The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90 (2), Page 3484-3487

The Outcome of Intramuscular Administration of Human Chorionic Gonadotropin to Restore Spermatogenesis in Patients with Non-Obstructive Azoospermia

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ABSTRACT

Background: Non-obstructive Azoospermia (NOA) is a common status among infertile men. The objective of the present study is to evaluate the efficacy of I.M administration of human chorionic gonadotropin (HCG) in men with NOA.

Patients and methods: This study included a total of 50 with NOA who were administrated I.M injection of HCG 5000 I.U twice weekly for 3 months. The effect of HCG on spermatogenesis was assessed by the presence of motile sperms in the ejaculate in two semen sample.

Results: The median of age was 39 (SD 11.37) years with the mean FSH of 28.16 (SD 16.44). Among 50 patients we found that sperms with a variable counts started to appear in semen of 25 patients which is statistically significant (p-value <0.001). Also, reduction of serum level of FSH was occurred to be 18.65 (SD 13.01) which is highly significant (p-value <0.001). **Conclusion**: Exogenous administration of HCG can improve spermatogenesis in patients with NOA and decrease level of FSH.

Keywords: non-obstructive Azoospermia, spermatogenesis, human chroinic gonadotropin, South Valley University.

INTRODUCTION

Azoospermia is defined as the absence of sperm in the ejaculate. Non-obstructive Azoospermia (NOA) is a subset of azoospermia induced by spermatogenic failure (STF) or hypogonadotropic hypogonadism (HH). Human chorionic gonadotropin (HCG) injection is thought to be the first step in treating NOA patients before microdissection testicular sperm extraction (micro-TESE) by hormonally stimulating spermtogensesis in those patients [(1)].

According to recent research, 60% of men with NOA are expected to produce some sperm in their testicles. However, some patients are still unable to receive treatment due to Sertoli cells and maturation arrest. The serum testosterone level does not actually correlate with intratesticular testosterone (ITT), and it is obvious that the serum testosterone and FSH levels do not reflect the focal sites of spermatogenesis that are discovered during micro-TESE, despite the fact that NOA is frequently accompanied by low serum testosterone levels and elevated serum FSH levels. ITT is present in the testes in high concentrations that are 100–1000 times greater than those seen in the circulation [(2)].

Since many men with NOA have low ITT, the aim of hormone therapy is to raise these levels. HCG, aromatase inhibitors, or anti-estrogens can all be used to treat this elevated amount. Exogenous HCG causes a rise in ITT and a downregulation of endogenous gonadotropin production, which in turn triggers spermatogenesis. The processes causing the start of spermatogenesis are the subject of therapeutic research, and histology results show that males with low spermatogenesis levels or late maturation arrest (MA) respond well to hormone therapy, suggesting that HCG can start spermiogenesis, a process that requires increased ITT levels [(3)].

PATIENTS AND METHODS

This study was an observational prospective study conducted on 50 eligible patients with infertility due to non-obstructive azoospermia in two seminal analyses, at Andrology Unit of Urology Department, Qena University Hospital.

Patients were considered eligible if they had infertility due to NOA in two seminal analyses with high level of serum FSH.

Exclusion criteria included: Patients with NOA with normal or low level of FSH, patients with serum testosterone <3 nmol/L, patients receive chemotherapy or radiotherapy at time of study, patients with unilateral or bilateral non-palpable testes and patients with elevated serum prolactin.

All Patients were administrated hormonal therapy (Beta HCG (5000 IU I.M) twice weekly for 3 months).

<u>All patients were subjected to the following:</u>

History and clinical examination:

Complete history taking from the patient, which included symptoms of urological or genital disease, with the onset, course, and duration of the presenting symptoms, duration of infertility, history of smoking status, and other comorbid conditions such as hypertension, and cardiac disease. Full clinical examination included assessment of general condition with stress on genital examination.

Received: 01/06/2022
Accepted: 08/08/2022

Laboratory Investigations: Semen analysis and Hormonal profile: [FSH, LH, Prolactin and serum testosterone (total and free)].
Imaging: Scrotal Doppler ultrasound and Trans rectal ultrasound.
Measuring Outcome: Detection of motile sperms in semen for more than 2 consecutive times (1 week between the 2 samples) the treatment will be considered effective and will be included into the statistical analysis.

Ethical considerations:

The study was approved by the local Ethics Committee of Qena Faculty of Medicine South Valley University. An informed written consent was taken from each participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data collected and encoded using Microsoft Excel software. Data were then imported into Statistical Package for Social Sciences (SPSS version 20.0) software for analysis. According to the type of data, qualitative represented as numbers and percentages, while quantitative data represented by mean ± SD. Chi-square test ($\chi 2$) and Fisher's exact test to calculate difference between two or more groups of qualitative variables. Independent samples t-test was used to compare between two independent groups of normally distributed variables. P-value was set at ≤ 0.05 for significant results, and ≤ 0.001 for highly significant results.

RESULTS

The median of age was 39 (SD 11.37) years. The range of duration of infertility was 1-45 years with the mean of 7.74 (SD 6.97). The smoker patients were 35 (70%) patients. Patients are classified according to type of infertility into primary infertility which counts 40 (80%) patients and secondary infertility 10 (20%) patients. Clinical evaluation for size of both testes revealed that 25 (50%) patients have relatively bilateral small size testes. Serum level of testosterone of all patients was not below 3ng/ml with mean level 5.47 (SD 2.86).

Thereafter, scrotal Doppler ultrasound was done to all patients the data obtained was: Free 13 (26 %) patients, bilateral varicocele 16 (32 %) patients, bilateral small sized testes 20 (40%) patients, and bilateral hydrocele 1 (2%) patient.

After three months of treatment, half of patients (25 patients) had a positive result as their semen analysis showed presence of sperms with variable counts with highly statistically significant (p-value <0.001).

The mean FSH showed high significant statically difference as pre hormonal administration it was 28.16 (SD 16.44) then it became 18.65 (SD 13.01) (p-value <0.001).

Level of serum testosterone showed no significant difference pre and post treatment; it was 5.47 (SD 2.86) then became 6.04 (SD 3.46) (p-value=0.178).

The range of age of the patients had positive result was 24-48 years old (nearly 92% of the total sample), except only two patients was 65 and 72 years old (nearly 8%) with no statistically difference between them, and those patients which show no sperms in their ejaculate (p-value=0.476).

Also, half of patients with 1ry infertility started to ejaculate few motile sperms in their semen and half of patients with 2ry infertility produce sperms (75000-5 million) in their semen with no statistically difference (p-value=1).

Eighteen patients with normal testicular size and 7 patients with bilateral Small sized testes had positive result which is highly statistically significant (p-value=0.002).

Table1: Characteristics of studied 50 patients with infertility due to non-obstructive azoospermia.

Age		39 ± 11.37
Duration of infertility		7.74 ± 6.97
Special habit	Smoker	35 (70%)
	Non smoker	15 (30%)
Type of infertility	Primary	40 (80%)
	Secondary	10 (20%)
Scrotal doppler US	Free	13 (26%)
	Bilateral varicocele	16 (32%)
	Bilateral small sized testes	20 (40%)
	Bilateral hydrocele	1 (2%)
Testes	Small size	25 (50%)
	Normal size	25 (50%)
Semen after 3 months treatment	Azoospermia	25 (50%)
	Presence of sperms	25 (50%)

Table 2: follow up of semen analysis, serum FSH and testosterone pre and post treatment

Variable	Hormonal therapy		P-value
	Pre	Post	
Semen	Azoospermia	Presence of sperms 25 (50%)	**<0.001**
FSH	28.16 ± 6.44	18.65 ±3.01	**<0.001***
Testosterone	5.47 ± 1.86	6.04 ± 1.46	0.178

Table 3: Sperm count (after 3 months of hormonal therapy) comparison among patients' characteristics

Variable		Sperm count (after 3 months of hormonal therapy)		P-value
		Azoospermia	Presence of sperms	
Age		40.16 ± 12.12	37.84 ± 10.69	0.476
Testosterone level after therapy		5.64 ± 3.89	6.43 ± 2.99	0.427
Special habit	**Smoker**	16 (64 %)	19 (76 %)	0.36
	Non smoker	9 (36 %)	6 (24 %)	
Type of infertility	**Primary**	20 (80 %)	20 (80 %)	1
	Secondary	5 (20 %)	5 (20 %)	
Size of testes	**Small size**	18 (72%)	7 (28%)	**0.002***
	Normal size	7 (28%)	18 (72%)	

DISCUSSION

Azoospermia is a complete sperm absence in the ejaculate. It is recognized in 15% of infertile men and is classified into obstructive Infertility (OI) and non-obstructive Infertility (NOI) [4,5,6].

Nearly 60% of individuals with azoospermia have NOI, which is characterized by defective spermatogenesis [4,5]. It develops from testicular failure (TF), either main or secondary, or from partial or ambiguous testicular failure [6,7,8].

The aim of treatment is to normalize or improve fertility state of the azoospermic patient.

Infertile men with pituitary insufficiency are treated with purified urinary gonadotrophins, HCG, human LH, and human FSH. They convince spermatogenesis in about 80% of patients [9,10].

In our study, we assess the effectiveness and impact of hormonal therapy using human chorionic gonadotropin in non-obstructive azoospermic individuals. While **Hu *et al.*** [11] (a case control pilot study) used Goserelin, a gonadotropin releasing hormone agonist (GnRHα) to suppress endogenous gonadotropin levels (gonadotropin reset) in the NOA patients, improving the sensitization of the Sertoli and Leydig cells. Then, human menopausal gonadotropin (hMG) and human chorionic gonadotropin (hCG) were injected to stimulate them to ameliorate the ability of testicular spermatogenesis.

As same as our study, **Shiraishi *et al.*** [12] used two groups to identify the effect of the daily subcutaneous injections of hCG for 4–5 months prior to the second micro-TESE. Recombinant FSH was added if endogenous gonadotropin levels decreased during the hCG stimulation.

Our study started with 50 patients with non-obstructive Azoospermia. The patients received hormonal therapy (Beta HCG (5000 IU I.M) twice weekly for three months). The mean patients age in was 39 ± 11.37.

In the study of **Shiraishi *et al.*** [12] included 48 patients which were divided into two groups; 28 patients received hormonal treatment protocol (subcutaneous self- injection of 5000 IU of HCG three times a week for 3 months before 2nd micro-tese) other 20 patients refuse hormonal protocol and undergoes 2nd micro-tese directly. The mean age in their study was 34 (SD 5.3) [Ranged from 23 to 47]. The range of age was wider in our study than his research; mean age 39 (SD 11.37) [Ranged from 23 to 72] but in other study mean age 34 (SD 5.3) [Ranged from 23 to 47].

In our study, the duration of infertility was 7.74 (SD 6.97). All patients of are azoospermic after centrifugation in two semen sample with high level of FSH (range 11-89 miu/ml) with the mean FSH in 28.16 (SD 16.44) and no significant difference to other study as **Shiraishi *et al.*** [12]. Serum level of testosterone of all patients was not <3 ng/ml, with mean level of 5.47 (SD 2.86).

After 3 months of treatment, there was a great respond to hormonal therapy, 25 (50%) patients had sperms in their semen without using centrifugation (18 patient had few motile sperms, one patients had 75000 sperms per ejaculate and other one had 187000 sperms per ejaculate (his wife got pregnant) and 5 patients had

sperm concentration ranges from 1- 5 million per ejaculate) with p-value is statistically significant (>0.001). In other study reported that return of spermatogenesis for azoospermic men or improved counts for men with severe oligospermia was documented in 47 (95.9%) men, with one (2.1%) additional man having a documented pregnancy without follow-up semen analysis. Our study was conducted only on selected non-obstructive azoospermic patients with high FSH, but with only half as many positive results as theirs. In **Shiraishi *et al*. [(12)]** study, the number of patients with successful sperm retrieval at the second micro-TESE was 6 (25%) patients from 28 patients.

Thus, our results were better than the other study without using any advanced maneuver as micro-TESE.

Those patients in our study with positive results underwent cryopreservation of semen for ICSI after preparation of their wife's.

Also, the follow up of FSH level was statistically significant >0.001 as the mean of FSH premedication was 28.16 (SD 16.44) [ranged from 11.7 to 89] this mean decreased after hormonal administration to reach 18.65 (SD 13.01) [ranged from 4.2 to 70]. So, our result was in consistent with the results of **Shiraishi *et al*. [(12)]** as the mean FSH decreased after hormonal protocol from 28 (SD 14.8) to 18 (SD 5.0) which is statistically significant (P value <0.001).

As regarding to the follow up of serum testosterone level, slight increase was observed as the mean elevated from 5.47 (SD 2.86) to reach 6.04 (SD 3.46) after hormonal therapy. This result is in similar to that of **Shiraishi *et al*. [(12)]**.

In our study, half of patients of 1ry infertility and half of patients with 2ry infertility had a positive result so type of infertility has no effect on treatment success.

Half of patients had normal testicular volume, of them 18 patients show presence of sperms in their ejaculate (72%) but only 7 patients with bilateral Small sized testes had positive result (28%) with statistically significant difference (P-value 0.002), so testicular volume has a great effect on our treatment protocol.

Age of patient has not a significant effect on the success of hormonal protocol (P-value 0.476) as our positive patients their mean age 37.84 (SD 10.69) years and those patients which still azoosprmic however hormonal administration the mean age 40.16 (SD 12.12).

In conclusion of our results, exogenous administration of HCG can improve spermatogenesis in patients with NOA and decrease level of FSH.

Limitation of the study

In spite of the patient sample in our study was double than any other study, but it needs to be increased. Duration of study was short only three months so, more follow up duration is needed. The cost of medication was high and the patients were poor.

The cost of hormonal assay and karyotyping limited the follow up visits.

- **Consent for Publication:** I confirm that all authors accept the manuscript for submission
- **Availability of data and material:** Available
- **Competing interests:** None
- **Funding:** No fund
- **Conflicts of Interest:** The authors declare no conflicts of interest regarding the publication of this paper.

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