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Evaluation of Fertility Parameters in Benign Prostatic Hyperplasia Patients Treated with 5 Alph-Reductase Inhibitor (Finasteride) in Amara city/Iraq

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Abstract
The current study aimed to determine the fertility parameters among BPH patients before and after 3 months of taking 5-α reductase (finasteride) by seminal fluid analysis method, 60 patients and 30 healthy individuals as control group from Amara city ,were involved in this study, their ages were between (40-59)year old. They all subjected to direct seminal fluid analysis before and after 3 months of treatment by 5α-reductase(finasteride)(the healthy individuals didn't take finasteride).The results showed that there is significant decreasing in **volume** ($P<0.05$) in post-treatment group compared to pre-treatment and control group ,while the concentration of semen (count and total count) found to non-significantly decrease in post-treatment compared with pre-treatment and decreases significantly ($P<0.05$) in comparison to control control group. On other hand, the **Motility**(high, moderate) observed to non significantly decreased in post-treatment group compared to pre-treatment group ,but significantly decreased ($p<0.05$) compared to control group, **The Morphology**(normal and abnormal) found to non significantly differences between pre-treatment group and post-treatment group, but that were significantly differences in control group compared to pre-treatment and post-treatment group. Concluded that BPH affects on fertility parameters.
Keywords: BPH. fertility. semen, finasteride .

Introduction

Prostate gland is single, it is a male accessory sex gland , a secretory endocrine gland that secretes part of semen , which is the fluid that carries sperm during ejaculation (Thuy,2006; Nawfal,2011).During male ejaculation, its secretes a complex protolytic milky fluid forms about 20% of semen volume, that contributes 0.5- 3ml of ejaculated seminal fluid (Benninghoff, 1993 Lee,*et al*.,2011;Elo,2013;Byrne,2014) the prostatic fluid help to increase the motility and fertility of the sperm this is only known function of the prostate gland. **(** Thuy,2006; Nawfal,2011).

In human prostatic secretions is contains components that nourish and maintain sperm such as fructose, as well as other components that provide a mechanical transport medium which improve spermatozoa motility through the female reproductive tract as well as alkalinize the vaginal canal to promote increased viability (Schauer and Rowley,2011) ,as calcium ,citrate ion, prostatic acid phosphates, spermine (for the motility of sperms), prostaglandins (for uterus stimulation),and zinc (500–1,000 times the concentration in blood). In addition, prostatic secretions have anti-bacterial properties, a clotting enzyme, prostate specific antigen (PSA) and a fibrinolysin (Benninghoff, 1993 ;Guyton, 2000; McNicholas 2008; Kukk, 2011; Praveen , 2013; Elo,2013) .Prostatic secretions are high in electrolytes, especially citrate, zinc, calcium, magnesium and potassium; which are important for metabolism and DNA stability of spermatozoa (Byrne, 2014). It is added to the seminal fluid at the time of ejaculation. When the smooth muscle in the capsule and stroma contract, the secretion from the many glands is squeezed into the prostatic urethra. A slightly alkaline characteristic of the prostatic fluid may be quite important for successful fertilization of the ovum as it helps to neutralize the acidity of the other seminal fluids during ejaculation, and thus enhances the motility and fertility of the sperms (Guyton, 2000; Kukk, 2011; Praveen , 2013).

BPH represents the most common nonmalignant condition of the abnormal growth of prostatic cells in aging men (Sahi,*et al*.,2013). It is considered as a common public health problem, causing high morbidity and essential worsening of men's quality of life. (Lu and Chen, 2014), and could be qualified clinically or pathologically.

Clinically, BPH is generally viewed as benign enlargement of the prostate, which shares in an array of urinary voiding difficulties that can range from bothersome to significantly influance quality of life among older men (Nawfal,2011,Roehrborn,2011).

Pathologically, BPH is the histological determination a proliferation of the epithelial and stromal elements within the prostate tissue and it is arise in the periurethral and transition zones of the prostate (Nicholson and Ricke ,2011;Jebor *;et al*.,2014; Tsujimura *et al.,*2015). Several hypotheses were found to explain the development of BPH the most accepted one is the dihydrotestosterone (DHT) hypothesis, the hypothesis

include the testosterone(T) converted by 5-alpha reductase(type II) to DHT, In recent studies reached to the drug finasteride inhibits 5α- reductase activity, especially type –II , Finasteride has shown to be effective in long-term treatment for progression of disease (Abd Al-Razaq,2007;Nicholson and Ricke ,2011).

Aim of the study

According to above the current study aimed to investigated reproductive (fertility)parameters for BPH patients before and after finasteride treatment, by the Seminal Fluid Analysis include: volume, sperm concentration ,sperm motility and sperm morphology.

Materials and Methods

Study population:

The present study involved (60) of BPH patients who attended to the consultant urologist at AL-Sadder Teaching Hospital in the period from April 2015 to April 2016. Their ages were between (40-59) years and (20) healthy individuals as control group from same age, Men who had a history of prostate cancer, prostate surgery or diabetes mellitus (DM), hypertension were excluded.

Experimental Design:

Patients completed a previously validated baseline questionnaire. prostate size and configuration was determined by digital rectal examination (DRE) and ultrasounds (transabdominl). Patients were treated with a 5mg/day dose of finasteride for at least 3 month, the semen take from the patients before start with drug (pretreatment) and after 3 month of the treatment(post treatment).

Seminal Fluid Analysis:

Seminal fluid from all subject enrolled in this study was obtained by masturbation after 3-5 days of sexual abstinence. Semen collected in sterile, wide mouthed, non-toxic container and processed in the laboratory within an hour of ejaculation, semen evaluation was based on sperm motility ,sperm morphology, semen concentration, total sperm number per ejaculation, and total semen volume .Briefly ,one drop of semen was dropped on a glass slide, and sperm motility was examined with a microscope at 40^x magnification. All semen specimens were evaluated according to World Health Organization guidelines (2010).

Microscopic Examination

Sperm Motility

The motility of spermatozoa was assessed directly after liquefaction, by applying a drop of a gently mixed seminal fluid on a clean slide and covered with a cover slip. After two minutes, the slide was exact microscopically (40x objectives) to determine the type of motility, and at least eight fields were examined. The categories of sperm movement system of (WHO, 2010) the percentage of motile sperm is determined and then the quality of motility is evaluated according to 4 classifications:

a) Rapid progressive motility (ie, >25µm/s at 37 C^o and >20 µm/s at 20 C^o. 25 µm is approximately equal to 5 head lengths or half a tall length).
b) Slow or Sluggish progression motility.
c) Non-progression motility (<5 µm/s).
d) immotility .

A normal semen analysis must contain at least 50% grade A and B progressively.

Semen Concentration

After liquefaction, the sample was mixed gently, and then 20 µl of the seminal was diluted with 380 µl of semen diluents. After mixing the diluted sample, 10 µl was applied to the surface of Neubauer Hemocytometer under the cover slip. After three minutes, the spermatozoa were counted in the middle 16 squares and by applying the following equation, the spermatozoa concentration was obtained and presented as million per ml.

Spermatozoa concentration (10^6/ml) = Number x dilution factor x multiplication (Dilution = 20, Multiplication =10000).

Sperm Morphology

Following Papanicolaou Giemsa staining of fresh specimen . One drop of semen was smeared on a glass slide and allowed to dry then, the slide was stained with Papanicolaou Giemsa stain ,the morphology is examined under a phase contrast microscope .Normal sperm have a regular oval form head (dimeter of length 3-5µm,diameter of width 2-3 µm).An intact midpiece (7-8 µm length)and tail of at least 45 µm length, acrosome cap should be visible and evaluated for the percentage of normal and abnormal sperm based on their morphology.

Statistical Analysis

All analysis was performed using the statistical package (SPSS) version 17. The data were expressed as mean, standard deviation SD, percentage. ANOVA was used to analyze repeated measurement. Results were determined as high significant ($P<0.01$) and significant at ($P< 0.05$) (Al –Rawi , 2000).

Results and Discussion

The results as shown in table (1) volume decreased significantly ($p<0.05$) in post-treatment group(2.7 ± 0.70ml) compared to pre-treatment group(3.03±0.69ml)and control group(3.5 ± 0.57ml) which there were significant differences between them ,figure (1),while **concentration** of semen(count ,total count) non significantly decreased in post-treatment group(26 ± 13.91×10^6, 82.66±49.49 ×10^6/ respectively)compared to pre-treatment group (36.03±14.14 ×10^6, 117.13±49.81 ×10^6/ respectively) but was significantly decreased compared with control group(77.82 ±38.67 ×10^6, 229.24±120 ×10^6/ respectively),as shown in figure (2). Considering **Motility** (high, moderate) no significantly decreased were found in post-treatment group(2.33±2.58%,7.33±4.16 % respectively) compared to pre-treatment group (5.07±4.37%,11.77±7.93% respectively),while significantly decreased compared to control group (21.93±7.54%,29.67±9.11% respectively), in motility(weak) no significantly differences (p 0.262) among study groups (30.33±13.57%,25.33±18.46%,23.67±8.04%respectively),as shown in figure (3)**.**

Morphology (normal and abnormal) no significantly differences were found in pre-treatment group (69.83±1.59%,30.17±1.59% respectively)compared with post-treatment group (70±0.0%,30 ± 0.0% respectively), while that were significantly differences in control group (76±7.60 %,24± 7.60% respectively) compared to pre-treatment and post-treatment group, figure (4). .

The decreasing in all semen parameters in pre-treatment group may be resulted from several causes such as the estrogen, and in particular the elevated plasma free estradiol/free testosterone ratio, the increase in serum and intraprostatic estrogen/androgen concentration ratios ,as a result of decline testicular function and increase peripheral aromatization rate , are associated with stromal hyperplasia (Joseph, *et al*.,2000).

It is mentioned that there is a correlation between sexual behavior, PRL release and prostate physiology. The correlation seems unidirectional since sexual activity influences prostatic function. The constant elevations of serum prolactin decreased sexual potency and increased the weight of the gland (Hernandez,*et al*.,2006). Males with hyperprolactinemia (hyper PRL) show a sever effect in the potency for penile erection. Generally take a longer time to ejaculate than control (Kooy ,*et al*.,1988; Hernandez ,*et al*.,2006) The time course effect of hyperPRL on sexual behavior seems to be around 10 to 15 days (Kooy, *et al*.,1988), high level of PRL reduces the sexual function of males.

Acute hyperprolactinemia is known to suppress testosterone synthesis and male fertility through prolactin induced hypersecretion of adrenal corticoids or by inhibiting the pulsatile secretion of GnRH through prolactin receptors on hypothalamic dopaminergic neurons which causes decreased pulsatile release of FSH ,LH .and T, which cause spermatogenic arrest , impaired sperm motility ,and altered sperm quality (Masud ,*et al.*,2007;Gill-Sharma,2009,Singh,*et al*.,2011).

Results of the study revealed that decrease in all semen parameters special in post-treatments group that due to finasteride treatment which were directly but reversibly with a reduction of semen parameters this agree with results of Liu, *et al.*(2008), Anith, *et al*.(2009), Tu and Zini (2011), Gude(2011), Samplaski, *et al*.(2013),and Bankhead(2013) ,the 5 mg dose of finasteride used to treat BPH has a reversible negative effect on semen parameters while 1 mg dose has been shown to have no negative effect on healthy men with normal spermatogenesis, but few case have impaired spermatogenesis. Discontinuation of the drug did not affect sperm motility ,or sperm morphology, may lead to improvement in semen parameters that will allow for less invasive fertility therapy, Anitha, *et al*(2009) observed decreased in all the semen parameters except sperm morphology ,they did not fall below the baseline levels to interfere with fertility(Gude,2011). Bankhead,(2013)and Samplaski, *et al*.(2013) reported after stopping finasteride increased mean sperm concentration ,sperm count including an 11.6-fold increase in sperm counts among nine men who were oligospermic (<15M/ml) before they stopped finasteride .The men with sever oligospermia (<5M/ml),57% had counts increase to >15 M/ml after finasteride cessation.

Other study found taking finasteride (1 mg) for 1 year ,diagnosed oligospermia (impaired spermatogenesis)5 years earlier, was found increased semen volume immediately after stop of finasteride and sperm concentration improved to more than 10x10^6/ml about 4 months later(Chiba, *et al*.,2011). Amory, *et al*(2007) observed that PSA and sexual function decreased during finasteride treatment and returned to baseline during follow-up, except sperm morphology ,all parameter are known to be compromised by finasteride (Gude,2011).

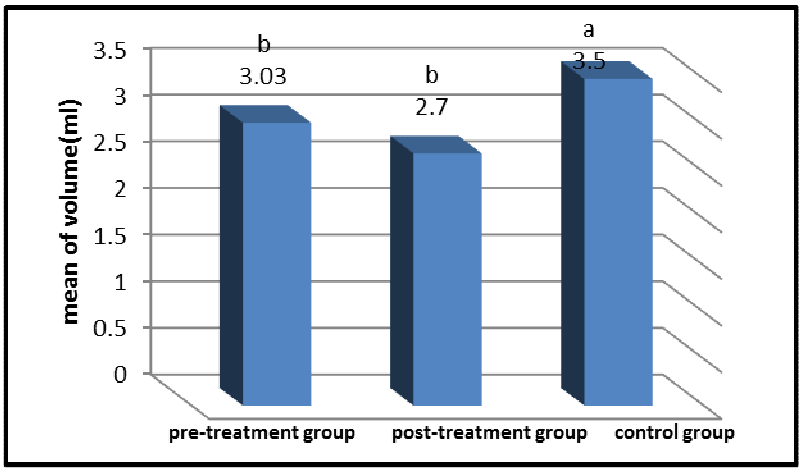

Figure (1): the effect of finasteride drug on the mean of semen volume (ml) in study groups.

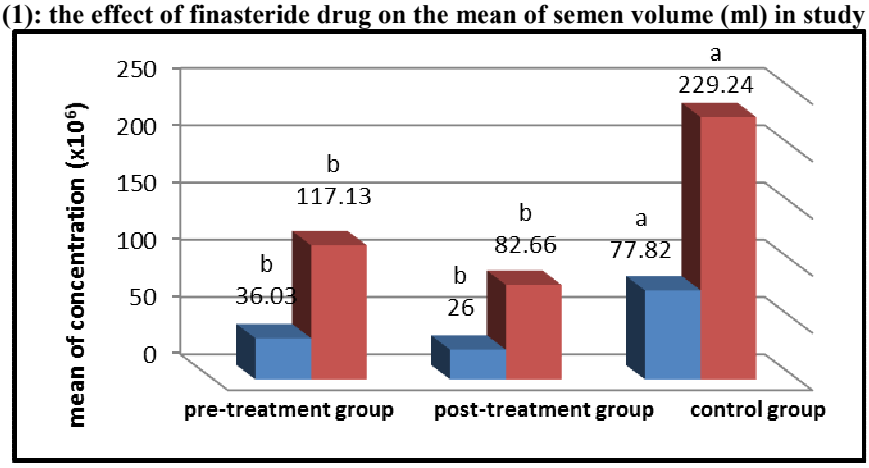

Figure (2): the effect of finasteride drug on the mean of concentration (count, total count) of semen for study groups.

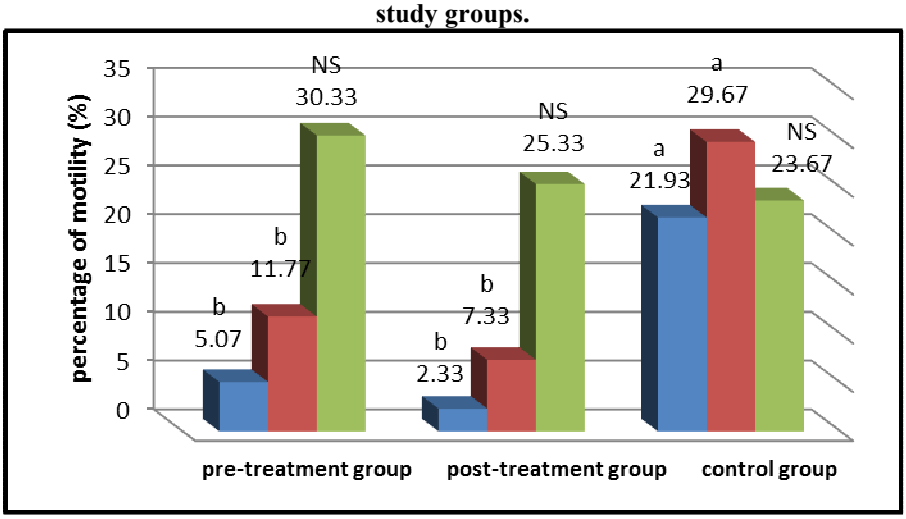

Figure (3): the effect of finasteride drug on the percentage (%) of motility (High ,Moderate, Weak) in study groups.

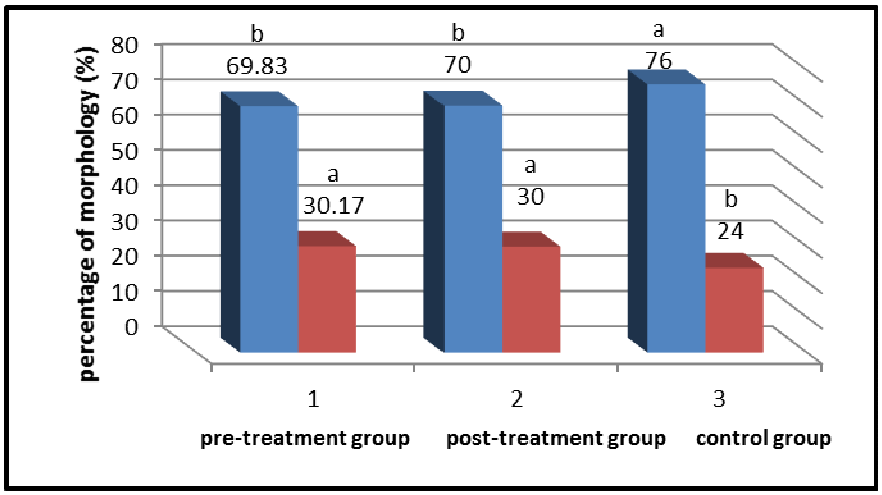

Figure (4): the effect of finasteride drug on the percentage (%) of morphology (normal ,abnormal) in study groups.

Table (1): The effect of finasteride drug on the mean ± SD of semen parameters in study groups.

Parameters		Pre-treatment group	Post-treatment group	Control group	P value
Volume(ml)		b 3.03 ± 0.69	b 2.7 ± 0.70	a 3.5 ± 0.57	0.000**
Concentration	Count(x10^6)	b 36.03±14.14	b 26 ± 13.91	a 77.82 ±38.67	0.000**
	T.Count (ejacul./x10$^{6)}$	b 117.13±49.81	b 82.66±49.49	a 229.24±120	0.000**
Motility (%)	High (%)	b 5.07±4.37	b 2.33±2.58	a 21.93±7.54	0.000**
	Moderate (%)	b 11.77±7.93	b 7.33±4.16	a 29.67±9.11	0.000**
	Weak (%)	30.33± 13.57	25.33±18.46	23.67±8.04	NS 0.262
Morphology (%)	Normal (%)	b 69.83±1.59	b 70±0.0	a 76±7.60	0.000**
	Abnormal (%)	a 30.17±1.59	a 30 ± 0.0	b 24± 7.60	0.000**
				*P <0.05 is significant	**P <0.01 is significant

Conclusions

This study conducted to the BPH affected on the fertility parameters(volume, concentration, motility ,and morphology) by observed the significant differences in fertility parameters in pre-treatment and post-treatment group compared to control group ,and the 5-alph reductase inhibitor (finasteride)cause deceasing significantly in fertility parameters in BPH patients.

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