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Effect of male age on reproductive function: A comparison of young and middle-aged men

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Purpose: There have been concerns regarding potential effects of older paternal age on male reproductive function. However, currently available data on this topic are insufficient and controversy exists. We analyzed semen characteristics and reproductive hormones in young men and middle-aged men to investigate the effect of age on male reproductive function.

Materials and Methods: This study examined healthy males of reproductive age who visited a single infertility center from January 2016 to July 2021. The young group consisted of men who were less than 35 years-old, and the middle-age group consisted of men who were more than 45 years-old.

Results: The two groups had no significant differences in sperm concentration ([89.9±59.4]×10^6/mL vs. [104.4±82.1]×10^6/mL, p=0.108) or sperm morphology (normal forms: 3.6%±1.5% vs. 3.4%±1.6%, p=0.131). However, the middle-age group had a smaller semen volume (3.2±1.5 mL vs. 2.5±1.4 mL, p<0.001), lower sperm motility (42.3%±9.8% vs. 31.2%±12.4%, p<0.001), lower progressive sperm motility (39.2%±10.3% vs. 28.4%±12.6%, p<0.001), and a higher serum follicle-stimulating hormone level.

Conclusions: Our results suggest that advanced male age might have a negative effect on fertility potential, as in women. This finding has important clinical implications because more couples are choosing to have children when they are older. Further studies on this issue, especially those that examine reproductive outcome, are warranted.

Keywords: Paternal age; Reproductive health; Semen analysis

INTRODUCTION

Infertility is a major public health issue. Approximately 15% of couples who are of reproductive age experience infertility, and male factor infertility is identified in approximately 30 to 50% of these cases [1]. Over the past decade, more women have delayed motherhood, mainly due to socioeconomic changes in modern societies [2]. Paternal age has also increased world-wide, in that many men decide to marry or remarry at an older age [3]. As more couples choose to postpone having children, it is increasingly important to understand the effects of age on reproductive potential and outcome. Female fertility is clearly linked to a woman's age, and women typically experience reduced fertility in their late 30s to early 40s due to a sharp decrease in oocyte production [4]. Increased maternal age also increases the risk for

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adverse reproductive outcomes and poor offspring health [5].

In contrast to females, males experience sustained reproductive function for many decades, and many elderly men father children with their partners. When assessing male fertility, a semen analysis that examines sperm count, sperm motility, and sperm morphology, is single most important test and is the cornerstone of male fertility evaluations. Previous studies that examined the effect of paternal age on semen quality reported that several indicators of semen quality such as sperm count, sperm motility, and sperm morphology had negative correlations with age [6-9]. However, currently available data on this topic are insufficient, and most prior studies are based on data from analysis of single semen samples, partly due to the difficulties of obtaining repeated samples from older men. The considerable variability among semen tests and the limited reproducibility of semen analysis results makes it difficult to properly interpret the clinical and real-world implications of prior studies [10,11]. Therefore, in this study, we analyzed semen characteristics and reproductive hormones in young men and middle-aged men who provided repeated semen samples to investigate the effect of age on male reproductive function.

MATERIALS AND METHODS

This study examined males of reproductive age who visited CHA Gangnam Medical Center from January 2016 to July 2021. The study protocol was approved by the Institutional Review Board of CHA Gangnam Medical Center (no. GCI-2021-07-006). As a retrospective study, the need for informed consent of the patients was waived off. All participants were healthy males of reproductive age who underwent fertility evaluations at our andrology clinic. The young group consisted of men who were less than 35 years old, and the middle-age group consisted of men who were more than 45 years old. Because semen analysis data have high inter-test variability, we only included cases who underwent at least 2 semen analyses within a 2-month period, so that data were collected within a single spermatogenesis cycle. Patients with chronic medical condition, a history of cryptorchidism, clinical varicocele, prior scrotal surgery, or exposure to gonadotoxin were excluded. Cases with low semen volume (≤1.0 mL), or severe oligozoospermia (≤5×10^6 cells/mL) were also excluded.

The evaluation consisted of a thorough personal history, physical examination, detailed semen analyses, and laboratory tests, including profiles of reproductive hormones. Physical examination was performed by an experienced andrologist and testicular volume was measured using an orchidometer. All semen samples were obtained by masturbation into a wide-mouthed plastic container while the participant was in a private room, and were collected after 2 to 14 days of sexual abstinence. Samples were allowed to liquefy for at least 20 min at 37℃ before analysis. Immediately after liquefaction, diagnostic semen analysis was performed according to World Health Organization (WHO) criteria [12]. Sperm concentration and motility were assessed using a Makler counting chamber, and sperm morphology was evaluated using Papanicolaou staining and the Kruger strict criteria. Serum reproductive hormones (follicle-stimulating hormone [FSH], luteinizing hormone [LH], and testosterone) were measured using an electrochemiluminescence immunoassay analyzer (Cobas E 601, Roche, Basel, Switzerland).

Statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Data were expressed as means±standard deviations. Semen parameters were presented as the means of the first and second samples. Student's t-test was used for inter-group comparisons. A p-value less than 0.05 was considered statistically significant.

RESULTS

We examined 1,843 males of reproductive age who visited our infertility center from January 2016 to July 2021. The medical records of all subjects were reviewed. After exclusion of ineligible subjects due to underlying chronic disease, prior scrotal surgery, ineligible age (35–44 years old), and lack of semen data from two tests, we enrolled 335 patients (Fig. 1).

The young group (<35 years old, n=172) had a mean age of 31.7 years (±1.8 years) and the middle-age group (≥45 years old, n=163) had a mean age of 47.0 years (±2.4 years)

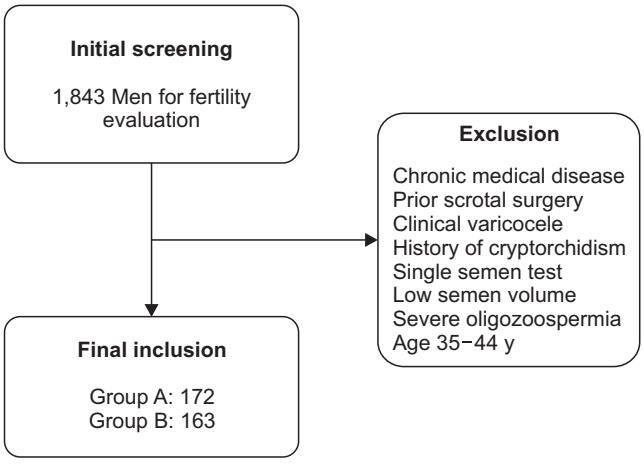

Fig. 1. Study design and enrollment of patients in the young group (n=172) and the middle-age group (n=163).

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Table 1. Baseline characteristics of the two groups

Parameter	Young group (<35 y)	Middle-age group (≥45 y)	p-value
Number	172	163	
Age (y)	31.7±1.8	47.0±2.4	<0.001*
BMI (kg/m^2)	24.5±3.1	25.2±2.9	0.204
Right testis volume	17.3±3.0	17.7±3.4	0.300
Left testis volume	17.2±3.0	17.6±3.4	0.275

Data are presented as number only or mean±standard deviation.
*Statistically significant p<0.05.

Table 2. Semen analysis data of the two groups

Parameter	Young group (<35 y)	Middle-age group (≥45 y)	p-value
Semen volume (mL)	3.2±1.5	2.5±1.4	<0.001*
Sperm concentration (×10^6/mL)	89.9±59.4	104.4±82.1	0.108
Sperm motility (%)	42.3±9.8	31.2±12.4	<0.001*
Progressive motility (%)	39.2±10.3	28.4±12.6	<0.001*
Strict sperm morphology (%)	3.6±1.5	3.4±1.6	0.131

Data are presented as mean±standard deviation.
*Statistically significant p<0.05.

(Table 1). The two groups had no significant differences in sperm concentration ([89.9±59.4]×10^6/mL vs. [104.4±82.1]×10^6/mL, p=0.108) or sperm morphology (normal forms: 3.6%±1.5% vs. 3.4%±1.6%, p=0.131) (Table 2). However, the middle-age group had a smaller semen volume (3.2±1.5 mL vs. 2.5±1.4 mL, p<0.001), lower sperm motility (42.3%±9.8% vs. 31.2%±12.4%, p<0.001), lower progressive sperm motility (39.2%±10.3% vs. 28.4%±12.6%, p<0.001), and a higher serum FSH level (5.5±3.2 mIU/mL vs. 6.3±2.8 mIU/mL, p=0.012). The older group also had a tendency for a lower serum testosterone level (4.4±1.3 ng/mL vs. 4.1±1.4 ng/mL, p=0.063). The two groups had no significant differences in serum LH and estradiol levels (Table 3).

Table 3. Reproductive hormonal data of the two groups

Parameter	Young group (<35 y)	Middle-age group (≥45 y)	p-value
FSH (mIU/mL)	5.5±3.2	6.3±2.8	0.012*
LH (mIU/mL)	4.6±2.1	4.9±2.0	0.178
Testosterone (ng/mL)	4.4±1.3	4.1±1.4	0.063
Estradiol (pg/mL)	24.1±3.1	23.5±4.2	0.236

Data are presented as mean±standard deviation.
FSH, follicle-stimulating hormone; LH, luteinizing hormone.
*Statistically significant p<0.05.

DISCUSSION

Our results indicated that middle-aged men may have a lower fertility potential than young men, as indicated by lower semen parameters. Not many previous studies investigated the issue of semen quality in older men, partly due to the difficulty of obtaining these data. The semen collection process, in which the male performs masturbation in a clinical setting, is embarrassing and unpleasant for most men, making it difficult to obtain multiple samples from same individual. In fact, most prior studies of the association male age with semen parameters were based on single semen samples [7-9]. However, semen data can have large within-subject variability among tests and limited reproducibility [10,11]. Because many prior studies only used single samples, this might explain their conflicting results. For example, one study that compared semen quality in young men and older men (50–65 years old) reported that older men had decreased progressive sperm motility, a smaller percentage of sperm with normal morphology, and a smaller semen volume [7], but they only analyzed single samples, limiting the reliability and reproducibility of these results. In fact, the authors acknowledged the wide range of values among individual semen parameters within each age group. Another prior study investigated multiple semen samples from older men (≥45 years old) [13] and reported that advanced age was associated with decreased semen volume and sperm motility, and poor sperm morphology. However, this study included semen data from 27 different institutions, therefore, was potentially limited by variability among these many centers. This study also did not consider semen data from young men.

For more clear contrast of the age effect, we performed a direct comparison of the semen data of men who were less than 35 years old and more than 45 years old. Our middle-age group had significantly lower total sperm motility (42.3% vs. 31.2%, p<0.001) and progressive motility (39.2% vs. 28.4%, p<0.001). Lower sperm motility is related with lower fertility potential and we suggest that the decreased sperm motility in our middle-age men might be related to abnormal function of their Sertoli cells, somatic cells that have critical roles in spermatogenesis process.

Previous studies reported that ejaculated semen volume gradually decreases after the age of 45 years due to functional decline of accessory glands in the male reproductive system [14,15]. Our study also showed significantly lower semen volume in the middle-age group (3.2 mL vs. 2.5 mL). Although we could not analyze data on sexual function in this retrospective analysis, we suggest that decreased overall sexual function in middle-aged men, such as poorer

maintenance of erection, also contributed to their decreased semen volume. The average volume of semen in an ejaculation is about 2 to 5 mL. The seminal fluids account for about 65% to 75% of this volume and secretions from the prostate gland account for about 25% to 30%. However, sperm cells, the main testicular component of semen, contribute account for less than 1% of this volume. Therefore, we think that the lower semen volume in older men by itself is unlikely to adversely affect male fertility.

Previous studies also suggested that the percentage of sperm with normal morphology, another important semen parameter, decreases with advanced age [16,17]. However, our two groups had no significant difference in sperm morphology (3.6% vs. 3.4%). We analyzed sperm morphology according to the fifth edition of the WHO guidelines using the Kruger strict criteria (normal forms ≥4%), criteria that are currently used in most fertility centers. Most previous studies that reported lower percentages of sperm cells with normal morphology in older men used less strict guidelines (normal forms ≥15% or 30%) [18]. Thus, we suggest that the use of a more subjective analysis with less strict morphological criteria could have affected the results of these prior studies. During spermatogenesis, somatic Sertoli cells produce factors that are required by developing germ cells in the testis. Testicular metabolism increases between the ages of 11 and 40 years, and then gradually decreases between the ages of 40 and 90 years [19]. There are also age-associated changes in the male hormonal profile and testicular physiology, including a decrease in the number of Leydig cells and decreased testosterone production [20]. A prior study reported that the serum FSH level had negative correlations with sperm concentration, sperm motility, and sperm quality, and that the serum LH level had a negative correlation with sperm concentration [13]. However, this prior study was limited by the use of data from many different institutions. Although we found that the serum FSH level was substantially increased in our middle-age group, the two groups had no significant difference in sperm concentration. Serum FSH level is a sensitive marker of seminiferous tubule function, and a markedly elevated level indicates severely impaired spermatogenesis, such as azoospermia [21]. We suggest that the increased serum FSH level in our middle-age group might suggest early stage of impaired spermatogenesis in the testis, not yet clearly manifested as decreased sperm concentration in semen analysis. We also found a tendency for a lower serum testosterone level in our middle-age group, although this difference was not significant. Age-dependent decrease of serum LH was not evident in our investigation.

This study had several shortcomings. Firstly, it had a retrospective design and examined a relatively small number of men. However, we only included healthy males who provided at least 2 semen samples to minimize inter-test variability, a major limitation of many prior studies. Secondly, we did not analyze the clinical effects of decreased semen parameters, such as pregnancy rate. However, analysis of reproductive outcome in a retrospective investigation is difficult due to many confounding factors that impact female fertility, such as old age and poor ovarian reserve. Although several prior studies reported that the pregnancy rate decreases as male age increases, many of these studies did not adjust for female-related factors in their analyses [22,23]. Several other studies suggested that increasing birth rates in older fathers is a concern because of evidence that advanced paternal age might be associated with an increased risk of pregnancy loss and developmental disorders in newborns [24,25]. In females, the primary oocytes in the ovary from birth continue to age over time. Therefore, an elderly female has an increased genetic risk such as chromosomal aneuploidy in female gamete. However, male germ cells are characterized to have fresh maturation cycle starting from a spermatogonial stem cell to mature sperm during each spermatogenesis cycle. Therefore, advanced paternal age is less likely to lead to detrimental effects in the offspring, although this topic needs further study.

CONCLUSIONS

Our results suggest that advanced male age might have a negative effect on fertility potential, as in women. This finding has important clinical implications because more couples are choosing to have children when they are older. Further studies on this issue, especially those that examine reproductive outcome, are warranted.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Seung-Hun Song. Data acquisition: Mihee Oh, Dong Hyuk Shin, and Won Hee Lee. Statistical analysis: Dong Suk Kim. Data analysis and interpretation: Dae Keun Kim. Drafting of the manuscript: Tae Ho Lee and Dong Suk Kim. Critical revision of the manuscript: Tae Ho Lee. Obtaining funding: Seung-Hun Song. Approval of the final manuscript: all authors.

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