

Empirical therapy for male factor infertility: Survey of the current practice

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Abstract

Background: Empirical therapy is sometimes used by urologists who desire to improve the outcomes for infertility patients. However, the literature on empirical therapies is scarce. Therefore, we aimed to assess the clinical practice of urologists regarding the use of empirical therapy in the treatment of infertility patients.

Methodology: An online survey using Google Forms was used to collect data during the Saudi Urological Association Annual Meeting, February 2019. Additional data were gathered electronically in March and April 2019 and sent to respondents. The study was closed in May 2019. No incentives were provided to the respondents.

Results: A total of 96 (80%) urologists participated in the survey, of whom 69.8% were consultants, and 20.8% were andrology-trained urologists. Empirical therapy was used by 86.5% of urologists for patients with idiopathic oligoasthenoteratozoospermia. The most commonly used empirical therapies were zinc, L-carnitine, clomiphene citrate, and L-arginine. The main factors that influenced the selection of empirical therapy were follicle-stimulating hormone, total testosterone, and luteinizing hormone levels.

Conclusion: Empirical therapy was used by more than three-quarters of the participants for idiopathic male infertility. There were no clear guidelines for the ideal therapy to be considered for individual patients while treating empirically. Our concern is that urologists use a wide variety of medications without significant data to support these medications.

Keywords: Empirical therapy, infertility, oligoasthenoteratozoospermia, survey, varicocele

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INTRODUCTION

Male factor infertility accounts for 40%–50% of all infertilities and affects around 7% of all men.^[1] Idiopathic oligoasthenoteratozoospermia (iOAT) is a condition in which the sperm concentration, proportion of motile sperms, and proportion of morphologically normal sperms

are below the World Health Organization reference values without a clear cause.^[2] iOAT is responsible for 30% of all male infertility.^[3] Studies on the treatment of iOAT patients show that multiple drugs can help with fertility, and these drugs are divided into three types: hormonal, antioxidant, and herbal medications.

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The most common empirical medications used for iOAT are clomiphene citrate, human chronic gonadotropin, and anastrozole.^[4] Magdi *et al.* demonstrated that sperm concentration and percentage of total and progressive motility were significantly increased in men with severe OAT after 6 months of lifestyle modification and antioxidant use, and abnormal sperm morphology was significantly reduced after therapy.^[5]

There are no clear guidelines for the treatment of iOATs; practices vary between countries. In this study, we conducted a survey to evaluate the practice of empirical therapy for the treatment of infertility by urologists in Saudi Arabia. We assessed the clinical practice in the following aspects: decision-making, treatment practice, and attitude toward empirical therapy.

METHODOLOGY

An online survey was conducted using Google Forms. Data were collected during the Saudi Urological Association Annual Meeting in February 2019. Additional data were gathered electronically in March and April 2019, and sent to respondents. The study was closed in May 2019. No incentives were provided to the respondents.

Survey

The survey consisted of 13 questions involving demographics and clinical practice. Demographics included age, gender, practice duration, position as per Saudi Commission for Health Specialties, sub-specialty, and the type of institute where the participant worked. Clinical practice questions included the number of infertility patients seen per week, use of empirical therapy for iOAT, frequency of multiple empirical drugs and herbal medications, factors that influenced the selection of the empirical therapy used, use of empirical therapy before surgical sperm retrieval (SSR), and duration before SSR. Participants were asked about their beliefs about the benefit of empirical therapy for multiple types of OATs and isolated teratozoospermia. The survey was validated using focus group validation.

Statistical methods

Statistical analysis was performed using IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. The Chi-square test was used for categorical variables.

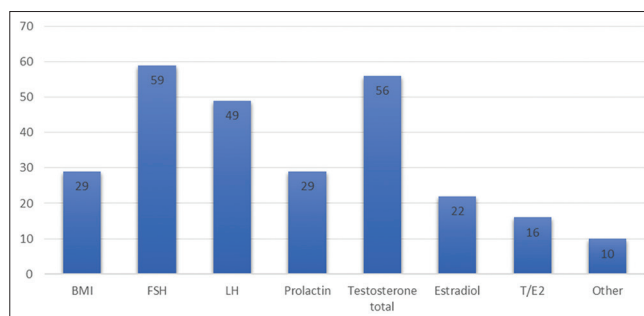
RESULTS

A total of 120 Saudi Urology Association (SUA) members were invited to participate in an electronic survey, of whom 96 (80%) were urologists. Of the respondents, 81.3% had more

than 10 years’ practice in urology, 69.8% were consultants, and 20.8% were andrologists trained in urology [Table 1].

Of the respondents, 47.9% saw >10 infertility patients each week. Empirical therapy was used for patients with iOAT by 86.5% of the urologists [Table 2]. The most used empirical therapies were as follows: zinc, with a use rate of 74%; L-carnitine, 72.9%; clomiphene citrate, 68.8%; and L-arginine, 65.6%.

The main factors that influenced the selection of empirical therapy were follicle-stimulating hormone (FSH), total testosterone, and luteinizing hormone (LH) levels [Graph 1].



Graph 1: Factors influencing the choice of empirical therapy

Table 1: Demographics

	<i>n</i>
Gender	
Male	95
Female	1
Age	
<30	13
30-40	41
41-50	22
>50	20
Years of practice	
<10	17
10-20	43
21-30	19
>30	12
Position	
Consultant	67
Nonconsultant	29
Subspecialty	
Andrologist	20
Nonandrologist	36
General urologist	40

Table 2: Clinical practice

	<i>n</i>
Number of infertility patients seen per week	
<10	50
10-20	26
>20	20
Use empirical therapy for patients with OATs	
No	13
Yes	83

OATs: Oligoastheno-teratozoospermias

Majority of the urologists agreed on the beneficial effects of empirical therapy on mild OAT and isolated teratozoospermia [Table 3], whereas they were divided on the efficacy of empirical therapy on severe OAT, OAT with varicocele, and azoospermia [Table 4]. The most commonly used empirical therapies in the practice were Clomiphene citrate, Zinc, L-arginine, L-carnitine [Table 5]. Of the 62 urologists who performed SSR, 72.6% used empirical therapy before surgery, of whom majority used it for 3–6 months before SSR.

Furthermore, we analyzed the difference in practice between andrologists and nonandrologists. Twenty of the participants specialized in andrology. There were multiple differences in the choice of empirical therapy used. Anastrozole, human chorionic gonadotropin, human menopausal gonadotropin, recombinant FSH, and coenzyme Q10 were mostly used by andrologists ($P = 0.0001$). The data also showed significant differences in other medications: l-arginine ($P = 0.006$), tamoxifen ($P = 0.013$), l-carnitine ($P = 0.015$), zinc ($P = 0.016$), antibiotics ($P = 0.032$), and combination formula ($P 0.044$). General urologists also tended to use herbal medications such as honey and royal jelly, although these were not sufficient [Graph 2]. Our data exhibited differences in the participants' beliefs concerning the efficacy of empirical therapy for OAT with varicocele ($P 0.013$) [Table 3].

Andrologists and nonandrologists agreed on administering empirical therapy prior to SSR for a certain duration, with the majority using it for 3–6 months in advance.

DISCUSSION

Of the 96 respondents, 83 urologists used empirical therapy

Table 3: Empirical therapy is beneficial for these cases

Empirical therapy is beneficial for these cases	Disagree (n)	Neither (n)	Agree (n)
Mild OAT	8	11	72
Severe OAT	30	24	32
OAT with varicocele	28	31	26
Isolated teratozoospermia	18	24	45
Azoospermia	47	18	27

OAT: Oligoasthenoteratozoospermia

Table 4: Empirical therapy is beneficial for these cases

	Andrologists			Nonandrologists			P
	Disagree %	Neither %	Agree %	Disagree %	Neither %	Agree %	
Mild OAT	5	5	90	9.8	14.1	76.1	0.393
Severe OAT	25	25	50	34.9	30.2	34.9	0.376
OAT with varicocele	21.1	21.1	57.8	36.4	40.9	22.7	0.013
Isolated teratozoospermia	10	25	65	23.9	28.3	47.8	0.304
Azoospermia	40	25	35	58.2	19.4	22.4	0.243

OAT: Oligoasthenoteratozoospermia

for iOATs. The most commonly used medications for empirical therapy were zinc, l-carnitine, clomiphene citrate, and L-arginine. The principal factors that influenced the choice of medication for iOATs were FSH, testosterone total, and LH levels. Among the 62 urologists who performed SSR, 45 used empirical therapy prior to surgery, with the majority using it for 3–6 months prior to SSR.

The literature contains significant data on the roles and positive effects of antioxidants in the treatment of male infertility; however, there are no well-controlled randomized trials on the use of antioxidants in the treatment of iOATs. Although antioxidants are used extensively, as shown in our results, there is a scarcity of studies with scientifically acceptable evidence. A prospective study investigated the effect of L-carnitine on 21 patients with asthenospermia during a 6-month period and showed no significant difference between the placebo group and the L-carnitine group.^[6]

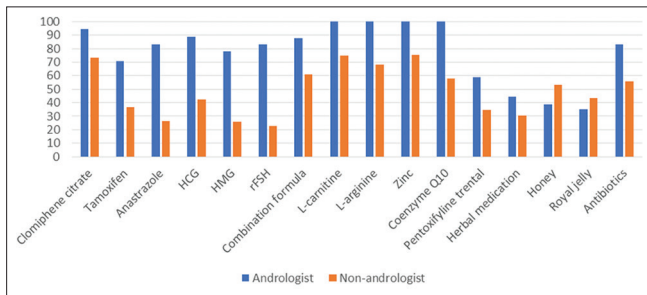
In our survey, 70.6% of andrologists used anastrozole, which correlates with a study in the USA, in which 61% of andrologists were reported to use anastrozole.^[4] Clomiphene citrate was used by most urologists in our research, as well as in the USA. In addition, the factors that influenced the urologists' choice of empirical therapy were FSH, total testosterone, and LH levels, whereas, instead of total testosterone in the US, sperm count is considered along with FSH and LH levels in choosing an empirical therapy.

Antibiotic use for idiopathic infertility has not been extensively researched in a randomized trial with a placebo group. Our results show that 61.7% of urologists used antibiotics without scientific evidence of their effects on idiopathic infertility from a well-controlled randomized trial. A systematic review was conducted on the effect of antibiotics on male infertility with leukocytospermia. Three randomized trials showed statistically significant improvement in sperm concentration and motility between the treated and untreated groups.^[7] Genital tract infections among infertile patients are often asymptomatic; therefore, evaluation of genital tract infection is recommended.^[8]

Table 5: Frequency of empirical therapies used for male factor infertility

Empirical therapy	Never (n)	Rarely (n)	Sometimes (n)	Often (n)	Always (n)
Clomiphene citrate	19	11	31	24	0
Tamoxifen	46	18	13	5	0
Anastrozole	51	14	9	9	0
HCG	39	20	15	8	0
HMG	50	21	9	0	0
rFSH	51	15	9	5	0
Combination formula	27	14	16	10	13
L-carnitine	17	7	27	18	18
L-arginine	21	11	27	15	10
Zinc	17	9	26	21	15
Coenzyme Q10	27	12	16	17	11
Pentoxifylline trental	47	14	11	5	1
Herbal medication	53	11	9	5	2
Honey	41	11	18	10	2
Royal jelly	45	16	10	4	2
Antibiotics	31	21	24	5	0

rFSH: Recombinant follicle stimulating hormone, HCG: human chorionic gonadotropin, HMG: human menopausal gonadotropin



Graph 2: Empirical therapy percentage

The majority of our respondents agreed on the minimal effect of herbal medication, honey, and royal jelly. There are few comprehensive studies on the use of alternative medicine as an empirical therapy for fertility. A recent review assessed the evidence for the use of complementary and alternative medicines (CAMs) during fertility treatment.^[9] The review included multiple aspects of CAM as follows: acupuncture, body work (e.g., massage), energy healing (e.g., reiki), herbal medicines (e.g., naturopathy), mind-body techniques (e.g., meditation, yoga), and traditional medicines (e.g., Chinese medicine). A total of 148 articles were reviewed, with the conclusion that only eight studies showed improvement in male fertility with Chinese herbal medication. Four level IV evidence showed an improvement in male fertility outcomes using herbal medications.

With the advancements in assisted reproduction techniques, the goal of empirical therapy may not be to enhance fertility in men but rather to augment spermatogenesis, thereby improving the success rate of *in vitro* fertilization. The majority of our respondents agreed on the use of empirical therapy before SSR. Most of them used empirical therapy

for 3–6 months before SSR. Studies have shown that clomiphene use before SSR helped in obtaining adequate sperm from SSR in 100% of patients with azoospermia.^[10] L-carnitine has also been shown to improve semen quality and sperm concentration and motility. However, most of the positive outcomes were results from uncontrolled, unblinded studies.^[11] Because of their encouraging results and lack of side effects, antioxidants are recommended as adjuvant therapies.

Varicocele causes a time-dependent decline in semen parameters and testosterone production.^[12,13] A recent study of 60 participants showed the positive effect of tamoxifen on semen concentration, progressive motility, normal morphology, and total motility after treatment for 3 months. However, no effect on vein diameter and the presence of reflux was observed in these patients.^[14] Our respondents gave conflicting responses regarding the benefit of empirical therapy for varicocele patients. Majority of the andrologists believed that empirical therapy was beneficial for such patients, whereas general urologists were divided concerning the usefulness of empirical therapy for varicocele patients. Nevertheless, empirical therapy was used by majority of our respondents.

CONCLUSION

The survey findings shed light on the difference in the management of iOATs between andrologists and nonandrologists. In addition, this research highlighted common medications and major factors affecting treatment outcomes. Thus, we suggest establishing treatment recommendations to guide urologists around the world to achieve the best outcomes for their patients.

The data were collected during the SUA 2018 conference, so we could not obtain responses from urologists who were absent from the conference. One strength of this survey is that most of the responses were from consultants in urology, majority of whom had >10 years of practice in urology.

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Conflicts of interest

There are no conflicts of interest.

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