Research Report

Etiologies of Male Infertility in Dr. Cipto Mangunkusumo Hospital, Jakarta

Etiologi Infertilitas Lelaki pada Rumah Sakit Dr. Cipto Mangunkusumo, Jakarta

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Abstract

Objective: To have description about the etiologies of male infertility in Dr. Cipto Mangunkusumo Hospital.

Method: This was a retrospective study of 315 male infertility patients treated at the Urology Department Dr. Cipto Mangunkusumo Hospital from January 2009 to June 2011.

Result: There were 78 patients excluded from the analysis due to incomplete or missing data. The available data consisted of 237 males, with a median age of 35 years old. The median duration of infertility was 4 years. Primary infertility was identified in 89.4% and secondary infertility in 10.6% of all cases. Semen analysis results were classified as normal 2.5%, aspermia 1.3%, azoospermia 41.4%, multiple abnormal parameters 38.0%, single abnormal parameter (oligozoospermia 7.6%, asthenozoospermia 6.8%, teratozoospermia 2.1%), and cryptozoospermia 0.4%. From 237 subjects, there were 39 men (15.9%) with multiple etiologies of male infertility. The most common etiology in this study was varicocele (48.5%). Other etiologies were idiopathic 27.8%, acquired factors 14.3%, obstruction 8.0%, congenital anomalies 6.3%, urogenital infection 2.5%, sexual factors 2.1%, endocrine disturbance 2.1%, no demonstrable cause 1.3%, and other abnormalities 0.8%. This study also found Y-chromosome microdeletions in 2.5% of subjects or 6/98 (6.1%) of azoospermic patients. Lifestyle factors associated with male infertility were smoking 31.6%, alcohol consumption 13.4%, hot-bathing 6.7%, and sauna 2.9%.

Conclusion: There are numerous possible contributing factors of male infertility, and varicocele was the most commonly identified etiology in this study. Some of our patients were presented very late for infertility treatment, therefore prompting the necessity to increase general awareness of male infertility in the society.

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Keywords: azoospermia, varicocele, risk factor

Abstrak

***Tujuan**: Untuk mendapatkan gambaran etiologi infertilitas lelaki di Rumah Sakit Dr. Cipto Mangunkusumo.*

***Metode**: Penelitian ini merupakan penelitian retrospektif pada 315 pasien infertilitas lelaki yang ditangani Departemen Urologi Rumah Sakit Dr. Cipto Mangunkusumo periode Januari 2009 - Juni 2011.*

***Hasil**: Sebanyak 78 pasien dieksklusi dari analisa karena ketidaklengkapan atau data yang hilang. Data yang dianalisa terdiri dari 237 pria dengan umur rata-rata 36 tahun. Durasi rata-rata infertilitas 4 tahun. Infertilitas primer teridentifikasi pada 89,4% dari seluruh kasus, dan infertilitas sekunder 10,6%. Hasil analisa semen dikategorikan sebagai normal 2,5%, aspermia 1,3%, azoozpermia 41,4%, multipel abnormal parameter 38,0%, abnormal parameter tunggal (oligozoospermia 7,6%; asthenozoospermia 6,8%; teratozoospermia 2,1%), dan cryptozoospermia 0,4%. Dari 237 subjek, 39 pria (15,9%) merupakan infertilitas lelaki dengan multipel etiologi. Etiologi paling sering pada penelitian ini adalah varicocele 48,5%. Etiologi lainnya yaitu idiopatik 27,8%, faktor-faktor yang didapat 14,3%, obstruksi 8,0%, anomali kongenital 6,3%, infeksi urogenital 2,4%, faktor seksual 2,1%, gangguan endokrin 2,1%, penyebab yang belum dapat dibuktikan 1,3%, dan penyebab lain 0,8%. Penelitian ini juga menemukan mikrodelesi kromosom Y pada 2,5% subjek kasus, atau 6/98 (6,1%) dari penderita azoospermia. Gaya hidup yang dihubungkan dengan infertilitas lelaki yaitu merokok 31,6%, konsumsi alkohol 13,4%, mandi air panas 6,7% dan sauna 2,9%.*

***Kesimpulan**: Terdapat beberapa faktor yang dapat berperan dalam infertilias lelaki, dan varicocele pada penelitian ini, diketahui sebagai etiologi tersering. Beberapa pasien datang dalam kondisi yang sudah sangat terlambat untuk dilakukan terapi infertilitas, sehingga desakan akan perlunya meningkatkan kesadaran mengenai infertilitas lelaki pada masyarakat sangat diperlukan.*

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***Kata kunci**: azoospermia, varicocele, faktor risiko*

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INTRODUCTION

Infertility is defined as the inability of a sexually active, non-contracepting couple to achieve pregnancy in one year.[1] It affects about 8 - 12% of all married couples.[2] Male factor infertility is the primary cause of infertility in approximately 20% of infertile couples, and contributes to 30 - 40% of both male and female factors.[3] Male factor was the most common cause of infertility (45%) in couples attending primary infertility clinics in Israel.[4]

Evaluation of the male partner of an infertile couple should include a thorough medical and reproductive history exploring all aspects that may be related to fertility. Male infertility is generally regarded as a condition that is difficult to treat, especially in the low-economic settings of many developing countries where advanced methods of assisted reproductive technology are not available. In developing countries, patterns of infertility are relatively different from those in developed countries. In general, the incidence of preventable infertility is much higher in developing countries. Since a lot of cases of male infertility are preventable and generally require sophisticated and expensive treatment, prevention of male infertility appears to be one of the priority tasks of infertility programmes in developing countries.[2] Nowadays, there are limited data about etiologies of male infertility in

Indonesia. The objective of this study was to determine the frequencies of the etiologies of male infertility in Dr. Cipto Mangunkusumo Hospital (CMH) Jakarta, a tertiary referral center in Indonesia.

METHODS

This was a retrospective study of 315 male infertility patients that attended the Urology Clinic in Dr. Cipto Mangunkusumo Hospital from January 2009 to June 2011. The information collected consisted of patient's age, type of infertility (primary or secondary), duration of infertility, history of systemic diseases with possible adverse effect on fertility, history of sexually transmitted disease, history of surgery, history of testicular injury or testicular torsion, history of therapeutic drugs, history of sexual and ejaculatory function, lifestyle factors (smoking, excessive alcohol consumption, hot-bathing, sauna), physical examination, semen analysis, hormonal investigations, scrotal ultrasonography, and genetic testing. The etiologies of male infertility in each patient was sorted out from the history, physical examination, laboratory, and imaging results.

Semen analysis results were classified according to 2010 World Health Organization (WHO) criteria/criterions. The results were classified as normal if sperm concentration > 15 x 10^6 per ml, normal sperm morphology > 4%, and total motility > 40%.[5] The etiologies of male infertility were grouped according to European Association of Urology (EAU) guidelines on male infertility on 2005.[6] Acquired factors consisted of systemic disease (diabetes mellitus, tuberculosis, liver dysfunction), orchitis, sexually transmitted disease, and history of surgery. Obstructive azoospermia means the absence of both spermatozoa and spermatogenic cells in semen and post-ejaculate urine due to bilateral obstruction of the seminal duct.[6] Congenital abnormalities consisted of genetic disorders (chromosome abnormalities, Y-chromosome microdeletions), testicular maldescent, and congenital bilateral absence of vas deferens (CBAVD). Sexual dysfunction included inadequate erection and ejaculatory dysfunction. The diagnosis of an endocrine cause was made in cases with normal or low serum FSH and low plasma testosterone or repeatedly elevated prolactin values. Men classified as having idiopathic male infertility have an unexplained reduction in semen quality with no history associated with fertility problems and have normal findings on physical examination and endocrine laboratory testing.[7,8] No demonstrable cause diagnosis was valid only if sexual and ejaculatory function were adequate and the semen classification was normal.[7]

RESULTS

There were 78 patients that were omitted from this study because of incomplete data. Subjects consisted of 237 men with a median age of 35 years old (range 26 - 58 years old). Median duration of infertility was 4 years (range 1 - 25 years). There were 89.4% of men with primary infertility and 10.6% of men with secondary infertility. Semen analysis results can be seen in Table 1. Etiologies and lifestyle risk factors that can contribute to male infertility are listed in Table 2.

Table 1. Semen analysis results (n=237)

Categories	n	Percentage
Normal	6	2.5%
Aspermia	3	1.3%
Azoospermia	98	41.4%
Multiple abnormal parameters (38.0%)		
Oligoasthenoteratozoospermia	56	23.6%
Oligoasthenozoospermia	23	9.7%
Asthenoteratozoospermia	7	3.0%
Oligoteratozoospermia	4	1.7%
Single abnormal parameter (16.9%)		
Oligozoospermia	18	7.6%
Asthenozoospermia	16	6.8%
Teratozoospermia	5	2.1%
Cryptozoospermia	1	0.4%

Table 2. Etiologies and lifestyle risk factors that can contribute to male infertility.

Etiologies and lifestyle risk factors	n	Percentage
Types of etiologies (n = 237)		
Varicocele	115	48.5%
Idiopathic	66	27.8%
Acquired factors	34	14.3%
Obstructive azoospermia	19	8.0%
Congenital abnormalities	15	6.3%
Urogenital infection	6	2.5%
Sexual dysfunctions	5	2.1%
Endocrine causes	5	2.1%
No demonstrable cause	3	1.3%
Other abnormalities	2	0.8%
Number of etiologies (n = 237)		
Single etiology	198	84.1%
Multiple etiologies	39	15.9%
Lifestyle risk factors (n = 209)*		
Smoking	66	31.6%
Alcohol consumption	28	13.4%
Hot-bathing	14	6.7%
Sauna	6	2.9%

**: There were 28 patients with no lifestyle risk factors data.*

DISCUSSION

There were 237 male infertility patients reviewed in this study. Median duration of infertility was 4 years (range 1 - 25 years). This result was similar to a survey in Iran in which mean duration of infertility was 7.4 ± 5.2 years.[9] However, our patients presented at a later time compared to a study on 2515 infertile couples that showed a mean duration of infertility 1.7 ± 1.8 years.[4]

In this study, 89.4% men had primary infertility and the other 10.6% had secondary infertility. This study showed that primary infertility was more common than secondary infertility. Some studies also showed similar results. A study in Iran showed that from 3734 infertility cases, 78.7% of couples had primary infertility and 21.3% had secondary infertility.[10] Another study showed that from 277 infertility cases, 61.4% of couples had primary infertility and 38.6% had secondary infertility.[11]

The median age of our patients were 35 years old (range 26 - 58 years old). This was similar to a study in which the mean age of infertile men was 33.6 ± 6.3 years old.[9] Quantification of the effect of a man's age on his fecundity is difficult because it is confounded by a lot of other factors. A study reported that there is a decline in male fecundity with advancing age. The likelihood of conception within 6 or 12 months was lower in older men. Compared to men < 25 years old, the adjusted odd ratios (OR) (95% confidence interval, CI) for conception in ≤ 12 months were 0.62 (0.40 - 0.98), 0.50 (0.31 - 0.81), and 0.51 (0.31 - 0.86) in men aged 30 - 34, 35 - 39 and ≥ 40 years respectively.[12]

The most common results of semen analysis in this study were azoospermia 41.4% and oligoasthenoteratozoospermia (OAT) 23.6%. From all subjects, abnormal semen parameters were found in 97.5% of men. This was much higher than a survey in Iran in which sperm disturbance was found in only 40.3% of subjects. In that study, normal sperm was found in 32.3% and OAT was found in only 8.5%.[9] The reasons for these differences were our study had used the 2010 WHO parameters, most of the patients in this study were referred to our clinic for some surgical reasons, and only a little of patients with normal sperm parameters were referred to our clinic.

From 237 subjects, there were 39 men (15.9%) with multiple etiologies of male infertility. The most common etiology in this study was varicocele (48.5%). Varicocele is a physical abnormality present in 2 - 22% of adult male population.[3] It is more common in men of infertile marriages, affecting 25 - 40% of those with abnormal semen analysis. Our result was bigger than other studies, possibly because most of the patients in this study were referred to the urology clinic for some surgical reasons, such as varicocele or suspicion of obstructive disorder. The exact association between reduced male fertility and varicocele is unknown, but analysis of the WHO data clearly indicates that varicocele is related to semen abnormalities, decreased testicular volume and decline in Leydig cell function.[6] A meta-analysis of randomized controlled trials and observational studies showed that surgical varicocelectomy significantly improved semen parameters in men with abnormal semen, but only in clinical varicoceles.[13] There is however an ongoing discussion on whether varicocele repair also results in an increased chance of natural conception.[1]

We found that 8.0% of subjects have obstructive azoospermia (OA). This was higher than data from EAU guideline that showed the frequency of OA only 1.7% from 10,469 patients.[1] This was because mostly our patients were referred to urology clinic to investigate a suspicion of obstructive disorder. In azoospermic subjects, OA occurred in 19/98 patients (19.4%) and non-obstructive azoospermia (NOA) occurred in 79/98 patients (80.6%). This is similar to the data in EAU guideline in which OA is less common than NOA and occurs in 15 - 20% of men with azoospermia. Common causes of OA are epididymal obstruction, vas deferens obstruction, and ejaculatory duct obstruction.[1] Epididymal obstruction is the most common cause of OA, affecting 30 - 67% of azoospermic men with a serum FSH of less than twice the upper limit of normal. Congenital forms of obstruction are rare. Among the acquired forms, those secondary to acute (gonococcal) and subclinical (e.g. chlamydial) epididymitis are considered to be most frequent. Ejaculatory duct obstruction is found in about 1 - 3% of OA. Vas deferens obstruction following vasectomy is the most frequent cause of acquired obstruction.[6] Our data showed that there were 7 patients who had vasovasostomy because of prior vasectomy.

Acquired factors caused male infertility in 14.3% of subjects. Diabetes mellitus caused testicular failure and ejaculation dysfunction. Tuberculosis caused epididymitis, prostatitis, and sperm transport failure. Operations that may have direct adverse effects for fertility include hernia repair, hypospadia, hydrocele, and vasectomy.[7] Many drugs, including nitrofurantoin, cimetidine, sulfasalazine, cocaine, and marijuana can impair spermatogenesis.[14]

Congenital abnormalities are the etiology of male infertility in 6.3% of subjects. Semen parameters in men with a history of cryptorchidism are often impaired. In 2 - 9% of infertile patients, a history of cryptorchidism is present. However, paternity in men with a history of unilateral cryptorchidism is almost equal (89.7%) to paternity in men without cryptorchidism (93.7%). In men with bilateral cryptorchidism, oligozoospermia can be found in 31% and azoospermia in 42%. In cases of bilateral cryptorchidism, paternity is only 35 - 53%.[6] Genetic disorders in male infertility consist of chromosomal abnormalities and Y-chromosome microdeletions.[6] This study found Y-chromosome microdeletions in 2.5% of subjects or 6/98 (6.1%) of azoospermic patients. Y-chromosome microdeletions were found in 8 - 12% of azoospermic men and 3 - 7% of oligospermic men. Men with microdeletions of the Y-chromosome do not have any phenotypic abnormalities other than abnormal spermatogenesis.[15] In a survey of pooled data from 11 publications including 9,766 infertile men, the incidence of chromosomal abnormalities was 5.8%. Of these, sex chromosome abnormalities accounted for 4.2% and autosomal abnormalities for 1.5%.[16] Immunologic causes were not reviewed in this study because it was not routinely done.

This study found that 2.5% subjects had urogenital infections. Male urogenital infections consisted of infection in epididymis, seminal vesicle, prostate, bladder, and urethra by bacteria, virus, or other microorganisms.[17] One study suggests approximately 28 - 71% of infertile men have evidence of a chlamydial infection.[18] Infections of the male accessory glands are potentially correctable causes of male infertility. However, concrete data are lacking to confirm a negative influence of these diseases on sperm quality.[6]

Sexual dysfunction only happened in 2.1% of subjects. This number was lower than the study in Pakistan in which sexual dysfunctions (decreased libido, premature ejaculation) were found in 34.6% of male infertility patients.[19] This was because most of male patients with sexual dysfunction in the infertility clinic were not referred to the urology clinic.

This study showed that 27.8% of male infertility had an idiopathic cause. Many men presenting with infertility are found to have idiopathic oligoasthenoteratozoospermia (OAT). Idiopathic cause of male in-

fertility is found in 40 - 75% of infertile men. The unexplained forms of male infertility may be caused by several factors, such as chronic stress, endocrine disruption due to environmental pollution, reactive oxygen species and genetic abnormalities.[6] This study also showed that only 1.3% subjects had no demonstrable cause. This low number might be caused by other patients with the same diagnosis were not referred to our urology clinic.

There are several lifestyle risk factors that can affect fertility such as smoking, alcohol consumption, hot-bathing, and sauna. In this study, history of smoking was found in 31.6% of subjects. In other study, smoking was found in 49.4% of infertile men.[19] The impact of smoking on male infertility is debatable. Cigarettes contain a range of chemical toxins which can impair the sperm function, motility and morphology. A proposed mechanism for this is the increase of seminal leukocyte into the semen as a result of an inflammatory reaction and higher levels of seminal oxidative stress.[20,21] A meta-analysis of 21 studies on the effect of smoking on semen quality revealed that smoking lowered sperm density by 13 - 17%, although 14 of the studies did not document an effect.[22] A case-control study showed that the risk of infertility was associated with smoking (adjusted OR 2.96 (95%) CI 1.98 - 4.42).[23] However, another study did not find a significant independent association between smoking and male infertility.[24] In this study, history of alcohol consumption was found in 13.4% of subjects. Alcohol consumption was found in 49.4% of infertile men.[19] Our finding was lower because the major religion in Indonesia is Islam in which alcohol consumption is forbidden. A case-control study showed that excessive alcohol consumption may decrease further an already low percentage of sperm with normal morphology.[25] However, a study in 258 infertile couples showed that there was no significant association between alcohol consumption and any semen parameter.[26] Long-term effects of chronic alcohol use include erectile dysfunction, reduced libido, and gynecomastia. One mechanism of these effects was a reduction in serum testosterone caused by decreased testicular production and increased metabolic clearance in the liver.[27] This study found that 6.7% of subjects frequently use hot tubs and 2.9% of subjects frequently use sauna. Impaired semen quality and spermatogenesis have known to result from experimental hyperthermia. The frequent use of hot tubs has been found to result in a 10% decrease in sperm motility. Therefore, the use of saunas and hot tubs should be discontinued in those patients with suboptimal semen analysis.[14]

This study has a limitation. This study was only done in a urology clinic. Further studies to monitor the results of male infertility treatment such as improvement in semen analysis and fecundity should be conducted.

CONCLUSION

There are numerous possible contributing factors of male infertility, and some of those are treatable. Varicocele was the most commonly identified etiology in this study. The frequency of varicocele was bigger than other studies, possibly because most of the patients in this study were referred to the urology clinic for some surgical reasons, such as varicocele or suspicion of obstructive disorder. Male infertility patients should also avoid the lifestyle risk factors. Some of our patients were presented late for infertility treatment, therefore prompting the necessity to increase general awareness of male infertility in the society.

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