Predicting The Ability To Successfully Retrieve Sperm In Infertile Men With Non-obstructive Azoospermia

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Research article

Keywords: testicular volume; hormonal profile; sperm retrieval; non-obstructive; azoospermia

Posted Date: July 3rd, 2019

DOI: <https://doi.org/10.21203/rs.2.11012/v1>

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Abstract

Objectives: to determine the ability of pre-surgical markers to predict the ability to retrieve sperm in non-obstructive azoospermia (NOA) undergoing surgical sperm retrieval. **Methods:** a cross-sectional descriptive analysis of 136 infertile patients with azoospermia, examined in the Hue Center for Reproductive Endocrinology and Infertility (HUECREI), Hue University Hospital from August 2014 to July 2018. Patients underwent surgical sperm retrieval in a stepwise manner via percutaneous epididymal sperm aspiration (PESA), testicular sperm aspiration (TESA) then testicular sperm extraction (TESE) until sperm were detected. Patient age, duration of infertility, body mass index (BMI), hormonal profile (FSH, LH & testosterone), and testicular volume were analyzed to determine the predictor of successful sperm retrieval. Analysis was done by univariate & multivariate generalized estimating equation modeling where the primary outcome was sperm retrieved at surgery. **Results:** In total of 136 infertile men with azoospermia, beside 45 cases with OA, surgical sperm retrieval was successful in 22/91 patients with NOA (24.2%). The group of men with successful sperm retrieval were more likely to live in urban area ($P=0.012$), higher proportion of normal testicular density ($P<0.05$), lower serum FSH and serum LH ($P<0.001$). By multiple logistic regression model, total testicular volume was found to be a only considerable predictor of sperm retrieval in NOA group (OR 1.09, 95%CI 1.013-1.178, $P=0.022$). **Conclusions:** The measurement of total testicular volume can be helpful for predicting the successful result of surgical sperm retrieval in Vietnamese infertile men with non-obstructive azoospermia. **Key words:** testicular ultrasound; endocrine profile; surgical sperm retrieval; non-obstructive; azoospermia.

Background

Azoospermia, reported in approximately 1% of male and 10 – 15% of infertile male, is one of the major reproductive disorders of male infertility [1]. It includes non-obstructive azoospermia (NOA) and obstructive azoospermia (OA) [2]. OA is less common than NOA and occurs in 15 to 20% of men with azoospermia [3]. NOA indicates impaired sperm production of the entire testis, although it has been observed that focal normal spermatogenesis can occur in 50-60% of men with NOA [4].

Abnormal spermatogenesis may be caused by any factors related to the hypothalamic – pituitary – testicle axis [5]. Due to the pathophysiology, OA patient may be treated by surgery to solve the obstruction if the etiologies are investigated accurately and the couple is able to conceive naturally [6]. In clinical practice, almost infertile man with azoospermia is appointed surgically sperm retrieval to extract sperm for treatment by assisted reproductive techniques.

Although there are different approaches for sperm retrieval including PESA (Percutaneous Epididymal Sperm Aspiration), TESA (testicular sperm aspiration) and TESE (testicular sperm extraction), these procedures are invasive with varying success in sperm extraction. Since mature sperm are not found in some cases, invasive procedures of sperm retrieval may be futile. Thus, it will be important to be able to predict spermatogenesis with the use of noninvasive testing. At present, accurate means of predicting spermatogenesis and sperm retrieval success do not exist.

Serum FSH and LH have been reported as important preoperative markers reflecting the testicular function [5]. Serum FSH and LH concentration is inversely related to sperm retrieval rate [7]. In a recent meta-analysis reported by Qi Yang *et al.*, FSH had moderate value in independently predicating successful sperm retrieval rate in men with NOA (area under curve >0.7). Therefore, they suggested that more detailed diagnostic testing should be anticipated in the future to confirm the diagnostic value of other noninvasive parameters [8].

Scrotal ultrasound has become a more common method in the assessment of testicle. Measuring the testicular volume by ultrasonography followed by the Lambert formula was the most accurate method [9]. Testicular volume has been noted to have a direct correlation with semen profiles [10] as well as the ability of sperm production in male [11]. In reality, many of studies demonstrated that testicular volume do not reduce in OA cases, spermatogenesis in these patients are normal so that sperm retrieval rates by PESA or TESA reaches approximately 100% [12]. Therefore, testicular volume is not considered as a prediction factor for sperm retrieval surgery outcome in OA patient in generally.

It is reported that the successful recovery of spermatozoa changes considerably from 16.7 to 45% of NOA cases and therefore the prediction of the success rate of sperm retrieval is very necessary before attempted surgery [11, 13]. So far, although there are numerous studies published, no single clinical finding or test that is able to exactly predict successful sperm retrieval has been found. Furthermore, the variety of optimal cut-off values for testes volume and endocrine profile for infertile males have been reported [7, 14-19] possibly due to the effects of study population and ethnicity [20]. This study aimed to identify pre-surgical markers that would predict successful sperm retrieval in Vietnamese infertile male with non-obstructive azoospermia.

Methods

Patient selection and evaluation

This was a cross sectional descriptive design which included 136 infertile males with azoospermia on semen analysis based on World Health Organization (WHO) 2010 standard criteria, who presented in the Hue Center for Reproductive Endocrinology and Infertility (HUECREI), Hue University Hospital from August 2014 to July 2018. Azoospermia is diagnosed by the complete absence of spermatozoa in the semen after two different centrifuged samples (3000 x g for 15 minutes) [2]. Azoospermia patients with successful PESA were categorized into OA group, the data of patients with OA were analysis particularly (Flowchart). The remaining were classified as NOA group; in our study, all of analyses, comparisons and discussions will concentrate on NOA group. Patients with acute systemic diseases, acute urinary tract infection, hepatic function disorders, malignant diseases, retrograde ejaculation, hypogonadotropic hypogonadism were excluded. All patients' general characteristics were recorded.

Scrotal ultrasound technique

Testicular ultrasound was performed to evaluate testicular echogenicity and homogeneity in 2D Ultrasound and the presence of varicocele was assessed in color Doppler ultrasound (CDUS). Ultrasounds were

performed in a warm room with the patient in a supine position and the penis resting on the lower abdomen. The testes were examined in two planes, along the long and transverse axes and each testicle was measured in three dimensions (length, width, height). The volume was then calculated by Lambert formula $V=0.71 \times L \times W \times H$. We used a high frequency linear probe (7.5MHz) for both power and spectral CDUS with Samsung Medison R5, Korea. Assessment of varicocele was done by measuring largest diameter and reflux in the vessels before and after Valsalva maneuver. Color Doppler parameters were optimized for the evaluation of slow flow (wall filter at minimum levels, gain at the maximum level permitted by the presence of artifacts, elective focus on the region of interest) and standardized using a simplified version of Sarteschi classification [21]. All examinations were taken by the same ultrasonographer.

Hormone assays

Venous blood samples were collected on the day of recruitment after the second semen analysis confirmed azoospermia. LH, FSH, and total testosterone levels were assessed by electrochemiluminescence (ECLIA) using Elecsys and Cobas E immunoassay analyzers (Cobas 4000/6000, Roche Diagnostics, Indianapolis, USA). The FSH's inter-assay coefficient of variation (inter-assay CV) is 3.95%, LH's is 2.1%, and testosterone's is 3.35%. All measurements were performed at the Hue University Hospital laboratory as per manufacturer instructions.

Surgical sperm retrieval procedures

All patients were underwent surgical sperm retrieval in HUECREI via three techniques: PESA, TESA, TESE consecutively, until sperm was found. Each procedure was carried out on the right and then left testis in turn. In the PESA procedure, the needle was gently advanced into the epididymis and the aspirated fluid was checked for sperm. TESA was done with a 20G butterfly needle in 3 different positions on the testis while applying suction with a 1ml Becton-Dickinson syringe. If both TESA and PESA failed to retrieve sperm, TESE was then performed by making a small incision (2 cm), just above each side of the testis, resecting a piece of testicular tissue and examining it under a microscope at x300 magnification to detect spermatozoa. The surgical procedure was stopped at any step once the lab staff found sperm successfully or after unsuccessful TESE on both sides, that is, if no sperm found at all.

Statistical analysis

Statistical analysis was carried out using SPSS software, version 20.0. NOA patients with successful vs unsuccessful sperm recovery were compared with Chi-square test, independent sample T-test or Mann-Whitney U as appropriate. Multiple logistic regression and generalize estimating equations were used to assess which factors were independently correlated with a successful sperm recovery. The backward stepwise method with condition significance level as 0.25 was carried out to selection independence variables in multiple logistic regression model. Fitting model was applied by using the R^2 ; AIC and AUC parameters. The prognosis of successful of sperm retrieval (SR) based on testicular volume which illustrated statistically significant in the final multiple logistic regression model. The probability of successful in SR and 95 confidence interval was illustrated by graph after adjustment with other covariates. The threshold for statistical significance was confirmed with $P < 0.05$.

Results

A total of 136 azoospermic patients, including 45 OA and 91 NOA. With 91 cases of NOA, we divided into two groups according to the result of surgery, surgical SR was successful in 22 of 91 patients (24.1 %). The age range of successful group was 26 - 70 years (mean of 36.7 ± 9.7 years) whereas the range was 24-50 years (mean 33.8 ± 5.7 years) for the patients in the unsuccessful group.

Table 1 shows the general and clinical characteristics of the patients stratified according to SR. There was no significant difference between the groups of patients with successful and unsuccessful SR in terms of the patient's age, geography, education, occupation, infertility duration, mumps, and history of surgery. There were significant differences in geography and testicular density between the 2 groups (0.012; 0.024, respectively).

Table 2 shows the endocrine tests of the patients according to SR. In the bivariate analysis, LH and FSH were statistically associated with result of SRs. The mean LH level of successful group of NOA was a half of that of unsuccessful group (6.34 mIU/ml compared to 13.42 mIU/ml, $p=0.0001$). Likewise, the mean FSH level of successful NOA was a quarter of that of unsuccessful NOA ($p<0.001$). Table 2 also shows the ultrasound parameters of the patients. With the exception of varicocele, all other parameters differed significantly between the two groups. Patients with successful SR had a greater mean testicular total volume than unsuccessful SR ($22.84 \pm$ ml versus $9.0 \pm$ ml, $P<0.001$). Generally, the OA patients had the characteristics of successful group with lower of LH, FSH level and greater mean testicular volume.

Analysis of the association between parameters of scrotal ultrasound and the result of SR (adjusted with age and FSH) showed for every unit increase in total volume, the chance of successful SR rises approximately by 11% (95%CI 1.3% - 18.0%; $P=0.022$) (Table 3).

Discussion

The study investigated the predictive value of ultrasound parameters and hormone level for successful SR in azoospermia. The results have shown that higher testicular volume is a good predictor for successful SR. The SR rate in this study was 24.2% (with NOA patients). SR rates ranged from 16.7 – 48.8% in the conventional TESE [11, 22]. Ramasamy *et al*/reported SR rate was 32% with conventional TESE and 57% with Micro-TESE, Ishikawa T *et al*/shown that SR rate was 42% as they performed Micro-TESE for NOA patients [23, 24]. The different results between these studies could be partially explained by the different characteristics of the patients (OA, NOA) and sperm recovery methods (TESA, PESA, TESE or Micro-TESE).

FSH is a glycoprotein that stimulates Sertoli function and some studies considered that it concerned to androgen production, which are necessary for fertility. Azoospermia has been a consistent finding in men with loss of function mutations in FSH β [25]. Serum FSH could predict the existence of sperm which was retrieved by conventional TESE [24]. Elevated plasma levels of FSH above 19.4 mIU/mL can suggest no spermatogenesis and hence unsuccessful SR [16]. Although FSH is useful marker for evaluation of the presence of sperm in NOA patients, it is dependent to the pathologic etiology of azoospermia and may not always be a good predictive factor [19, 20]. The different demographic characteristics in each study may

explain these differences in the results. Li *et al.* considered FSH to only reflect the global spermatogenesis function but stated that FSH cannot determine the function of an isolated area in a testis. Micro-TESE is able to retrieve sperm even if the spermatogenesis function of the testis was very low, which could be the reason why FSH could not precisely predict the SR rate of micro-TESE [20]. In our study, we found that the FSH levels did indeed differ greatly in patients with whom sperm was retrieved successfully vs patients where sperm was not retrieved (see table 2).

LH was not commonly investigated as a predictor of SR outcome. In contrast to FSH, LH appears to have little role in spermatogenesis outside of inducing gonadal testosterone production. Cissen *et al.* found that LH was predictive for successful SR [7]. Enatsu *et al.* demonstrated older age and non-idiopathic etiology were significantly associated with the probability of successful SR; however, they found no significant effects of testicular volume, FSH, LH, or testosterone on SR [17]. We found that LH seemed to be higher in unsuccessful patient than successful patients, with 13.42 mIU/ml and 5.86 mIU/ml, respectively ($p = 0.0001$).

In our study, varicocele was found in 13 cases (11.2%). Varicoceles were present in 26% of Chinese infertility patients [26]. The diagnosis of varicocele by spectral Doppler analysis has a sensitivity of approximately 97% and a specificity of 94% [27]. Although the relation between varicocele and male infertility has been demonstrated in many studies, the exact mechanism of the effect of varicocele on spermatogenesis is still unknown [26]. In our study, there was no significant difference between varicoceles and SR outcome. Scrotal ultrasound has a role in the diagnosis of the etiologies of male infertility. Abdulwahed *et al.* divided 268 infertile males into OA versus NOA based on histopathology, they found that decreased testicular volume and varicoceles (intra- and extra-testicular) were the most common abnormalities of NOA patients using ultrasonography. In contrast, epididymitis, spermatocele and duct ectasia were the most common in OA patients with a sensitivity 87% but only 30% specificity. Therefore scrotal ultrasound is used to exclude these diagnoses [14].

In this study, the mean total testicular volume of NOA was 13.67 ± 12.1 ml (Right testis 6.77 ± 5.8 ml, left testis 6.9 ± 6.66 ml). Sharath *et al.* (2013) found, mean testicular volume is 15 ml (right testis 7.62 ± 4.056 ml, left testis 6.99 ± 3.60 ml) in male with abnormal semen analysis [10]. There is a distinction in selection of sperm recovery methods in OA patients (TESA, Percutaneous Biopsy, PESA, MESA) vs NOA patients (TESE, micro TESE). Testicular volume was found to be statistically significant between OA and NOA (mean testicular volume of OA and NOA patients are 11.6 ml and 8.3 ml, respectively, $p < 0.05$) [28]. Huang *et al.* showed that a combination of FSH > 9.2 mIU/ml and right testis size < 15 ml might be used to distinguish NOA from OA, the positive predictive value for NOA was 99.2% and 81.8% for OA [18]. There was a significant difference in testicular volume between successful and unsuccessful SR group (22.84 ml versus 9.0 ml, $P < 0.001$), higher testicular volume increased the chance of a successful SR. With a total volume lower than 7.8 ml there is a 96.47% of having absence of sperm, and with a total volume higher than 28 ml there is of 88.89% chance of sperm present in the sample. Tang WH *et al.* and Enatsu N *et al.* found that testicular volume of successful SR was higher than that of unsuccessful SR but there was no statistical significance between the two groups [17, 29]. Salehi *et al.* (2017) performed TESE and micro-TESE in 170 NOA patients and found that testicular volume was related to surgical SR results (OR, 10.5, $p < 0.01$) [11]. The result was similar to

Boitrelle's study [15]. In OA sperm production was totally normal so SR rate by TESA or PESE was very high. Levine *et al.* assessed the effect of PESA and TESA in NOA and OA and found that SRR in NOA was 47% and OA this rate amounted to 100% [12].

In fact, it is difficult to predict the outcome of surgical SR with only testicular volume or any hormone values as well because many factors can affect process of spermatogenesis so a combination of these values might prove to be more reliable. After multivariate logistic regression analysis, the proportion of sperm improved with increasing of total testicular volume particular in NOA patients. It was found that, for every unit increase in total volume, the chance of successful SR rises by approximately 11%. Boitrelle *et al.* found that there was no significant difference between two groups (sperm present and no sperm) with age, testosterone, LH but they found that a combination of FSH concentration, inhibin B, and total testicular volume was the best predictor of TESE outcome (AUC=0.663) [15]. Li H *et al.* analyzed five studies with a total of 1764 cases involving testicular volume and found AUC=0.6389, indicating a low predictive [20]. Some studies showed that testicular volume did not affect the SR rate for micro-TESE. They suggested that testicular volume was an influential factor on successful SR, as it is correlated with spermatogenesis, but topographical variations in testicular pathology can occur, so testicular volume may not be a good predictive factor for successful SR for ICSI [19].

From our research, preoperative variables, namely FSH and testicular volume may predict success of SR in men with non-obstructive azoospermia and the combination of the variables may be even more predictive. Boitrelle *et al.* developed a formula to predict TESE outcome, including three parameters: total testicular volume, FSH and inhibin B, shown to be the best predictor of successful TESE (positive likelihood ratio:+3.01) [15]. Histopathological examination has been the most reliable predictive factor of SRR to date. However, it is not recommended to perform the testicular biopsy just to predict the SRR of microdissection TESE [20]. We believe that the trial for SR should not be denied to any azoospermic men based solely on the values of the preoperative variables. The patient should be informed, prior to the operation that finding mature cells may not be guaranteed (even in cases with normal FSH and testicular volume) and allowed to make an informed decision on whether to proceed.

Conclusions

Although there are numerous studies published and the variety of optimal cut-off values for testes volume and endocrine profile for infertile males have been reported, testicular volume is valuable, noninvasive parameters in predicting SR outcome in Vietnamese infertile male in non-obstructive azoospermia. The combination of different noninvasive parameters should be studied in further researches for the possibility of predicting SR outcomes more accurately.

Abbreviations

ART: assisted reproductive technologies; AUC: area under the curve; BMI: Body Mass Index; CDUS: color Doppler ultrasound; FSH: Follicle stimulating hormone, HUECREI: Hue Center for Reproductive Endocrinology and Infertility; ICSI: intracytoplasmic sperm injection; IVF: in-vitro fertilization; LH: Luteinizing

hormone; NOA: non-obstructive azoospermia; OA: obstructive azoospermia; PESA: percutaneous epididymal sperm aspiration; Se: Sensitivity; Sp: Specificity. SR: sperm retrieval; TESA: Testicular sperm aspiration; TESE: testicular sperm extraction; WHO: World Health Organization.

Declarations

Please include the full name of the ethics committee (and the institute to which it belongs to) that approved the study and the committee's reference number if appropriate in the "Ethics Approval and Consent to Participate" subsection of the Declarations. Please also confirm whether the consent you obtained from study participants was written or verbal. If verbal consent was obtained, please clearly state the reason or if this was approved by the ethics committee.

This work was approved by the Ethics Committee of Hue University of Medicine and Pharmacy, Vietnam. All participants were explained and agreed with written consent form.

Consent for publication: We are all agree to participate and consent for publication

All data and materials are available as requested.

Competing interests: The authors have no competing financial or other interests to declare in relation to this manuscript.

Funding: This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Authors' contributions: L.M.T, N.T.T.T, N.V.Q.H, T.T.N.Q, C.N.T participated in the study design, data collection, data analysis, manuscript drafting and critical discussion. L.D.D participated in data analysis, manuscript drafting and critical discussion. J.M.J, T.D.L, and M.J.H participated in interpretation of data, manuscript drafting and critical discussion. All authors have involved in drafting the work or revising it critically for important intellectual content of the final manuscript.

Acknowledgements: N/A

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Tables

Table 1. General and clinical characteristics of OA and NOA groups

Variables	Total (n=136)	OA (n=45)	Non OA (n=91)		p-value
			Successful (n=22)	Unsuccessful (n=69)	
Age (Mean $\pm$ SD)	35.54 $\pm$ 8.36	37.71 $\pm$ 10.44	36.64 $\pm$ 9.73	33.77 $\pm$ 5.68	0.250
<35	78 (57.3)	23 (51.1)	11 (20.0)	44 (80.0)	
$\geq$ 35	58 (42.7)	22 (48.9)	11 (30.6)	25 (69.4)	
Geography					
Urban	56 (41.2)	19 (42.2)	14 (63.6)	23 (33.3)	0.012
Rural	80 (58.8)	26 (57.8)	8 (36.4)	46 (66.7)	
Education					
School grade	83 (61.0)	27 (60.0)	11 (50.0)	45 (65.2)	0.201
University grade	53 (39.0)	18 (40.0)	11 (50.0)	24 (34.8)	
Occupation					
Office work	47 (34.6)	16 (35.6)	11 (50.0)	20 (29.0)	0.070
Manual work	89 (65.4)	29 (64.4)	11 (50.0)	49 (71.0)	
Infertility type					
Primary	125 (91.9)	39 (86.7)	19 (86.4)	67 (97.1)	0.054
Secondary	11 (8.1)	6 (13.3)	3 (13.6)	2 (2.9)	
Infertility duration (years)	3 (2 -6)	4 (2-7)	2.5 (2-5)	3 (2-5)	
<3 years	56 (41.2)	16 (35.6)	11 (50.0)	29 (42.0)	0.512
$\geq$ 3 years	80 (58.8)	29 (64.4)	11 (50.0)	40 (58.0)	
Mumps					
Yes	46 (33.8)	12 (26.7)	10 (45.5)	24 (34.8)	0.368
No	90 (66.2)	33 (73.3)	12 (54.5)	45 (65.2)	
History surgery					
Yes	20 (14.7)	10 (22.2)	(18.2)	6 (8.7)	0.215
No	116 (85.3)	35 (77.8)	18 (81.8)	63 (91.3)	
Testicular Density					
Normal	77 (56.6)	34 (75.6)	15 (68.2)	28 (40.6)	0.024
Abnormal	59 (43.4)	11 (24.4)	7 (31.8)	41 (59.4)	

OA: Obstructive Azoospermia; SD: Standard Deviation

Table 2. Endocrine tests and characteristics of scrotal ultrasound of OA and NOA groups

Groups Median (IQR)	OA (n=45)	Non OA		p-value
		Successful (n=22)	Unsuccessful (n=69)	
Endocrine tests				
LH (mIU/ml)	5.25 (4.11-6.67)	6.34 (4.17-9.02)	13.42 (7.41-20.52)	0.0001
FSH (mIU/ml)	5.83 (3.76-7.33)	7.66 (4.71-18.97)	27.93 (17.17-36.77)	<0.001
Testosterone (nmol/L)	4.44 (3.21-5.30)	3.29 (2.61-4.04)	3.12 (1.72-4.39)	0.7005
Testicular volume				
Right volume	12.98 (8.86- 14.61)	11.87 (6.26-14.2)	4.40 (1.92-6.61)	<0.001
Left volume	11.81 (9.37-15.51)	10.65 (6.47-16.70)	4.39 (1.67 - 6.61)	<0.001
Total volume	24.46 (19.2-29.28)	22.84 (12.19-32.98)	9.0 (3.91-13.39)	<0.001
Varicocele Right n(%)	1 (2.22)	0 (0.0)	3 (4.35)	N/A
Varicocele Left n(%)	4 (8.89)	0 (0.0)	10 (14.5)	N/A

OA: Obstructive Azoospermia; IQR: interquartile range

Table 3. Multiple logistic regression model for result of sperm retrieval in NOA group.

Factors	Crude OR (95%CI)	Adjusted OR (95% CI)	p
Age	1.06 (0.988 - 1.131)	1.08 (0.979 - 1.196)	0.122
FSH (mIU/ml)	0.92 (0.874 - 0.961)	0.96 (0.903 -1.013)	0.131
Total volume	1.13 (1.061 - 1.196)	1.09 (1.013-1.178)	0.022
R ²	N/A	0.297	
AIC		77.78	
AUC		0.8366	

AIC: Akaike Information Criterion; AUC: Area Under Curve; FSH: Follicle Stimulating Hormone; OR_{Ad}: Adjusted Odds ratio; N/A: non analysis

Figures

Figure 1

Prediction of the successful probability of sperm retrieval based on total testicular volume by adjusted age (35 year old) and FSH 10 mIU/ml and 20 mIU/ml

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [ComplementFlowchartofrecruitment.png](#)