KnE Medicine

ASPIRE Conference Proceedings
The 6th Congress of the Asia Pacific Initiative on Reproduction (ASPIRE 2016), Volume 2016

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Conference Paper

Cut-off Value of Testosterone and FSH Level in Patient with Azoospermia

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Abstract

Follicle-stimulating hormone(FSH) and Testosterone are important for spermatogenesis. Increased serum FSH and decreased testosterone are related to abnormal spermatogenesis. Azoospermia can be classified as obstructive and non-obstructive azoospermia. This study aims to discover cut-off value of Testosterone and FSH in predicting obstructive and non-obstructive azoospermia. From 1064 patients, 120 fulfilled inclusion and exclusion criteria. There were 66.7% in obstructive with 33.3% in non-obstructive group. No difference in terms of age (36,83 vs 36,62 y.o). Testosterone were 405.54 ± 186.14 ng/dL vs 298.84 ± 161.45 ng/dL ($p = 0.002$) while FSH was 8,53 ± 8,43 mIU/mL vs 20,12 ± 11,89 mIU/mL ($p < 0.001$) for obstructive and non-obstructive azoospermia respectively. Average testicular were 17.74 ± 4.03 cc and 17.50 ± 4.23 cc while in non-obstructive group are 12.97 ± 5.18 cc and 13.37 ± 5.31 cc for right and left testis respectively. FSH value above 10.36 mIU/mL has sensitivity 82.1% and specificity 79.5% for predicting non-obstructive azoospermia. Unfortunately, Testosterone could not be used in predicting azoospermia classification. Obstructive and non-obstructive azoospermia could be predicted using FSH but not testosterone serum level. Higher testosterone population should be used for further study.

Keywords: Hormone, FSH, Testosterone, azoospermia, infertility

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Received: 24 August 2016
Accepted: 25 September 2016
Published: 4 October 2016

Publishing services provided by Knowledge E

Selection and Peer-review under the responsibility of the ASPIRE Conference Committee.

OPEN ACCESS

1. Introduction

Infertility is a condition in which there is a failure to achieve and maintain successful pregnancy during 12 months of regular sexual intercourse without any protection that could prevent pregnancy [1,2]. More than 8% of married population are suffered from infertility, however it prevalence is vary globally depends on risk factors which are specific in each country. In Canada, the prevalence is around 11.5% to 15.7% while in Asia is around 9% [3-5].

Infertility could affect personal, interpersonal, social, religion, as well as financial problems. These circumstances will lead patient into incompetency and guilty [2]. The old paradigm points women as the cause of infertility. As the knowledge increases, the community nowadays already realizes that this condition could be caused by men as well. In a study done in Israel, 45% of infertility is believed to be caused from men factors [6].

The etiology of infertility could be categorized as pre-testicular and post-testicular causes [7]. Pre-testicular problems are hormonal imbalances, and sexual intercourse disorder (erectile and ejaculation problems). A study done in Nigeria showed that the prevalence of hormonal problems in infertile patients was more than 7.3% [8]. Hormonal imbalances could be screened using follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone examination [9].

FSH is the main hormone used to stimulate the production of sperm in the testis and has a negative feedback from this condition [10]. Testosterone, in another hand is produced in the testis. The increase serum FSH and the decrease testosterone level relate to alteration of spermatogenesis, for example primary testicular failure. Previous study already showed FSH concentration in different categories of sperm concentration in infertile men such as azoospermia and oligozoospermia [11]. Completely no sperm production found, called azoospermia, could be classified as obstructive and non-obstructive azoospermia [12,13]. Azoospermia affects more than 40% of infertile patients with 10% of all infertile men suffered from altered spermatogenesis while non-obstructive azoospermia affects more than 10% of infertile men [13-15]. Patient with non-obstructive azoospermia who will undergo artificial fertilitzation should have biopsy of testicular tissue [16].

Artificial fertilization is quite expensive, especially in developing countries such as Indonesia. By knowing the appropriate treatment needed for patient, will prevent any unnecessary financial expenditure. In Jakarta, reconstructice surgery of obstructive azoospermia is expensive and time consuming, thus sperm retrieval surgery is the best approach for artificial fertilization. Percutaneous Epidydimal Sperm Aspiration (PESA), Microscopic Epidydimal Sperm Aspiration (MESA), and Testicular Sperm Extraction (TESE) are some options of sperm retrieval surgery for obstructive azoospermia patient while TESE is the only option for patient with non-obstructive azoospermia. Until now, we could not predict the occurence of obstructive and non-obstructive azoospermia. Thus, this study aims to discover Testosterone and FSH value in predicting obstructive and non-obstructive azoospermia.

2. Experimental Details

2.1. Patients

This is a retrospective study based on secondary data acquired from infertility database. Database was conducted from 2005 to 2015. The infertility database consists of patients who attended urology clinic in Cipto Mangunkusumo Referral Hospital, ASRI Hospital Jakarta, and Bunda Hospital Jakarta with chief complaint in difficulty to have offspring.

Patients were diagnosed of infertilty based on anamnesis fulfilled WHO criteria of infertility and etiology came up based on physical examination, supporting examination, and therapeutical approach. Inclusion criteria are infertile patients with azoospermia and had already done testosterone and FSH examination. Patients' characteristic

including age, testosterone level, FSH level, Johnson criteria, testicular volume, and the occurrence of varicocele were collected and recorded.

Exclusion criteria are patients who did not yet have sperm retrieval surgery. Classification of obstructive and non-obstructive azoospermia are based on sperm retrieval surgery results. If sperm were found during sperm retrieval surgery, patient would be considered to have obstructive azoospermia, while if no sperm were found patients would be considered as non-obstructive azoospermia. Sperm retrieval surgery consists of Percutaneous Epididymal Sperm Aspiration (PESA), Microsurgical Testicular Sperm Extraction (MESA), and/or Testicular Sperm Extration (TESE).

2.2. Statistical Analysis

Secondary data that fullfilling inclusion on and exclusion criteria were analized using SPSS ver. 20. Results are showed as means ± std. Deviation. A previous study showed that FSH valued more than 19.4 mIU/mL was a reliable criteria for sperm retrieval surgery [16]. However, there is no data in determining descripancy of obstructive and non-obstructive azoospermia.

Study done in 2008 showed that testosterone level below 300 ng/dL was related to non-obstructive azoospermia in more than 40% of infertile patients [17]. In our lab, testosterone was measuremed using ECLIA Testosterone II with lower limit of normal testosterone level of 249 ng/dL. Receiver operating characteristics are used in order to see the cut off point of testosterone and FSH in this population. The value with the highest specificity and sensitivity well be further analysed using chi-square crosstabulation.

3. Results and Discussion

3.1. Result

There were 1064 patients came to Urology Clinic from 2005 until 2015, but only 120 patient fullfiled the inclusion and exclusion criteria. There were 66.7% and 33.3% of patients belonged to obstructive and non-obstructive group respectively. Regarding the Johnson Criteria, patients with non-obstructive azoospermia had lower means of Johnson score compared with the obstructive azoospermia patients (3 vs 6). There were no different between two group in term of age (36.83 vs 36.62 y.o). Testosterone and FSH level were quite different between the two groups. Testosterone level were 405.54 ± 186.14 ng/dL vs 298.84 ± 161.45 ng/dL ($p = 0.002$) while FSH level were 8.53 ± 8.43 mIU/mL vs 20.12 ± 11.89 mIU/mL ($p < 0.001$), obstructive and non obstructive azoospermia respectively (Table 1).

Means of testicular volume in obstructive group were 17.74 ± 4.03 cc and 17.50 ± 4.23 cc while in non-obstructive group are 12.97 ± 5.18 cc and 13.37 ± 5.31 cc for right and left testis respectively. In tem of varicocele, both group mostly had bilateral varicocele, 35% vs 40% for non-obstructive and obstructive group respectively. Unilateral varicocele

	Obstructive (n = 80)	Non-Obstructive (n = 40)	
Age (years)			
Mean ± SD	36.83 ± 6.12	36.62 ± 5.65	p = 0.72
Range	27-58	26-49	
Testosterone (ng/dL)			
Mean ± SD	405.54 ± 186.14	298.84 ± 161.45	p = 0.002
Range	31.8-918.3	16.0-680.0	
FSH (mIU/dL)			p < 0.001
Mean ± SD	8.53 ± 8.43	20.12 ± 11.89	
Range	1.4-41.3	0.3-66.8	
Johnson Criteria	6	3	
Testicular Volume (cc)			
Right	17.74 ± 4.03	12.97 ± 5.18	p < 0.001
Left	17.50 ± 4.23	13.37 ± 5.31	p < 0.001

Table 1: Testosterone and FSH Level in Obstructive and Non-Obstructive Patients. (FSH = Follicle Stimulating Hormone; SD=Standard Deviation).

Varicocele Category	Obstructive (n = 80)	Non Obstructive (n = 40)
Bilateral	32 (40.0%)	14 (35.0%)
Unilateral	10 (12.6%)	6 (15.0%)
Right	1 (1.3%)	1 (2.5%)
Left	9 (11.3)	5 (12.5%)
No Varicocele	28 (35.0%)	18 (45.0%)
No Data	10 (12.5%)	2 (5.0%)

Table 2: Varicocele in Non Obstructive and Obstructive Azoospermia Patients.

was observed in 15% of patients in non-obstructive group while in obstructive group it around 13%. Most unilateral varicoceles were occurred in the left side (Table 2).

None of the patients in both group exposed to chemical substances, electromagnetic, kitchen stove, and persistenct machinary works. There is significant difference in the smoking habit between the two groups. Smoking habit is 50% vs 33 % in obstructive and non-obstructive azoospermia group respectively. In obstructive group, alcohol consumption is 11.5% of patients while in non-obstructive is 7.7% of patients. There is no different in term of sauna habit in between the two groups, both are 2.6%. There is no patient in non-obstructive group ever had hot water bathing while in obstructive there is 3.8% have it as a habit. No patient in both group wear tight pants and place laptop in the tight as their habit.

This study used receiver operating characteristics (ROC) as statistical tools in order to determine cut off point of testosterone and FSH to predict the occurence of obstructive and non-obstructive azoospermia (Figure 1). Table 3 shows that Testosterone value is below 0.5 (0.355) while FSH values is 0.839

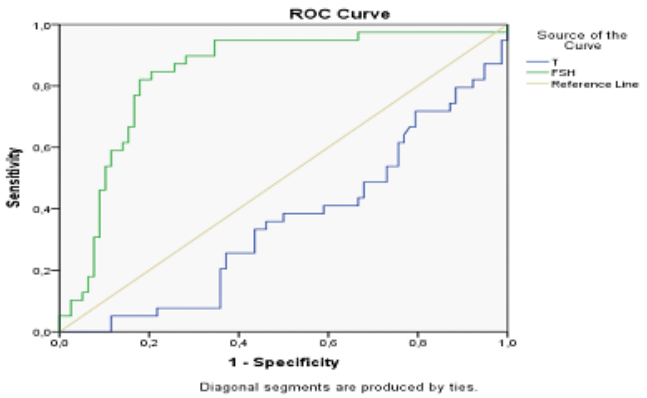

Figure 1: ROC of Testosterone and FSH in Determining Cut-off Value of Azoospermia Category. (ROC = Receiver Operating Characteristics; FSH = Follicle Stimulating Hormone; T = Testosterone).

Test Result Variable(s)	Area	SE[a]	Asymptotic Sig.	Asymptotic 95% CI	
				Lower Bound	Upper Bound
Testosterone	0.355	0..053	0.011	.251	.459
FSH	0.839	0.040	0.000	.760	.918

Table 3: Testosterone and FSH Level Test Results Variables. (FSH = Follicle Stimulating Hormone; SE = Standard Error; CI = Confident Interval).

The cut off value of FSH with highest specificity and sensitivity is 10.36 mIU/mL. This value have specificity of 79.5% and sensitivity of 82.1%. We used chi-square crosstabulation as statistical tools in order to measure the significancy of FSH level of 10.36 mIU/mL and Testosterone level of 275 ng/dL. The results are significant for both FSH and Testosterone with p value of p = 0.000 and p = 0.017 ($p < 0.05$).

4. Discussion

The caused of male infertility are varied, thus many diagnosing approach are postulated in order to decide the etiologi. Testicular biopsy, spermiography, and vasography are some approach to decide the etiology, however these approach are not usualy accepted by patients [18]. Hormonal assays is simple and quite cheap compared to these modalities and postulated as the means tools to diagnosed the caused of infertility. Hormone such as FSH and Testoterone are necessarily to be evaluated in order to search the etiology of male infertility. Age of patients in our population (36.83 vs 36.62 y.o), as well as testicular volume are similar with previous study [8,19].

As we already know that FSH serum concentration is inversely correlated with spermatogenesis process. Which mean that if the spermatogenesis process is altered, FSH serum concentration will be elevated. Previous study done by Gowri et al showed that FSH level in non-obstructive azoospermia patient with spermatogenic failure was higher compared to that with proper spermatogenesis [11,20]. Our study had same result that non-obstructive azoospermia patiens had higher FSH serum concentration compared to obstructive azoospermia (20.12 ± 11.89 vs. 8.53 ± 8.43). Previous study

showed that testosterone serum concentration between azoospermia patient was 494 ± 98 ng/dL while in our study it was 405.54 ± 186.14 ng/dL [11]. Babu et al study reported that testoterone level in patient with testicular abnormality has similar result with patient with normal testicular histology [11]. In our study, a groups of patient with non-obstructive azoospermia was relatively had lower Testosterone level compared with the obstructive group (405.78 ng/dL vs 298.84 ng/dL, p = 0.002).

In our study, we found that are under the curve from ROC for Testosterone are 0.355 ± 0.053 which mean that Testoterone in our study population could not be used to classify between obstructive and non-obstructive azoospermia. In another hand, FSH had area under the curve was 0.839 ± 0.04 (>0.5) with a 95% of Ci for the area between 0.760 – 0.918. With that value of FSH, it could be used as predictive assay to predict the occurence of obstructive and non-obstructive patient in our study population, as well as in bigger population. A cut-off value of 10,36 mIU/mL had the highest specivicity and sensitivity (80% and 84,6%) in order to differentiate between non-obstructive and obstructive azoospermia. A study done by Chen et al showed cut off value of FSH at the level of 13.7 mIU/mL in order to differentiate between azoospermia with normal spermatogenesis and failure of spermatogenesis.16 However, these two values was predicted to have low sperm retrieval rate based on study done by Tahereh [21]. Tahereh et al showed that FSH level below 15.25 mIU/mL had sperm retrieval rate less than 12% [21]. In our study, group of patients with non-obstructive azoospermia have lower testicular volume compared to obstructive group, but according to Campbell et al testicular volume would not affect sper retrieval rate [22].

5. Conclusion

FSH level could be used as predictive factor of non-obstructive and obstructive azoospermia but not Testosterone level. We could suggest that azoospermia patient with FSH level above 10.36 mIU/mL do not need to undergo TESE since it is estimated no sperm will be found.

Acknowledgments

The authors like to give gratitude to Prof. Akmal Taher dan Prof. Rainy Umbas as senior surgeon and urologist for their advice and guidance in writing this study. Authors also like to say thank you to dr. Ariel Pradipta and dr. Chrystie Amanda for their advice in term of statistical analysis.

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