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ORIGINAL ARTICLE

Male Infertility

Analysis of semen quality of 38 905 infertile male patients during 2008–2016 in Wenzhou, China

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This study analyzed the trend in semen quality of infertile male patients in Wenzhou, China, based on the data obtained from 38 905 patients during 2008–2016 in The First Affiliated Hospital of Wenzhou Medical University (Wenzhou, China). The results showed that only 24.9% of the patients had normal semen quality. For the semen quality of infertile male patients, that of the workers and 40-year-olds was significantly worse than the other occupational and age groups. For all the infertile patients, low semen volume, asthenozoospermia, and teratozoospermia accounted for 8.4%, 50.5%, and 54.1%, respectively. During 2008–2016, the annual mean percentage of fast forward motile spermatozoa, percentage of total forward motile spermatozoa, and percentage of spermatozoa with normal morphology decreased linearly with slopes of –2.11, –2.59, and –0.70, respectively. The proportion of patients with asthenozoospermia and multi-abnormal spermatozoa increased during 2008–2016 with slopes of 4.70 and 4.87, respectively, while for low semen volume, it decreased with a slope of –0.47 in the same time period. The proportion of patients with teratozoospermia increased from 2008 to 2011 and from 2011 to 2016 with slopes of 17.10 and 2.09, respectively. In general, the deteriorating trend of semen quality of infertile male patients in Wenzhou was obvious. Future efforts should be made to reveal the adverse influences on semen quality, such as occupational exposure, environmental quality, and living habits. Furthermore, more pervasive reproduction health education is necessary.

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Keywords: distribution; infertile male patient; semen quality; symptoms; time trend

INTRODUCTION

Infertility has been a serious social problem in many countries and regions. According to the National Institutes of Health, of all infertility cases, 1/3rd are caused by male reproductive problems, and approximately 10%–15% of men who are infertile have a complete lack of spermatozoa. Among infertility couples, the rate of male infertility with or without female infertility factor has reached as high as 50%, and it is likely to continue to rise owing to pathological factors, environmental pollution, and poor lifestyles.[1,2] At present, the overall trend of semen quality in men worldwide is still controversial, but quality decline in local areas has been recognized.[3–5] From the perspective of regional disease prevention and control, it is of great significance to grasp the distribution characteristics and trend of semen quality of infertile male patients. There are many epidemiological studies on semen quality in male infertility patients, mainly focusing on semen quality,[6,7] and factors influencing it.[8–10] However, there are relatively few studies on the long-term trend of semen quality in patients with male infertility because of a lack of many samples and long series of data.[11]

Wenzhou is a prefecture-level city having 9 million people in the south of Zhejiang province, eastern China. It is one of the economically developed areas in China that ranks 49th in comprehensive Competitiveness Ranking of China cities. It is also one of the typical areas where environmental protection has lagged behind economic development for a long time. With the continuous advancement of urbanization and industrialization, a trend of low fertility and aging is intertwined. According to the Wenzhou Statistical Yearbook, the birth rate in 2018 decreased by 2.2/1000 compared with that in 2017. One of the underlying reasons is the increase in the incidence of infertility.

The main goal of this article was to analyze the distribution of infertile male patients, identify the population differences of semen quality and changing trends, and provide a basis for local governments and health management departments to improve residents' reproductive health.

PATIENTS AND METHODS

The Center for Reproductive Health of The First Affiliated Hospital of Wenzhou Medical University began to establish a database of male infertility patient samples and medical records from 2006 and has accumulated a long-term series of datasets. Infertile male patient, is defined as the wife possesses normal reproductive capability but is not becoming pregnant after 1 year's continual unprotected intercourse. In this study, datasets from January 2008 to November 2016 were used. Patients whose cohabitation life and family history were normal after

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marriage were excluded from the study, as were those with organic diseases and female infertility. In general, a total of 38 905 male infertile patients were screened, with an average age of 32.3 years (standard deviation [s.d.]: 6.3). All the data from The First Affiliated Hospital of Wenzhou Medical University database were de-identified, and the extracted data did not require informed consent. Besides, the study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University (issuing No. 2020160).

All patients were required to abstain from sexual intercourse for 3-7 days before semen provision. Semen was collected by masturbation in a clean cup in a specific semen collection room of the hospital and placed in a 37°C incubator for liquefaction. The degree of liquefaction was checked every 10 min, and the test was performed immediately after the specimen was liquefied. If the semen had not liquefied after 60 min, the sample was mechanically pipetted and mixed before analysis. Semen volume, color, viscosity, and liquefaction time were assessed according to the method of the WHO Laboratory Manual for the Examination and Processing of Human Semen (4th and 5th Edition;[12,13] there is no difference between the two editions in methodology). The computer-assisted semen quality analysis system was SCA-H-01 (MICROPTIC S.L. Company, Viladomat, Barcelona, Spain). In order to make a unified judgment standard, we used the WHO 5th reference values.[13] In this study, semen is defined as normal if it meets all the following requirements: semen volume ≥1.5 ml, sperm concentration ≥15 × 10^6 ml^{-1}, total forward motile spermatozoa ≥40% or fast forward motile spermatozoa ≥32%, spermatozoa with normal morphology ≥4%, and liquefaction time ≤60 min, whereas semen is defined as abnormal when it did not meet one or more of these requirements. The characteristics of abnormal semen were classified as low semen volume (semen volume <1.5 ml), asthenozoospermia (total forward motile spermatozoa <40% or fast forward motile spermatozoa <32%), and teratozoospermia (normal sperm morphology <4%). We defined the abnormality of two or more of the above-stated four criteria as multi-abnormal sperm disease (MSD).

Statistical analysis was performed in R programming language for statistical computation (the R foundation, version 3.4.3, St. Louis, MO, USA). The comparison of measurement data between groups used single-factor analysis of variance and the Student–Newman–Keuls (SNK) *post hoc* test, while the variance was tested as homogeneity; otherwise, Kruskal–Wallis multiple comparison was used. Time trends of semen quality and semen abnormalities were analyzed by means of linear regression models.

RESULTS

Distribution of the patients

We collected four common semen quality parameters of the 38 905 patients and made a descriptive statistic (**Supplementary Table 1**). Among the 38 905 infertile male patients, those with normal semen quality accounted for 24.9%. For age distribution, the proportions of age ≤25 years, 25 years < age ≤30 years, 30 years < age ≤35 years, 35 years < age ≤40 years, and age >40 years were 6.4%, 32.9%, 33.5%, 18.3%, and 9.0%, respectively. For occupational distribution, workers, peasants, intellectuals, businessmen, and others accounted for 87.6%, 2.0%, 6.5%, 3.4%, and 0.4%, respectively. For spatial distribution, 68.4%, 82.8%, and 17.2% of the addresses of the patients were in Wenzhou city, Zhejiang province, and other provinces, respectively. For time distribution, the number of patients showed a linear upward trend ($r^2 = 0.96$, $P < 0.001$) during 2008–2016, with an average annual increase of about 647 cases (**Supplementary Figure 1**).

Overall situation and group differences in semen quality

Among the different age groups, the mean values of percentage of fast forward motile spermatozoa, total forward motile spermatozoa, spermatozoa with normal morphology, and semen volume for patients over 40 years old were significantly different from those of the other age groups (**Table 1**). Among the different occupational groups, the mean values of percentage of fast forward motile spermatozoa, total forward motile spermatozoa, and spermatozoa with normal morphology for workers were significantly different from those of the other occupational groups (**Table 2**).

Changes of semen quality with time

Figure 1 shows the semen quality of the 38 905 patients during 2008–2016. The annual mean percentage of fast forward motile spermatozoa and percentage of total forward motile spermatozoa for peasants continued to decline from 44.7% to 58.9% in 2008 to 31.3% and 45.0% in 2016, respectively. The annual mean percentage of spermatozoa with normal morphology decreased from 10.1% in 2008 to 4.2% in 2011, and then decreased to 3.4% in 2016. The annual mean semen volume increased from 2.9 ml in 2008 to 3.1 ml in 2016. Univariate linear regressions were performed with the annual average of each parameter as the dependent variable and year as the independent variable. During 2008–2016, the annual mean percentage of fast forward motile spermatozoa, percentage of total forward motile spermatozoa, and percentage of spermatozoa with normal morphology decreased linearly with slopes of −2.11, −2.59, and −0.70, respectively (**Figure 2a–2c**). However, the annual mean semen volume had no significant linear time trend ($P = 0.39$; **Figure 2d**).

Symptoms of the patients

For all the patients, low semen volume, asthenozoospermia, and teratozoospermia accounted for 8.4%, 50.5%, and 54.1%, respectively. The proportion of patients with teratozoospermia increased from 9.9% in 2008 to 64.9% in 2016 (**Figure 3**). The proportion of patients with asthenozoospermia and MSD increased from 26.7% and 8.9% in 2008 to 61.7% and 47.8% in 2016, respectively. The proportion of patients with low semen volume had a linear downward trend, from 12.4% in 2008 to 8.5% in 2016.

Similarly, a univariate linear regression equation was established with the proportion of patients with each symptom as the dependent variable and time as the independent variable. All the models showed significant linear relationships in results, and the r^2 values ranged from 0.73 to 0.97 (**Figure 4**). The proportion of patients with asthenozoospermia and MSD increased from 2008 to 2016 with

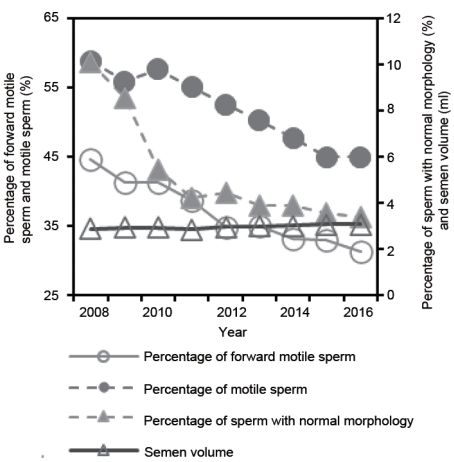

Figure 1: Semen quality of the 38 905 patients during 2008–2016.

Table 1: Comparison of semen quality in infertile male patients of different age groups

Parameter	*Age ≤25 years (n=2472)*	*25 years < age ≤30 years (n=12 783)*	*30 years < age ≤35 years (n =13 047)*	*35 years < age ≤40 years (n =7116)*	*Age >40 years (n=3487)*
Percentage of fast forward motile spermatozoa (%), median (IQR)	36.00[a] (24.70, 46.10)	36.40[ab] (25.30, 46.80)	36.80[b] (26.00, 47.00)	35.60[a] (24.60, 45.70)	33.4[c] (21.25, 43.65)
Percentage of total forward motile spermatozoa (%), median (IQR)	50.80[a] (39.30, 49.14)	51.80[b] (40.80, 63.40)	52.10[c] (41.10, 63.70)	50.60[a] (39.20, 62.10)	47.7[d] (34.80, 59.40)
Percentage of sperm with normal morphology (%), median (IQR)	3.40[a] (1.60, 5.60)	3.50[ab] (1.60, 6.10)	3.80[c] (1.80, 6.50)	3.60[bc] (1.80, 6.20)	3.40[ab] (1.60, 5.70)
Semen volume (ml), mean (s.d.)	3.17[a] (0.35)	3.10[a] (1.79)	2.97[b] (1.43)	2.89[c] (1.87)	2.71[d] (1.31)

Significance level is 0.05. Among columns, figures with the same superscript are not significantly different, whereas those with different superscript are significantly different. The comparison of measurement data between groups used single-factor analysis of variance and the SNK test, while the variance was tested as homogeneity, otherwise Kruskal–Wallis multiple comparison was used. IQR: interquartile range; s.d.: standard deviation; SNK: Student–Newman–Keuls

Table 2: Comparison of semen quality in infertile male patients of different occupational groups

Parameter	*Worker (n=34 094)*	*Peasant (n=788)*	*Intellectual (n=2529)*	*Businessman (n=1319)*	*Others (n=175)*
Percentage of fast forward motile spermatozoa (%), median (IQR)	35.90[a] (24.70, 46.20)	38.60[bc] (28.57, 49.17)	34.8[d] (24.00, 45.00)	40.50[be] (29.70, 51.95)	40.00[ace] (28.05, 49.00)
Percentage of total forward motile spermatozoa (%), median (IQR)	51.20[a] (40.0, 62.70)	54.65[b] (43.42, 65.33)	49.40[a] (38.30, 61.00)	56.40[c] (44.70, 68.45)	54.80[bc] (41.95, 66.60)
Percentage of spermatozoa with normal morphology (%), median (IQR)	3.5[a] (1.70, 6.10)	4.00[b] (2.10, 7.00)	3.50[c] (1.70, 6.00)	5.4[d] (2.55, 8.90)	5.40[abc] (2.30, 7.90)
Semen volume (ml), mean (s.d.)	2.99[a] (1.6)	3.0[ab] (1.43)	3.0[a] (2.39)	2.8[bc] (1.29)	2.8[ac] (1.25)

Significance level is 0.05. Among columns, figures with the same superscript are not significantly different, whereas those with different superscript are significantly different. The comparison of measurement data between groups used single-factor analysis of variance and the SNK test, while the variance was tested as homogeneity, otherwise Kruskal–Wallis multiple comparison was used. IQR: interquartile range; s.d.: standard deviation; SNK: Student–Newman–Keuls

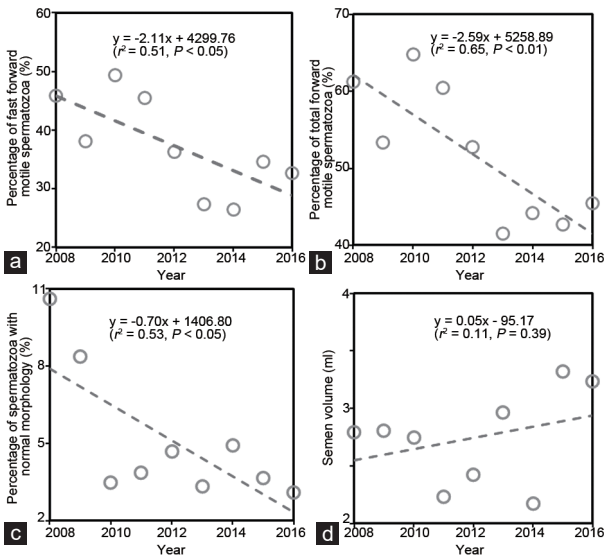

Figure 2: Linear models between the annual mean values of the four semen quality parameters and time. (**a**) The percentage of fast forward motile spermatozoa, (**b**) the percentage of total forward motile spermatozoa, and (**c**) the percentage of spermatozoa with normal morphology were declining year by year and showed a linear trend. (**d**) Semen volume was increasing year by year and showed a linear trend.

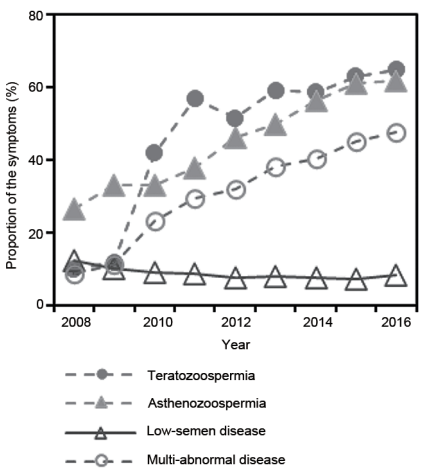

Figure 3: Percentages of the symptoms of the 38 905 patients during 2008–2016.

slopes of 4.70 and 4.87, respectively. The proportion of patients with teratozoospermia increased from 2008 to 2011 and from 2011 to 2016 with slopes of 17.10 and 2.09, respectively, while for low-semen disease, it decreased with a slope of −0.47 in the same time period.

DISCUSSION

Semen quality is an important reference index for evaluating male fertility, which is of great significance for the diagnosis, treatment, and prevention of male infertility. There are many factors that affect male semen quality, such as occupation (polluting workshops, long-term driving, *etc.*), environment (air pollution, environmental endocrine disruption, *etc.*), and lifestyle (smoking, alcohol abuse, staying up late, *etc.*).[1,8,10] The semen quality of male workers who were infertile in Wenzhou was significantly lower than that of the rest, especially for sperm motility. The workers in this study are mainly drivers, renovation workers, stone practitioners, and general staff and a majority are shoe factory workers. Owing to the nature of the work, these people are often exposed to the reported risk factors of infertility. The current articles have reported that ionizing radiation, radiant heat, inorganic lead, the fungicide ethylene dibromide, and ethylene glycol ethers have become established male reproductive toxicants in humans in the last 30 years.[14] Wang *et al.*[15] revealed the adverse effects of formaldehyde exposure on semen quality, especially on sperm motion parameters. The shoe-making industry is flourishing in Wenzhou, and a large

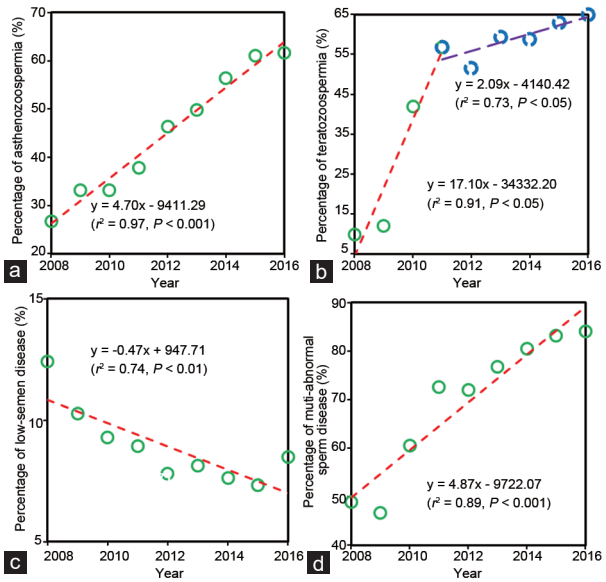

Figure 4: Linear models between the annual percentages of the symptoms and time. (**a**) The percentage of asthenozoospermia was increasing year by year and showed a linear trend. (**b**) The percentage of teratozoospermia was increasing year by year and showed a linear trend during 2008–2011 and 2011–2016, respectively. (**c**) The percentage of low-semen disease was declining year by year and showed a linear trend. (**d**) The percentage of multi-abnormal sperm disease was increasing year by year and showed a linear trend.

number of workers in shoe factories are exposed to air-borne pollutants such as benzene. The results of this study showed that workers may have greater fertility problems in the study area, which is consistent with the findings of Katukam *et al*.[16] However, more research is required to confirm this conclusion. The semen quality of patients over 40 years of age was worse than that in other age groups, indicating that age is one important factor affecting semen quality, which is consistent with that of other regions in China.[9]

During the study period, the percentages of fast forward motile spermatozoa, total forward motile spermatozoa, and spermatozoa with normal morphology in male infertility patients in Wenzhou area showed a significant downward trend. How to curb the decline in semen quality and improve regional reproductive health is an urgent and important issue in many countries and regions.[4,17] The main symptoms of male infertility can be divided into azoospermia, low semen volume, asthenozoospermia, and teratozoospermia. Studying the main types, composition, and trends of abnormal semen symptoms in male infertile populations is important for guiding the prevention and treatment of regional male infertility. The proportion of patients with teratozoospermia, asthenozoospermia, and MSD increased during the study period. This fully shows that the time trend of deteriorating semen quality of infertile male patients in Wenzhou continues to develop, and the time trend of semen abnormalities is becoming increasingly obvious. Wenzhou is an industrialized city and is one of the banners of the private economy in China. Manufacturing industries such as footwear and electrical appliances are the main components of the private economy and have been developing rapidly over the past 20 years in Wenzhou. However, these industries are always highly polluting, which may affect the health of workers. The findings of the study indicate that the prevention and control of occupational hazards is a very important and urgent task in Wenzhou, as well as in many other industrialized cities in China and other countries and regions.

The main influencing factors of the health can be divided into three categories of genetic factors, environmental factors, and lifestyle habits, that also influence semen quality.[10,18] Genetic factors are congenital and are impossible to change, but we can start with acquired factors. Among the different populations in Wenzhou, the semen quality of male infertile patients in the worker group was significantly worse than that of other occupational groups, and the semen quality of male infertile patients in the 40-year-old group was significantly worse than that of other age groups. For government departments, it is necessary to focus on the worker group for occupational disease prevention and control, to manage industrial enterprises in accordance with laws and regulations, and to create a good working environment for workers. For male infertility patients, they should actively create a good working and living environment and cultivate good living habits. This is the most significant both to them and to their family and future generations.

Reproductive health is closely related to improving the quality of life. It is a prerequisite for a happy life, and it is the basis for social stability and economic development. The main purpose of this article is not to study the influencing factors of semen quality of male infertility patients, but to focus on revealing the population differences and time trends of semen quality, and to provide decision-making basis for regional reproductive health management. Wenzhou has been intertwined with a low birth rate and an aging population, and the semen quality of male infertility patients has shown a significant decline overall. Reversing this situation requires the joint efforts of the government, health and disease control departments, academia, business, and individuals, which will be a long and arduous task.

Substantial limitations apply to our study, which suffer from the lack of specific information on occupation, especially the history of poison exposure.

AUTHOR CONTRIBUTIONS

ZGW, WKC, and QJF drafted the manuscript. ZGW, YLL, and XDL collected data and performed the statistical analysis. XJS and HH conceived the study and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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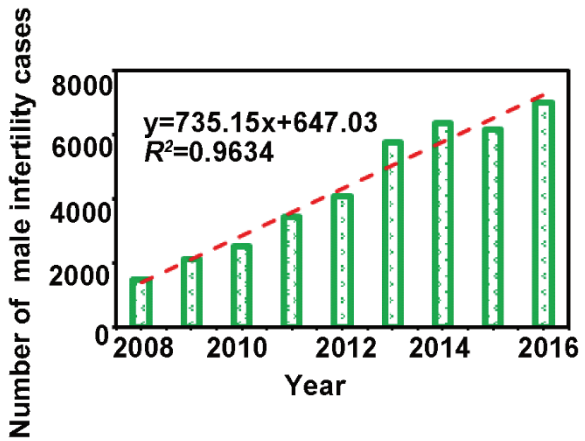
Supplementary Table 1: Descriptive statistics on the four common semen quality parameters

Group	*Normal group (n=9686)*	*Abnormal group (n=29 218)*	*Total (n=38 905)*
Percentage of fast forward motile spermatozoa (%)	48.10 (41.90, 55.10)	31.30 (25.00, 46.40)	36.10 (25.00, 46.40)
Percentage of total forward motile spermatozoa (%)	64.80 (57.80, 72.05)	45.90 (34.40, 56.20)	51.30 (40.10, 62.90)
Percentage of sperm with normal morphology (%)	6.90 (5.30, 9.50)	2.60 (1.30, 4.30)	3.60 (1.70, 6.20)
Semen volume (ml)	3.11 (1.28)	2.95 (1.75)	2.99 (1.65)

Data of percentage of fast forward motile spermatozoa, percentage of total forward motile spermatozoa, and percentage of spermatozoa with normal morphology presented as median (first quartile, third quartile), while for semen volume presented as mean (s.d.). s.d.: standard deviation



Supplementary Figure 1: The number of patients (2008–2016).