D. Male Infertility in Lebanon: A Case-Controlled Study

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Objective. The impact of risk factors, such as consanguinity and familial clustering, reproductive infections, traumas, and diseases, lifestyle factors and occupational and war exposures on male infertility, was investigated in a case-controlled study conducted in Lebanon.

Study Design. One-hundred-twenty males and 100 controls of Lebanese, Syrian or Lebanese-Palestinian descents were selected from two in-vitro fertilization (IVF) clinics located in Beirut, Lebanon. All cases suffered from impaired sperm count and function, according to World Health Organization guidelines for semen analysis. Controls were the fertile husbands of infertile women. Data were collected using a semi-structured interview, laboratory blood testing and the results of the most recent semen analysis. Univariate, bivariate and multivariate logistic regression analyses were used for data analysis, along with checks for effect modification and control of confounders.

Study Results. Consanguinity and the familial clustering of male infertility cases, as well as reproductive illnesses and war exposures were independently significant risk factors for male infertility. The odds of having infertility problems in the immediate family were 2.6 times higher in cases than controls. The odds of reproductive illness were 2 times higher in cases than controls. The odds of war exposures were 1.57 times higher in cases than controls. Occupational exposures, such as smoking and caffeine intake, were not shown to be important risk factors.

Conclusion. This case-controlled study highlights the importance of investigating the etiology of male infertility in Middle Eastern communities. It suggests the need to expand research on male reproductive health in the Middle East in order to improve the prevention and management of male infertility and other male reproductive health problems. (*Ethn Dis*. 2007;17[Suppl 3]:S3-33–S3-38)

Key Words: Male Reproductive Health, Infertility

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Introduction

Infertility affects more than 80 million people around the globe, with one in 10 couples experiencing primary or secondary infertility. Infertility is more prevalent in those countries defined as the infertility belt, namely the central and the southern African countries, where as many as one-third of the couples in some populations are unable to conceive.[1] Globally, the overall prevalence ranges between 8%–12%, with a core prevalence of primary infertility of about 5%.[1,2] The causes of infertility have been attributed to a variety of anatomical, genetic, endocrinological and immunological factors.[3]

The majority of the gynecological workload in the developing world is attributed to infertility problems.[4] Infertility problems are understudied at all biological, clinical and epidemiological perspectives; up to 30% of the causes of infertility are idiopathic.[5] Prevention and appropriate treatment of infertility in terms of concrete strategies of actions are lacking.

Infertility poses severe ramifications at the cultural, social and emotional levels. It directly affects the lives of married couples resulting in distress, anxiety, blame and marital and sexual problems.[6] This is compounded by the limited availability of infertility treatments especially in the poorest and most affected developing countries.[1,4]

Epidemiological studies assessing the prevalence of, and risk factors for, infertility are relatively scarce in the developing world. On one hand, there is international community neglect, as infertility is considered a natural check on population growth in countries with high fertility levels. On the other hand, a range of logistical and methodological problems exists pertaining to carrying out epidemiological infertility research in the developing world. Conducting sound studies on infertility, in general, and male infertility, in particular, is significantly controversial in male patriarchal societies, which relate fertility with masculinity. Many cases of male infertility in those societies remain unidentified. As such, the accurate estimation of the prevalence of this condition and its contributing factors or causes is an issue of major uncertainty globally.[1,7] This is especially true in the Middle East, where 10%–15% of all married couples are estimated to have infertility problems.[8]

This case-controlled study seeks to assess the underlying factors of this condition in a Middle Eastern society. It specifically aims to investigate the impact of various risk factors on male infertility – consanguinity, reproductive infections, traumas and illness, lifestyle and occupational and war exposures. Lebanon is a country characterized with both westernized and traditional lifestyles. It has high rates of consanguineous marriage (11%–17%), 15 years of civil war, and high rates of smoking and caffeine intake.

Materials and Methods

Study Design and Population

A total of 220 cases and controls (120 cases and 100 controls) of either Lebanese, Syrian, or Lebanese-Palestinian men were selected from two of the busiest and most successful infertility clinics located in Beirut. The American University of Beirut-Medical Center (AUB-MC) is a private, university-based teaching hospital catering to a religiously mixed patient population of Muslims (Sunni and Shiìite), Christians, Druze and various immigrant and refugee populations. The FIRST IVF is a stand-alone private infertility clinic catering primarily to southern Lebanese Shiìtes and occasionally Muslim Sunnis and Christians coming from either Lebanon or neighboring Syria. A total of 146 cases and controls were selected from AUB-MC and 74 cases and controls from the FIRST IVF.

There were no major exclusion criteria regarding the demographic, socioeconomic characteristics or history of reproductive infections. Cases and controls were tested for comparability and no remarkable differences in baseline characteristics were observed. The inclusion criteria for the cases were: 1) inability to conceive a child during at least the past 12 months; and 2) confirmed semen results of one or more of these conditions: oligospermia (low-sperm count, less than 20 million per mm^3), asthenospermia (low motility, $<$ than 40%, teratozoospermia (bad morphology), and azoospermia (no sperm in the ejaculate). The inclusion criteria for the controls were: 1) confirmed semen results of the absence of these aforementioned conditions; and 2) confirmed results of an infertile spouse or unexplained infertility.

Data Collection

Upon obtaining informed consent, data were collected using a combination of methods including structured interview technique, blood testing for toxic metal analysis and semen analysis results.

The interview questionnaire collected information on demographics, socioeconomic parameters, reproductive history, presence of chronic diseases, lifestyle factors, and occupational and war exposures. The laboratory data provided blood analysis for the following heavy elements: lead, arsenic, vanadium, manganese, copper, molybdenum, zinc, and selenium. The most recent semen analysis was reported; the semen analysis results were processed at the time the interview was being conducted or within a few hours following its completion.

Table 1. Distribution of sociodemographic factors among cases and controls

Variables		Male Infertility Cases	Male Infertility Control
Age	Mean (SD)	38.6 (6.7)	39.30 (5.9)
		P value=.538	
Years of education	Mean (SD)	13.5 (4.2)	14.2 (5.5)
		P value=.589	
Salary (US$)	Mean (SD)	1721 (2435)	1885 (2230)
		P value=.380	
		N **(%)**	***N*** **(%)**
Current residence			
Beirut		42 (35.3%)	46 (46.0)
South		25 (21.0%)	8 (8.0%)
Mount Lebanon		14 (11.8%)	10 (10.0%)
Else where in Lebanon		13 (10.9%)	8 (8.0%)
Outside Lebanon		25 (21.0%)	28 (28.0%)
		X^2= 9.39 *P value*=.052	
Religion			
Christian		30 (25%)	29 (29.0%)
Muslim		86 (71.0%)	66 (66.0%)
Druze		4 (3.3%)	5 (5.2%)
		X^2= .949 *P* value=.622	
Profession			
Blue collar		16 (13.3%)	6 (6.3%)
Clerical related		19 (15.8%)	21 (21.2%)
Business/teaching		42 (35%)	37 (37.4%)
Doctor/lawyer/diplomat/professor		29 (24.2%)	28 (28.3%)
Government employee		14 (11.7%)	6 (6.1%)
		X^2= 5.19 *P* value=.268	

Data Management and Analysis

Data were coded and entered, using the FoxPro version 2.6, and were analyzed using the Statistical Package for Social Sciences (SPSS-v12, Chicago, Ill.). Univariate and bivariate analyses, utilizing chi-square Fisher's exact test were used to test the association between the main outcome variable (male-infertility) and the different exposure and confounding variables. The Multivariate Backward Logistic Regression model was used where odds ratios, *P*-values and confidence intervals (CI) were computed at type I error, alpha of 5%. The final model incorporated the independent variables that displayed the most significant odds ratios.

RESULTS

Sociodemographic Characteristics

There were no significant differences in sociodemographic characteristics between the cases and the controls (Table 1). The average age in both groups was 39 years of age, with the average years of education being 14 years. The average monthly reported income in both groups was approximately US$1,800. The majority of the subjects resided in Beirut and South Lebanon. The religious backgrounds were similarly heterogeneous between the two groups. The controls were slightly more likely to be in higher-status professions; yet, the professional background of both the cases and the controls was relatively similar.

Consanguinity and Infertility

Twenty-four percent of the controls reported being married to a cousin as opposed to 16% of the cases; however, this difference was not significant. The cases were more likely to report cousin marriages among their parents and grandparents. The odds of infertility problems in the immediate family

Table 2. Bivariate analysis of the various risk factors among cases and controls

	Male Infertility	
	Cases	Controls
	N (%)	*N* (%)
Familial clustering of infertility via consanguinity		
Kinship to wife		
Wife closely related	19 (16.2)	24 (24.0)
Wife not closely related	98 (83.8%)	76 (76.0)
	X^2=2.04 *P* value=.153	
Relationship between parents/grandparents		
None are related	64 (53.8%)	62 (62.6%)
Parents or grandparents are related	34 (28.6%)	28 (28.3%)
Both parents and grandparents are related	21 (17.6%)	9 (9.1%)
	X^2=3.61 *P* value=.165	
Reported infertility problems in immediate family		
Yes	49 (41.2%)	17 (17.0%)
None	70 (58.0%)	83 (83.0%)
	X^2=15.085 *P* value=.0000	
Reproductive histories, infections and illnesses		
Age at marriage Mean (SD)	32.1 (6.4)	32.3 (6.7)
	P value=.875	
Wife's age at marriage Mean (SD)	25.7 (5.5)	27.5 (6.4)
	P value=.024	
No. of sexual partners Mean (SD)	38.8	33.5
	P value=.752	
Age of sexual activity Mean (SD)	22.5 (6.8)	20.7 (5.35)
	P value=.036	
Reproductive health index*		
No event	21 (17.8%)	49 (49.0%)
One event	51 (43.2%)	33 (33%)
Two events	31 (26.3%)	14 (14.0%)
Three events	15 (12.7%)	4 (4.0%)
	X^2= 26.54 *P* value=.000	
Lifestyle factors		
Coffee intake (cups/day) Mean (SD)	3.2 (4.7)	2.9 (4.7)
	P value=.574	
Soft drink intake (bottles/day) Mean (SD)	2.6 (12.6)	1.09 (1.4)
	P value=.221	
Smoking		
Years of smoking Mean (SD)	19.66 (6.8)	20.4 (8.9)
	P value=.621	
No. of cigarettes per day Mean (SD)	27.1 (19.8)	27.7 (16.0)
	P value=0.868	
Water pipe smoking		
Yes	32 (27.1%)	26 (26.0%)
No	86 (72.9%)	74 (74.0%)
	X^2=0.035 *P* value=.852	
Exercise		
No	37 (31.1%)	26 (26.3%)
Used to	41 (34.5%)	33 (33.3%)
Yes	33 (27.7%)	27 (27.3%)
Not regularly	9 (7.4%)	12 (12.5%)
	X^2=2.764 *P* value=.429	
Self-reported stress		
Stressed	39 (35.1%)	31 (31.3%)
Not stressed	72 (64.9%)	68 (68.7%)
	X^2=.344 *P* value=.558	

among the cases was 2.6 times higher than that among the controls, suggesting a familial clustering of male infertility that may be related to consanguinity and possibly a resultant of genetic mutations of the Y-chromosome micro-deletions. (Tables 2 and 3)

Reproductive History

No major differences between the cases and the controls existed in the age at marriage, number of sexual partners and age of sexual activity initiation. The cases and the controls had an average age of 32 years upon the first marriage, and an average of 34 lifetime sexual partners for the controls and 38 for the cases. The cases were slightly older than the controls upon their sexual activity initiation. The history of reproductive illnesses and infections was shown to be a highly significant independent risk factor. The odds of suffering from one reproductive event were 2.4 times higher among the cases than controls; the odds of suffering from two or more events were 4.8 times higher among cases than controls (Tables 2 and 3).

Lifestyle Practices

Both the cases and the controls reported similar rates of caffeine consumption. Similarly, there were no significant differences in the smoking habits and practices. Both cases and controls reported similar exercise habits, with 27% engaged in regular exercise. On the other hand, cases were slightly more likely to report that they have stress in their lives; this difference (35% vs 32%) was not significant. (Tables 2 and 3)

Occupational Exposures

Both cases and controls were equally likely to report some type of occupational exposure. The most common exposures reported were those associated with chemicals used in agriculture or manufacturing. These were followed by driving-related exposures to gasoline and high heat, and construction-related

Table 2. Continued

	Male Infertility	
	Cases	Controls
	N (%)	*N* (%)
Occupational exposures		
None	50 (42.0%)	55 (55.0%)
Chemical exposure	25 (21.0%)	16 (16.0%)
Agricultural-related exposures	8 (6.7%)	6 (6.0%)
Driving-related exposures	18 (15.1%)	13 (13.0%)
Construction-related exposures	11 (9.2%)	6 (6.0%)
More than one occupational exposures	7 (5.9%)	4 (4.0%)
	X^2= 3.98 *P* value=.553	
War exposures**		
No event	45 (39.5%)	51 (51.0%)
One event	44 (38.6%)	32 (32.0%)
Two or more exposures	25 (21.9%)	17 (17.0%)
	X^2= 2.89 *P* value=.236	

* Reproductive health index is a non-weighted index of the summation of the presence of one of these self-reported conditions: adult onset mumps, varicoceles, testicular injuries, sexually transmitted diseases, spinal cord injuries, impotence, premature ejaculation.

** War exposure index is a non-weighted index of the summation of the presence or absence of one of these self-reported events: close residential proximity to violence, self injury, family injury, taking part in the war as a fighter, being displaced, and being subject to kidnap or torture.

exposures to cement and dust. Occupational exposures were not shown to be a significant risk factor in the etiology of male infertility in this study (Tables 2 and 3).

War Exposures

War exposures were reported by the study subjects in terms of exposure to one or more of the following war-related events: close residential proximity to violence; self-injury; family injury; taking part in the war as a fighter; being displaced; and being subjected to kidnap or torture. This exposure was shown to be a significantly independent risk factor. Twenty-two percent of the cases were exposed to two or more war events as opposed to 17% of the controls. The odds of exposure to war events is 57%, borderline significantly higher among cases than controls (Tables 2 and 3).

DISCUSSION

This study demonstrated that consanguinity, reproductive illnesses and war exposures are important risk factors for male infertility. The odds of having infertility problems in the immediate family were 2.6 times higher in cases than controls. The odds of reproductive illness were 2 times higher in cases than controls, and the odds of war exposures were 1.57 times higher in cases than controls. Occupational exposures, smoking practices and caffeine intake were not shown to be important risk factors in this case-controlled study.

A significant proportion of the study sample reported consanguineous marriage patterns, in terms of either having married to a relative or having their parents and/or grandparents married to a relative. Male infertility tended to cluster strongly in families often with several male relatives affected by infertility. This familial infertility could serve as an important proxy of the genetic disposition in the etiology of male infertility. Major studies in the literature relate the micro-deletions along the Y-chromosome to azoospermia, the potential of cystic fibrosis gene mutations among azoospermic men with congenital absence of the vas deferens and seminal vesicles, as well as germ cell alterations associated with inadequate DNA repair that is associated with increased frequency of DNA mutations resulting in meiotic arrest.[9–12] The rates of such mutations substantially increase among consanguineous communities.

Reproductive illnesses, traumas and infections are important risk factors in the etiology of male infertility. The study showed a gradient increase in the odds ratio as the number of reported reproductive disorders increased. Cases were significantly more likely to report more than one reproductive problem than controls, including varicoceles, sexually transmitted infections, spinal cord injuries, adult-onset mumps and testicular injuries.

Various studies have shown the adverse impact of sexually transmitted diseases, mumps, delayed treatment of undescended testes, repair of inguinal hernia and endocrine disorders in the etiology of male infertility.[10,13] Varicoceles have also been implicated in causing direct effect on the testes via

Table 3. Multi-variate analysis-logistic regression

Variable	Adjusted OR	*P* value (95% CI)
Infertility problems in immediate family (yes/no)	2.58*	.057 (.971–6.8)
Kinship between parents and/or grandparents (yes/no)	.865	.756 (.34–2.17)
Reproductive Health Index (No. of events)	1.98*	.009 (1.18–3.1)
Intake of coffee (cups/day)	1.05	.288 (.96–1.14)
Intake of soft drinks (bottles/day)	1.07	.677 (.77–1.47)
Cigarette smoking (cigs × years/day)	.999	.183 (.998–1)
Occupational exposures (yes/no)	1.32	.556 (.527–3.29)
War exposures (No. of events)	1.57*	.056 (.989–2.49)

R^2 = 29.5% *P* value= .001.

causing ipsilateral testicular damage resulting in reduced testicular volume resulting in a reduction in spermatogenesis and semen counts, as well as poor sperm morphology. These effects are attributed to a decrease in the germ cell/steroli cell ratio, where by the percentage of germ cells in their late stage, (ie, spermatids and spermatozoa) are reduced. The impact of varicoceles tend to be bilateral on both testes, even in men with unilateral varicoceles.[14–16] Varicoceles have also been implicated by having indirect effects on the spermatogenesis process by causing hypothermia, hormonal dysfunction, production of anti-sperm antibodies, and release of oxidative stress.[16,17]

This study demonstrated the importance of war-related exposures in the etiology of male infertility. There was a significant gradient increase in the odds of male infertility as exposure to war-related events increased. This assessment relied on objective measures of exposures, such as close residential proximity to violence, self and family injury, taking part in the war, being displaced or subject to kidnap or torture, that are less likely to be subject to recall bias. This finding suggests the importance of conducting more comprehensive studies specifically in this region of the world, which has been undergoing extensive periods of war turmoil and political instability. The ramifications of war-related exposures on male infertility and developmental disorders can not be taken lightly, as the use of various chemicals with long half-lives will not only affect the fertility of current generations but could extend to futures generations.[18–20]

The impact of smoking on male infertility is debatable. Cigarettes contain a range of chemical toxins such as nicotine, carbon monoxide, cadmium and other mutagenic compounds, which can impair the sperm function, motility and morphology. A proposed mechanism for such impairment is the increase in seminal leukocyte infiltration into the semen as a result of an inflammatory reaction triggered by the smoking metabolites in the male genital tract.[21] Other studies failed to confirm this mechanism and postulated that smoking impacts on male infertility could be attributed to the coexistence of other etiological factors mediating the association such as caffeine and alcohol intakes.[22,23] This study did not find a significant independent association of smoking on male infertility. Both cases and controls tended to be heavy smokers of both cigarettes and water pipes and had approximately the same number of years of exposure to smoking. This suggests the importance of other etiological factors that could be affecting the condition and the need for additional studies to be conducted among heavy smokers.

In terms of occupational hazards, both cases and controls had similar levels and durations of such exposures. Many studies documented the negative impact of chemical and pesticides exposures, radiation, and heat on spermatogenesis resulting in alterations in sperm quantity and quality.[24–27] On the other hand, some studies suggest that the association of certain occupations and male infertility is highly dependent on the organ susceptible and the individual's age at exposure. Accordingly, an observed negative association could either mean that the concentration of a specific chemical may have not reached its latency period for the incurred damage to take place or it could simply reflect a true negative association. Additional studies are needed to further understand the etiology of different occupational exposures in terms of toxic effects, dose and duration.[24, 27]

The major limitation of this study relates to its external validity, since a clinic-based convenience sample was used in contrast to a population-based random sample. However, the fact that the study population was selected from two major infertility clinics in Lebanon might overshadow the ability to generalize the overall population. A larger sample size is also needed for increasing the power of this study; this problem is difficult to correct, owing to the fact that the actual reporting on male infertility is compromised due to the negative social connotations associated with this condition. For every man who agreed to participate in this study during an 8-month period in 2003, at least one man refused to participate for unspecified reasons. In addition, the quality of the measures is high, due to employing multiple validation techniques. No major problems existed for adjusting for missing and non-response data.

In summary, the current case-controlled study suggests the importance of consanguinity, reproductive illnesses and war-related exposures as risk factors for male infertility. Unlike some studies, no observed associations were made in terms of lifestyle factors and occupational exposures. This suggests the importance of investigating the etiology of this condition in the context of the communities where it arises. It also highlights the need for expanded research targeting male infertility in the Middle East and the development of constructive strategies to alleviate this condition and to resolve social disparities arising from this condition.

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