Combination clomiphene citrate and antioxidant therapy for idiopathic male infertility: a randomized controlled trial

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Introduction

- **Male infertility**
  - alone responsible for 30% of couple infertility
  - + female factor contribute to additional 20%

- Empirical medical treatment for idiopathic male factor infertility is a ***controversial*** issue.

Medical treatment

- FSH
- **antiestrogen**
- L-carnitine
- **antioxidants**

antiestrogen therapy

- yield pregnancy rate 20-40% following 6-9 months of therapy
- commonly used for idiopathic oligozoospermia and/or asthenozoospermia
- interfere with normal negative feedback →↑GnRH, FSH, LH → stimulating spermatogenesis

- Whether there is also an additional ***direct effect*** on spermatogenesis or steroid genesis at the testicular level ? ***– uncertain***

- **Clomiphene citrate** (25 mg daily) and **tamoxifen** (20 or 30 mg daily)
  - ***predominant antiestrogen effect***
  - Tamoxifen is favored (∵ has weaker estrogenic effect which can possibly suppress spermatogenesis in higher dose)
  - usually administered for 3-6 months (spermatogenic cycle ≒ 75 days)

antioxidant therapy

- Oxidative stress precipitates pathologic conditions thought to affect male reproductive system.
- ROS mediated damage to sperm plasma membrane may account for defective sperm functions observed in a higher proportion of infertility patients.

- High level of ROS in semen have been correlated with reduced sperm motility and damage to sperm nuclear DNA.

- vit C, vit E, astaxanthin, glutathion, Q10 *(reported to be benefit to male infertility)*, carnitine, arginine, Zn, selenium, vit B12

- no well-defined therapeutic protocol in male infertility and some suggesting combination

objective

- to assess the effect of treatment with combination of clomiphene citrate (as antiestrogen) and vit E (as antioxidant) on incidence of pregnancy and sperm variables in men with idiopathic oligozoospermia and infertility

Materials and Methods

- Design: prospective, randomized, double-blind, placebo-controlled
- Setting: Cairo University Hospital, andrology outpatient clinic
- Patients: 60 infertile men
  - Age: 20-40 y/o (31.8 ± 8.1 years)
  - Mean duration of infertility: 4.5 years (min. of 1 year)
  - Primary infertility (86%); secondary infertility (14%)

Inclusion criteria

- *unexplained* oligoasthenozoospermia
  - Sperm concentration < 20 x 10^6 repeatedly
  - Sperm total motility < 50%
  - Sperm forward progressive motility < 25%
  - Normal sperm morphology > 30%

Exclusion criteria

- known etiology
- apparent physical finding
- leukocytospermia
- ↓testicular volume
- varicocele (by clinical exam or sonography)
- abnormal FSH
- Couples with combined male and female factors

- reviewed and approved by IRB
- no conflict of interest
- informed consent
- clinical evaluation
  - history, PE and genital exam
  - ♂ : semen analysis, U/A, expressed prostatic secretion, serum FSH, total T and scrotal duplex
  - ♀ : ovulation observation, hormone profile, pelvic ultrasound, HSG, cervical mucus exam ➔ *only couples with no female factor infertility included*

- Interventions: ***randomly*** *assigned to*
  - placebo (n = 30)
  - Clomiphene citrate (25 mg/day) + vit E (400 mg/day) (n = 30)
  - treatment continued for 6 months

- Outcomes
  - primary – incidence of pregnancy
  - secondary – main sperm variables (*)

(*) semen analysis performed at least twice before and at the end of treatment

Results

- Age
  - mean age of patients : 31.8 ± 8.1 years
  - mean age of partners : 25.5 ± 5.4 years
  - comparable between two groups
- Average infertility duration : 4.5 years

TABLE 1

Comparison between combination therapy group and placebo group regarding the incidence and timing of pregnancy.

	Active treatment	Placebo
Cases	30	30
Pregnancies (1–3 mo)	4	3
Pregnancies (3–6 mo)	7	1
Total pregnancies	11 (36.7%, $P = 0.037$)	4 (13.3%)

Ghanem. Combination therapy for male infertility. Fertil Steril 2010.

- Odds ratio (OR) = 3.76 (95% CI, 1.03-13.64)
- groups differed significantly at 6 months of tx

TABLE 2

Effect of combination therapy versus placebo on semen parameters.

Group	Semen parameters before treatment: Volume (mL)	Count ($\times 10^6$)	TM (%)	FPM (%)	ABF (%)	Semen parameters after treatment: Volume (mL)	Count ($\times 10^6$)	TM (%)	FPM (%)	ABF (%)
Combined (n = 30)										
Min	1	2	10	0	25	1	1	0	0	15
Max	6.5	18	70	20	85	5.5	60	70	40	80
Mean	2.6	10.2	33	4	41	2.8	18[a]	34	7[b]	38
SD	1.34	4.14	19	6	16	1.2	15	21	10	18
Placebo (n = 30)										
Min	1	3	10	0	13	1.5	5	10	0	20
Max	6	19	70	30	80	5	25	60	30	90
Mean	2.7	11.3	30	5	41	3.2	12	24	2	51
SD	1.0	7.13	18	7	15	1.4	8.6	16	3	14

Note: TM = total motility; FPM = forward progressive motility; ABF = abnormal forms.

[a] $P = 0.0025$.

[b] $P = 0.0286$.

Unremarkable change

Ghanem. Combination therapy for male infertility. Fertil Steril 2010.

Discussion

- Clomiphene citrate + vit E for men with idiopathic infertility
  - ***safe***
  - ***inexpensive***
  - ***easy to administer***

- combination therapy for male infertility evaluated by other investigator
- obstacle in conducting RCT using combination therapy – no industry support

- Effectiveness of combined tamoxifen citrate and testosterone undecanoate treatment in men with idiopathic oligozoospermia.

  Fertil Steril 2003;80:914–20

- 212 pts with treatment for 6 months
- incidence of spontaneous pregnancy:
  - active treatment group (33.9%)
  - placebo group (10.3%)
  - OR of 3.195 (95% CI, 2.615–3.765)
  - most occurred between 4–6 months of treatment

- Combined conventional antioxidant "Astaxanthin" treatment for male infertility: a double blind, randomized trial.

Asian J Androl 2005;7: 257–62

- 30 men with tx for 3 months
- Astaxanthin (16 mg/day)
- total pregnancy rates:
  - placebo group (10.5%)
  - Astaxanthin group (54.5%)(P=0.028)

- A recent review assessing evidence-based treatment for make infertility elucidated several methodological difficulties.
  - ***short duration***
  - ***limited sample size***
  - ***patient selection***

- short duration
  - diagnosis of infertility > 1 year
  - study duration only average 3 months
  - cumulative pregnancy rates may differ if observation period is long enough

(ex, improved pregnancy rate between 4-6 months)

- limited size of study group
  - further trials → multicenter basis
- patient selection
  - heterogeneous etiology
  - clearly defined inclusion / exclusion criteria

Conclusion

- The combination of clomiphene citrate and vit E can significantly increase the pregnancy rate and improve semen parameter in cases of idiopathic oligoasthenozoospermia.

The end ~