Consanguinity and family clustering of male factor infertility in Lebanon

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Objective: To investigate the influence of consanguineous marriage on male factor infertility in Lebanon, where rates of consanguineous marriage remain high (29.6% among Muslims, 16.5% among Christians).

Design: Clinic-based, case-control study, using reproductive history, risk factor interview, and laboratory-based semen analysis.

Setting: Two IVF clinics in Beirut, Lebanon, during an 8-month period (January–August 2003).

Patient(s): One hundred twenty infertile male patients and 100 fertile male controls, distinguished by semen analysis and reproductive history.

Intervention(s): None.

Main Outcome Measure(s): Standard clinical semen analysis.

Result(s): The rates of consanguineous marriage were relatively high among the study sample. Patients (46%) were more likely than controls (37%) to report first-degree (parental) and second-degree (grandparental) consanguinity. The study demonstrated a clear pattern of family clustering of male factor infertility, with patients significantly more likely than controls to report infertility among close male relatives (odds ratio = 2.58). Men with azoospermia and severe oligospermia showed high rates of both consanguinity (50%) and family clustering (41%).

Conclusion(s): Consanguineous marriage is a socially supported institution throughout the Muslim world, yet its relationship to infertility is poorly understood. This study demonstrated a significant association between consanguinity and family clustering of male factor infertility cases, suggesting a strong genetic component. (Fertil Steril® 2009;91:1104–9. ©2009 by American Society for Reproductive Medicine.)

Key Words: Male infertility, consanguinity, inbreeding, recessive genetic disorders, Lebanon, Middle East, Muslim world

Consanguinity is usually defined as the intermarriage of two individuals who have at least one ancestor in common, the ancestor being no more distant than a great-great grandparent. The progeny of such consanguineous marriages are usually referred to as inbred (1).

Consanguinity may increase the rate of homozygous genotype expression, making the offspring of consanguineous marriages at increased risk for recessively inherited disorders (2, 3). Closely biologically related couples may produce offspring with recessive autosomal mutations of nonphenotypic origins, mutations that may lead to a range of specific, rare recessive disorders (1, 4–7). Recent studies suggest that consanguinity is highly correlated with rare genetic sperm-defect syndromes, involving the sperm head (e.g., round heads, heads with craters) or sperm tail (e.g., stunted, immotile, or detached tails) (8, 9). These syndromes impact sperm motility, are incurable, will be present throughout a man's lifetime, and may be transmitted over generations to male offspring (8). Consequently, assisted reproductive technologies, particularly intracytoplasmic sperm injection (ICSI), should be practiced with caution and be accompanied by accurate sperm ultrastructural investigation and comprehensive genetic counseling (8).

According to a recent overview of genetic mutation research, Mediterranean, and Muslim Mediterranean populations in particular, rank highest in the world in terms of increased frequency of recessive disorders linked to consanguinity (10). This finding is a result of the high rates of consanguineous marriages across the Middle Eastern region, ranging in most societies from 20% to 55% of all marital unions (1, 5, 7, 11–14), with an exceptionally high rate (78%) recorded for one province of Iran (15). As a result, Middle Eastern Muslim populations have high frequencies of autosomal recessive disorders, homozygosity of autosomal and X-linked traits, and a plethora of new genetic syndromes and variants, the majority of them autosomal recessive (16–18).

The high rates of male factor infertility in the Middle East—higher than those observed in the West (19)—may be related to the genetics of consanguinity (10). Many infertile male patients are initially seen with severe oligospermia, asthenospermia, and teratozoospermia, as well as azoospermia of nonobstructive origin. It is widely speculated in the Middle Eastern assisted reproductive community that these severe forms of male factor infertility are attributable to genetic causes (19). However, few

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TABLE 1

Distribution of sociodemographic factors among cases and controls.

Variables	Male factor infertility status: Present (cases)	Absent (controls)
Age (y), mean (SD)	38.54 (6.6)[a]	39.39 (6.1)
Years of education, mean (SD)	13.67 (4.2)[b]	14.2 (5.5)
Salary (US$ monthly), mean (SD)	1,768 (2,500)[c]	1,829 (2,130)
Current residence, n (%)		
Beirut	43 (35.8)[d]	45 (45.0)
South Lebanon	25 (20.8)[d]	8 (8.0)
Mount Lebanon	16 (13.3)[d]	8 (8.0)
Elsewhere in Lebanon	12 (10.0)[d]	10 (10.0)
Outside Lebanon	24 (20.0)[d]	29 (29.0)
Religion, n (%)		
Christian	32 (26.7)[e]	27 (27.0)
Muslim	84 (70.0)[e]	68 (68.0)
Druze (Muslim sect)	4 (3.3)[e]	5 (5.0)
Profession, n (%)		
Blue collar	17 (14.2)[f]	6 (6.0)
Clerical	18 (15.0)[f]	22 (22.0)
Business/teaching	40 (33.3)[f]	40 (40.0)
Physician/lawyer/diplomat/professor	31 (25.8)[f]	26 (26.0)
Government employee	14 (11.7)[f]	6 (6.0)

Note: Reproductive history data from 2003.
[a] $P = .901$, compared with control.
[b] $P = .606$, compared with control.
[c] $P = .541$, compared with control.
[d] $P = .034$, compared with control.
[e] $P = .721$, compared with control.
[f] $P = .151$, compared with control.

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genetic studies of male factor infertility have been undertaken in the Middle Eastern region (20, 21), and no studies have attempted to examine the association between male factor infertility and consanguineous marriage practices.

MATERIALS AND METHODS

This case-control study seeks to investigate the influence of consanguineous marriage practices on male factor infertility in Lebanon. Two hundred twenty men who were seeking assisted reproduction at two major IVF centers in Beirut (American University of Beirut Medical Center and FIRST-IVF) were included in the study. All patients were unable to conceive a child for at least 12 months before the study. The patients were divided into two groups according to their fertility status on the basis of repeated semen analyses. Cases included 120 men who were deemed infertile on the basis of World Health Organization (WHO) semen analysis criteria (22). The control group included 100 men who had repeated normal semen analyses but who were seeking fertility treatment because of female factor infertility, including tubal, polycystic ovary syndrome, unexplained, or endometriosis-related infertility. Subjects underwent confirmatory semen analysis (for volume, count, motility, and morphology) at the time of the study, generally on the day of study recruitment at the IVF centers, to confirm the results of previous analyses. Semen analysis was reliable and standardized to reflect current WHO guidelines (22). The study was approved by Institutional Review Boards in the United States and Lebanon, and patients were not entitled to any financial reimbursement.

After informed consent, data were collected through a semi-structured interview, which included baseline information on demographics (age, religion, place of residence, education, income) and reproductive and sexual history (age at first sexual intercourse, number of sexual partners, age at marriage, and number of marriages, pregnancies, and births). Questions were also posed about general health status and behaviors (e.g., history of hypertension, tobacco consumption) and reproductive illnesses (e.g., sexually transmitted infections, undescended testicles). Detailed questions were asked about consanguineous marriage practices between spouses (first cousin, second cousin, distant relative) and between the research subject's parents (i.e., first-degree consanguinity) and grandparents (i.e., second-degree consanguinity, of maternal or paternal relatives or both). In addition, questions were posed about other known cases of male factor infertility in the immediate family (i.e., brothers, cousins, uncles, fathers, grandfathers).

After data collection, data were coded and entered with use of FoxPro version 2.6 (MicroSoft, Redmond, WA). Data were analyzed with use of the Statistical Package for Social Sciences (version 12, SPSS Inc., Chicago, IL). Univariate analysis consisted of frequency and percentage distributions for the different categorical variables in the study. Means, SDs, and ranges were computed for the different continuous variables, with checking for normality and outliers.

Bivariate analysis mainly used χ^2–Fisher's exact test to determine the association between the main outcome variable (male factor infertility) and the various exposure and confounding variables. The purpose of this analysis was to examine crude associations and to check for potential confounders and effect modification.

Multivariate analysis involved a backward logistic regression model, where analysis included the different exposure and confounding variables that yielded significant results during bivariate analysis. Odds ratios, *P* values, and confidence intervals were computed at a type I error–α of 5%. The final model incorporated the exposure and confounding variables that displayed the most significant odds ratios (OR).

RESULTS

As shown in Table 1, there were no statistically significant differences between cases and controls in terms of sociodemographic background. The average age in both groups was 39 years, and most subjects had completed high school. The average monthly income in both groups was around US$1,800. The majority of cases and controls resided in Beirut (46% vs. 35%). The religious backgrounds of cases and controls were similarly heterogeneous; approximately one quarter of the cases and controls were Christians and three quarters were Muslims. Controls were slightly more likely to be white-collar professionals; however, the professional background of both groups was relatively similar. Reflecting Lebanon's comparatively high educational levels, approximately 60% of cases and controls held professional sector jobs, including physicians, engineers, professors, and businessmen.

As shown in Table 2, rates of consanguineous marriage were relatively high among the study sample, with 16% of cases and 24% of controls reporting consanguineous marriage to a related spouse, a difference that was not statistically significant. The cases were more likely than controls to report first-degree (parental) consanguinity, second-degree (grandparental) consanguinity, or both, but the difference (46%

TABLE 2

Bivariate analysis of consanguinity among cases and controls.

	Male factor infertility	
	Cases, n (%)	**Controls, n (%)**
Consanguineous marriage to wife		
Wife is a relative (maternal or paternal cousin)	19 (15.8)[a]	24 (24.0)
Wife is not a relative	101 (84.2)[a]	73 (73.0)
Relationship unknown	0 (0)[a]	3 (3.0)
Type of consanguineous marriage		
Wife: maternal cousin	8 (6.7)[b]	16 (16)
Wife: paternal cousin	10 (8.3)[b]	7 (7)
Wife: both paternal and maternal cousin	1 (0.8)[b]	1 (1)
Wife: unspecified cousin	3 (2.5)[b]	0 (0)
Wife is not related	98 (81.6)[b]	76 (76)
Consanguineous marriage between parents and/or grandparents		
None are related	64 (53.4)[c]	60 (60.0)
Parents or grandparents are related	34 (28.3)[c]	29 (28.0)
Both parents and grandparents are related	22 (18.3)[c]	8 (8.0)
Relationship unknown	0 (0)[c]	3 (3.0)
Reported male factor infertility problems in immediate family		
Yes	52 (42.6)[d]	14 (14.0)
None	68 (57.4)[d]	85 (85.0)
Unknown	0 (0)[d]	1 (1)

Note: Reproductive history data from 2003.
[a] $P = .102$, compared with control.
[b] $P = .107$, compared with control.
[c] $P = .113$, compared with control.
[d] $P < .001$, compared with control.

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cases vs. 37% controls) was not statistically significant. The socioeconomic and educational backgrounds of those who reported first- and second-degree consanguinity in the parental and grandparental generations did not differ significantly from those who did not report such consanguineous backgrounds. Both groups were equally likely to have married a related wife (i.e., paternal or maternal cousin), suggesting that consanguineous marriage practices in Lebanon are continuing over the generations. The key difference between the groups reflected religious background. As shown in Table 3, those who reported first- or second-degree consanguinity (or both) were more likely to be Muslims or Druze (a Muslim minority sect in Lebanon) (83%) than Christians (17%).

As noted above, cases were more likely than controls to report first- or second-degree consanguinity or both (46% vs. 37%) (Table 2), suggesting that infertility in men may be the product of consanguineous marriage practices in prior generations. Nonetheless, this difference was not found to be statistically significant, either in the bivariate (Table 2) or multiple regression analyses (Table 4). However, a clear family clustering of male factor infertility cases was detected in this study. Controlling for other risk factors, the odds of reported infertility problems among immediate family members—particularly brothers, male cousins, uncles, and, in some cases, fathers and grandfathers—was 2.58 times as high among cases as controls, as shown in Table 4.

In addition, when only men with azoospermia and severe oligospermia ($<1 \times 10^6$ sperm/mL) were separated from the rest of the cases of male factor infertility, the consanguinity and family clustering effects were amplified, as shown in Table 5. Exactly 50% of these men reported first- or second-degree consanguinity or both in their families, and more than 40% reported known male factor infertility problems among close relatives. In other words, half of the most severely infertile Lebanese men in this study came from consanguineous families. Male factor infertility clustered among the men in these families, suggesting a strong genetic component for their sperm defects.

DISCUSSION

The epidemiology of consanguinityand its impacts on infertility are poorly understood, including for the Middle Eastern region, where consanguineous marriages are common. In Middle Eastern Muslim societies, first-cousin marriages—especially patrilateral parallel, or father's brother's son/daughter marriages (*ibn 'amm*, *bint 'amm*)—are the preferred form, with partners having at least one set of grandparents in common, and sometimes two (1, 3).

Lebanon, the focus of this study, has the lowest rate of consanguineous marriages in the Middle Eastern region (1). However, levels of consanguinity in Lebanon may be increasing; current figures demonstrate that nearly one third (29.6%) of all Lebanese Muslims and nearly one fifth (16.5%) of all Lebanese Christians marry consanguineously, even though many Christian sects technically forbid close kinship in marriage. In our study of both Muslim and Christian men, 20% of men (16% of cases, 24% of controls) were married to their cousins

TABLE 3

Distribution of socioeconomic background by consanguinity status.

Variables	First or second consanguinity status: Present	Absent
Age at marriage (y), mean (SD)	32.1 (6.1)[a]	32.4 (6.8)
Wife's age at marriage (y), mean (SD)	26.3 (5.5)[b]	26.8 (6.3)
Years of education, mean (SD)	14.2 (5.6)[c]	13.77 (4.1)
Monthly salary (US$), mean (SD)	1925 (2921)[d]	1723 (1847)
Kinship to wife, n (%)		
Wife related	21 (50.0)[e]	21 (50)
Wife not related	68 (39.3)[e]	105 (39.3)
Religion, n (%)		
Christian	18 (17.3)[f]	6 (6.6)
Druze	2 (1.9)[f]	6 (6.6)
Muslim	84 (80.8)[f]	67 (73.6)

Note: Reproductive history data from 2003.
[a] $P = .725$, compared with absent.
[b] $P = .577$, compared with absent.
[c] $P = .384$, compared with absent.
[d] $P = .539$, compared with absent.
[e] $P = .207$, compared with absent.
[f] $P = .207$, compared with absent.

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TABLE 4

Multivariate logistic regression analysis of consanguinity and family clustering of male factor infertility.

Variable	Adjusted OR	*P* value (95% confidence interval)
Male factor infertility problems in immediate family (yes/no)	2.58	.057 (0.971–6.8)
Consanguineous marriage between parents and/or grandparents (yes/no)	0.865	.756 (0.34–2.17)

Note: Reproductive history data from 2003.

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(Table 2), indicating the persistence of consanguineous marriage practices in this population over time.

Although the presence of first-degree (parental) and/or second-degree (grandparental) consanguinity did not prove to be directly associated with male factor infertility outcomes, two findings of this study are significant. First, male factor infertility problems clearly clustered among men born into consanguineous families (OR = 2.58, Table 4). Second, among the "most infertile" Lebanese men in this study—those with either azoospermia or severe oligospermia—half were the offspring of consanguineous unions among the parental or grandparental generations (or both) (Table 5). Furthermore, >40% of these severely infertile men had close male relatives who were infertile; male factor infertility clearly clustered in the families of infertile men in this study.

Together, these findings suggest a genetic predisposition to male factor infertility in Lebanon. Our findings are supported by a growing literature linking consanguinity to rare recessive genetic sperm defects (8, 9). A variety of abnormalities in both the Y and X chromosomes, as well as genetic abnormalities of the hypothalamic-pituitary-gonadal axis involved in the production of reproductive hormones, are now well-established causes of male factor infertility (23, 24). Probably the most frequent molecular genetic cause of infertility in men involves microdeletions of the long arm of the Y chromosome; these deletions are associated with spermatogenic failure (25–27). Such genetic sperm defects have been linked to consanguinity in two recent studies (8, 9).

There is a significant paucity of data in the Middle East on the genetic component of male factor infertility. In recent studies emerging from Kuwait (20, 21), a short arm deletion of chromosome 21 appears to be associated with male factor infertility (20). Similar studies ascertaining the underlying mechanisms of genetic male factor infertility should be repeated in other Middle Eastern countries. Such genetic studies should then be linked to epidemiologic studies of consanguinity as a male infertility risk factor.

Moreover, molecular genetic testing of infertile Middle Eastern men is necessary and represents one of the major limitations of our own study, in which genetic testing was not feasible. However, because of the availability of rigorous and standardized semen analysis data, objective evidence of azoospermia and severe oligospermia was provided in this study, which proved critical to the analysis. Furthermore, the quality

TABLE 5

Consanguinity and family clustering of male factor infertility among men with severe oligospermia and azoospermia.

	Men with severe oligospermia and azoospermia	
	No.	%
Distribution of first- or second-degree consanguinity		
None	33	50.8
First or second degree	19	29.2
Both first and second degree	13	20.0
Distribution of infertility problems in immediate family		
None	38	58.5
Male factor	25	38.4
Female factor	2	3.1

Note: Reproductive history data from 2003.

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of the measures in this study was high, because of the use of multiple validation techniques (i.e., an in-depth reproductive history and risk factor interview, carried out by M.C.I. in either Arabic or English). No major problems existed in terms of adjusting for missing and nonresponse data, and the size of the sample approximated computed statistical power calculations. Although the study relied on self-reported family data, research subjects usually had no difficulty providing this information. Some even volunteered to sketch their family's genealogy, marking the relevant male factor infertility cases at the time of the interview.

Given the findings of this study, counseling infertile Middle Eastern couples about possible genetic causes of male factor infertility seems necessary, especially in light of the rapid expansion of ICSI in this region (28). For example, in Lebanon, a relatively small country of only 10,452 km^2 area and 4.3 million people (29), more than 15 IVF centers serve the population, one of the highest rates per capita in the world (19). The use of ICSI in this population may be inadvertently perpetuating genetic disorders into future generations in a population with limited comprehension of the basic principles of heredity.

Indeed, in Lebanon, as in other regions of the Middle East, religion is often invoked to explain genetic diseases (and other serious conditions) as manifestations of God's will (30, 31). Furthermore, consanguineous marriages are common, but genetic conditions, such as thalassemia and cystic fibrosis, are relatively uncommon. Thus, community members are often unwilling to link consanguinity to genetic disorders, particularly when the Prophet Muhammad married his daughter Fatima to his first cousin Ali (5, 30, 31). Understanding the relationships between consanguinity and genetic disorders, including those underlying male factor infertility, will require not only basic medical and epidemiologic research, but also comprehensive religious, governmental, and media-based intervention programs, which set in place the basic groundwork for effective prevention and counseling (32).

In conclusion, rare genetic recessive disorders, including those linked to male factor infertility, are more often observed among inbred populations. This study in Lebanon has demonstrated relatively high levels of consanguinity over multiple generations, resulting in family clustering of male factor infertility cases and the likelihood of genetically based infertility disorders among Lebanese men with azoospermia and severe oligospermia.

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