ERECTILE DYSFUNCTION

Erectile Dysfunction is Predictive Symptom for Poor Semen in Newlywed Men in Japan

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ABSTRACT

Introduction: As a continuous decline in semen concentration has been reported, the concept of male infertility has gained increased attention. Although several surveys of semen quality have been conducted in young men in general, no study has reported only on newlywed men.

Aim: The aim of this study was to evaluate semen quality and assess its characteristics in newlywed men.

Methods: This study included 564 men visiting our hospital or clinic for fertility screening just before their wedding or as newlywed men. Based on the World Health Organization criteria, the rates of men who did not have a semen volume of $\geq$1.5 mL, a sperm concentration of $\geq$15 million/mL, and a sperm motility rate of $\geq$40% were calculated. The characteristics of the poor semen findings group with any 1 of the 3 items of semen volume, sperm concentration, or sperm motility rate not reaching the reference value were evaluated.

Main Outcome Measure: Independent factors, which are involved in the poor semen findings group, were evaluated.

Results: The poor findings in semen volume, sperm concentration, and sperm motility were found in 11.0%, 9.2%, and 10.6%, respectively. The poor semen findings group included 143 men (25.4%) with any 1 of the 3 items not reaching the reference value. As compared to the normal group, age and body mass index were significantly higher, testicular volume was significantly smaller, and blood gamma-glutamyltransferase and fasting blood sugar levels were significantly higher in the poor semen findings group. Logistic multivariate analysis, including symptom questionnaire scores, blood biochemistry items, and endocrinological items, showed 3 independent factors were involved in the poor semen findings group: age, luteinizing hormone, and erection (Erection Hardness Score).

Conclusion: It was clarified that even among men beginning their attempts at pregnancy, semen findings were poor and erectile dysfunction was involved in poor semen quality in one-quarter of the men. **Tsujimura A, Hiramatsu I, Nagashima Y, et al. Erectile Dysfunction is Predictive Symptom for Poor Semen in Newlywed Men in Japan. Sex Med 2019;8:21–29.**

INTRODUCTION

Most developed countries, including Japan, have been facing a decline in the rate of total fertility and an aging population over the last few decades. With respect to this point, the concept of male infertility has gained increasing attention and poses very serious problems even from economical and national aspects, even though infertility has been recognized as a female problem for a long time. In relation to male infertility, several surveys of semen quality have recently been reported. A continuous decline in semen concentration of about 1.9% per year was reported in a longitudinal survey with a sample of 26,609 men whose infertile wives underwent assisted reproductive technology procedures in

France over a 17-year period from 1989−2005.[1] Exposure to certain kinds of chemical substances and insecticides, smoking, stress in highly advanced and complicated societies, obesity with change in nutrition, and increased infection rate have been speculated to cause these alterations.[2] Even lower urinary tract symptoms are speculated to be associated with semen quality. It is easy to imagine that this worldwide trend of worsening semen quality has induced the serious demographic problem of declining birthrates in contemporary society. In addition to these environmental factors, the aging process also worsens semen quality (eg, sperm concentration and motility[3]). These data indicate that male age needs greater recognition as a potential contributor to the negative pregnancy outcomes associated with delayed first reproduction. In spite of these facts, there is a serious tendency for late marriages and late births in most developed countries, especially in Japan, because men and women of reproductive age often wish to keep working for career advancement or economic reasons.

In Japan, a nationwide survey of male infertility in 2017 indicated that the etiology of infertility included testicular factors (82.6%), sexual dysfunction (13.5%), and seminal tract obstruction (3.9%).[4] Thus, most male infertility should be caused by problems related to ejaculated semen. A general survey of the semen quality of 1,559 young Japanese men (median age 21.1 years; range 18−24 years) from 1999−2003 showed a median sperm concentration of 59 (95% CI 52−68) million/mL and median sperm motility of 67% (65−68%).[5] This shows that even when semen samples were obtained from young men, particularly excellent findings, such as a sperm concentration of 100 million/mL or more or sperm motility of 90% or more, cannot necessarily be expected. These results caused us to be concerned about the semen findings of Japanese men whose first marriage was delayed when they start to actively have their partner become pregnant. However, there are no studies so far of the semen of newly married men or men just before marriage who are expecting to have a baby in the future. Likewise, there have been no reports on the patient background of men whose semen findings deteriorate at the start of attempts to get their wife pregnant.

AIMS

In the present study, we investigated the characteristics of semen quality in newlywed men or men just before marriage. Especially, we analyzed the biochemical and endocrinological factors that influenced poor semen quality and the scores of specific questionnaires addressing several symptoms, including lower urinary tract symptoms, sexual function, and late-onset hypogonadism.

METHODS

Participants

This study included 293 newlywed men and 271 men just before marriage who visited our hospital or affiliated clinic for fertility screening. Newlywed men meant persons who just started trying to conceive after the first semen test in their life. For them, the average duration between the semen test and the marriage was 8.6 months.

Procedure

A semen test was performed after 4 or more days of abstinence by use of a Makler semen counting chamber.

First, based on the 2010 World Health Organization (WHO) criteria, the rates of men who did not have a semen volume of 1.5 mL or more, a sperm concentration of 15 million/mL or more, and a sperm motility rate of 40% or more were calculated. Next, the men in whom any of these 3 measures did not reach the reference value were assigned to the poor semen findings group, and the rates were calculated and compared against the men assigned to the normal semen findings group.

5 independent factors, including age, body mass index (BMI), smoking habit, and bilateral testicular volumes evaluated by orchidometer were assessed. Serum concentrations of 20 factors evaluated by biochemical blood tests were assessed: total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, blood urea nitrogen, creatinine, urinary acid, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, total bilirubin, total protein, albumin, albumin globulin ratio, sodium, potassium, chloride, fasting blood sugar, and hemoglobin A1c. 8 endocrinological factors were also assessed: luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone, estradiol, prolactin, dehydroepiandrosterone sulfate, insulin-like growth factor 1, and cortisol. 5 symptomatic factors were assessed as scores evaluated by several specific questionnaires, including the International Prostate Symptom Score for voiding symptoms, the Sexual Health Inventory for Men, the Erection Hardness Score (EHS) for sexual function, the Aging Males Symptom rating scale for late onset hypogonadism, and the Beck Depression Inventory for depression. This study was approved by the institutional review board of Juntendo University Urayasu Hospital (2018-033).

Data Analysis

The Mann−Whitney U test was used to compare these factors between the normal semen findings group and the poor semen findings group. Statistical significance was set at $P < .05$. Further, using logistic univariate analysis, factors predictive of the poor semen findings group were identified ($P < .10$), and logistic multivariate analysis (initial model) was subsequently conducted. Finally, using backward elimination, factors causing poor semen findings were identified ($P < .05$).

MAIN OUTCOME MEASURES

In all 38 factors incorporated as independent variables, factors predictive of the poor semen findings group were identified.

Table 1. Clinical characteristics of 564 men just before wedding or newly wed

Case	564	
Unmarried, N (%)	271 (48)	
Married, N (%)	293 (52)	
(Duration after marriage [months] 8.6 ± 3.3)		
Age, years	35.5 ± 6.7	(21–66)
BMI, kg/m^2	22.7 ± 3.0	(12.1–37.6)
Smoking, N (%)	86 (15.2)	
Testicular volume, mL		
Right	20.6 ± 3.8	(2–30)
Left	19.6 ± 4.2	(1–30)
Total cholesterol, mg/dL	196.0 ± 32.9	(99–305)
HDL cholesterol, mg/dL	60.2 ± 13.3	(30–115)
LDL cholesterol, mg/dL	120.2 ± 30.7	(45–226)
Triglyceride, mg/dL	91.8 ± 61.2	(19–658)
BUN, mg/dL	12.9 ± 2.9	(6.6–21.7)
Creatinine, mg/dL	0.8 ± 0.1	(0.6–1.2)
Urinary acid, mg/dL	6.0 ± 1.2	(0.7–10.3)
AST, U/L	22.8 ± 12.7	(12–233)
ALT. U/L	26.0 ± 20.5	(7–178)
γ-GTP, U/L	35.8 ± 34.5	(9–295)
ALP, U/L	195.0 ± 48.9	(60–403)
Total bilirubin, mg/dL	0.9 ± 0.3	(0.2–2.9)
Total protein, g/dL	7.4 ± 0.4	(6.1–8.5)
Albumin, g/dL	4.8 ± 0.3	(3.9–5.6)
A/G	1.8 ± 0.2	(1.2–2.8)
Na, mEq/L	142.2 ± 1.5	(139–148)
K, mEq/L	3.9 ± 0.3	(3.0–5.7)
CL, mEq/L	103.3 ± 1.8	(98–109)
FBS, mg/dL	87.0 ± 9.7	(65–157)
HbA1c, (%)	5.3 ± 0.3	(4.5–7.3)
LH, mIU/mL	3.3 ± 1.8	(0.1–16.8)
FSH, mIU/mL	4.3 ± 3.8	(1.1–60.1)
Testosterone, ng/mL	5.5 ± 1.9	(1.1–14.7)
Estradiol, pg/mL	25.0 ± 9.6	(10–86)
Prolactin, ng/mL	24.5 ± 156.3	(4.1–3,605.0)
DHEA-S, μg/dL	300.8 ± 105.6	(65–777)
IGF-1, ng/mL	152.2 ± 38.9	(59–389)
Cortisol, μg/dL	9.7 ± 4.6	(0.2–35.4)
IPSS	3.4 ± 3.7	(0–24)
BDI	5.4 ± 5.4	(0–42
SHIM	18.9 ± 5.3	(1–25)
EHS	3.5 ± 0.7	(1–4)
AMS	24.9 ± 7.6	(17–61)

A/G = albumin to globulin ratio; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AMS = Aging Males Symptom; AST = aspartate aminotransferase; BDI = Beck Depression Inventory; BMI = body mass index; BUN = blood urea nitrogen; CL = chloride; DHEA-S = dehydroepiandrosterone sulfate; EHS = Erection Hardness Score; FBS = fasting blood sugar; FSH = follicle-stimulating hormone; γ-GTP = gamma-glutamyltransferase; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; IGF-1 = insulin-like growth factor-1; IPSS = International Prostate Symptom Score; K = potassium; LDL = low-density lipoprotein; LH = luteinizing hormone; Na = sodium; SHIM = Sexual Health Inventory for Men.

Table 2. Rates of semen volume, sperm concentration and sperm motility exceeding the lower limit of normal

Semen volume <1.5 mL	62 (11.0%)
Sperm concentration <15 × 10^6/mL	52 (9.2%)
≥5 × 10^6/mL	31 (5.4%)
<5 × 10^6/mL	11 (2.0%)
Azoospermia	10 (1.8%)
Sperm motility <40%	60 (10.6%)

RESULTS

Patient characteristics are shown in Table 1. The subjects included 271 men just before marriage (48.0%) and 293 newlywed men (52.0%), with the married men visiting this hospital for screening an average of 8.6 months after their marriage. The mean age was 35.5 years, and the testicular volumes of both groups averaged around 20 mL, but patients with extremely small testicular volumes also existed. Almost no items in the biochemical blood tests deviated from the reference values, but endocrinological testing showed 1 man who had an abnormally high prolactin value of 3,605.0 ng/mL. This man had pituitary adenoma and was referred to the Department of Endocrinology, where control with medical treatment was given priority.

Results of the semen examination are shown in Table 2. 62 men (11.0%) had a semen volume of <1.5 mL. Similarly, 52 men (9.2%) had a sperm concentration of less than 15 × 10^6/mL. Surprisingly, azoospermia was found in 10 men (1.8%). Additionally, 11 men (2.0%) were found who had sperm concentrations of <5 × 10^6/mL, which would cause difficulty in initiating a spontaneous pregnancy. Furthermore, 60 men (10.6%) were found whose sperm motility rate was less than the reference value of 40%. The poor semen findings group included 143 men (25.4%) with any 1 of the 3 items of semen volume, sperm concentration, or sperm motility rate not reaching the reference value, who hoped for fertility in the future.

Results of the normal semen findings group can be compared with those of the poor semen findings group in Table 3. Age and BMI were significantly higher and testicular volume was significantly smaller in the poor semen findings group. Among the biochemical blood tests, gamma-glutamyltransferase, and fasting blood sugar were significantly higher in the poor semen findings group, and the involvement of hepatic dysfunction and glucose metabolism disorder were suspected. The results of the endocrinological tests revealed that only FSH involved in spermatogenesis was significantly high in the poor semen findings group. In the comparison of symptom scores, every symptom score was worse in the poor semen findings group.

The results of logistic analysis are shown in Table 4. First, univariate analysis demonstrated associations of 11 factors ($P < .10$), and the logistic multivariate analysis using these 11

Table 3. Semen quality the normal group and poor group

	Normal	Poor	
	(N = 421; 74.6%)	(N = 143; 25.4%)	P value
Age, years	34.3 ± 5.9	38.8 ± 7.7	< .001
BMI, kg/m^2	22.6 ± 2.9	23.2 ± 3.2	.013
Smoking, N (%)	63 (15.0)	23 (16.1)	.788
Testicular volume, mL			
Right	20.9 ± 3.5	19.7 ± 4.6	.015
Left	20.0 ± 3.9	18.6 ± 5.1	.003
Total cholesterol, mg/dL	194.4 ± 32.9	200.8 ± 32.3	.128
HDL cholesterol, mg/dL	60.4 ± 12.8	59.5 ± 14.9	.203
LDL cholesterol, mg/dL	119.0 ± 30.6	123.9 ± 30.9	.133
Triglyceride, mg/dL	88.6 ± 56.0	101.6 ± 74.4	.051
BUN, mg/dL	12.9 ± 2.8	12.9 ± 3.0	.708
Creatinine, mg/dL	0.8 ± 0.1	0.8 ± 0.1	.208
Urinary acid, mg/dL	6.0 ± 1.2	5.9 ± 1.2	.146
AST, U/L	22.7 ± 13.8	23.1 ± 8.7	.098
ALT, U/L	25.3 ± 20.1	28.2 ± 21.7	.050
γ-GTP, U/L	33.6 ± 31.6	42.7 ± 41.5	< .001
ALP, U/L	195.0 ± 48.4	195.0 ± 50.5	.700
Total bilirubin, mg/dL	0.9 ± 0.3	0.9 ± 0.4	.687
Total protein, g/dL	7.4 ± 0.4	7.4 ± 0.4	.450
Albumin, g/dL	4.8 ± 0.3	4.8 ± 0.3	.132
A/G	1.8 ± 0.3	1.8 ± 0.2	.943
Na, mEq/L	142.2 ± 1.5	142.3 ± 1.6	.553
K, mEq/L	3.9 ± 0.3	3.9 ± 0.3	.159
CL, mEq/L	103.3 ± 1.8	103.5 ± 1.9	.161
FBS, mg/dL	86.0 ± 8.1	90.0 ± 13.1	.002
HbA1c, %	5.3 ± 0.3	5.3 ± 0.3	.132
LH, mIU/mL	3.2 ± 1.5	3.6 ± 2.5	.088
FSH, mIU/mL	3.8 ± 1.9	5.8 ± 6.8	.001
Testosterone, ng/mL	5.6 ± 1.9	5.4 ± 1.9	.231
Estradiol, pg/mL	24.8 ± 9.1	25.5 ± 10.9	.976
Prolactin, ng/mL	26.8 ± 179.5	17.2 ± 9.2	.080
DHEA-S, μg/dL	305.3 ± 106.5	286.8 ± 101.9	.245
IGF-1, ng/mL	153.3 ± 38.9	148.7 ± 38.5	.125
Cortisol, μg/dL	9.6 ± 4.4	9.8 ± 5.5	.653
IPSS	3.2 ± 3.5	4.1 ± 4.2	.014
SHIM	19.4 ± 5.1	17.5 ± 5.8	< .001
EHS	3.5 ± 0.7	3.3 ± 0.7	< .001
AMS	24.3 ± 7.2	26.7 ± 8.5	< .001

A/G = albumin to globulin ratio; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AMS = Aging Males Symptom; AST = aspartate amino-transferase; BDI = Beck Depression Inventory; BMI = body mass index; BUN = blood urea nitrogen; CL = chloride; DHEA-S = dehydroepiandrosterone sulfate; EHS = Erection Hardness Score; FBS = fasting blood sugar; FSH = follicle-stimulating hormone; γ-GTP = gamma-glutamyltransferase; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; IGF-1 = insulin-like growth factor-1; IPSS = International Prostate Symptom Score; K = potassium; LDL = low-density lipoprotein; LH = luteinizing hormone; Na = sodium; SHIM = Sexual Health Inventory for Men.

factors is shown in model 1. In addition, using backward elimination from model 1, model 2, which analyzed significant factors associated with the poor semen findings group ($P < .05$), finally indicated an association of 3 factors: age, LH, and EHS. In other words, even if a man was starting actively to get his partner pregnant, the risk of poor semen findings increased as he got older. Likewise, on the basis of the reference value for serum LH of 2.29 mIU/mL or more and <3.10 mIU/mL, even if the value decreased to 2.29 mIU/mL or lower or rose to 3.10 mIU/mL or higher, the risk of poor semen findings increased. Moreover, in terms of erectile function, in men who did not reach EHS 4 (the penis is completely hard and stiff), that is, men who were aware of a lack of hardness of their erection, the risk for poor semen findings was high.

Table 4. Independent factors influencing semen analysis in the poor group

Variable	Category	N	Poor case	Multivariate analysis model 1		[Variable P]	Multivariate analysis model 2		[Variable P]
				Odds ratio			Odds ratio		
				Point estimation	95% CI	Category P	Point estimation	95% CI	Category P
Age	21−<30	87	9 (10.3%)	Reference	-	[0.149]	Reference	-	[0.009]
	30−<34	130	23 (17.7%)	1.903	(0.791, 4.578)	0.151	1.794	(0.775, 4.150)	0.172
	34−<39	134	33 (24.6%)	2.170	(0.924, 5.099)	0.075	2.563	(1.134, 5.791)	0.024
	39−65	129	43 (33.3%)	2.778	(1.158, 6.665)	0.022	3.545	(1.591, 7.900)	0.002
Rt. testicular Volume	2−<18	86	29 (33.7%)	0.661	(0.186, 2.355)	0.523			
	18−<20	44	11 (25.0%)	0.437	(0.132, 1.449)	0.176			
	20−<24	214	39 (18.2%)	0.457	(0.220, 0.953)	0.037			
	24−30	136	29 (21.3%)	Reference	-	[0.168]			
Lt. testicular Volume	2−<18	117	37 (31.6%)	2.208	(0.718, 6.783)	0.167			
	18−<20	77	17 (22.1%)	2.408	(0.918, 6.318)	0.074			
	20−<22	90	21 (23.3%)	2.133	(0.971, 4.684)	0.059			
	22−30	196	33 (16.8%)	Reference	-	[0.196]			
SHIM	1−<18	119	35 (29.4%)	0.886	(0.424, 1.850)	0.747			
	18−<21	114	30 (26.3%)	1.060	(0.534, 2.106)	0.867			
	21−<23	80	13 (16.3%)	0.619	(0.277, 1.382)	0.242			
	23−25	167	30 (18.0%)	Reference	-	[0.590]			
EHS	0−3	206	61 (29.6%)	1.829	(1.031, 3.245)	0.039	1.844	(1.167, 2.913)	0.009
	4	274	47 (17.2%)	Reference	-	-	Reference	-	-
γ-GTP	9−<18.5	120	18 (15.0%)	Reference	-	[0.469]			
	18.5−<24	113	21 (18.6%)	1.198	(0.566, 2.534)	0.636			
	24−<39	126	36 (28.6%)	1.649	(0.819, 3.322)	0.161			
	39−295	121	33 (27.3%)	1.586	(0.768, 3.275)	0.213			
Creatine	0.55−<0.77	117	27 (23.1%)	Reference	-	[0.148]			
	0.77−<0.83	112	18 (16.1%)	0.885	(0.426, 1.841)	0.744			
	0.83−<0.90	124	24 (19.4%)	0.968	(0.485, 1.931)	0.925			
	0.90−1.20	127	39 (30.7%)	1.733	(0.913, 3.289)	0.093			
FBS	65−<81	109	17 (15.6%)	0.935	(0.419, 2.086)	0.870			
	81−<85	103	18 (17.5%)	Reference	-	[0.261]			
	85−<90.5	148	35 (23.6%)	1.468	(0.734, 2.936)	0.278			
	90.5−157	120	38 (31.7%)	1.770	(0.861, 3.636)	0.120			
LH	0.92−<2.29	118	30 (25.4%)	2.634	(1.230, 5.639)	0.013	2.604	(1.263, 5.366)	0.010
	2.29−<3.10	119	13 (10.9%)	Reference	-	[0.034]	Reference	-	[0.002]
	3.10−<4.015	123	26 (21.1%)	2.210	(1.023, 4.773)	0.044	2.267	(1.088, 4.727)	0.029
	4.015−16.79	120	39 (32.5%)	2.958	(1.351, 6.477)	0.007	3.941	(1.937, 8.019)	<0.001

Table 4. Continued

Variable	Category	N	Poor case	Multivariate analysis model 1				Multivariate analysis model 2			
				Odds ratio		[Variable P]		Odds ratio		[Variable P]	
				Point estimation	95% CI	Category P		Point estimation	95% CI	Category P	
FSH	1.10–<2.59	119	23 (19.3%)	1.858	(0.862, 4.005)	0.114					
	2.59–<3.565	121	18 (14.9%)	Reference	-	[0.192]					
	3.565–<4.99	120	25 (20.8%)	1.688	(0.794, 3.585)	0.173					
	4.99–60.11	120	42 (35.0%)	2.255	(1.042, 4.880)	0.039					

EHS = Erection Hardness Score; FBS = fasting blood sugar; FSH = follicle-stimulating hormone; γ-GTP = gamma-glutamyltransferase; LH = luteinizing hormone; SHIM = Sexual Health Inventory for Men.

DISCUSSION

Although the main potential confounders, such as age or sexual behavior of the participating men were not clarified, results suggesting a decrease in sperm count have been reported since the early 1990s. Recently, researchers in the United States, Brazil, Denmark, Israel, and Spain conducted meta-regression analyses to assess 185 study results on sperm counts from 1973 through 2011 and sensationally reported that at least for men in North America, Europe, Australia, and New Zealand, their sperm concentrations and sperm counts had decreased by 52.4% and 59.3%, respectively, over this period.[6] The reason is not clear, but smoking may be 1 factor associated with poor semen quality.

Although the rate of smoking is gradually decreasing, it was reported in a new systematic review and meta-analysis comprising 5,865 men that cigarette smoking was associated with reduced sperm count and motility.[7] In that review, deterioration of semen quality was more pronounced in moderate and heavy smokers.

It is a well-known fact that 32 to 33°C is the ideal temperature for spermatogenesis, but the possibility that obesity can worsen semen findings by raising the scrotal temperature has been pointed out. A clinical study in which scrotal temperatures were measured over time showed that although the scrotal temperatures of nonobese men are high during sleep at around 36°C, the temperatures decrease to around 30−33°C after the men get out of bed, and especially while walking after breakfast, a coffee break, or a lunch break. In contrast, the scrotal temperatures in obese men rarely decrease and are maintained at about 35°C or more.[8]

Likewise, it is also reported that if a laptop computer is rested on the thighs while the user is in a sitting position, scrotal temperatures increase significantly compared with times when the users are just sitting down.[9] Furthermore, it was also recently reported in an in vitro study that sperm motility in semen placed near laptop computers connected to the Internet via WiFi for 4 hours decreased and sperm DNA fragmentation increased.[10] Interesting clinical studies have also been reported about underwear. In a study using self-reported questionnaires, men who reported primarily wearing boxers had a 25% higher sperm concentration and 17% higher total sperm count than men who reported primarily not wearing boxers.[11]

In Japan, it is customary not only to take a shower but also to then bathe in a bathtub in hot water at 40°C or more. It is also reported that when Westerners who did not usually take baths used a sauna (80−90°C) for around 15 minutes twice a week for 3 months alone, their sperm counts decreased.[12] Therefore, the increase in scrotal temperature caused by the Japanese habit of taking a bath may not have a little influence on spermatogenesis. Additionally, psychological stress was also reported to be involved in semen findings. Results of a clinical study of young men with an average age of 19 years that evaluated stress using questionnaires and analyzed the relationship with the semen findings

showed that the men with the highest stress levels had a 38% lower sperm concentration, 34% lower total sperm count, and 15% lower semen volume than the men with intermediate stress levels.[13]

Needless to say, dietary habits are also related to semen findings. It is reported that a "Western diet" and "high-sweet snacks & sugar-sweetened drinks" are related to a reduction in sperm concentration.[14] As described above, in modern society, the involvement of various environmental factors, endocrine disrupters, social stress, socially induced changes in diet or lifestyle, or metabolic factors, is suspected, but a definitive cause has not yet been discovered. We think that the importance of evaluating the semen findings of men who start activity to get their partner pregnant is high as the birthrate declines and the men get older.

In Japan, the age of men at first marriage exceeds 31 years, and the tendency to marry later is increasing. The mass media often reports the importance of a women's age in relation to sterility from the point of view of "aging of the ovum." As the concept of "aging of ova" has spread, the interest level of men's age in terms of sterility is also gradually increasing. Recently, a systematic review and meta-analysis using data from 90 studies (93,839 subjects) clearly showed age-associated declines in semen volume, total sperm count, percentage of sperm motility, progressive motility, and normal morphology.[15] Therefore, the risk of a tendency toward later marriage has become a concern, and those who desire a so-called bridal check to confirm their own fertility before marriage is currently on the increase. However, it is also true that some couple's marriages were canceled when the results clarified that the man's fertility was extremely low, and, thus, a bridal check may not necessarily contribute to the happiness of a couple. As infertility should be discussed and overcome by a couple, it is still necessary to know about fertility before marriage in the first place. Although the thought of a bridal check is considered in a negative light, it is thought that a semen examination before marriage is very important for the couple or the family on the woman's side to avoid psychosocial, economical, and biological troubles after the marriage. Actually, when the pros and cons of fertility testing were recently investigated using questionnaires in 740 randomly chosen adults before marriage (>18 years old, 364 men, 382 women), 523 respondents (70.11%) reportedly had a positive attitude toward applying fertility testing for men before marriage.[16]

Moreover, this tendency is not influenced by sex, age, BMI, smoking history, income, education level, and infertility of the relatives. In addition, a different report found that infertility factors on the male side were present in 28.4% of the infertile couples who had practiced contraception in the past.[17] More specifically, this report pointed out that if a man had undergone a semen examination early in the marriage and was found not to need to practice contraception, it was emphasized that had he understood the situation beforehand, he might start actions to get pregnant immediately. The report concluded that from the point of view of a man's future life plan, an early semen examination would be important, even at the stage where he is not yet concretely hoping for a child just before or after marriage. In such circumstances, it may be understandable that bridal checks are spreading in Japanese men as an international trend.

Now, a large number of reports have been published on semen findings, especially those of ordinary young men. Recently, multiple studies, including a study of Japanese over the past 15 years, reported median sperm concentrations of $41-55 \times 10^6$/mL in young men (mean age 18−21 years) from the general population.[18] However, we could find no studies limited to men just before starting activity to get their partner pregnant. The present study revealed that even among men before marriage or at the start of activity to get pregnant, those who did not reach the 2010 WHO criteria of semen volume, sperm concentration, and sperm motility rate, accounted for 11.0%, 9.2%, and 10.6%, respectively. When sperm concentration, sperm motility, and morphology were recently examined and the semen findings of 1,165 young men of 16−29 years of age were classified into low, intermediate, and high semen quality, low semen quality was present in 11−15%, intermediate semen quality in 37−50%, and high semen quality in 38−52% of the men.[19] In other words, a considerable number of young men have worsening semen findings. Even our study found that 1 in 4 (25.4%) young men in whom any 1 of the factors of semen volume, sperm concentration, or sperm motility did not reach the WHO reference values were classified into the poor semen findings group. These men were slightly older than those in the normal semen findings group, but their BMI, gamma-glutamyltransferase, and fasting blood sugar values were significantly higher, and, therefore, it would presumably be important for them to continue to improve their lifestyle and diet.

Surprisingly, the data in our study showed that azoospermia was present in 1.8% of the men. There are only a few clinical studies evaluating the rate of azoospermia in Japanese men, and in all of these reports studying men in general or young men, the rate was <1%.[5,20] In addition, 2.0% of the men had a sperm concentration of $<5 \times 10^6$/mL, and combined with those with azoospermia, the rate was 3.8%, much higher than the 1.2% reported in a previous evaluation of young men.[5]

It must be admitted that the men undergoing screening for marriage purposes comprised a group with vague anxiety about fertility, and it is not necessarily appropriate to compare them with studies of men in general, but the rates of azoospermia and severe oligozoospermia seemed to be higher than the usually estimated rates. Furthermore, it was reported by The Japan Society of Obstetrics and Gynecology that in 2016, there were 447,790 assisted reproductive technology cycles that were registered and 54,110 neonates were recorded, accounting for 1 in 18.1 neonates born in Japan (total number of neonates was 976,979 in 2016).[21] Consequently, it is assumed that a considerable number of patients are forced to undergo in vitro fertilization due to male reproductive-related factors.

In the present study, we conducted a multivariate analysis of risk factors in men at the start of activity to get their partner pregnant who were already included in the poor semen findings group. As a result, the 3 factors of age, serum LH value, and EHS were recognized as independent factors. It is a well-known fact that older age adversely affects spermatogenesis, and it is incontrovertible that the younger the man, the more desirable he is to initiate activity to get his partner pregnant. Interestingly, as an endocrinological finding, not the serum FSH value, which originally had a stronger relationship with spermatogenesis, but the serum LH value was recognized as a factor involved in spermatogenesis. At least, men with a low level of serum LH showed characteristics of central testicular dysfunction, whereas men with a high level of serum LH showed characteristics of peripheral (testicular) dysfunction, and it is important to maintain normal gonad function. From the results obtained in the present study, the fact that erectility not reaching EHS 4 (ie, decreased erectility was present), was a risk factor of poor semen findings is of interest. It was previously reported that the prevalence of erectile dysfunction increases as a function of the severity of semen quality impairment[22] and that male sexual function tends to decrease with low sperm count.[23]

In men of older age or with a decreased serum testosterone value, both fertility and erectility decline naturally. However, the most interesting finding in the present study was that, based on a multivariate analysis including the above factors, EHS remained an independent predictive factor. For example, arteriosclerosis is a representative risk factor of erectile dysfunction, but at the same time there is a report of animal experimental results in which it impaired spermatogenesis.[24] More specifically, the results suggest that men with decreased vascular endothelial function may have erectile dysfunction and decreased spermatogenesis simultaneously. Because arteriosclerosis and vascular endothelial function were not included as end points in this study, we can only speculate about further possibilities, but we are now measuring the flow-mediated dilatation reaction of men whose erection ability and semen findings were evaluated, and we plan to conduct an additional analysis in the future.

This study has limitations related to the semen test. First, it was reported that the results of semen testing using the Makler semen counting chamber are not accurate for measurements of sperm concentration and sperm motility rate.[25] We understand that the semen test recommended by the WHO is a reliable method, but the method is complicated and takes time to obtain test results. We were forced to use the Makler semen counting chamber as a screening test that provided results immediately while we were interviewing the patients. However, we excluded evaluation of the sperm morphology ratio by the Makler semen counting chamber from the examination items. Second, the test was conducted only once. It is well-known that semen findings change depending on physical conditions, but a recent clinical study reported the possibility that even the change of seasons has an influence on semen findings.[26]

Thus, we cannot necessarily say that semen findings are always poor just because they did not reach the level of the reference criteria one time. In fact, in a report of men whose first semen test was normal, 27% showed abnormal findings at the second semen test, and, in contrast, among men whose first semen test was abnormal, 23% showed normal findings at the second semen test.[27] Third, the detailed backgrounds of the men are unclear. This study did not cover all such related information, for example, whether each man was being treated for a disease or received some other kind of medical treatment. However, despite these limitations, even in young men who start activity to get their partner pregnant from now on, it is possible that semen findings may have already deteriorated, and, moreover, there is an undeniable risk of semen findings worsening when the ability to sustain an erection decreases.

CONCLUSIONS

We clearly showed that even among men beginning their attempts at pregnancy, semen findings were poor and erectile dysfunction was involved in poor semen quality in one-quarter of the men. The present findings should be noted in the field of treatment of male infertility. We further believe that the clinical significance of the findings will not diminish over time.

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COI Statement: The authors report no conflicts of interest.

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