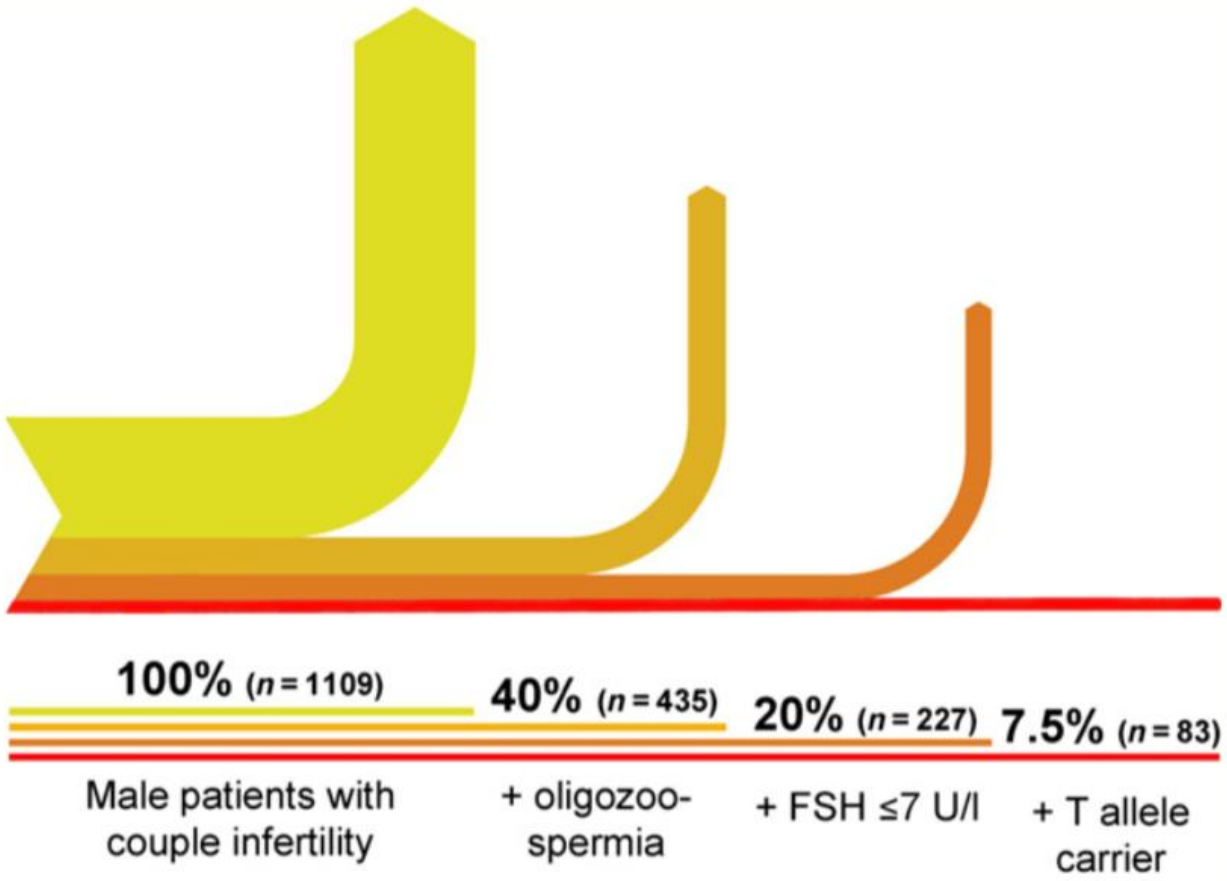
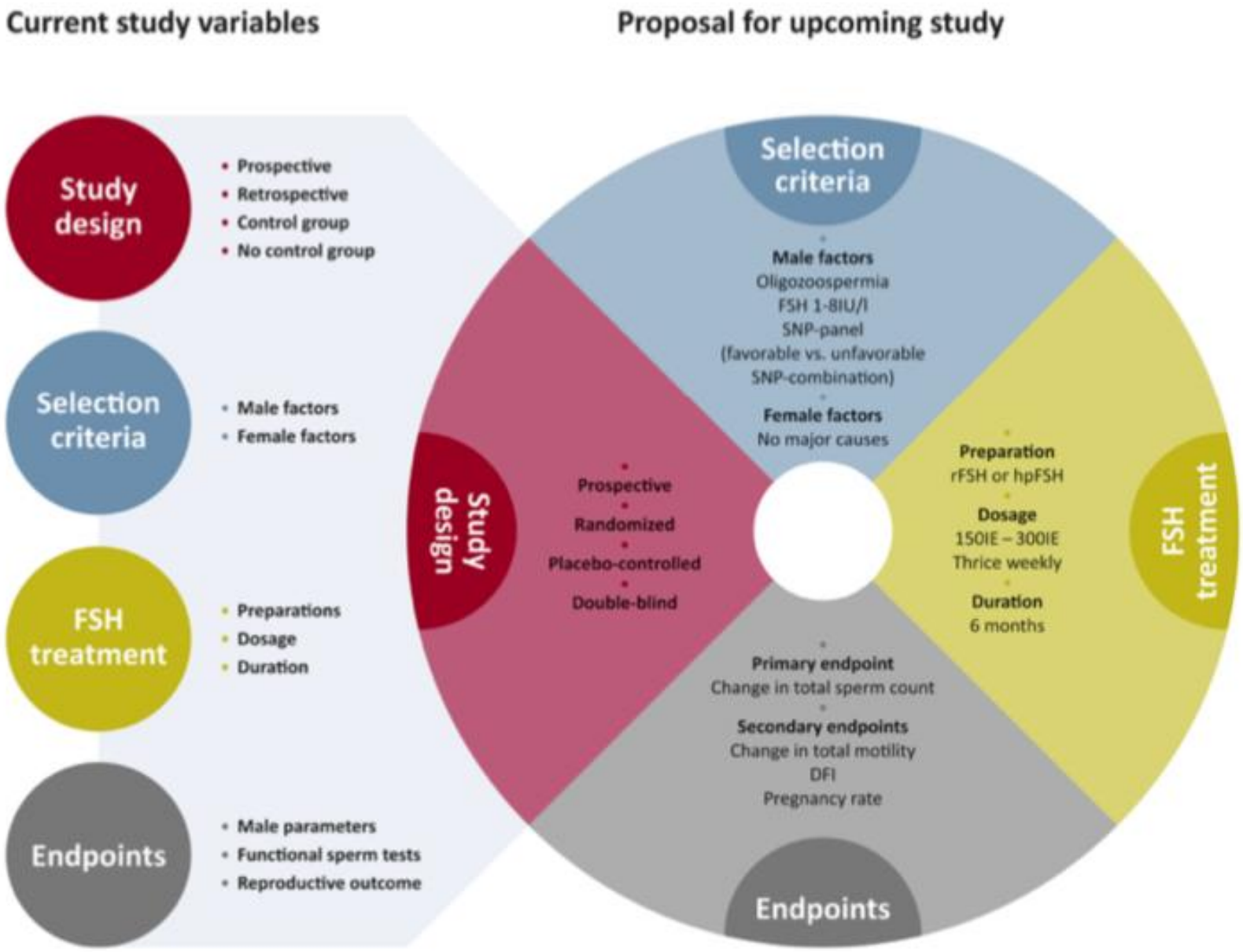
A pharmacogenetic approach



Busch AS, et al. Andrology 2015;3:1050



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How?

How can we conclude?

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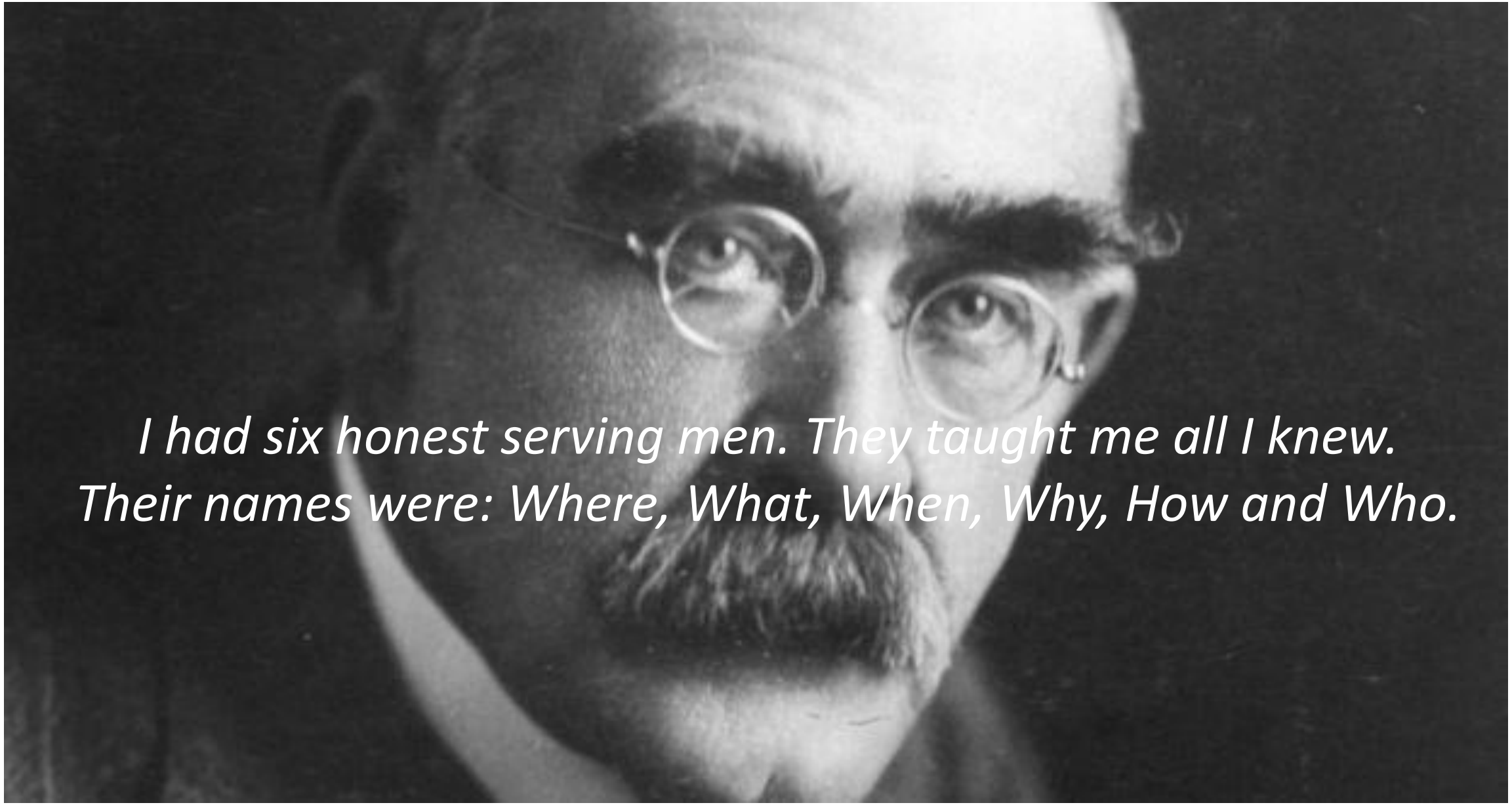
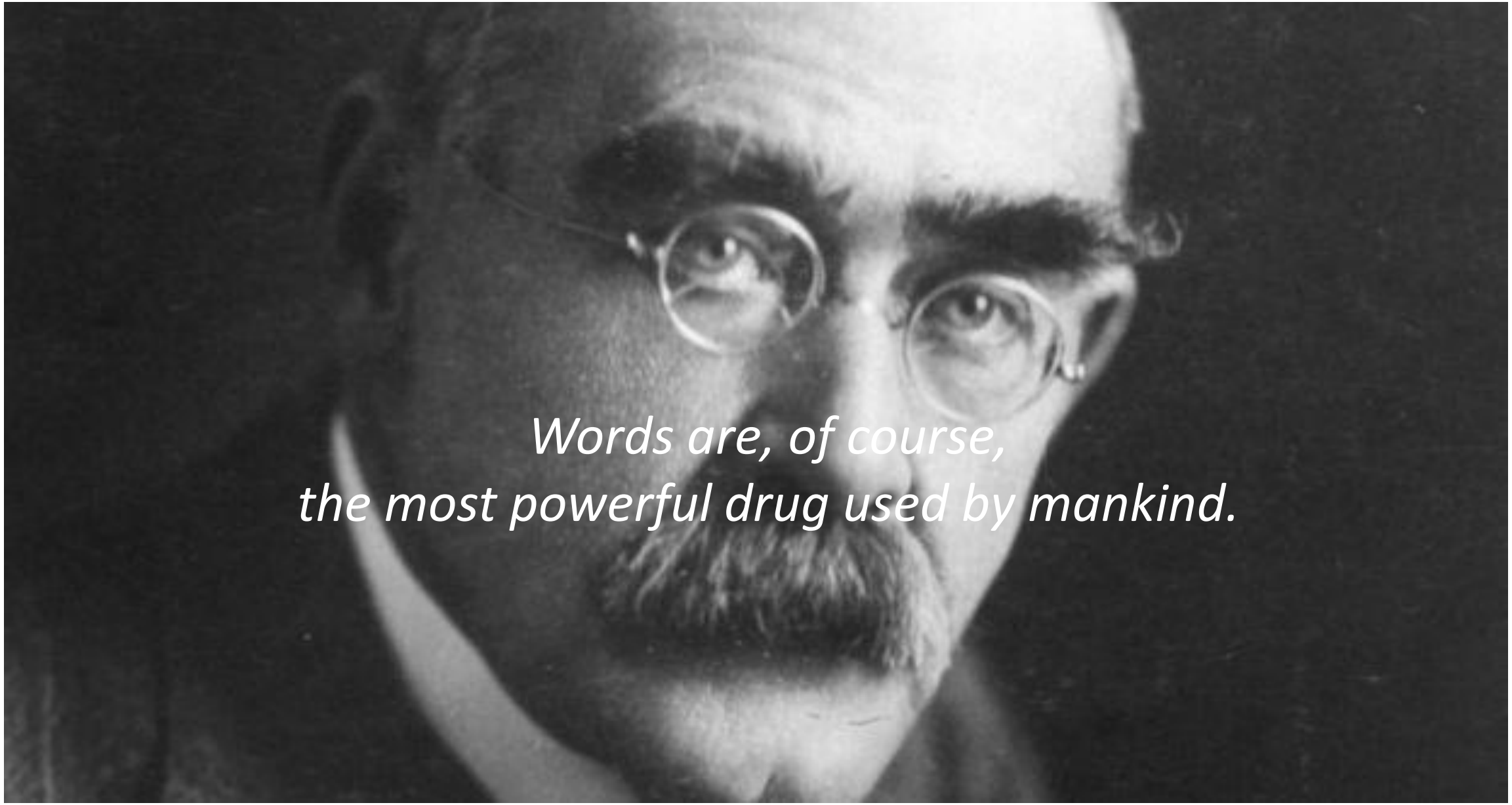
Aims

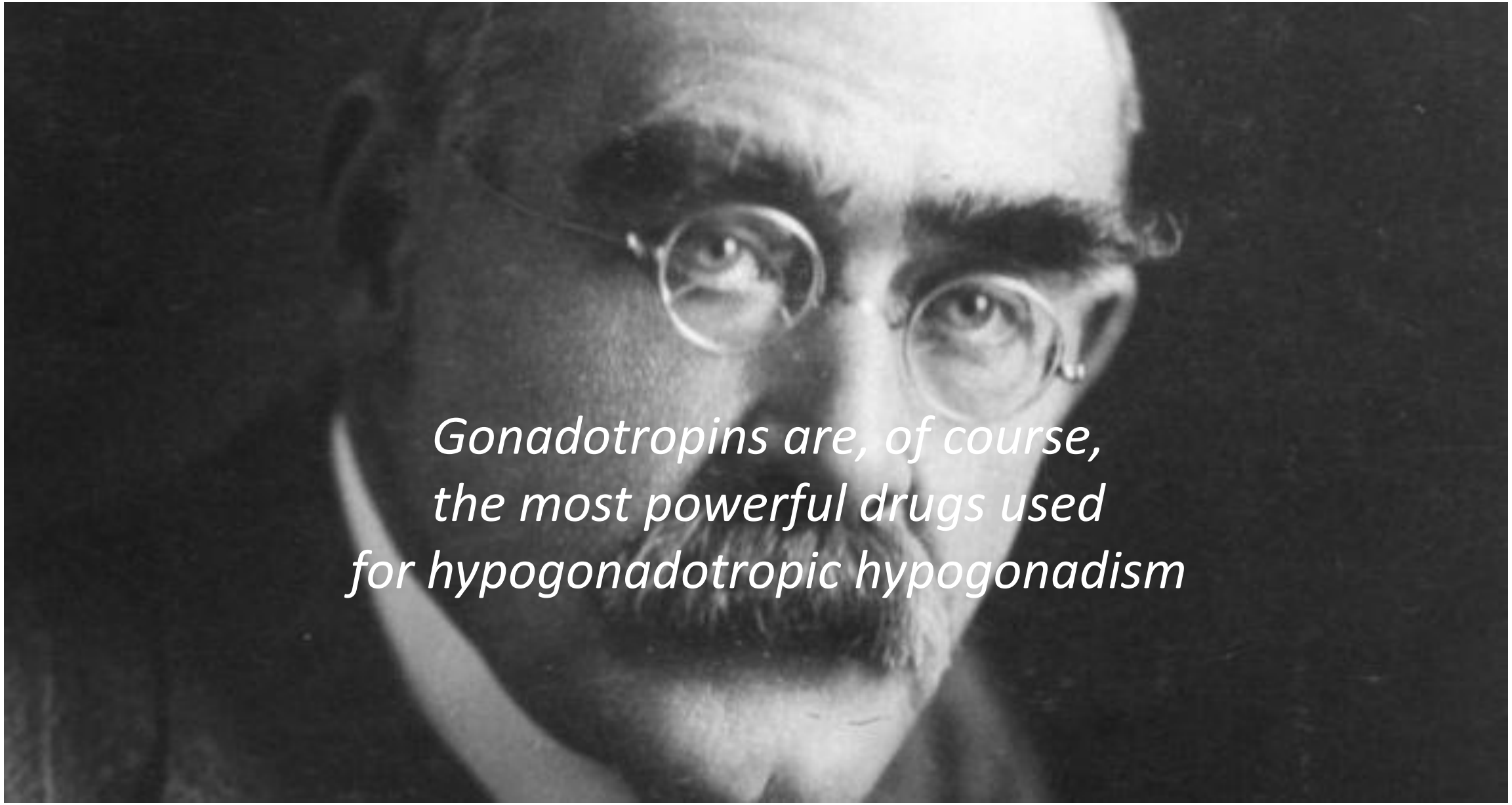
- Gonadotropins for induction of spermatogenesis
- Gonadotropins for idiopathic infertility



Rudyard Kipling (1865 - 1936)



Rudyard Kipling (1865 - 1936)



Rudyard Kipling (1865 - 1936)

If—

BY RUDYARD KIPLING

('Brother Square-Toes'—Rewards and Fairies*)*

If you can keep your head when all about you
  Are losing theirs and blaming it on you,
If you can trust yourself when all men doubt you,
  But make allowance for their doubting too;
If you can wait and not be tired by waiting,
  Or being lied about, don't deal in lies,
Or being hated, don't give way to hating,
  And yet don't look too good, nor talk too wise:

If you can dream—and not make dreams your master;
  If you can think—and not make thoughts your aim;
If you can meet with Triumph and Disaster
  And treat those two impostors just the same;
If you can bear to hear the truth you've spoken
  Twisted by knaves to make a trap for fools,
Or watch the things you gave your life to, broken,
  And stoop and build 'em up with worn-out tools:

If you can make one heap of all your winnings
  And risk it on one turn of pitch-and-toss,
And lose, and start again at your beginnings
  And never breathe a word about your loss;
If you can force your heart and nerve and sinew
  To serve your turn long after they are gone,
And so hold on when there is nothing in you
  Except the Will which says to them: 'Hold on!'

If you can talk with crowds and keep your virtue,
  Or walk with Kings—nor lose the common touch,
If neither foes nor loving friends can hurt you,
  If all men count with you, but none too much;
If you can fill the unforgiving minute
  With sixty seconds' worth of distance run,
Yours is the Earth and everything that's in it,
  And—which is more—you'll be a Man, my son!

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Professor emeritus J. Papadimas

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C. Dimopoulou (endocrinologist)
E. Kintiraki (endocrinologist)
S. Paschou (endocrinologist)
P. Anagnostis (endocrinologist)
I. Litsas (endocrinologist)
I. Koutsogiannis (urologist)
A. Kouthouris (urologist)
G. Kanakis (endocrinologist)
G. Mintziori (endocrinologist)
A. Mousiolis (endocrinologist)
E. Billa (endocrinologist)
K. Papadimitriou (endocrinologist)
V. Harizopoulou (midwife)
E. Tsirou (endocrinologist, dietician)
E. Taousani (midwife)
D. Savvaki (physical education)
M. Grammatikopoulou (dietician)
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