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THE IMPACT OF VOLUME OF PROSTATE ON SEMENOGRAM IN INFERTILE MEN- A CROSS-SECTIONAL STUDY

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ABSTRACT
Prostate is a male accessory sex organ vital for normal fertility. Secretions of prostate gland play a crucial role in protection of sperm within the female reproductive tract. The objective of the present study is to evaluate the status of prostate volume and its impact on semen characters in the different infertile male subgroup. The study being conducted in Mediwave IVF and Fertility Research Hospital (MIFRH) Mysore, Karnataka, India. A group of 274 males aged between 21-50 years, clinically diagnosed with infertile or sub-fertile conditions were included as cases and 130 men with proven fertility were considered as control group. Semen samples were collected and processed according to WHO guidance. The dimensions of prostate glands were measured using Trans Rectal Ultrasound Scan and values were tabulated. A significant decrease (p<0.05) in prostate dimensions were observed among the infertile men (12.38±3.98cc) when compared to the control subjects. Further it is evident that the reduced mean value of the prostate is observed in azoospermic and oligospermic infertile male groups but idiopathic cases showed increased prostate volume when compared to control group. Correlation study showed association between altered prostate volume with abnormal semen character which demonstrates the altered functional status of the spermatozoa.

KEYWORDS: Prostate glands, TRUS, spermiogram, male infertility.

INTRODUCTION
Infertility is a common clinical problem, with 15% of couples unable to conceive with regular unprotected intercourse over a year period.[1] The etiology of infertility is multifactorial. Twenty percent of infertility cases are secondary to male factor alone and 50% of all infertility cases have a male factor component.[2] Approximately 8% of men of reproductive age seek medical attention for infertility problems.[3] Up to 12% of male infertility cases are caused by male genital tract infections, including prostatitis, epididymitis, and orchitis.[4] Male genital tract infections are a major and correctable etiology of male infertility. Prostatitis has been linked with male infertility and treatment may restore male reproductive function. Earlier studies have reported that 0.5–7.9% of men were reported with anatomical changes in prostate gland.[5] All available literature mainly focuses on pathology of prostate such as Prostatitis, benign prostatic hyperplasia (BPH), prostatic cysts and infertility. But till today not much information is available on the comparison of prostatic volume in infertile and fertile individuals. Generally urologist concentrate on enlarged prostate which interfere normal fertility potentials but regression of prostate is most deserted and is considered among the poorly understood medical problems. Systematic studies on reduced prostate volume in correlation with varied semen parameters are sparse. Several biochemical markers are traced in the seminal fluid which is involved during the time of ejaculation and prostatic secretion is one among them.[6] The secretions of the accessory glands may not be absolutely essential for fertilization but they optimize condition for sperm motility, transport and survival in both the semen and female reproductive tract.[7,8] The prostate gland is the largest male accessory genital gland, weighing approximately 20 g.[9] A healthy human prostate is classically said to be slightly larger than a walnut, any variation in the volume indicates pathology. Hence an attempt has been made to evaluate the dimensional variation of prostate gland by Trans-rectal ultrasound scan among infertile and fertile individuals with respect to different sperm characters.

MATERIALS AND METHODS
After obtaining the institutional ethical clearance from the University of Mysore (IHEC-UoM No. 54/Ph.D/2011-12) and with the informed written Consent from the cases and control subjects present study was conducted in Mediwave IVF and Fertility Research Hospital (MIFRH), Mysore, Karnataka, India, over a period of 3 years, January 2010 to Jan 2013. A total of 274 males of age group 21 to 50 years who had

the inability to have a child and 130 normozoospermic men with proven fertility were included in the present study. A detailed family, medical and reproductive history and life style factors including age, duration of married life, duration of infertility, frequency of coitus, premature ejaculation, psychological status, libido alcoholism, smoking and substance abuse were recorded. Special conditions like occupational exposure to radiation, heat and pesticides were recorded. Significant past history of infection like mumps, measles, pneumonia, sexually transmitted diseases (STD), tuberculosis and any surgical procedure were also noted. A thorough general physical, genital and systemic examination were conducted. Prostatitis, benign prostatic hyperplasia (BPH), prostate cysts, and calcification in prostate gland, anemia, tuberculosis and diabetes mellitus were excluded. Clinical dimension of prostate gland was confirmed by TRUS procedure.

Semen collection and preservation

Semen samples were collected in the laboratory room in a clean, dry, sterile biologically inert container after 3-5 days of ejaculatory abstinence by the process of masturbation (WHO, 2010). In case of oligospermics or azoospermics, repeated three samples were collected with three days interval. The collected samples were allowed to liquefy at 37°C for 30 minutes and analyzed within one hour of collection.

Semen analysis

Single blended semen analysis was done. Physical and microscopic examinations were conducted with respect to liquefaction time, color, pH, count, density, motility, and morphology of the sperm according to WHO protocol (2010). Absence of spermatozoa's was confirmed by the centrifuged pellets in Azoospermic cases. Seminal citric acid level were estimated by Polakoski and Zaneveld, (1977) method.[10]

Examination of Prostate through TRUS

Transrectal ultrasound (TRUS) has the advantage of being non-invasive technique which allows visualization of seminal vesicles, prostate and ejaculatory ducts. Procedure was performed in lithotomy positions. Knee joints were supported using supportive strands attached to a gynecological examination table. The patients were explained the technique of the scanning. The ultrasound transmission gel was applied to the endorectal transducer and it was covered with a sterile probe or a sterile condom. 7.5MH_2 transducer was used in this study. Scanning begins in the axial plane, and the base of the prostate and seminal vesicles were visualized first. A small amount of urine in the bladder facilitates the examination. Volume assessment of the prostate is an important and integral part of this procedure. Several formulas have been used, the most common of which is the ellipsoid formula, which requires measurement of three prostate dimensions. The length and breadth of the prostate was taken in the longitudinal axis of the prostate. Thickness was taken in the transverse axis. Prostatic volumes were calculated by using the ellipsoid volume formula of: length × breadth × thickness × 0.52.

This was available in inbuilt calculator of volume in the software of the scanning machine. Prostatic scanning was done in various slices. The prostate is divided into three zones such as the central zone comprises the central part of the gland which surrounds the urethra and is often hyperechoic. The transition zone portion of the gland is between the central zone and peripheral zone. The transition zone is often filled with cystic spaces in patients with benign prostatic hyperplasia (BPH). The peripheral zone forms most of the gland. It is the sub-capsular portion of the posterior aspect of the prostate gland that surrounds the diatal urethra. Echoes are described as isoechoic and closely packed. Scanning at the level of the verumontanum and observation of the Eiffel tower sign (anterior shadowing) help to identify the urethra and the verumontanum. The prostate distal to the verumontanum is mainly composed of the peripheral zone. The capsule is a hyperechoic structure that can be identified all around the prostate gland. Several hypoechoic rounded structures can be identified around the prostate gland. These are the prostatic venous plexi. The position of the neurovascular bundles can often be identified by the vascular structures. Imaging in the sagittal plane allows visualization of the urethra. Even the median lobes of the prostate are often visualized through TRUS.

Statistical analysis

The obtained data were recorded and analyzed using statistical software SPSS version 14. Independent't'-test and one way analysis of variance (ANOVA) was employed to analyze the significant mean difference between case and control groups. Pearson correlation analysis was done to find out the significant co-relation between prostate gland with different semen parameters

RESULT

Comparison of different semen characters between infertile and control groups was depicted in table 1, significance difference in the all the semen characters was observed (p<0.05). The Results of the Trans rectal ultrasound scanning (TRUS) of prostrate gland was depicted in table 2, which showed significant (p<0.05) decreased in the prostate mean volume in the infertile subjects case (12.38±3.980cc) when compaierd to control subjects. Table 3 shows the condition wise distribution of TRUS analysis of prostate gland, where azoospermia (11.0±0.45) and oligospermic (12.4±0.42) condition showed decreased in the volume but idiopathic subject showed increased in the mean prostatic volume (14.3±0.72) compaierd to control. Comparison of seminal citric acid level between infertile and controls were depicted in table 4. No significant mean differences found to be exist between both the study groups but decrease in the seminal citric acid was observed in the azoospermic and Oligo-Astheno-Teratozoospermic (OAT) infertile conditions than the control (table 5).

Further it is also observed that the increased seminal citric acid level in asthenospermic conditions. Correlation table showed a significant positive relation between prostate volume with Age, BMI and different semen variables like semen volume, sperm count, total sperm count, motility, morphology and viability (Table 6). Figure 1, Illustrates the ultrasound scanning of prostate gland in different infertile condition, plate A shows the transverse and longitudinal view of normal prostate gland. B & C: Image of Ultrasound scanning of the prostrate with calcification in different subjects D: Image of Ultrasound scanning of the prostate with midline cyst.

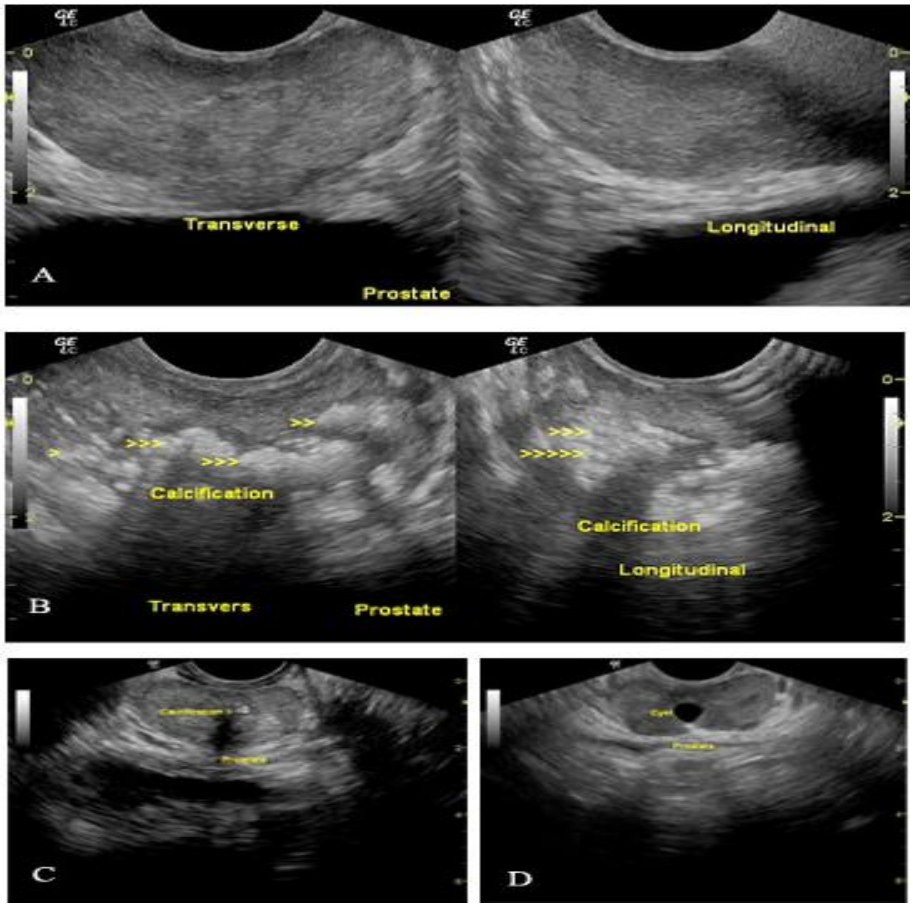

Figure 1:
A: Image of Ultrasound scanning of the normal prostate in transverse and longitudinal view.
B & C: Image of Ultrasound scanning of the prostrate with calcification in different subjects
D: Image of Ultrasound scanning of the prostate with midline cyst.

Table 1: Comparison of different semen characters between infertile and control groups

Semen parameters	Condition	N	Mean± Std. Error	t test	*P value*
Seminal volume	Infertile	163	1.68±0.01	3.323	0.001*
Sperm count	Control	130	1.96 ± 0.06		
	Infertile	163	20.5±1.8	5.949	0.001*
Total sperm count	Control	130	62.9±1.9		
	Infertile	163	33.9±3.5	13.566	0.001*
Sperm motality (a+b)	Control	130	125.0±6.07		
	Infertile	163	20.0±1.46	15.469	0.001*
Morphology	Control	130	55.6±0.9		
	Infertile	163	8.5±0.6	13.566	0.001*
Viability	Control	130	17.3±0.7		
	Infertile	163	50.4±1.7	19.158	0.001*
pH	Control	130	72.1±0.9		
	Infertile	260	8.0±0.03	8.851	0.001*
	Control	128	7.7±0.02		

Liquefaction time (min)	Infertile	260	47.2±2.5	10.314	0.001*
	Control	129	43.7±3.3		

Azoospermic condition (N=97) is excluded for sperm parameters like count, motility, viability and morphology. Aspermic condition (N=14) is excluded for all the semen parameters.
**p* is significant at the 0.05 level

Table 2: Description of the study groups for prostate volume assessment, cc=cubic centimeter.

Condition	Number of study subjects	Prostate volume (cc)	t	Sig. (2-tailed)	95% CI	
Infertile	274	12.38±0.25	2.89	0.004*	2.66	0.87
Control	130	13.71±0.4				

***p* is significant at the 0.05 level**

Table 3: Distribution of prostatic volume between different infertile and control subjects

Conditions	N	Mean± Std. Error (Prostate volume in cc)	95% CI		F value	*P value*
			Lower Bound	Upper Bound		
Aspermia	14	13.2±1.71	9.5036	16.9121	4112	0.001*
Asthenospermia	29	13.7±0.82	12.0140	15.3984		
Azoospermia	97	11.0±0.45	10.1668	11.9794		
Oligospermia	75	12.4±0.42	11.5699	13.2451		
OAT	44	13.1±0.57	11.9510	14.2831		
Idiopathic	15	14.3±0.72	12.8315	15.9552		
Control	130	13.7±0.41	12.8875	14.5456		

***p* is significant at the 0.05 level**

Table 4: Comparison of seminal citric acid level between infertile and control male groups. (N=Number of subjects).

	general	N	Mean± Std. Error Mean	t-value	p value
Seminal citric acid	Infertile	101	43.56±5.4	0.110	0.913
	control	54	44.42±3.1		

Table: 5 Distribution of levels of seminal citric acid between different infertile and control subjects.

	N	Mean± Std. Error	95% CI		F value	*P-value*
			Lower Bound	Upper Bound		
Asthenospermia	13	66.3±22.3	17.6378	115.1160	1.263	0.283
Azoospermia	34	34.3±4.24	25.7249	43.0040		
Oligospermia	32	43.2±12.2	18.2458	68.1604		
OAT	11	31.6±6.8	16.4670	46.9057		
Idiopathic	11	57.9±18.8	16.0302	99.9662		
control	54	44.4±3.1	38.1637	50.6941		

***p* is significant at the 0.05 level**

Table: 6 Pearson correlation between prostate volume and different parameters.

	BMI	SV	SC	TSC	TSM	Morphology	Viability	Prostate
Age	0.151**	0.059	-0.057	-0.024	-0.076	-0.025	0.022	0.139**
BMI		0.052	-0.041	-0.021	-0.018	0.064	0.015	0.163**
SV			0.152**	0.395**	0.202**	0.185**	0.204**	0.216**
SC				0.883**	0.817**	0.588**	0.753**	0.154**
TSC					0.751**	0.569**	0.666**	0.247**
TSM						0.653**	0.823**	0.176**
Morphology							0.681**	0.155**
Viability								0.174**

SV=Seminal Volume, BMI=Body Mass Index, SC=Sperm Count, TSC=total Sperm count, TSM=Total Sperm Motility, **(**Azoospermic condition is excluded for sperm parameters like count, motility, viability and morphology. Aspermic condition is excluded for all the semen parameters.
* Correlation is significant at the level 0.05, ** Correlation is significant at the level 0.001

DISCUSSION

Physical abnormality of the male reproductive tract is mainly due to structural abnormalities that can injure or block the functional aspect of testes, epididymis, seminal ducts, or prostatic utricles and ultimately decrease the fertility. Widespread implementation of imaging techniques such as TRUS and End rectal MRI has increased the detection of anatomical changes such as cystic lesions of the prostate.[5,11] Prostate pathology such as Prostatitis, BPH, prostatic cysts is well established factor for male infertility.[12] We direct our study on the sole factor, that the association of male infertility and reduced prostate volume in cases who were not suffered from any of the causes resulting in reduced prostate volume with no female factor infertility. The result of this study reveals that there may be a positive relation between reduced prostate volume and male fertility.

In the present investigation, a considerable number of infertile subjects, were found with a decreased prostate volume (< 12 cc) with a $p<0.05$ (Table 1) when compared to the normal ranges (12-20 cc) with different value of deviation from 0.2 cc to 8 cc which is statistically significant. The Decrease in the semen quality was also evident in our study could be due to reduced prostate secretions may be the underlying etiology for varied semen quality.

Normal human ejaculate volume ranges from 1.5 to 5 ml. Mature spermatozoa represent a minimal amount of the total ejaculate volume. The main contribution to ejaculate volume is from the secretions of the sex accessory glands including the seminal vesicles, prostate, and epididymis. Prostatic secretions contribute up to 30% of semen volume. In general as such human semen has high buffering capacity compared to most of the other body fluids. This enables the semen to maintain the pH near neutral in the acidic vaginal environment.[13] During ejaculation, the prostatic capsule and vas deferens simultaneously contract, secreting a homogeneous, serous, slightly acidic fluid (pH 6.8). Reduction in the size of prostate may reduce prostate secretion hence semen volume, is probably reduced and spermatozoans were unable to sustain. Decreased motility and morphological changes of the sperm was probably due to reduced micronutrients which were abundant in the prostate secretion such as high amount of zinc, citric acid, calcium, phosphate, which are important for sperm function[8]. Prostate gland has highest concentration of zinc in the human body.[14] The concentration of zinc increases at puberty and reaches the maximum level at 34–40 years of age. (15) Stabilization of chromatin in human sperm is mainly dependent on zinc concentration[16], loss or deduction in zinc concentration causes DNA damages such as fragmentation.[17] Zinc plays an essential role in male reproduction as an antimicrobial agent.[18] Sperm development is depended on angiotensin converting enzyme (ACE) whose activity depends on zinc concentration hence deficiency of zinc may lead to ACE impairment and subsequent testosterone depletion, as well as decreased spermatogenesis[15]. Hypoplastic prostate resulting insufficient secretions might have resulted in zinc deficiency resulting morphological changes in spermatozoa in our study.

Another important component of prostate secretion is citric acid which is at high concentrations in prostate secreted by prostatic epithelial cells.[19] The level of citric acid in prostate is 100 folds more than seminal vesicle,[20] which plays an important role in prostatic function and maintains seminal pH.[21] In the present investigation estimated citric acid levels between controls and in infertile cases, as well as different infertile conditions though less but statistically not significant. Apart from mitochondrial index increased sperm motility is influenced by prostatic profibrinolysin which lyses the semen coagulum, leading to increased motility of sperm.[22] This allows sperm progression within the female reproductive system and ultimately encourages fertilization and pregnancy. The importance of prostate gland is also evidenced by the conversion of free testosterone into dihydrotestosterone (DHT), a potent androgen that is 2–10 times more active than testosterone 5 -reductase type 2 enzymes is necessary for male external genitalia growth.[12] Varied testosterone levels between cases and control subjects once again accent the importance of prostatic secretions.

Even variation in the levels of Prostate specific antigen (PSA) is a member of the human kallikrein gene family and is secreted by the prostate gland into the seminal fluid at high concentrations.[23] PSA functions in the liquefaction of seminal ejaculate to encourage sperm motility. Prostatic secretion play a vital role in liquefaction of semen the ejaculate coagulum prevents loss of semen out of the vagina just after ejaculation. However, liquefaction must occur to enable sperm to become motile and progress into the upper regions of the female reproductive tract. PSA is elevated in the presence of many prostatic diseases, including inflammation, malignancy, and benign prostatic hyperplasia.[23] Varied liquefaction was well marked in the present investigation could be due to reduced PSA may perhaps a factor in abnormal semen parameters among individuals with hypoplastic prostate gland.

In our study, the prostate volume was calculated from control comprising healthy normal men who had 13.71 cc who initiated pregnancies earlier. The composite score calculated with respect to Seminal volume, Sperm count, Total sperm motility, Liquefaction time (Table 1) for these men was representative of the fertile group, and scores significantly above the scores of the patients being infertile. Furthermore, using the area under the curve for these variables the probability

of correctly identifying patients in any given clinical diagnosis as either fertile or infertile can be achieved.

CONCLUSION

In conclusion, our study describes the size of prostate as revealed in TRUS, a novel measure of semen parameters in discriminating between fertile and infertile men. We found that infertile men with male factor or idiopathic diagnoses had significantly varied in prostate volume than controls. Therefore, the prostate volume may serve as an important measure in identifying the deficiency in semen parameters in those patients with a clinical diagnosis of male infertility.

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