

THE EFFECT OF SYSTEMIC ISOTRETINOIN ON FERTILITY IN MALE PATIENTS WITH ACNE VULGARIS

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ABSTRACT

Background: Acne vulgaris is a common dermatological problem that affects males and females in the adolescent period and early adulthood. Isotretinoin is the treatment of choice for moderate to severe cases of acne vulgaris, as it provides complete cure with minimal scarring. Males receiving isotretinoin are always concerned about its adverse effects, especially on their fertility potential. **Objective:** To study the effect of systemic isotretinoin on semen parameters of male patients treated for acne vulgaris. **Materials and Methods:** This study was carried on 30 male patients with acne vulgaris presented to the Dermatology Clinic, Tishreen University Hospital, Lattakia. A dose of 0,5 mg/kg of systemic isotretinoin was given to all patients over a period of 6 months. Semen analysis was done for all patients before and after 6 months of use. **Results:** After the course of systemic isotretinoin, a statistically significant increase in sperm concentration (million/ml), total concentration (million) and progressive sperm motility % was observed, without any statistically significant increase in morphologically normal sperm% after isotretinoin use. **Conclusion:** Systemic isotretinoin in acne vulgaris is a safe modality of treatment with no harmful adverse effects on semen parameters, after 6 months of use.

KEYWORDS: Acne vulgaris, systemic isotretinoin, semen parameters.

INTRODUCTION

Acne vulgaris is a multifactorial disorder of the pilosebaceous unit. The clinical picture can vary significantly, from mild comedonal acne to fulminant systemic Disease.^[1] Although all age groups may be affected by its many variants, the peak incidence is during adolescence. With a peak incidence during adolescence, acne affects approximately 85% of young people between 12 and 24 years of age and is therefore a physiologic occurrence in this group.^[1] The development of acne involves the interplay of a variety of factors, including: (1) follicular hyperkeratinization; (2) hormonal influences on sebum production and composition; and (3) inflammation, in part mediated by P. acnes.^[1]

Treatment of AV depends on disease type, severity, and complications, and it ranges from topical therapies including topical antibiotics, retinoids, sulfur, azelaic acid and benzoyl peroxide in mild conditions to oral therapy including systemic antibiotics, hormonal therapy,

and systemic isotretinoin in moderate to severe condition.^[2]

Isotretinoin is known to be the active metabolite of retinol, which is vitamin acid.^[3]

Its molecule contains 13-cis-retinoic acid (RA), which is a tretinoin stereoisomer. It gains its high and rapid response by affecting cell survival, cellular differentiation, cell-cycle progression, and apoptosis.^[4]

The spermiogram is a technique which evaluates certain characteristics of a male's semen and the sperm contained therein. It is done to help evaluate male fertility, whether for those seeking pregnancy or to verify the success of.^[5] Despite much technological progress, the spermiogram is still the most widely used procedure to evaluate male fertility. It includes an examination of the color, pH, ejaculate volume, motility, morphology, vitality and leukocyte count.^[6] Reference values for the standard spermiogram are evidence-based, using results from prospective studies with nearly 1800 men who were able

to father a child within one year of unprotected intercourse.^[7] The reference values for a spermogram are listed in Table 1.

Effect of isotretinoin on male fertility was studied in earlier studies, which revealed increased semen parameters after isotretinoin intake like sperm concentrations and sperm motility.^[8] More recently, positive effects of isotretinoin on sperm parameters were found in male patients receiving isotretinoin. These effects were referred mostly to its proliferative and regenerative effects on the testes in addition to its neutral effect on sex hormone levels.^[9]

Isotretinoin has been used for a long time for the treatment of severe or refractory acne. However, there are very few prospective studies about its effect on male fertility in the literature. For this reason, we aimed to evaluate the effects of systemic isotretinoin on male fertility and conducted this study.

Table-1: Evidence-based reference values of the spermogram Parameters).^[7]

Ejaculate volume	≥1.5 ml
Sperm concentration	≥15 million/ml
Sperm count/ejaculate	≥39 million
Progressive motility	≥39% sperm
Vitality	≥58% living sperm
Normal morphology	≥4% normomorph sperm

MATERIALS AND METHODS

Acne vulgaris is one of the most common skin diseases affecting the pilonidal-seborrheic follicle unit.

Systemic isotretinoin is one of the best therapeutic options available for the treatment of moderate and severe acne vulgaris, in addition to its role in the process of spermatogenesis and differentiation and its effect on sperm count and motility, hence the importance of our research in studying the positive effect of systemic isotretinoin on semen analysis and removing common concerns about its use as a treatment option.

Main objective: To study the effect of systemic isotretinoin on fertility in male patients with acne vulgaris.

Secondary objectives

Study the effect of systemic isotretinoin on fertility according to the following variables

1. Age (in years)
2. Dose of Isotretinoin

Study population and methods

Study Design: After approval by local research ethics committee, a prospective (Before and after) study was conducted in Department of Dermatology and Venereology at Tishreen University Hospital in Lattakia, Syria between 2022-2023.

Inclusion Criteria

Male patients aged more than 18 years, with normal semen analysis and treated with systemic isotretinoin for AV.

Exclusion criteria

1. Patients who used systemic isotretinoin before or had medical contraindications to its use.
2. Azoospermia or leukocytospermia.
3. Andrological or medical conditions affecting semen parameters.

The final research sample consisted of 30 patients who underwent treatment with isotretinoin.

The data in this study were collected prospectively, and all research participants were fully aware of the procedure, and their written informed consent or their families' consent to participate in the research was obtained after receiving sufficient information. This study did not face serious ethical challenges.

Upon admission, research participants underwent a clinical and laboratory evaluation and then initiation of treatment

Clinical evaluation

It involved taking a detailed clinical history and documenting the following information:

1. Age
2. Weight
3. Severity of acne vulgaris
- 4- Previous treatment

Clinical, and laboratory examination

- Before starting treatment
- Laboratory analyses were performed, including
- Blood count and formula, liver enzymes (ALT, AST), kidney function (creatinine, urea), blood sugar.

Before starting treatment

Patients were weighed, and a semen analysis for each patient was performed, we gave them the appropriate initial dose of isotretinoin at a rate of 0.5 mg/kg patients were followed-up every month and re-evaluation of laboratory test.

A second semen analysis was performed at the end of the treatment period, and we compared the results with the analysis before treatment.

RESULTS

The research sample included 30 male patients with acne vulgaris undergoing treatment with systemic isotretinoin who fulfilled the inclusion criteria.

The patients' ages ranged from 18 to 36, with a mean age of 23.83 ± 5.1 years, patients' weights ranged from 59 to 89 kg, and the average weight was 73.86 ± 7.7kg. 6.7% of the research sample had a mild degree of acne, while

both moderate and severe degrees amounted to 46.7%. And 43.3% of the patient sample used the dose of 40 mg of isotretinoin, while 56.7% of the sample used the dose of 30 mg.

Changes in semen analysis

We noticed that there were no statistically significant differences regarding the mean values of pH, as it was before treatment 8.11 ± 0.3 and after treatment 8.10 ± 0.3 with p-value = 0.5 (Table-2 Fig-1), There were also no statistically significant differences regarding the mean values of the volume, as it was before treatment 2.79 ± 0.5 and after treatment 2.93 ± 0.5 with p-value = 0.1. (Table-3 Fig-2).

We found statistically significant differences regarding the mean values of sperm concentration, as before treatment it was 51.33 ± 24.5 and after treatment it increased to 56.45 ± 22.7 with p-value = 0.0001. (Table-4 Fig-3), we also found Statistically significant differences regarding the mean values of the total sperm count, as it was before treatment 138.1 ± 65.3 , and after treatment it

increased to 164.5 ± 70.1 with p-value = 0.0001 (Table-5 Fig-4), there were statistically significant differences regarding the mean values of sperm motility, as before treatment it was 36.53 ± 2.9 and after treatment it increased to 40.50 ± 4.5 with a p-value = 0.04. (Table-6 Fig-5).

Unfortunately, There were no statistically significant differences with regard to the average values of normal sperm forms, as it was before treatment 73.23 ± 3.5 and after treatment it was 75.36 ± 3.8 with a p-value = 0.08. (Table-7 Fig-6).

In the end, we noticed that there were statistically significant differences in the changes in sperm count and age, the changes were higher with ages over 25 years but there were no differences between changes in concentration and sperm motility with age (Table-8).

We also did not notice any statistically significant differences between the semen parameters and the dose of isotretinoin used (Table-9).

Table-2: Changes in semen PH before and after treatment.

Time	Mean \pm SD	Range	P- value
Before treatment	8.11 ± 0.3	7 - 9	0.5
After treatment	8.10 ± 0.3	7 - 8.50	

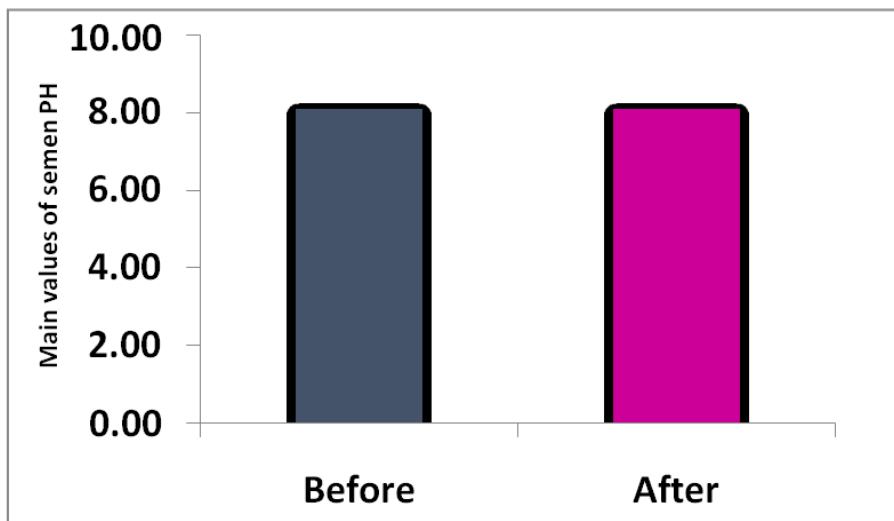


Fig. 1: Changes in semen PH before and after treatment.

Table-3: Changes in semen volume before and after treatment.

Time	Mean \pm SD(ml)	Range(ml)	P- value
Before treatment	2.79 ± 0.5	2 - 4.50	0.1
After treatment	2.93 ± 0.5	2 - 4	

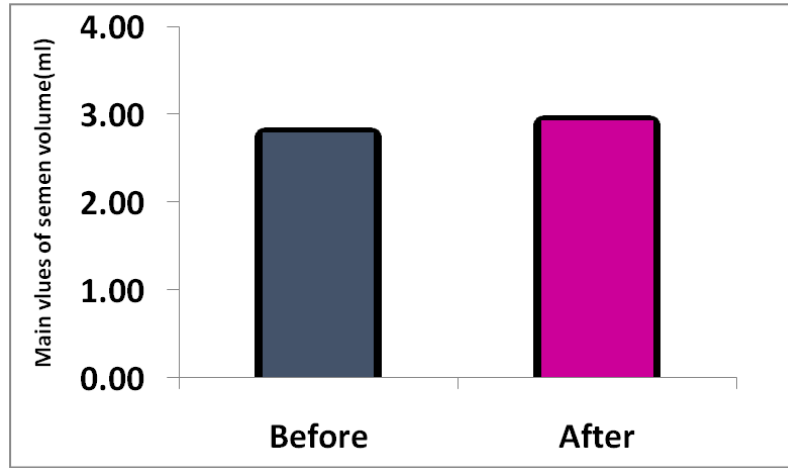


Fig. 2: Changes in semen volume before and after treatment.

Time	Mean ± SD(million/ml)	Range(million/ml)	P- value
Before treatment	51.33±24.5	4.8 – 97.4	0.0001
After treatment	56.45±22.7	12.6 - 95	

(Table-4 Changes in sperm concentration before and after treatment)

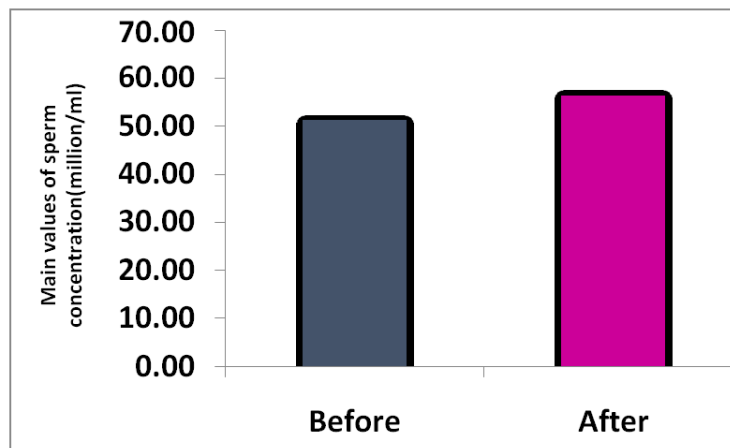


Fig. 3: Changes in sperm concentration before and after treatment.

Table-5: Changes in total sperm count before and after treatment.

Time	Mean ± SD(million)	Range(million)	P- value
Before treatment	138.1±65.3	20.4 – 248.82	0.0001
After treatment	164.5±70.1	37.8 – 291.9	

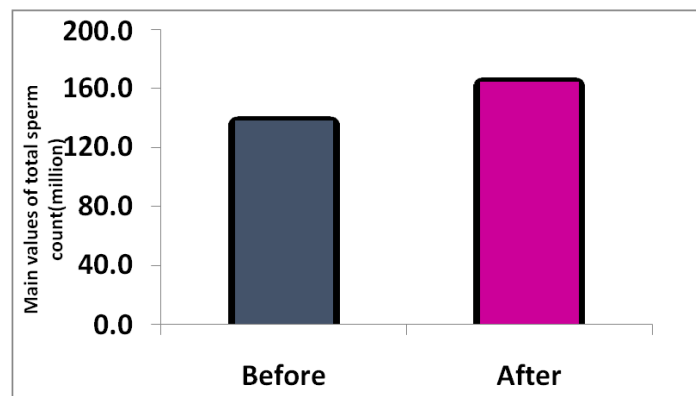


Fig. 4: Changes in total sperm count before and after treatment

Table-6: Changes in sperm motility before and after treatment.

Time	Mean ± SD (%)	Range (%)	P- value
Before treatment	36.53±2.9	34 – 50	0.04
After treatment	40.50±4.5	37 - 60	

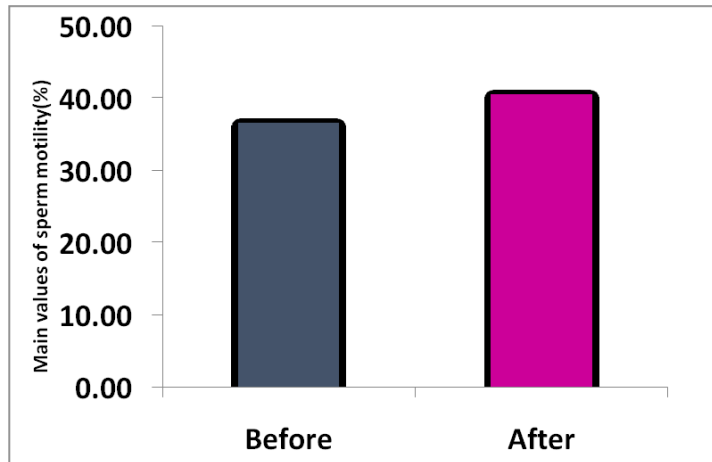


Fig. 5: Changes in sperm motility before and after treatment.

Table-7: Changes in normal morphology of sperm before and after treatment.

Time	Mean ±SD(%)	Range(%)	P- value
Before treatment	73.23±3.5	70 - 80	0.08
After treatment	75.36±3.8	70 - 81	

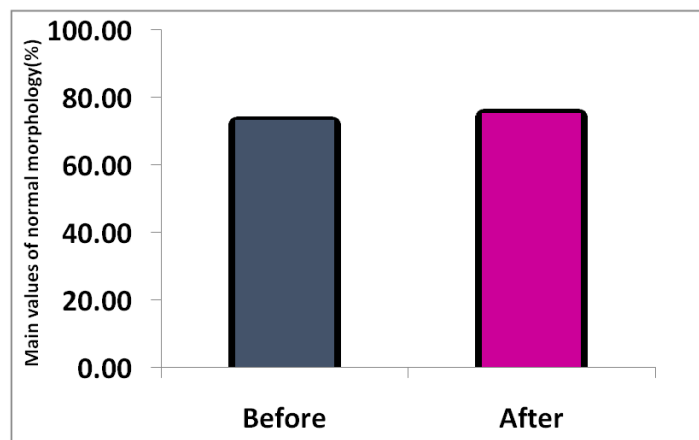


Fig. 6: Changes in normal morphology of sperm before and after treatment.

Table 8: Changes in total number, concentration and motility of sperm and their correlation with age.

Age group	The mean values of changes in:		
	Sperm concentration	Total number of sperm	Motility of sperm
≤25	5.2±4.6	17.8±23.5	2.9±2.01
>25	5.4±6.4	41.5±23.6	3±2.9
P-value	0.9	0.01	0.9

Table-9: Changes in total number, concentration and motility of sperm and their correlation with dose.

Dose	The mean values of changes in:		
	Sperm concentration	Total number of sperm	Motility of sperm
30	5.8±4.8	19.4±24.8	2.2±1.1
40	4.8±5.6	32.01±26.1	3.5±2.8
P-value	0.6	0.1	0.1

DISCUSSION

Systemic isotretinoin is the only drug which affects all the pathogenic mechanisms of acne. For this reason it has been used in the treatment of severe or refractory acne for more than 30 years.^[10] It has many well-known but acceptable side effects. Besides these, teratogenicity is the most frightening complication of systemic isotretinoin.^[11] Although, many of the side effects of isotretinoin have been well established, its influence on male fertility is still unclear. In humans, systemic isotretinoin was reported to have a favorable positive effect on male fertility through its regenerative and proliferative effects on the testes.^[9] Retinoid receptors are abundantly expressed in the fetal and neonatal testes.^[12] RA has been shown to be a potent endocrinologic regulator of the development of fetal and neonatal testes. For this reason, the effects of RA on the male reproductive system have attracted the attention of researchers recently. Even so, there are very few studies concerning the effects of retinoids on adult male fertility. When considered from this point of view, our study seems to be one of the most comprehensive prospective human studies about isotretinoin's effect on male fertility. In the present study, we tried to determine the actual effect of systemic isotretinoin on male fertility by semen analysis before and after treatment course (6 months).

In the current work, we found that main semen parameters significantly improved after systemic isotretinoin therapy, the mean values of sperm concentration increased from 51.33 ± 24.5 before treatment to 56.45 ± 22.7 after treatment with p -value = 0.0001, and mean values of the total sperm count increased from 138.1 ± 65.3 before treatment to 164.5 ± 70.1 after treatment with p -value = 0.0001, and there were statistically significant differences regarding the mean values of sperm motility, as before treatment it was 36.53 ± 2.9 and after treatment it increased to 40.50 ± 4.5 with a p -value = 0.04. Unfortunately, there were no statistically significant differences with regard to the average values of normal sperm forms.

When comparison our results with the results of global studies, we found

Our study agreed with The study published by Moustafa et al in Egypt in 2020, the study included 40 male patients who were treated with systemic isotretinoin at a dose of 0.5 mg / kg for a period of six months. In this study, it was found that there were statistically significant changes in sperm concentration and motility, and this is consistent with our study. They also found a statistically significant difference in the normal shapes of sperm, and this is not consistent with our study (this may be explained by our inability to conduct an accurate study of the normal morphology of sperm using electron microscopy).^[13]

As for the study of Çinar L and et al in Turkey in 2015, the study included 80 male patients with acne vulgaris

treated with systemic isotretinoin at a dose of 0.5 mg / kg for a period of six months, it was found at the end of the study that there was a statistically significant correlation in all variables of semen analysis and this contradicts with our study (probably due to the small size of the sample in our study).^[9]

As for The study published in 2017 in America by John et al, the study included 19 patients with acne vulgaris, males treated with isotretinoin at a dose of 20 mg for all patients for a period of 20 weeks, and this does not correspond to the dose used in our study, as it was shown through the results that there is a statistically significant correlation in sperm concentration without having a statistical significance in motility and this is not consistent with our study.^[14]

There were some limitations in our study; The sample size was small and unavailability of electron microscope examination. Another limitation of the study was follow up of semen parameter changes only at the end of isotretinoin treatment course. It would be better if semen parameter changes had been re-measured again after 3 or 6 months after the end of isotretinoin course.

CONCLUSION

Systemic isotretinoin has no harmful effect on semen parameters. Isotretinoin had a positive effect on some semen parameters (sperm concentration, total number of sperm and progressive sperm motility). Systemic isotretinoin after 6 months of use had no negative effects on sperm morphology.

RECOMMENDATIONS

We recommend the following

1. Use of systemic isotretinoin in male patients with acne vulgaris without any concern for their reproductive health.
2. Discussing the possibility of including vitamin A derivatives (retinoic acid) within the treatment plan for male infertility who suffer from delayed childbearing.
3. Conducting future studies that include a larger sample of patients and follow-up for longer periods after treatment and using better techniques in semen examination.

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