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Changes in hormonal profile and seminal parameters with use of aromatase inhibitors in management of infertile men with low testosterone to estradiol ratios

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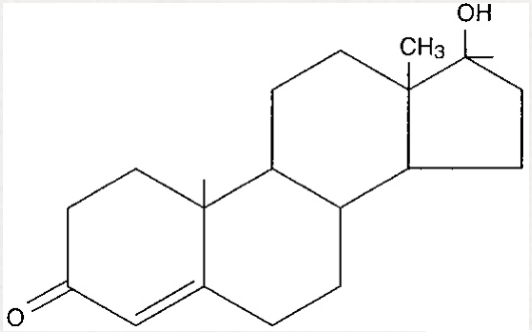
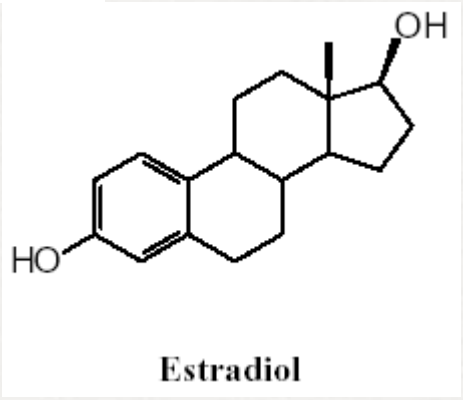
INTRODUCTION

Aromatase

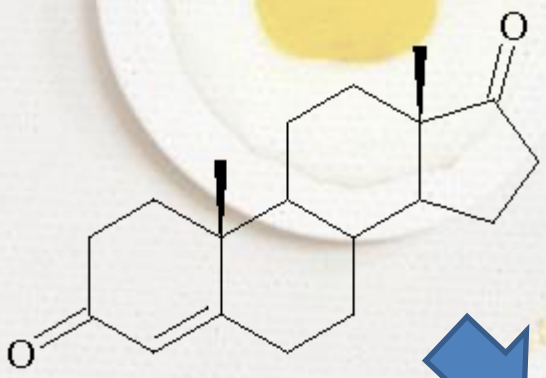
- ✓ Cytochrome p450 enzyme
- ✓ In the ovaries, testis, adipose tissue, brain

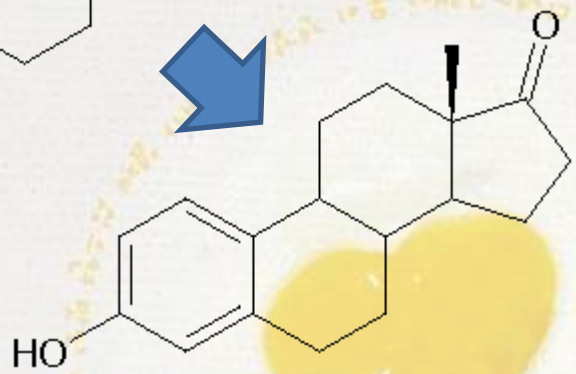
Testosterone → E2





Androstenedione → Estrone





Aromatase inhibitors

- Interact with aromatase enzyme in Estrogens-secreting tissues

  →Preservation of **T level**

  →Limiting **Estrogens** production
- Widely used for endocrine **treatment** of:
  - Endometriosis, uterine leiomyomata
  - Endometrial & breast cancers
  - Impaired sperm production, ovulation induction

Previous study

- Men with normal gonadotropins and **idiopathic oligospermia**
  → Treated with aromatase inhibitors
  → Improved semen quality

This study

- Prospective, randomized trial
- Subset of infertile men with low T/E2 ratios
- 2.5 mg Letrozole ⇔ 1 mg Anastrazole daily
- Effect on the Hormonal & semen profiles

- Letrozole: Nonsteroidal, selective, potent 3rd generation aromatase inhibitor
- Anastrazole: Nonsteroidal agent, 4th generation of aromatase inhibitors

Inhibiting Aromatization

- Blocking estrogen production
  → Conversion of androstenedione & T → estrogen

- **Hypo**estrogenic state
  → Release the hypothalamic–pituitary axis from estrogenic negative feedback
  → Lead to ↑ FSH secretion and to the development of sperm production

MATERIALS AND METHODS

- Aretaieion Hospital, Athens
- March 2008 ~ July 2011
- Prospective, non randomized study
- 29 infertile men with a low serum T/E2 ratio (<10)
  - Group A: 15 x → 2.5 mg letrozole orally, QD x 6m
  - Group B: 14 x → 1 mg anastrazole orally, QD x 6m
  - *Monitor Liver function testsevery month*
- Serum hormones & semen parameters: Compare the beginning & the end of treatment

Patient Selection and data collection

- Thorough history, physical examination
- No therapeutic regimen for at least 3 months before the study, except occasional use of analgesics (e.g., paracetamol)
- Inclusion criteria:
  - Sperm concentrations < 1 x 10^6 spermatozoa/Ml
  - T/E2 ratio <10
  - T levels <300 ng/dL

Semen analyses

- Semen sample: Masturbation after 2–4 days of sexual abstinence, processed within 1 hour of ejaculation

- In the same andrology lab. according to WHO criteria

- Other information
  - Volume of ejaculate (in ml)
  - Sperm concentration (in millions /ml)
  - Motility (%)

Serum hormonal evaluation

- FSH, LH, T, E2, PRL, TSH
  - Blood samples in the early morning, 7:00 ~ 8:00 AM
  - Commercially available kit (Vidas, bioMerieux)

Reference ranges of the assays	
FSH	0.1–110 mIU/MI
LH	0.1–100 mIU/mL
E2	9–3,000 pg/mL
T	0.1–13 ng/mL
PRL	0–200 ng/mL
TSH	0–60 mIU/mL

- Testicular volume: ultrasound (length x height x width x 0.71)
- Karyotype analysis:
  - Y chromosome microdeletion & patients with a total sperm count < 1 x 10^6 → genetic analysis for cystic fibrosis
  - Exclusion: Abnormal karyotype or Y chromosome microdeletion

Idiopathic oligozoospermia

1. [FSH] within the normal range of reference values
2. Average value from the 2 most recent semen analyses < normal (WOH classification)
3. Absence of any abnormality that could be responsible for the impaired semen values: infection, trauma, autoimmunity, varicocele, epididymal factor
4. Negative results of the hormonal & other investigations

Total functional sperm fraction (TFSF, x 10^6)

- An overall index of seminal quantity & quality
- Includes quantitative & qualitative factors of the semen
- Calculated by multiplying the sperm count (10^6) by motility (%) and by normal morphology (%)
- Comparison from pretreatment to post treatment

Statistically analysis

- Medcalc statistical software (version 12.0.4.0)
- Mean ± SE (standard error of mean)
- Student's t test to compare pre- and post treatment
  - Sperm parameters
  - Serum hormone levels
  - Testicular volumes
- $P < 0.05$ → statistically significant difference

RESULTS

Both drugs were well tolerated

- **Letrozole group**
  - No improvement: 4/15, 26.6%
  - 1 x asymptomatic mild ↑ serum GOT/GPT, transient → medication was continued
  - 2 x transient weakness, 1 x nausea lasted for 10 days, 2 x mild headache

Both drugs were well tolerated

- **Anastrazole group**
  - No improvement: 3/14, 21.4%
  - 2 x asymptomatic ↑ serum GPT
  - 1 x mild diarrhea (at 1 month of use)
    →lasted for 3 days
    →subsided on its own without further sequelae
  - 2 x transient nausea and
  - 1 x mild headache

Group A (Letrozole)

Results of semen analysis and hormonal tests before and after 6 months of treatment with letrozole 2.5 mg/d.

Parameter	Before treatment	After treatment	*P* value
Body mass index (kg/m^2)	29.86 ± 2.53	30.1 ± 2.13	>.05
Testicular volume (mL)	14.89 ± 4.32	15.01 ± 4.30	.94
Serum FSH (mIU/mL)	8.35 ± 2.03	8.41 ± 1.95	.93
Serum LH (mIU/mL)	9.55 ± 1.84	9.28 ± 1.80	.69
Serum T (ng/dL) ↑	275 ± 29	495 ± 65	<.001
Serum E_2 (pg/mL) ↑	26.7 ± 1.75	14.98 ± 2.58	<.001
T/E_2 ratio ↑	9 ± 0.2	36 ± 4.5	<.001
Ejaculate volume (ml) ↑	2.85 ± 0.36	3.35 ± 0.20	.005
Sperm count ($\times 10^6$) ↑	3.5 ± 1.43	5.19 ± 1.62	.001
Motility (%) ↑	11.05 ± 2.48	22.13 ± 4.37	.001
TFSF[a] ($\times 10^6$) ↑	1.71 ± 0.87	2.51 ± 1.09	.013

Group B (Anastrazole)

Results of semen analysis and hormonal tests before and after 6 months of treatment with anastrazole 1 mg/d.

Parameter	Before treatment	After treatment	*P* value
Body mass index (kg/m^2)	30.14 ± 3.1	30.0 ± 2.75	>.05
Testicular volume (mL)	13.65 ± 3.95	13.89 ± 3.42	.86
Serum FSH (mIU/mL)	8.35 ± 1.95	8.45 ± 1.93	.89
Serum LH (mIU/mL)	11.15 ± 1.58	11.01 ± 1.53	.81
Serum T (ng/dL) ↑	265 ± 25	513 ± 65	<.001
Serum E_2 (pg/mL) ↑	24.1 ± 2.01	15.15 ± 1.95	<.001
T/E_2 ratio ↑	8 ± 0.5	34 ± 5.9	<.001
Ejaculate volume (ml) ↑	2.40 ± 0.15	3.18 ± 0.52	<.001
Sperm count ($\times 10^6$) ↑	4.15 ± 3.38	8.9 ± 2.11	<.001
Motility (%) ↑	12.35 ± 3.89	22.85 ± 3.38	<.001
TFSF[a] ($\times 10^6$) ↑	1.91 ± 1.25	2.41 ± 1.06	.005

TFSF value comparison

(Total functional sperm fraction)

- Statistical comparison using Student's t test
- For independent samples (all samples follow normal distribution)
- Letrozole ⇔ Anastrazole group: No statistically significant difference
  - Value Before treatment (P = 0.62)
  - Value After treatment (P = 0.81)

☆ **Both groups are comparable with respect to TFSF before and after treatment**

TFSF value comparison

(Total functional sperm fraction)

- ↑ Average TFSF After treatment - pretreatment
  - Letrozole group: ↑ 31.6%
  - Anastrazole group: ↑ 21.1%

- Detect the statistically significant difference between above increasing value

  →Type I error 0.05/Type II error 0.20

  →273 patients are required in each group

DISCUSSION

- △ E2 within the male physiologic range
  → Significant change of LH
  (through an effect at the level of the pituitary gland)
- Aromatase inhibitor → ↓ E2 → ↑ LH, FSH, T
- FSH release:
  - Mainly under the control of inhibin
  - Circulating E2 has a strong effect in men

Aromatase inhibitor treatment

- *Earler study:*
  - Using Anastrozole or Testolactone → Positive action on sperm concentration & motility
- *Another study:*
  - Using testolactone → No significant improvement of sperm quality in men with oligospermia
- *Recent study:*
  - Idiopathic oligoasthenoteratozoospermia & ↓ T/E2
  - Anastrozole + Tamoxifen vs. Tamoxifen → ↑ pregnancy rate

Saylam et al.

- 27 infertile men with a low serum T/E2 ratio (<10)
- 2.5 mg letrozole orally QD > 6 months
  - T/E2 ratio, ejaculate volume, sperm motility, total motile sperm count (TMSC) significantly ↑
  - 10 x oligospermic men

    →2 x achieved spontaneous pregnancy
  - Azoospermia

    →23.5% presented spermatozoa in the ejaculate

    →76.5% remained azoospermic

Patry et al.

- One 31-year-old man with primary infertility, normal serum FSH levels, and pattern of **non obstructive azoospermia**

➔Aromatase inhibitor letrozole orally for up to 4 months

➔Final testicular biopsy: normal spermatogenesis

Raman et al.

- 140 sub fertile men with abnormal **T/E2 ratios**

→**Testolactone 100–200 mg** or **anastrazole 1 mg** daily

- Comparison of the efficacy of these two therapies on both hormonal and semen parameters: **similar effects**

Others Published data

- In Klinefelter's syndrome patients

  →Aromatase inhibitors before testicular sperm extraction → with favorable results

- In patients having oligospermia

  →Clomiphene citrate → Azoospermia

  – Not used in these patients

- Many infertile men with severe oligospermia

  – Can exhibit a ↓ T/E2 ratio → Aromatase inhibitor

  →Normalize values & improve semen quality

The present study

- Some men with
  - Severe oligospermia (<5x10^6/mL)
  - Low T levels (<300 ng/dL)
  - T (ng/dL) to E2 (pg/mL) ratio <10
  - Normal gonadotropins concentration

  →may have a treatable **endocrinopathy**

Endocrine evaluation

- Estimation of E2
- Calculation of the T (ng/dL) to E2 (pg/mL) ratio
  - <10 → might benefit from aromatase inhibitor → Improve T levels & possibly the seminal parameters

Aromatase inhibitor treatment

Letrozole ⇔ Anastrazole

- Efficacy of improving the seminal parameters: similar
  - Nonresponse rate: 26.6% ⇔ 21.4%
  - T levels & T/E2 ratio → Improved in all patients (so that control arm was not used)
- Side effects
  - Both well tolerated & subsided with time
  - No significant difference in the incidence and severity of side effects between the two groups

- Both anastrazole and letrozole
  - Are equally effective in the improvement of T levels and seminal parameters
  - In patients with severe oligospermia (<5 x 106/mL), low T levels (<300 ng/dL), and a T (ng/dL) to E2 (pg/mL) ratio <10
  - Presented side effects are mild, well tolerated, and subside with the time

Long-term use

- In men: no available data
- Postmenopausal women with breast cancer
  - At 5 years of use of letrozole
  - Main potential concerns: risk of osteoporosis
    - Letrozole vs. placebo:
      - Reporting osteoporosis: 6.9% vs. 5.5%
      - Bisphosphonates (↑bone strength) use: 21.1% vs. 18.7%
  - Possible mild ↑ cholesterol levels

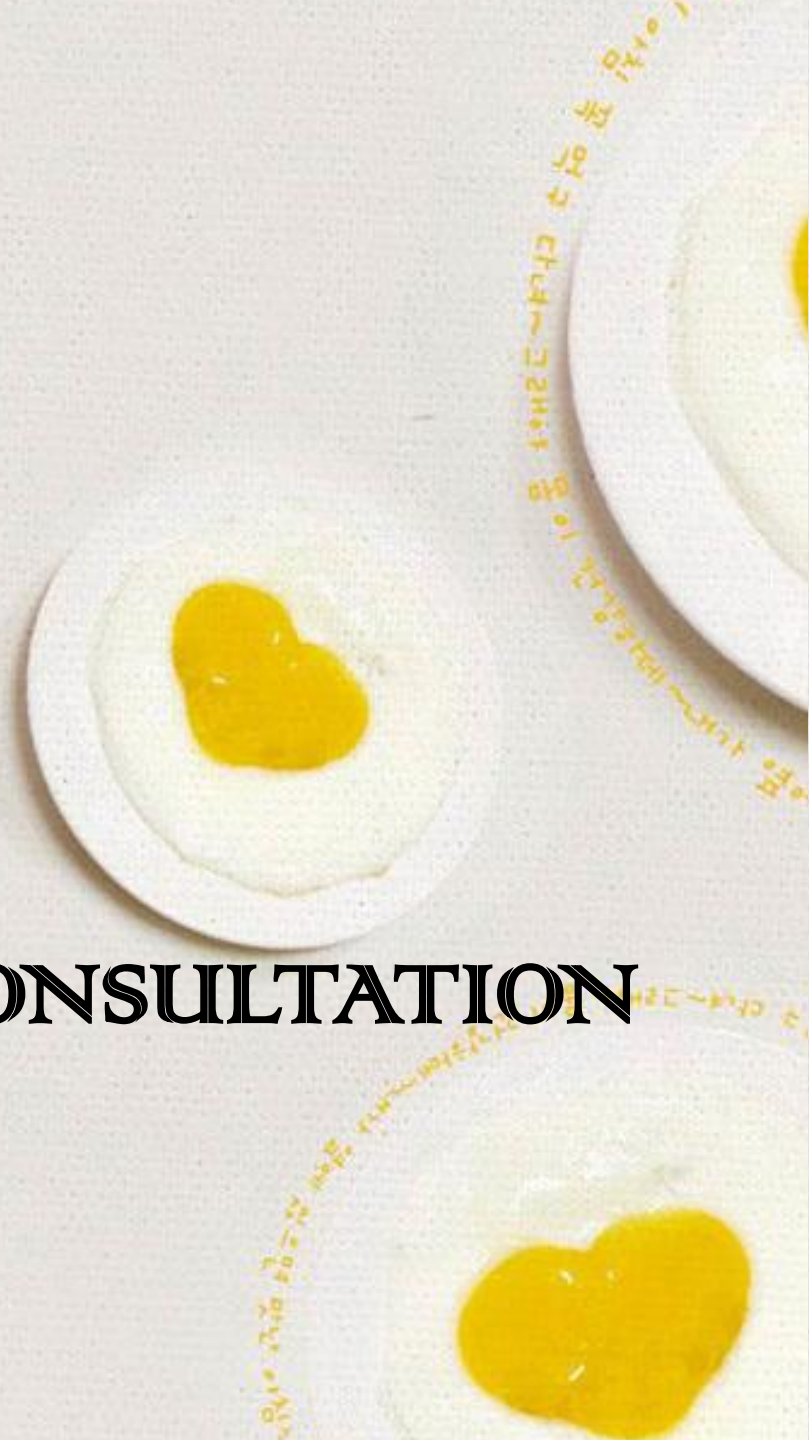
Possible limitations

- Relatively small numbers of participating patients in each group

- No data about Rates of IUI/IVF & Pregnancy outcomes
  - Pregnancy achievement rates → Clinical significance of the improvement of semen parameters

- A control arm was not used → in the study given the previously published reports describing benefit of aromatase inhibition in men with E2/T ratios >10:1

- Need further prospective, randomized, blinded, placebo controlled studies → clarify the role of aromatase inhibitors in the management of male infertility



THANK YOU FOR CONSULTATION