SQU Med J, December 2010, Vol. 10, Iss. 3, pp. 350-353, Epub. 14th Nov 10
Submitted 22nd May 10
Accepted 20th July 10

CLINICAL & BASIC RESEARCH

Comparison of the Demographics, Semen Parameters and Hormone Profiles in Men with Primary and Secondary Infertility

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مقارنة الديموغرافيا ومؤشرات المني وشاكلة الهورمونات لدى الرجال المصابين بالعقم الأولي والثانوي

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الملخص: **الهدف:** دراسة مقارنة بين الديموغرافيا، ومؤشرات السائل المنوي وشاكلة الهورمونات لدى الرجال المصابين بالعقم الأولي والثانوي.**الطريقة:** اعتمدنا في هذه الدراسة على التحليل الاستعادي للبيانات التي تم جمعها من الرجال المراجعين لعيادة العقم المشتركة (التي تدار من قبل اختصاصيي المسالك البولية وأمراض النساء) في الفترة من يناير 2005 إلى ديسمبر 2008 في مستشفى جامعة السلطان قابوس (مستشفى رعاية ثالثي) في سلطنة عمان. **النتائج:** أحيل ثمانية وتسعون رجلا على التوالي مع واحد أو أكثر من التشوهات في السائل المنوي لعيادة العقم المشتركة حيث أجري فحص بدني كامل من قبل اختصاصي المسالك البولية تلاها فحص للهرمونات التالية: الهُرْمونُ المُنَبِّهُ للجُرَيب وهُرْمونٌ مُلوتن وهرمون التستوستيرون وهرمون البرولاكتين من كل المرضى. مؤشرات المني والهورمون الذكري لا تختلف عند المصابين بالعقم الأولي أو العقم الثانوي. المرضى المصابون بالعقم الأولي أصغر سنا من أولئك المصابين بالعقم الثانوي. كان 24% من المصابين بالعقم الأولي و16% من المصابين بالعقم الثانوي فاقدي النطف مع وجود مستويات طبيعية لهرمون موجه الغدة التناسلية في 9 رجال مصابين بالعقم الأولي ورجل واحد مصاب بالعقم الثانوي. **الخلاصة:** فقدان النطف أكثر انتشارا عند المصابين بالعقم الأولي وبناء على مستويات هرمون موجه الغدة الجنسية يظهر أن انسداد المسالك التناسلية يكون أكثر عند المصابين بالعقم الأولي أيضا.

مفتاح الكلمات: عقم الرجال؛ العقم الأولي؛ العقم الثانوي؛ دوالي الخصية؛ الهرمونات الجنسية؛ مؤشرات المني؛ عُمان.

ABSTRACT: ***Objectives:*** The objectives of this study were to compare the demographics, semen parameters and hormone profiles in men with primary and secondary infertility. ***Methods:*** The study was designed as a retrospective analysis of data collected from men attending a combined infertility clinic (seen together by urologist and gynaecologist) from January 2005 to December 2008 at Sultan Qaboos University Hospital, a tertiary care hospital in Oman. Ninety-eight consecutive male patients with one or more abnormalities in semen analysis were referred to the combined infertility clinic. A complete physical examination was carried out by a urologist followed by hormone evaluation of follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone (T) and prolactin (PRL). ***Results:*** The semen parameters and the sex hormone evaluation were not significantly different between the men with primary and secondary infertility. The men with primary infertility were younger than the men with secondary infertility. A total of 24% of the men in the primary group and 16% in the secondary group were azoospermic with normal gonadotropin values in 9 men and 1 man in the primary and secondary group respectively. ***Conclusion:*** Azoospermia was more common in the primary infertile group and, based on gonadotropin levels, obstructive causes seemed more prevalent in the primary group compared to secondary group.

Keywords: Male infertility; Primary infertility; Secondary infertility; Varicocele; Sex Hormones; Semen parameters; Oman

Advances in knowledge

1. This is one of the first studies from the Arabian Gulf region on male infertility

2. Hormonal evaluation results for all men with azoospermia/oligospermia is not very different in primary or secondary types of infertility.

Application to patient care

1. Based on the results of this study, men with primary subfertility need to be more thoroughly investigated for obstructive causes.

2. Serum hormone level estimation obviates the need for invasive procedures on the testes.

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Infertility is a common problem faced by the clinician and could arise from male factors, female factors or both. Though infertility is conventionally divided into primary and secondary types, the aetiology is not always different.[1] Semen analysis is an integral part of evaluation of an infertile couple. In males with abnormal semen parameters, including reduced sperm count or sperm motility, sex hormones are evaluated to rule out testicular causes and aid in the management. Low levels of follicle stimulating hormone (FSH) suggest a hypothalamo-pituitary axis problem and high levels of FSH signify testicular failure. Primary testicular failure and hypothalamic causes are more likely to result in primary male infertility than causes like sexually transmitted diseases, trauma, environmental factors and social habits like smoking and consuming alcohol. Obstructive azoospermia secondary to sexually transmitted infection is a preventable cause of secondary male infertility. Bayasgalan *et al*. found a high prevalence of obstructive azoospermia (8.4%) and acquired testicular damage (5.4%) in their study.[2] This study aimed to examine and compare the semen and serum hormone parameters in the two groups of men with primary and secondary infertility.

Methods

The study was approved by the institutional ethics committee and was designed as a retrospective analysis of data collected from men attending the combined infertility clinic (seen together by urologist and gynaecologist) from January 2005 to December 2008 at Sultan Qaboos University Hospital, Oman, a tertiary care centre. Semen analysis was done as part of initial evaluation for all couples with infertility. Men with abnormal semen analysis (reduced count, reduced motility and/or abnormal sperm morphology) were referred to the combined infertility clinic. A thorough history and complete examination of the male partner was carried out by the urologist. Sex hormone assays of follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone (T) and prolactin (PRL) on the male partner and/or ultrasound of the testes with Doppler was requested. The optimal treatment modality was chosen based on the results of investigations of both the female and male partners.

Semen specimens were collected at the study site and transferred immediately to the laboratory. Men were asked to abstain for 72 hours prior to collection. Sperm concentration was determined by counting the two sides of a haemocytometer. Semen volume was measured in a graduated pipette. Motility was evaluated as the proportion of sperms that were progressively motile at 370° C using a Makler chamber. Men were considered azoospermic if no sperms were seen. Dried semen smears were treated with Berg's stain (carbol fuchsin and methylene blue) and assessed for morphological abnormalities by one examiner using strict criteria.

Serum concentrations of FSH, LH, T and PRL were measured using the Access® system (Beckmann Coulter Inc.). The Access hFSH and LH assays were sequential two-step immunoenzymatic (sandwich assay) with a sensitivity of 0.2 miu and a coefficient of variation less than 10%. The Access testosterone assay was a competitive binding immunoenzymatic assay. PRL was also measured by a sandwich technique, immunochemical method (Access® system, Beckmann Coulter Inc.) with a sensitivity of 0.25 ng/ml and coefficient of variation of 10%. The analytical sensitivity for testosterone was 0.1 ng/mL and the interassay and intraassay coefficients of variation were 2.71% and 5.65% respectively.

Descriptive statistics were used for the data. For categorical variables, frequencies and percentages were reported. Differences in prevalence of varicocele between groups (primary and secondary infertility) were analysed using Pearson's chi-squared test. For continuous variables, means and standard deviations (SD) were presented. Since the distributions of the continuous variables (age, duration, volume, motility, count, abnormal forms, FSH, LH, PRL and T) were significantly non-normal, the analysis was conducted using the Mann-Whitney test. An *a priori* two-tailed level of significance was set at the 0.05 level. Statistical analysis was conducted using STATA, Version 10.1, (STATA Corporation, College Station, TX).

Results

The total number of men during the study period (January 2005 to December 2009)

Table 1: Demographics and semen characteristics of the primary and secondary infertility groups

Parameter	Primary infertility (n = 67)	Secondary infertility (n = 31)	*P* value
Age, mean ± SD	32.72 ± 8.08	36.71 ± 10.09	0.002
Duration, mean ± SD	6.07 ± 5.83	5.17 ± 4.15	0.663
Volume, mean ± SD	2.54 ± 1.40	3.39 ± 4.12	0.888
Motility, mean ± SD	30.62 ± 26.74	23.71 ± 19.83	0.359
Count, mean ± SD	32.05 ± 59.19	27.66 ± 37.61	0.904
Abnormal forms, mean ± SD	26.51 ± 33.58	39.231 ± 35.59	0.075
Varicocele, n (%)	30 (45%)	11 (35%)	0.386

Note: Analysis was conducted using the Mann-Whitney test for all the variables except for the varicocele variable for which Pearson's chi-squared test was used.

Legend: SD = Standard deviation.

was 98. There were 67 men with primary and 31 with secondary infertility. Hormone analysis was done for 46 patients in the primary group and 25 in the secondary group. Men in the primary infertile group were significantly younger than the men in secondary infertility group (33 versus 37 years; P = 0.002). The duration of infertility as well as volume, sperm motility, sperm count and abnormal forms of the semen were not significantly different between the primary and secondary groups [Table 1]. There were also no statistical differences in the hormonal parameters between the two groups [Table 2]. Furthermore, the prevalence of varicocele was also not significantly different between the groups. Only nine men admitted to smoking in the primary group and six men in the secondary group. There was no clinical evidence or history of sexually transmitted disease except for one in the primary infertility group. A history of diabetes was present in four men and cardiomyopathy in one in the primary group. Azoospermia was present in 16 of 67 (24%) men in the primary group and 5 of 31 (16%) men in the secondary group. Serum gonadotropin values were normal in 9 of 16 (56%) in the primary group and one out of the five (20%) in the secondary group. There was weak negative correlation between LH and sperm counts in both groups (-0.0971 and -0.08897 in primary and secondary respectively). The testosterone levels correlated positively with sperm motility in both groups (0.400 and 0.315 in the primary and secondary groups respectively).

Discussion

In the present study, except for the age of men in the primary infertility group which was significantly less than in men with secondary infertility, the other assessed parameters were not significantly different. There were only six men with FSH equal to or more than 15 IU in the primary infertile group, but seven in the secondary group. In the secondary infertility group, the cause for elevated FSH was due to orchidectomy in one man and bilateral small testes in another, but there was no obvious cause in the others except a history of smoking in two men. The FSH levels and the sperm counts correlated inversely in the primary and secondary infertility groups, (0.28157, -0.2702 respectively) and this fits with other observations in the literature.[3,4,5] Although the serum gonadotropin values were not significantly different between the two groups, analysis of serum FSH levels in both groups, after excluding men with

Table 2: Sex hormonal characteristics of the primary and secondary infertility groups

Sex Hormone	Primary infertility (n = 46)	Secondary infertility (n = 25)	*P* value
FSH, mean ± SD	5.68 ± 7.12	9.20 ± 10.32	0.106
LH, mean ± SD	4.17 ± 3.82	5.48 ± 5.41	0.414
PRL, mean ± SD	124.40 ± 145.54	131.32 ± 129.81	0.623
Testosterone, mean ± SD	10.97 ± 9.85	12.51 ± 7.21	0.551

Legend: SD = standard deviation; FSH = follicle stimulating hormone; LH = luteinizing hormone; PRL = prolactin;

Note: Analysis was conducted using the Mann-Whitney test.

very high values (≥15 iu), revealed a mean higher FSH value in the primary group compared to the secondary group with a trend to significance. A negative correlation between LH and sperm count and a positive correlation between testosterone and sperm motility go with the reports of Meeker *et al.* in 2007.[6]

Measuring serum FSH and LH will help in the diagnosis of hypothalamic hypogonadotropic causes and possible treatment with gonadotropin injections in such males. There was no patient with a hypothalamic/hypopitutary disorder in the present study. The usefulness of measuring the hormonal parameters is only to diagnose obstructive causes versus testicular failure especially in men with azoospermia.

Although compared to other populations the prevalence of clinically evident sexually transmitted disease appeared to be much lower in this population, obstructive azoospermia was present in at least 9 patients in the primary group based on serum gonadotropin values. The only patient in the secondary group who had normal serum gonadotropin values gave a history of trauma to posterior urethra and false passage. Of the nine men with normal serum gonadotropin values in the primary group, testicular biopsy was done in 2 patients and there was history of Behçet's disease, right inguinal hernia repair and epididymal cyst in three others. A thyroid stimulating hormone test was not routinely performed in all men.

According to Bayasalgan *et al.,* sexually transmitted infections (STI) as a predictor of azoospermia had a very high odds ratio, being 5.6 in patients with gonorrhea and 7.6 in patients with other STIs in Mongolia. The same authors concluded that a history of pathology involving testicular damage appeared to have the strongest impact on male infertility in Mongolia. STIs have less impact on semen quality except when complicated by orchitis, epididymitis and vasal obstruction.[7] Obstructive azoospermia was present in 8.4% men in a Mongolian study along with previous testicular damage, and testicular biopsy or vasography was done in 16 patients.[2] The numbers are comparable to this group, but testicular biopsy was done only in 2 patients in our study.[2] Based on serum gonadotropin levels in the present study, obstructive azoospermia was found to be more common in the primary infertile men compared to secondary infertility.

The major limitations of the present study include the retrospective nature of the study and the absence of sex hormonal evaluation in all patients. Also testicular biopsy to obtain the final diagnosis of testicular failure versus obstruction was performed in only two patients with azoospermia. Finally, the cause of obstructive azoospermia was not discovered in this study.

Conclusion

In this study, while the seminal parameters and sex hormonal evaluation were not significantly different in males with primary and secondary infertility based on normal serum FSH values, obstructive causes seemed more prevalent in primary infertile males compared to those with secondary infertility. Further well constructed prospective studies with larger numbers of patients are needed to verify this hypothesis.

CONFLICT OF INTEREST

The authors reported no conflict of interest.

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