Relationship between semen production and medical comorbidity

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Objective: To study the relationship between semen quality and current health status in a cohort of men evaluated for infertility.
Design: Cross-sectional study.
Setting: Fertility clinic.
Patient(s): Nine thousand three hundred eighty-seven men evaluated for infertility between 1994 and 2011.
Intervention(s): None.
Main Outcome Measure(s): Charlson comorbidity index, medical diagnoses by organ system.
Result(s): At the time of evaluation, 9,387 men with a mean age of 38 years had semen data available. Of these men, 44% had at least one medical diagnosis unrelated to infertility. When stratifying the cohort by the Charlson comorbidity index (CCI), differences in all measured semen parameters were identified. Men with a higher CCI had lower semen volume, concentration, motility, total sperm count, and morphology scores. In addition, men with diseases of the endocrine, circulatory, genitourinary, and skin diseases all showed significantly higher rates of semen abnormalities. Upon closer examination of diseases of the circulatory system, men with hypertensive disease, peripheral vascular and cerebrovascular disease, and nonischemic heart disease all displayed higher rates of semen abnormalities.
Conclusion(s): The current report identified a relationship between medical comorbidites and male semen production. Although genetics help guide a man's sperm production, his current condition and health play an important role. (Fertil Steril® 2015;103:66–71. ©2015 by American Society for Reproductive Medicine.)
Key Words: Fertility, hypertension, male infertility, oligospermia, vascular disease

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Aberrations in reproductive fitness may be a harbinger of medical diseases in men. Indeed, recent studies in men from Europe and the United States have demonstrated links between malignancies and fertility in men (1–3). Moreover, data demonstrate that impaired semen parameters can predict mortality, suggesting that a semen analysis may represent a biomarker of overall health and fitness (4, 5). As approximately 15% of the male human genome is involved in reproduction, it is conceivable that other health ailments may also be linked to defects in fertility (6, 7). In addition to shared genetic origins, investigators have hypothesized that hormone, environmental/lifestyle, or in utero factors could explain a link between a man's reproductive and somatic health.

However, the relationship between fertility and health is likely complex, as many confounding factors may impact both. For example, obesity and smoking are known to adversely affect semen parameters, health, and life expectancy (8–11). Medical conditions and their treatments may also directly impact fertility. Diabetes mellitus has been associated with impaired semen parameters in case-control studies (12, 13). However, as some of the diabetic men from these studies were fathers, the clinical importance is uncertain. More consistently, diabetes has been shown to impact male fertility through ejaculatory and erectile impairments (14). Hemoglobinopathies can lead to gonadal dysfunction and impaired sperm production through both manifestations of the disease (e.g., testicular iron deposition in thalassemia) and its treatment (e.g., hydroxyurea for sickle cell disease) (15–17). Recent data also suggest a relationship between hypertension and

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TABLE 1

Characteristics of cohort.

Characteristic	Value
No. of patients	9,387
Age at SA, mean (SD)	37.8 (6.33)
Age at SA, n (%)	
20–29	648 (6.9)
30–39	5,812 (61.92)
40–50	2,546 (27.12)
50+	381 (4.06)
Year of evaluation	
1991–1995	31 (0.33)
1996–2000	1,664 (17.73)
2001–2005	3,991 (42.52)
2006–present	3,701 (39.43)
CCI	
Mean ± SD	0.07 (0.54)
0	9,071 (96.63)
1	149 (1.59)
2	114 (1.21)
≥3	53 (0.56)

Note: CCI = Charlson comorbidity index; SA = semen analysis; SD = standard deviation.

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poor sperm quality as assessed by markers of DNA fragmentation and abnormal sperm morphology (18). However, the methodologic limitations and a paucity of data for many human ailments make interpretation of the relationship between somatic and reproductive health difficult.

As up to half of all infertile couples have a male factor to explain their reproductive difficulties, further examination of a link between health and male infertility has implications for millions of men in the United States, especially given that the U.S. paternal age is rising (19–21). With the wide uptake of electronic health records and advanced linkage, extraction, and analytic techniques available through the big data revolution, relationships between disparate medications, conditions, and treatments can be explored to allow improved counseling and treatment. Using this strategy, we sought to determine the relationship between semen quality and current health status in a cohort of men evaluated for infertility.

MATERIALS AND METHODS

Study Population

After institutional review board approval, a study cohort was identified with data from 1994 to 2011 in the Stanford Reproductive Endocrinology and Infertility semen database. The clinic evaluates and treats infertile couples who have both male and female infertility. The laboratory performs a high volume of semen analyses for fertility evaluations and sperm preparations for use with assisted reproduction technology (ART).

Men evaluated for infertility were self-referred or referred by an internist, gynecologist, urologist, or reproductive endocrinologist. For men with multiple semen analyses, only the first test was analyzed for our present study. The methods used for analysis of semen (sperm concentration, motility, volume, morphology) were previously described elsewhere (22–24). Morphology scoring was performed as described by Kruger et al. (24).

TABLE 2

Association of Charlson comorbidity index (CCI) and semen parameters.

	CCI				
Semen parameters	**0**	**1**	**2**	**3+**	***P* trend**
No. of patients (all)	9,071	149	114	53	
Volume (mL)					
Mean (SD)	3.1 (1.8)	2.8 (1.6)	2.67 (1.5)	2.23 (1.5)	<.01
<1.5 mL	868 (10.0)	23 (16.4)	15 (14.0)	12 (25.5)	<.01
Concentration (M/mL)					
Mean (SD)	64.9 (51.6)	58.7 (41.2)	47.32 (56.7)	43.4 (46.1)	<.01
<15 M/mL	1,057 (12.5)	16 (12.3)	36 (36.4)	14 (35)	<.01
Motility (%)					
Mean (SD)	47.6 (23.8)	43.3 (23.8)	37.7 (25.7)	30.5 (22.7)	<.01
<40%	3,103 (36.7)	62 (47.7)	49 (51.0)	26 (65)	<.01
Total sperm (M)					
Mean (SD)	193.2 (179.9)	164.8 (140.0)	132.7 (178.4)	92.8 (100.8)	<.01
<39 M	1,243 (14.7)	17 (13.1)	41 (41.8)	15 (37.5)	<.01
Total motile sperm (M)					
Mean (SD)	109.9 (126.6)	87.14 (98.3)	78.4 (127.9)	44.3 (61.6)	<.01
<9 M	1,276 (15.1)	21 (16.2)	34 (35.8)	17 (42.5)	<.01
Morphology (%)					
Mean (SD)	10.6 (6.1)	10.59 (5.6)	9.3 (6.51)	8.37 (4.9)	.04
<14%	4,086 (71.3)	67 (71.3)	52 (74.3)	25 (83.3)	.31
No. semen abnormalities					
0	4,757 (55.8)	59 (43.4)	41 (40.2)	13 (28.9)	<.01
1	2,601 (30.5)	57 (41.9)	25 (24.5)	16 (35.6)	
2+	1,164 (13.7)	20 (14.7)	36 (35.3)	16 (35.6)	

Note: Semen parameters assessed as continuous values (mean (standard deviation) listed) and categorical (n, percentage in subfertile range based on WHO 5th ed. criteria) (26). Analyses adjusted for age and year of evaluation.

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