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The Effect of Advancing Paternal Age on Seminal Fluid Parameters in Iraqi Males Attending Infertility Center: An Observational Study

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ABSTRACT

Background: Age can affect seminal fluid parameters (SFPs); many studies reported that SFPs are reduced in older men. Although these alterations may not necessarily cause infertility, they can make it harder for older men to conceive.
Objectives: We aimed to examine which SFPs are mostly affected by age among Iraqi population.
Materials and methods: A retrospective observational study recruited 120 eligible male participants attending an infertility center, Bagdad, Iraq. The participants were grouped according to their ages into 3 groups as follows: Group I: 21-30 years (41/120); Group II: 31-40 years (43/120), and Group III > 40 years (36/120). For each participant, we collected firstly male demographic and clinical criteria that include age, infertility type, and its duration, in addition to abstinence days. Secondly, SFPs, that include volume, viscosity, liquefaction time, sperm concentration, viability, motility, normal and abnormal morphology, and round cell count. The correlation of age with SFPs was examined.
Results: Analysis showed insignificant differences in seminal fluid volume, total motility, and viscosity among the three groups. Group I showed the lowest liquefication time, and had the highest sperm counts and normal morphology. Abnormal sperm morphology was highest in group III and was statistically meaningful across the groups.
Conclusion: SFPs of older men > 40 years had the lowest number of sperm number and live sperm the highest immotile, non -progressive, and abnormal morphological sperms. Since the average paternal age is rising, it is imperative to educate men that advancing age reduces fertility potential and impacts offspring health.
Keywords: Age; Seminal fluid parameters; Sperm number, Sperm morphology; Iraqi men

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INTRODUCTION

Aging is a normal biological process that affects all living beings, including humans. Our bodies endure various changes as we age, including alterations in the reproductive systems [1]. While women's fertility declines with age, men endure a more significant decline in their reproduction ability [2, 3]. Earlier research has discussed negative impact of aging on seminal fluid parameters. These changes were attributed to reduced testosterone levels and other age-related hormonal changes [3, 4]. In addition to increased erectile dysfunction caused by low testosterone and the effect of chronic diseases such as diabetes, heart disease, and ailments that interfere with reproduction, such as prostate and testicular cancer. All these changes can make it difficult or even impossible to conceive [5]. Seminal fluid analysis (SFA) is an important method for assessing male fertility; it provides vital information about a man's reproductive status, diagnose and treat any underlying medical issues that contribute to infertility, and finally determine the fertility status of men [6]. Numerous confounding variables, like lifestyle circumstances and drugs, can have a

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Table 1. The normal sperm parameters based on WHO Criteria 2010.

Parameter	Normal Range (2010 WHO Criteria)
Semin volume	$\geq$ 1.5 milliliters (mL)
pH	7.2 to 8.0
Sperm concentration	$\geq$ 15 million sperm per mL
Total sperm Count	$\geq$ 39 million per ejaculate
Motility	$\geq$ 40% of sperm have forward progression, or $\geq$ 32% have rapid progression (Grade A)
Normal morphology	$\geq$ 4% of sperm are morphologically normal
Viability	$\geq$ 58% of sperm are live sperm
Round Cell	$<$ 1 million per mL

considerable impact on the reliability of SFA results [7].

Clinicians must consider variables affecting SFA when interpreting test results. Previous studies have demonstrated that elderly men showed decreased sperm counts and motility than younger men, but the precise mechanisms remain unknown [8].

Additionally, research exploring prospective novel medicines or therapies that could increase male fertility with aging is sparse [9]. Recent work in the field hypothesized a possibility of heterogenic age-related change based on the socio-demographic aspects and the geographic location of males [2]. The current study was designed to examine which age category mostly affects semen parameters in Iraqi males and how this alters their fertility potential.

MATERIALS AND METHODS

A retrospective observational study was conducted in our "in vitro fertilization" (IVF) fertility center from July 2021-June 2022 in Baghdad, Iraq. During the reference period, all male partners attending our fertility center were checked for eligibility. We enrolled couples with normal male partners, i.e. couples with female cause of infertility and normal SFA of a male partner, according to WHO criteria 2010 [2] as shown in Table 1.

We excluded males with chronic diseases like diabetes mellitus, hypertension, and thyroid disease. Couples with idiopathic infertility, prior or current infection or varicocele and those on medication that interfere with sperm production and motility, and a history of smoking were excluded. An exclusion was made for 37 cases, as described in Figure 1.

Ethical approval

The study protocol, subject data, and consent form were reviewed and approved by the College of Medicine, Department of Obstetrics and Gynecology, Mustansiriyah University's local ethics committee dated January 22, 2021 with reference number 189.

Finally, 120 participants satisfied our inclusion criteria, and they were grouped into 3 groups based on paternal age. Group I: 21-30 years (41/120), Group II: 31-40 years (43/120), and Group III $>$ 40 years (36/120). For each participant, 2 sets of data were collected from our database as follows:

1. The male demographic criteria include age, infertility type and duration, and abstinence days.

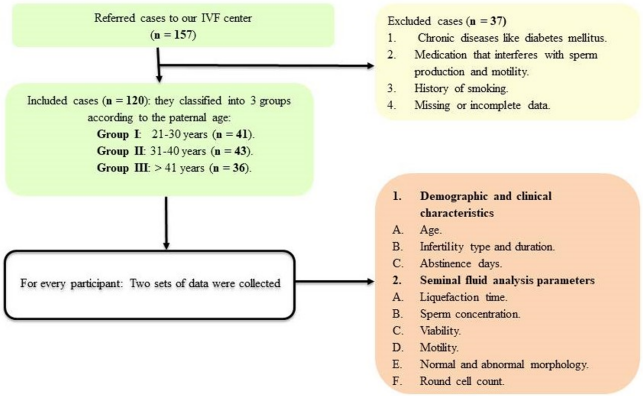

Figure 1. Study flowchart. IVF = in vitro fertilization.

2. Seminal fluid analysis parameters include volume, viscosity, liquefaction time, sperm concentration, viability, motility, normal and abnormal morphology, and round cell count.

Semen fluid analysis technique

The semen samples were obtained by masturbation at the laboratory after 3–7 days of abstinence in a clean, sperm-friendly container and kept in an incubator at a temperature of 37 degree centigrade for 30-60 minutes, allowing for liquefication to be completed. The sample was analyzed according to the WHO laboratory manual of human semen [10].

Sperm volume was first assessed, followed by sperm count (done in the hemocytometer post-dilution), motility (assessed under the microscope), and viability (evaluated using the Eosin-Nigrosin stain). Sperm morphology was studied using smears stained with hematoxylin and eosin. The pH value was assessed with pH paper and compared the result with a calibration strip. To reduce the individual variations, the measurement of semen parameters was done at same time by two qualified technicians using the same sample.

Statistical Analysis

The data normality was checked by the D'Agostino test; data were expressed as mean and standard deviations as well as numbers and percentages when appropriate. Different means were compared by one-way ANOVA or Chi-square test for parametric and categorical data respectively. Pearson's correlation tested the correlation between the age versus the seminal fluid parameters. All tests were done by MedCalc® Statistical Software version 20.211. P-value $<$ 0.05 was statistically significant for all tests.

RESULTS

The age and duration of infertility were lowest on Group I and were statistically significant among the three groups. As for the type of infertility and abstinence days, there were no statistical differences among the groups described in Table 2.

In Table 3, the seminal fluid volume and viscosity were statistically insignificant among the groups (P-value = 0.650 and 0.612, respectively). While, liquefication time was significantly lowest in Group I (P-value = 0.019). The sperm counts and normal morphology were statistically highest in Group I (P-value $<$ 0.001, and $<$ 0.001, respectively).

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Table 2. The demographic and clinical criteria of the study participants.*

Variables		Group I (n=41)	Group II (n=43)	Group III (n=36)	P-value
Age per year (mean ± S D)		27.073 ± 2.66	34.69 ± 3.23	45.88 ± 5.53	< 0.001
Type of infertility	Primary	29	29	17	0.073*
	Secondary	12	14	19	
Duration of infertility per years (mean ± S D)		3.32 ± 0.26	4.75 ± 0.48	4.76 ± 0.56	0.016
Abstinence days (mean ± S D)		3.85 ± 1.62	4.09 ± 2.11	4.11 ± 1.86	0.83

* Analysis is done by Chi-square test.

Table 3. Seminal quality of infertile Iraqi men.*

Variables		Group I (n=41)	Group II (n=43)	Group III (n=36)	P-value
Volume per ml (mean ± SD)		2.81 ± 1.35	3.11 ± 1.28	2.97 ± 0.28	0.650
Viscosity	Normal	37	41	34	0.612*
	High	4	2	2	
liquefaction (min)		30.0 ± 1.118	31.0 ± 0.001	32.83 ± 5.0	0.019
Sperm concentration (million/ml)		35.53 ± 11.26	19.95 ± 4.11	15.71 ± 3.50	< 0.001
Motility	progressive%	27.56 ± 3.89	13.70 ± 4.24	2.3 ± 0.24	< 0.0001
	non-progressive%	18.00 ± 8.197	31.86 ± 2.45	43.19 ± 5.75	< 0.001
	immotile type%	57.44 ± 18.51	51.63 ± 11.63	54.86 ± 15.87	0.002
Total motility		45.56 ± 5.66	45.58 ± 2.92	45.19 ± 5.08	0.921
normal morphology%		321.60 ± 14.33	2.23 ± 2.22	0.00	< 0.001
Abnormal morphology	abnormal head%	89.02 ± 15.16	97.16 ± 0.37	98.55 ± 0.87	< 0.001
	abnormal neck%	0.658 ± 0.48	0.9 ± 0.02	3.22 ± 2.72	< 0.001
	abnormal tail%	0.66 ± 0.48	0.89 ± 0.01	1.88 ± 1.74	< 0.00
Round cells count		(34.2%)	(35.8%)	(30.0%)	0.6*

* Analysis is done by Chi-square test.

Sperm viability showed meaningful differences across the three groups, highlighted in Figure 2. The number (No.) of dead sperms was insignificantly (P-value = 0.3) higher among Group III (57.44 ± 18.51), followed by Group I (54.86 ± 15.88); and the least was Group II (51.63 ± 11.64). While the No. of viable sperm were significantly highest (P-value < 0.001) in Group I (59.68 ± 6.82) followed by Group II (51.30 ± 2.49); the least was Group III (25.69 ± 14.88).

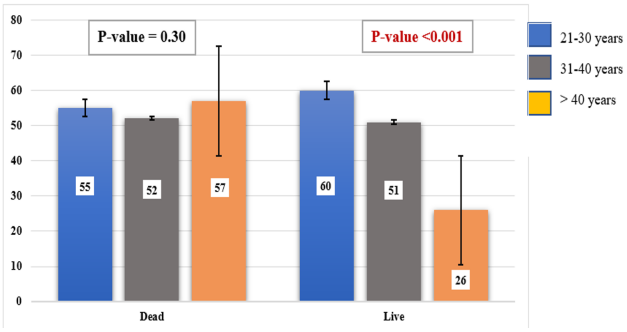

Figure 2. The number of live and dead sperm based on age category. The number of dead sperms was insignificantly higher among Group III followed by Group I and lastly Group II (57.44 ± 18.51), (54.86 ± 15.88) , (51.63 ± 11.64), P-value = 0.3 respectively. While the number of viable sperm were significantly highest in Group I followed by Group II, and the least were Group III; (59.68 ± 6.82) ; (51.30 ± 2.49); (25.69 ± 14.88) ; P-value < 0.001.

Table 4. Pearson's correlation of age versus different semen parameters of infertile men.

Parameters tested (n = 120)	r	P-value
Age *vs.* sperm count	- 0.9	0.001
Age *vs.* volume	- 0.003	0.975
Age *vs.* total motility	- 0.17	0.0574
Age *vs.* progressive sperm	- 0.93	< 0.000
Age *vs.* non-progressive sperm	0.94	< 0.0001
Age *vs.* immotile sperm	0.07	0.4384
Age *vs.* live sperm	- 0.94	< 0.0001
Age *vs.* dead sperm	0.07	0.438
Age *vs.* normal morphology sperm	- 0.7	< 0.0001
Age *vs.* abnormal head	0.49	< 0.0001

The percentage of progressive sperms were significantly higher in Group I (P-value < 0.0001), as for the percentage of non-progressive sperms it was highest in Group III (P-value < 0.001).

The total motility (sum of progressive and non-progressive sperms) was not statistically significant (P-value = 0.921). Abnormal sperm morphology was highest in Group III, including percentages of the abnormal head, abnormal neck, and abnormal tail and was statistically meaningful across the groups (P-value < 0.001).

In Table 4, the age was correlated inversely and strongly with sperm counts, the number of progressive sperms, and the number of live sperms. Correlation to normal morphology sperm was moderate with r = 0.7. The age was positively

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and strongly linked with non-progressive sperm and a weak positive correlation to abnormal head sperm with r = 0.49.

DISCUSSION

Infertility is now the third most often diagnosed condition, with a global incidence of 15 percent; half of these situations are attributable to male causessee [3]. There was in-consensus regarding the criterion of advanced paternal age; forty years and above was the most often used criterion as what the current study adopted [3, 11]. While the British Andrology Society and the ASRM issued a paternal reference age of 45 years for sperm donation due to the deleterious effect of paternal age diseases [12].

Our analysis showed that older men had the highest liquefaction time, number of dead, and abnormally morphologic sperms. Conversely, they showed the lowest sperms count, number of viable sperms, and lowest number of progressively motile sperms. Advanced paternal age exhibited inverse correlations with sperm counts, volume, motility, and viable morphological normal sperms. This result was in line with studies that linked increased paternal age with substantial decreases in several aspects of SFA, including sperm count, motility, morphology, and viability [13, 14].

Johnson *et al.*s meta-analysis included ninety studies (93,839 participants) that discussed a decline in SFA, including seminal volume, total and progressive motility, and morphologically normal cells. The reduction was statistically meaningful, and the evidence was strong. However, their results showed that sperm counts did not decline with advanced paternal age [1]. Increased semen liquefaction time may contribute to male infertility, as hyper-viscous semen inversely impacts sperm motility and quality [15].

Sperms viability was consistently reduced in advancing age [16]. Verón *et al.* s study set an age of forty years among males as a cut-off value to examine age's impact on sperms viability; their study confirmed a meaningful reduction of sperm viability in males above forty vs. those below [17]. Another study set an age of fifty to examine the reduction of sperm motility; their results showed that males above fifty suffered a 2-fold reduction compared to those below [11, 18]. Interestingly, this study finding is inconsistent with a recent study by Sandfoss *et al.* that signified that both sperm progressive motile sperms and morphology were not age-dependent [19].

The evidence behind abnormally morphologic sperm in relation to age was scarce. Poor sperm morphology associated with implantation and pregnancy failure are not overcome by intracytoplasmic sperm injection. More research is needed to understand the mechanisms involved [20]. The effect of advanced paternal age on sperm counts was conflicting with the literature. In line with our results, Dong *et al.* s review discussed an inverse correlation of sperm production with paternal age, with a 30 percent reduction among males older than fifty years [21] while others set the age at forty for reducing sperms production [11].

The inverse effect of paternal age on sperm concentration, motility, and viability may be due to that age-dependent alteration of the testicular environment, which triggers ROS (Reactive oxygen species) [22] or may be due to hormonal changes, oxidative stress, and genetic damage [23].

Conversely, other researchers reported increased sperm counts since 30 years of age [17]. Begueria *et al.* discussed that sperm concentration positively increased with advancing age; one explanation could be the reduction of semen volume with advanced age [24]. Other explanations may be the inconsistency in the study population, methodological variation, and different SFA techniques.

In accordance with earlier studies, the sperms motility was significantly reduced in males above forty and was inversely linked to advancing paternal age. Some discussed 1.3% reduced motility every five years of paternal age. Likewise, sperms kinetics was negatively linked to advancing age [17, 24]. Previous research has shown that semen properties might differ depending on the geographical area and the chronological age. Asif *et al.* study tested the impact of aging on SFA in the Indian population; they declared a significant relationship between advancing paternal age and reduced sperm motility and normal morphology. In line with our result, semen volume and viscosity were not associated with advancing age [25].

Consistent with our study; Borges *et al.* s [26] study that examined the decline of seminal fluid parameters (SFP) over ten years among Brazilian infertile men. The findings of their study confirmed a notable decline over time in the quality of SFP, specifically in terms of sperm concentration and count, as well as a decrease in the proportion of morphologically normal sperm. There was a statistically significant increase in the occurrences of oligospermia and azoospermia. The implementation of lifestyle modifications has been suggested as a means to mitigate the adverse consequences associated with the progression of paternal age [26].

Akang *et al.* [27] conducted a study on infertile males in South Africa and Nigeria; the study signified a rapid falling trend in SFP, including normal sperms morphology, progressive motility, and sperms count. There was a worrisome rise in astheno- and teratozoospermia among South Africa and Nigeria, respectively, which was the main contributor to male infertility. They confirmed a negative correlation between advanced paternal age vs. all tested SFP [27].

The decline in male infertility with age, mirrored by changes in SFA, was previously researched and can be explained based on many causes. Mitochondria changes are the most notable factor that impedes the sperm's normal function [10]. To begin with, mitochondria produce adenosine triphosphate which is needed for sperm mobility; second, it has a crucial role in ROS signaling; third, it is responsible for sex-hormone synthesis; and finally, cell apoptosis. Considering these facts, antioxidants' ability to scavenge ROS holds considerable promise for developing effective therapeutic techniques to treat male infertility [28].

Men are prone to germ-cell mutations in an age-dependent way; it is generally accepted that older men are more likely to pass on the genetic material of lower quality than their younger peers, which may affect fertility rates, pregnancy odds, and offspring health [29].

Some researchers hypothesize that observed correlations of SFPs with increasing men's age are not merely the result of aging but rather a surrogate for the cumulative impacts of lifelong exposures to toxins and pollution [11, 18].

In light of increasing paternal age, men need a deeper insight into semen changes associated with aging, including reduced fertility potential, a significant decrease in the live birth rate in IVF cycles, a higher abortion rate, and adverse pregnancy outcomes. Additionally, negative offspring health was reported, including congenital, psychological, and structural abnormalities [24]. Study strengths: The current study had strict sampling criteria; all the tests were done in the same lab to avoid inter-observational disparities.

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Future observational and multicenter studies with representative samples of the population as a whole and considering adding sperm DNA fragmentation test are required to corroborate whether or not the quality of sperm is deteriorating.

Study limitations: This was a single-center study; it recruited only attendees of the infertility clinics, and the results were not compared with otherwise healthy Iraqi fertile males of the same age groups. Therefore, we were unable to globalize its result. The infertility period for Group III was higher than other groups, which may raise concerns for bias as the SFP tends to be worse for longer infertility periods. A sperm DNA fragmentation test could improve our insight into the effect of aging on SFP. Unfortunately, not all patients did the test. Finally, the study was conducted during the COVID-19 pandemic which inversely affected the sample size, additionally the effect of the infection and vaccination status of the participants were not addressed. Earlier work has shown that COVID-19 infection and vaccines caused reversible changes in SFP; this is another study limitation [5].

CONCLUSION

The reduction in several seminal fluid parameters, including liquefaction time, sperm counts, viability, normal morphology, and motility, in older men was a significant finding of this study. Importantly, these changes were strongly associated with advanced paternal age, suggesting that aging significantly influences fecundity. There is an urgent need for older men to focus on lifestyle interventions to mitigate the effects of detrimental factors that can potentially improve fertility. Implementing preventative strategies or fertility guidelines helps men make informed decisions about family planning. Future research should elucidate mechanisms of age-related changes in semen parameters and explore potential interventions.

ETHICAL DECLARATIONS

Acknoweldgements

None.

Ethics Approval and Consent to Participate

The study was done under the umbrella of Helsinki Declaration ethics. Informed consent was waived due to the retrospective nature of the study. The study protocol, subject data, and consent form were reviewed and approved by Mustansiriyah University's local ethics committee dated January 22/2021with reference number 189.

Consent for Publication

Not applicable (no individual personal data included).

Availability of Data and Material

Data generated during this study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that there is no conflict of interest.

Funding

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Authors' Contributions

Nori W and Helmi ZR were responsible for the conception and conducting formal analysis. Helmi ZR and Humadi MH were responsible for data collection. Nori W wrote and drafted the manuscript. Kassim MAK and Pantazi AC conducted the literature review. All authors agreed to the final version of the manuscript.

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