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Impact of Sperm Telomere Length on Sperm Quality and Male Fertility

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Abstract

Background: Telomeres are specialized chromatin structures found at the ends of eukaryotic chromosomes; their length is an important factor in the early stages of embryonic development in humans. While studies have shown that different sperm preparation methods affect concentration, motility, and morphology, little is known about the probable association between telomere length and sperm preparation methods.

Aim of Study: The purpose of this research was to examine the comparison of a raw sample with a sample prepared by gradient.

Material and Methods: Thirty semen samples were obtained from thirty patients for this prospective cohort study. From January 2021 to October 2021, participants admitted to the Obstetrics and Gynecology Department, in vitro fertilization (IVF) unit, Faculty of Medicine, Cairo University, were evaluated. Following clearance from Cairo University's Local Ethical Committee. Gradient was approved to select sperm with longer telomere length.

Results: STL is positively associated with progressive sperm motility.

Conclusion: Thus, the use of assisted reproductive technologies to choose sperm with longer telomeres boosts the success rate of pregnancies and births, which in turn enhances the progeny's longevity.

Key Words: Reproductive technology – Density gradient centrifugation – Infertility – Sperm – telomere length.

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Introduction

INFERTILITY, defined as the inability to conceive after a year of unprotected sexual activity, affects 15% of reproductive-age couples. As such, the use of assisted reproductive technology (ART) to assist infertile couples in becoming pregnant has increased. Male factor infertility is the root cause of infertility in over half of infertile couples **[1]**. 15% of married couples experience infertility. About 50% of the time, one sex is to blame for infertility. A genetic anomaly such as a chromosomal aberration, translocation, microdeletion, single-gene mutation, or dysregulated gene expression is present in more than 15% of these instances **[2]**. Scientists have discovered a number of genes that may predispose a couple to idiopathic infertility, which is brought on by poor-quality sperm or eggs. The term "assisted reproductive technology" refers to a broad category of techniques used to modify human gametes outside of the body (ART). Globally, the adoption of ART procedures is increasing because of variables including longer average marriage ages and deteriorating gamete quality **[3]**. Because of its high rate of fertilization, intracytoplasmic sperm injection (ICSI), one of the most popular assisted reproductive technology (ART) treatments, has given birth to over 5 million babies globally. Despite the high success rate of ICSI, 1% to 5% of cycles result in a failed fertilization attempt. Apoptosis, oxidative stress, and a lack of protamine are just a few of the functional factors that can fragment DNA and compromise sperm's genomic integrity **[4]**. One process that contributes to the increase in DNA fragmentation is the oxidative state becoming unbalanced due to an excess of reactive oxygen species (ROS) or

a decrease in antioxidant capacity. These pathways were previously explored. Moreover, aberrant histone/protamine and epigenetic aberrations expose DNA to reactive oxygen species (ROS) and fragmentation. Another element that affects the integrity of chromosomes and chromatin is the length of DNA telomeres **[5].** There aren't many studies looking into how telomeres affect human reproduction or the effectiveness of assisted reproductive technologies. When combined, these results demonstrate that spermatozoa from lower-quality sperm samples and infertile guys with typical semen characteristics have shorter telomere lengths. Some studies indicate that this anomaly affects the capacity of embryos to develop normally **[6].** The purpose of this research was to examine the comparison of a raw sample with a sample prepared by gradient.

Patients and Methods

Study design and populations:

Thirty semen samples were obtained from thirty patients for this prospective cohort study. From January 2021 to October 2021, participants admitted to the Obstetrics and Gynecology department, in vitro fertilization (IVF) unit, Faculty of Medicine, Cairo University, were evaluated. The median age of the patients was 35 years (range: 18–59). A comprehensive clinical history of patients was obtained, including details such as the man's identity, date of birth, personal code number, length of abstinence, date of collection, completeness of the sample, and analysis interval, which were documented in the report. Individuals suffering from severe asthenozoospermia or oligozoospermia were excluded. The study protocol was approved by the ethics commission of Cairo University, and all participants signed a written informed consent.

Characterization of sperm parameters:

After three to six days of not having sex, seminal fluid was obtained via masturbation, allowed to liquefy at room temperature for thirty minutes, and then examined in accordance with World Health Organization guidelines. Sperm concentration, total number, progressive motility, no-progressive motility, total motility, and sperm morphology were all assessed. Individuals with sperm counts less than 15 million/ml, sperm motility below 40%, or sperm volumes less than 2ml were disqualified from the study. Sperm that were still intact and unfixed were submerged in an inert agarose microgel, and an acid treatment was used to denature the DNA fragmentation. Nuclear proteins were removed by the lysis solution. Each sample had at least 300 sperm counted, and the Sperm DNA Fragmentation Index (SDFI) was computed using the following formula:

$$\text{SDFI (\%)} = \frac{\text{Fragmented + degraded}}{\text{Total numderof counted sperm}} \times 100$$

Processing:

A density gradient centrifugation utilizing an 80–40% pure sperm gradient (ORIGO GradientTM) was used to separate the sperm from debris and any other somatic cells. After suspending the pellet in 2 milliliters of sperm washing media (ORIGIO® Sperm Wash), the combination was centrifuged. Furthermore, sperm washing medium was used to purify and suspend the supernatant. After processing, the concentration, motility, and SDFI were determined after everything was ready.

DNA extraction for telomere length calculation:

The procedure for Isolation of Genomic DNA from Forensic Case Work Samples from the QIAamp® DNA Micro Kit 08/2003 (QIAGEN) was used to extract DNA from sperm samples. We followed standard procedure with a few small modifications: prior to the DNA sample's final elution, 20 µl of elution buffer was added to the QIAamp-MinElute Column, and it was centrifuged after 15 minutes of room temperature incubation. Using the Invitrogen Qubit® 2.0 Fluorometer (Thermo Fisher Scientific), the DNA concentration of each sample was determined. The concentrations ranged from 0.73ng/µl to 42.5ng/µl. Prior to qPCR analysis, extracted DNA samples were kept in a refrigerator at 4°C. Before qPCR analysis, samples were kept in a refrigerator at 4°C.

Real time PCR (qPCR):

The housekeeping gene 36B4, a single copy gene (S) on chromosome 12, was amplified in relation to the amplification of the telomeric repeat region (T) **[7].** Given that the amplicon is proportional to the number of primer-binding sites in the first cycle of the PCR reaction, the telomere to single copy (T/S) ratio was formerly believed to be related to the average telomere length of the sample. The samples were all performed on 96-well plates with an Applied Biosystems, USA, 7500 Real-Time PCR System. Amplifications were carried out in 20ml reactions containing 20ng (5 ml×4 ng/ml) genomic DNA and 1×SYBR Green reaction mix (Qiagen, 204054). For the telomere PCR, 300nm of the forward primer (5'-CGGTTTGTTTGGGTTTGGGTTTGGGTTTGGGTTTGGGTT-3') and 700 nm of the reverse primer (5'-GGCTTGCCTTACCCTTACCCTTACCCTTACCCTTACCCTTACCCT-3') were used. For the 36B4 PCR, 300nm of the forward primer (5'-CAGCAAGTGGGAAGGTGTAATCC-3') and 500nm of the reverse primer (5'-CCC ATTCTATCATCAACGGGT ACAA-3') were used. For both the telomere and 36B4 PCR reactions, the cycling conditions were 95°C for 10min followed by 30 cycles of 95°C for 15s and 56°C for 1min.

Sperm Telomere Length (STL) calculation:

Mean Ct values were used to compute the sperm telomere length using the T/S ratio according to the following formulas:

$\Delta Ct_{sample} = Ct_{telomere} - Ct_{control}$; $\Delta\Delta Ct = \Delta Ct_{sample} - \Delta Ct_{reference\ curve}$

Sperm telomere length of the target sample to the reference sample (fold) = $2^{-\Delta\Delta Ct}$

Statistical analysis:

The relationship between STL and the patient's age and sperm count was examined using Pearson correlation (*rp*). The correlation between STL and each patient's age and sperm count was estimated using the partial Pearson's correlation coefficient (*r*). Multivariable linear regression was used to analyze the link between STL and the pregnancy rate in order to determine the relationship between STL and clinical factors. In the regression analysis, we employed the following independents: Age, volume, abstinence period (days), count per milliter, total count, sperm motility, progressive motility, aberrant forms, and DFI. The Statistical Program for Social Sciences (SPSS Inc., Version 25.0, Chicago, IL, USA) was used for all statistical analyses. $p<0.05$ was the threshold for statistical significance.

Results

Table (1): Preliminary parameters of study group and seminal fluid parameters before & after processing regarding age, abstinence period, volume, concentration, total count, sperm motility, progressive motility, abnormal forms & DFI before proceeding in addition to motility & DFI after processing.

Parameter	Mean ± SD
Preliminary Data:	
Age (years)	35.00±5.39
Abstinence period (days)	3.77±1.01
Volume (ml)	3.56±1.11
Sperm Concentration ($\times10^6$/ml)	38.5±18.86
Total Sperm Count ($\times10^6$)	133.17±67.17
Sperm Motility Before Processing (%)	59.33±7.74
Progressive motility Before Processing (%)	26.67±9.25
Sperm Abnormal Forms (%)	97.20±1.35
DFI Before processing (%)	17.21±7.57
After Processing Data:	
Sperm Motility (%)	92.83±2.84
DFI	14.62±7.12

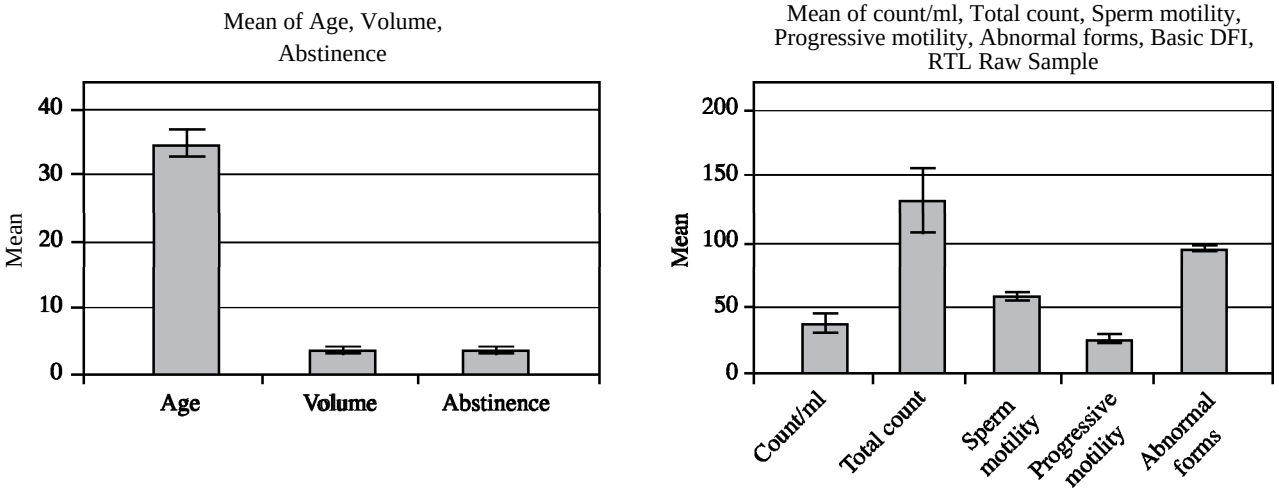

Fig. (1): Preliminary parameters of study group and seminal fluid parameters.

Table (2): Results of comparing parameters of seminal fluid before & after processing regarding sperm motility & DFI shows a significant difference (*p*-value >0.05). The sperm telomere length results of the studied group shows a non-statistically significant difference between the experimental groups' values (*p*-value <0.05). Association between pregnancy rate and age revealed a significant difference (*p*-value > 0.05).

Variable	Mean ± SD	*p*-value
Sperm Motility (%)	Before Processing: 59.33±7.74 After Processing: 92.83±2.84	0.000
DFI	Before Processing: 17.21±7.57 After Processing: 14.62±7.12	0.000
Sperm Telomere Length (STL)	Raw: 0.73±0.26 Pellet: 1.05±1.75	0.347
Age	Pregnancy Positive (N = 23): 33.70±4.050 Pregnancy Negative (N = 7): 39.29±7.251	0.014

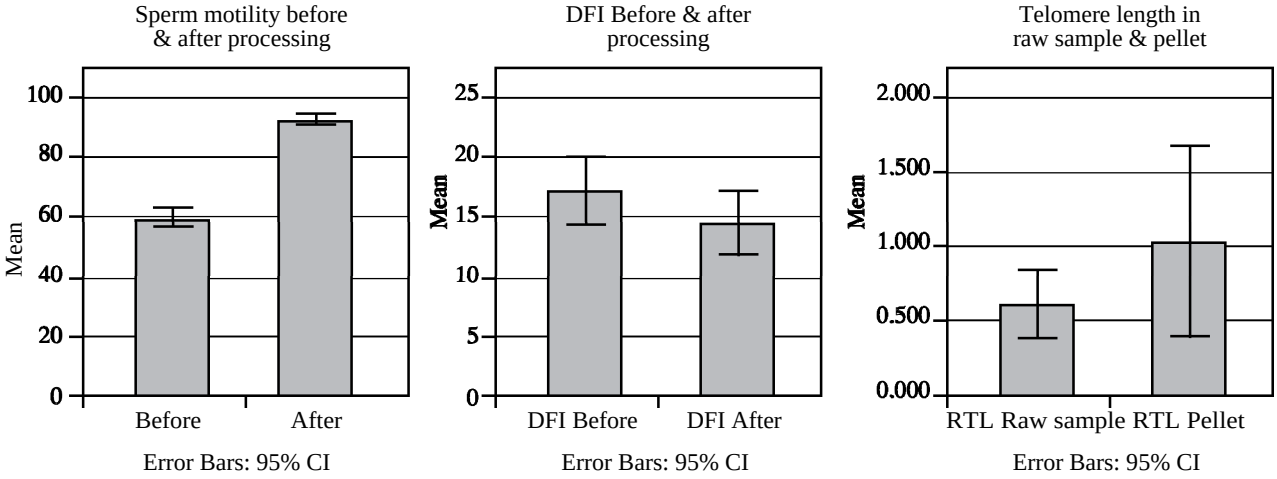

Fig. (2): (Left): The average sperm motility prior to & after processing. (Middle): The average DFI prior to & after processing. (Left): Sperm telomere length of raw & pellet samples.

Table (3): Pearson correlation between STL & other parameters shows significant correlation regarding progressive motility (r_p 0.514; p=0.04) & a non-significant negative correlation with age (r_p -0.176; p=0.353) & other parameters.

Parameter	Pearson Correlation (p-values)
Age (years)	-0.176-(0.353)
Sperm Concentration ($\times 10^6$/ml)	-0.084- (0.659)
Total Sperm Count ($\times 10^6$)	0.052(0.787)
Sperm Motility (%)	0.102 (0.592)
Progressive motility (%)	0.514 (0.04)
Sperm Abnormal Forms (%)	-0.176-(0.352)

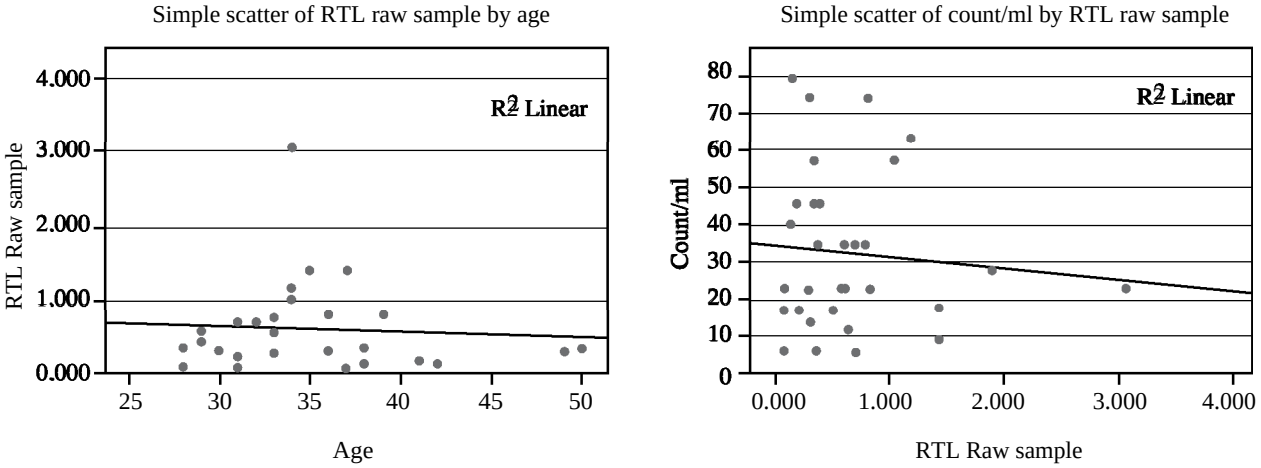

Fig. (3): (Left): STL & age. (Right): Sperm telomere length of and count.

Table (4): In order to analyze the associations between STL and pregnancy rate, we performed linear regression analyses. The results showed that there was no significant association between STL and the pregnancy rate (regression coefficient: 0.164; p=0.60) as summarized in Table (4).

Table (4): STL & pregnancy rate linear regression.

Model	Independent variables	Regression Coefficient	95% CI of regression coefficient	p-value
	(Constant)		From -32.999- to 59.563	0.554
	Age	0.227	From -.040- to 0.090	0.427
	Volume	1.029	From -.459- to 1.560	0.267
	Abstinence	-0.351-	From -.564- to 0.150	0.239
	Count/ml	0.781	From -.067- to 0.116	0.578
	Total Count	-1.481-	From -.039- to 0.013	0.311
	Sperm motility	-0.047-	From -.073- to 0.066	0.914
	Progressive motility	0.286	From -.053- to 0.090	0.596
	Abnormal Forms	-0.465-	From -.583- to 0.174	0.271
	DFI	0.348	From -.083- to 0.137	0.610
	Pregnancy Rate	0.164	From -.665- to 1.119	0.600

Discussion

The current study's findings indicate that spermatozoa from older men have shorter telomeres since there is a weak negative association between sperm telomere length and male age. This conclusion is supported by Rocca et al., who found a negative correlation between all variables and sperm telomer length **[8]**. The influence of various factors, including oxidative stress, aging, psychological stress, obesity, sickness, smoking, way of life, food, and others, on telomere length may account for these results **[9-11]**. There was no correlation found in this investigation between STL and sperm motility, count, or concentration. This finding was in line with the findings of other earlier research projects **[8,11]**. Consistent with the results of the current study **[12,13]**, recent research has demonstrated that STL levels have decreased in ten ICSI patients with a history of low fertilization rates **[14]** and are positively linked with embryo quality **[15]**. A different analysis was unable to find any connection between sperm parameters and STL **[16].** However, studies looking into the connection between sperm quality and STL have found a favorable correlation between total sperm count and STL **[17,18].** In the current study, there was a significant positive correlation (p=0.004) between increased motility and STL. The current study's finding that STL positively correlates with increasing motility and vitality is in line with earlier studies that found that STL is associated with shorter telomeres in oligozoospermic and infertile men compared to normozoospermic and fertile men **[15,17].** Furthermore, using normozoospermic samples, Rocca et al., revealed that in previous studies, STL was found to be negatively linked with sperm DNA fragmentation and positively associated with sperm progressive motility and viability **[8]**. Zhao et al. also found a significant and positive correlation (p=0.003) between STL and the rising motility of total sperm. However, the STL was negatively and strongly correlated with other variables **[13].** Conversely, Berneau, et al. **[19]** reported no direct correlations between the STL and progressive motility **[18]**. According to WHO guidelines **[20],** sperm quality is currently assessed without taking into account molecular andrology processes such as sperm DNA integrity and STL **[11].** Therefore, in addition to typical sperm features, molecular integrity may affect the quality of spermatozoa and their ability to fertilize. In the current paper, Ghorbani-Sini et al.'s STLs analysis revealed a negative correlation between telomere length and the percentage of abnormal sperm morphology. Thus, this study further emphasizes the significance of sperm telomere length as an indicator of sperm quality **[21]**. Studies have indicated that sperm DNA fragmentation can be reduced by selecting sperm based on the electrical charge on their surface **[22-24]**. It should be noted that Lafuente and associates used the fluorescence in-situ hybridization (FISH) technique to measure telomere length in their research. They clarified that problems with sample size and technique could be the cause of the disparity. On the other hand, decreased levels of oxidative stress could be the cause of the shorter telomere length observed in different experimental groups **[10]**. The precise nature of the relationship between STL and semen characteristics was ascertained by analyzing raw semen samples for sperm DFI. The STL and DFI were shown to be adversely linked in this study. These findings concur with those of a previous study **[8,15],** which discovered a relationship between the STL and the most significant standard semen features as well as sperm quality. Since telomere shortening has been linked to DNA damage as a cause as well as an effect, previous studies have suggested that telomere shortening alone is responsible for DNA damage **[25,26],** which helps to explain these results. Furthermore, sperm DNA fragmentation may be the cause of telomere shortening, as per the findings of Ramrez et al., **[27].** However, it is impossible to pinpoint exactly which of DNA fragmentation and telomere shortening is the cause and which is the result; additionally, it is plausible that specific stimuli could cause both processes. Furthermore, as shorter telomeres are linked to more fragmented DNA and a lower fraction of viable and motile cells may both induce and result from high fragmentation, it is also

possible that sperm DNA integrity determines STL, sperm motility, and sperm vitality. To fully understand how oxidative stress affects the post-meiotic regulation of STL (when telomerase is unable to restore telomere length), more research is obviously needed. The current study's findings indicated that a lower age significantly influenced the success rate of conception. Numerous factors can be used to explain these findings. First, according to *[28]*, the age threshold used in this study is 36 years old, which is also the age at which the reduction in male fertility is thought to have started. The second confounding factor is the correlation between aging and fertility issues, such as a decline in male hormone levels and sperm quality *[29]*. Studies have indicated that a higher parental age at conception has a detrimental effect on the overall fitness of human progeny *[30,31]* as well as the survival of both children in mice *[32]*. Given the crucial role telomeres play in meiosis and the maintenance of genomic integrity, it is conceivable that errors in segregation and/or germ cell death could jeopardize spermatogenesis in the event of shorter telomeres *[33]*. The study's findings indicate that there was no meaningful correlation between STL and the pregnancy rate. These findings contradict those of Cariati and associates, who noted that IVF patients with an aberrant STL did not experience any more pregnancies *[18]*. In contrast to couples who successfully conceived naturally with spermatozoa holding a longer STL, spermatozoa with a shorter STL were associated with lower rates of natural conception *[10]*. Individuals with oligozoospermia consistently had shorter STLs than samples from normozoospermic patients; this suggests that spermatogenesis may be compromised due to reduced STLs resulting from meiotic segregation errors *[10,15,17]*. Therefore, some age threshold (e.g., 30 years versus 50 years or older) is required in order to assess the impact of age or STL on pregnancy rate *[28,34]*. Although statistical analysis did not show a significant difference in the results of the experimental groups, our inquiry did show a significant discrepancy in STL phases being longer in pellets than raw samples. Our findings were emphasized by *[15,21]*. Noted that there was a substantial difference in the average sperm telomere length between the raw semen group and the post-processed sperm group, which is consistent with our findings. According to *[15]*, this shows that raw semen can be purified using density gradient centrifugation to create sperm with longer telomeres, which can be employed in assisted reproductive procedures.

Limitations: We used a modest cohort design in our single-center investigation. Our findings need to be validated by conducting additional statistical analysis.

Conclusion: There was a positive link seen in the semen between telomere length and increasing sperm motility. Thus, choosing sperm with longer telomeres and using assisted reproductive techniques to increase the pregnancy rate result in children who live longer and a higher live birth rate.

Fund: NIL.

Conflict of Interest: NIL.

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تأثير طول تيلوميرالحيوانات المنوية على جودة الحيوانات المنوية وخصوبة الذكور

التيلوميرات هى هياكل كروماتينية متخصصة توجد فى نهايات الكروموسومات حقيقية النواة. يعد طولها عاملاً مهمًا فى المراحل المبكرة من التطور الجنينى عند البشر. فى حين أظهرت الدراسات أن طرق تحضير الحيوانات المنوية المختلفة تؤثر على التركيز والحركة والتشكل، لا يُعرف سوى القليل عن الارتباط المحتمل بين طول التيلومير وطرق تحضير الحيوانات المنوية بالمعامل المختصة بالتلقيح والاخصاب الصناعى.

يهدف هذا البحث الى دراسة مقارنة العينة الخام مع العينة المحضرة بالمعمل بطريقة التدرج Gradient.

لاجراء هذا البحث تم الحصول على ثلاثين عينة من السائل المنوى من ٣٠ (حالة) مريضاً فى الفترة من يناير ٢٠٢١ إلى أكتوبر ٢٠٢١، تم تقييم الحالات المشاركين المقبولين فى قسم أمراض النساء والتوليد، وحدة الإخصاب والتلقيح الصناعى (IVF) بكلية الطب، جامعة القاهرة.

بعد موافقة اللجنة الأخلاقية المحلية بجامعة القاهرة. تمت الموافقة على التدرج لتحديد الحيوانات المنوية ذات طول التيلومير الأطول، حيث وجد انه يرتبط sperm with longer telomere length (STL) بشكل إيجابى بحركة الحيوانات المنوية. وبالتالى، فإن استخدام تقنيات الإنجاب المساعدة (التلقيح والاخصاب الصناعى) لاختيار الحيوانات المنوية ذات التيلوميرات الأطول يعزز معدل نجاح الحمل والولادة، والذى بدوره يعزز طول عمر النسل.