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Expression and correlation of male reproductive hormone levels with abnormal semen liquefaction time

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ABSTRACT

Objective: To explore the reproductive hormone levels and their correlation in males with abnormal semen liquefaction time, providing evidence-based medical insights for the diagnosis and treatment of abnormal semen liquefaction.

Methods: A total of 36 male patients who exhibited a sperm liquefaction time exceeding 60 min in the Maternal and Child Health Hospital of Hubei Province from January 2021 to January 2023 were included. They were classified into the delayed liquefaction group. During the same period, 138 male patients with a sperm liquefaction time of ≤60 min were assigned to a normal liquefaction group. Comparative analysis was performed on reproductive hormone levels between the two groups, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone (T), estradiol (E2), prolactin (PRL), as well as semen parameters such as normal morphology sperm rate, forward motility sperm rate, and sperm concentration. Pearson's correlation analysis was employed to investigate the relationship between reproductive hormones and semen liquefaction time. The effectiveness of biomarkers in predicting delayed semen liquefaction time was assessed using receiver operating characteristic (ROC) curves.

Results: Patients with delayed semen liquefaction had significantly lower rates of normal morphology sperm, forward progressive motility, and sperm concentration when compared to patients with normal liquefaction. Significantly lower FSH, LH, and T levels were observed in patients with delayed semen liquefaction than those with normal liquefaction. Furthermore, a negative correlation was identified between serum FSH and T levels in male infertility patients and semen liquefaction time. The sensitivity of FSH for predicting semen liquefaction defects is 72.2%, whereas testosterone exhibits a sensitivity of 94.4%.

Conclusion: The semen liquefaction time of male infertility patients is closely correlated with semen parameters and reproductive hormone levels. Specifically, FSH and T exhibit a negative correlation with semen liquefaction time.

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Semen liquefaction; reproductive hormones; semen parameters

1. Introduction

The constituents of seminal plasma provide nourishment and protection to spermatozoa within the female reproductive tract, protecting them from the acidic environment and preventing potential DNA damage. Seminal plasma is a composite of secretions from the testes, epididymis, seminal vesicles, prostate, and bulbourethral glands [1]. The process of semen liquefaction is a protein hydrolysis mechanism wherein the gel-like ejaculate undergoes a transition to a fluid state due to the enzymatic activity of prostate-derived serine proteases in the female reproductive tract [2]. Liquefaction involves the breakdown of gel formed by seminal vesicle proteins, resulting in a more liquid texture of semen [2]. Standard semen coagulates (forming a clot) within seconds of ejaculation and liquefies within 30 min. As outlined in the guidelines of the National Institute for Health and Care Excellence (NICE), liquefaction within 60 min is deemed physiologically normal [3]. The process of liquefaction is crucial for maintaining sperm vitality and facilitating their successful transportation to the site of fertilization within

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the fallopian tube. Non-liquefaction of semen can lead to asthenozoospermia and diminished sperm motility, and is one of the main causes for male infertility or reduced fertility potential [4]. Currently, there are approximately 12% of individuals with infertility experiencing non-liquefaction of semen [5].

Semen liquefaction may be a result of combined enzymatic reactions in the reproductive tract, and abnormal liquefaction implies disruptions in the internal environment that facilitates the production of semen [6]. The process of semen liquefaction is primarily governed by the secretions emanating from accessory glands, the regulatory mechanisms of which are modulated, directly or indirectly, by reproductive hormones within the body. Hormones related to male reproduction mainly include testosterone (T), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2), which have an impact on the environment and biological functions of sperm [7].

Recent research has underscored the significant influence of hormones on male fertility. These studies have examined how hormonal imbalances and environmental exposures affect reproductive health in both humans and animals. For example, Toghan et al. [8] investigated the protective effects of folic acid against reproductive toxicity in male albino rats, highlighting the crucial relationship between hormonal health and fertility outcomes. El-Sawy et al. [9] showed that Artemisia annua extract enhanced testicular function and spermatogenesis in rats subjected to high-fat diets. In veterinary research, Hamed et al. [10] assessed chemical castration methods and utilized anti-Müllerian hormone levels as indicators of reproductive effects. Research on female fertility also emphasizes the role of hormones. Studies by Amin et al. [11,12] explored the effects of hormonal treatments on the reproductive health of dairy cows and how postpartum complications influence hormone profiles. Amin et al. [13] looked into the effects of aflatoxin exposure on reproductive hormones in buffalo. Furthermore, Amin et al. [14] described how Trypanosoma evansi infection disrupted hormonal profiles and reproductive indices in camels. Collectively, these findings highlight the importance of reproductive hormones in fertility, offering insights into therapeutic strategies and the impact of environmental and physiological stressors on reproductive function. So, hormones play a pivotal role in initiating and sustaining male reproductive functions. Nevertheless, the relationship between hormone levels and the duration of semen liquefaction remains elusive.

The present study recruits reproductive-age male patients with abnormal semen liquefaction time admitted to the Maternal and Child Health Hospital (MCHH) of Hubei Province, with the aim of investigating the correlation between reproductive hormone levels and the duration of semen liquefaction.

2. Materials and methods

2.1. Baseline profiles

This study is a cross-sectional investigation that enrolled 36 male patients of age between 20 and 40 years old with a sperm liquefaction time of >60 min admitted to the MCHH of Hubei Province from January 2021 to January 2023 as research subjects and included them in a delayed liquefaction group.As per the criteria for normal liquefaction group, during the same period, 138 male patients with a sperm liquefaction time of ≤60 min who sought medical attention in the same hospital due to male diseases were recruited as controls and assigned to a normal liquefaction group. Informed consent was obtained from all patients.

With a significance level set at 0.05 and a predetermined statistical power (1–β), the necessary sample size for the control group can be calculated using sample size estimation formulas based on these parameters.

$$n = \left(\frac{\left(Z_{\alpha/2} + Z_{\beta} \right)^2 \cdot \left(\sigma_1^2 + \sigma_2^2 \right)}{\left(\mu_1 - \mu_2 \right)^2} \right)$$

Where n represents the required sample size for each group. $Z_{\alpha/2}$ is the critical value from the standard normal distribution corresponding to the significance level. Z_{β} is the critical value from the standard normal distribution corresponding to the statistical power. σ_1 and σ_2 denotes the standard deviations of the two groups, while μ_1 and μ_2 represent the means of the two groups.

2.2. Baseline Patient profiles

The general information between the two groups is presented in Table 1. In the delayed liquefaction group, the mean age was 30.14 ± 3.05 years, duration of infertility was 1.76 ± 0.29 years, abstinence duration was 4.66 ± 1.15 days, and body mass index (BMI) was 25.36 ± 3.02 kg/m^2, with 11 patients being smokers and 13 patients being alcohol consumers. In the normal liquefaction group, the mean age was 31.14 ± 4.11 years, duration of infertility was 1.81 ± 0.34 years, abstinence duration was 4.73 ± 1.36 days, and BMI was

Table 1. Baseline patient profiles.

	Delayed liquefaction	Normal liquefaction	t/χ^2	P
n	36	138		
Age, years ($\bar{x}$±s)	30.14 ± 3.05	31.14 ± 4.11	1.364	0.174
Infertility time, years ($\bar{x}$±s)	1.76 ± 0.29	1.81 ± 0.34	0.809	0.420
Abstinence time, days ($\bar{x}$±s)	4.66 ± 1.15	4.73 ± 1.36	0.283	0.777
BMI, kg/m^2 ($\bar{x}$±s)	25.36 ± 3.02	25.17 ± 3.44	0.302	0.763
Current smokers (n)			1.571	0.210
Yes	11	58		
No	25	80		
Current alcohol consumers (n)			1.220	0.269
Yes	13	64		
No	23	74		

25.17 ± 3.44 kg/m^2, with 58 patients being smokers and 64 patients being alcohol consumers. The two groups were well-balanced in terms of baseline characteristics ($p > 0.05$).

2.3. Delayed liquefaction group inclusion and exclusion criteria

Inclusion criteria: (1) age between 20 and 40 years old; (2) infertility, as defined by the World Health Organization, is defined as couples having more than three vaginal sexual encounters within a month without being separated from each other, unprotected sex between couples who have been diagnosed with male infertility for at least a year; (3) resistance lasting three to seven days; (4) sex partners' hormone levels and uterine and ovarian function tests are normal; (5) no past history of using medication for inferiority within the previous month.

Exclusion criteria: (1) Klinefelter syndrome was identified by karyotype analysis (47, XXY); azoospermia factor, or microdeletion of the Y chromosome; lack of the vas deferens at birth; presence of illnesses related to the reproductive system, such as prostatitis or orchitis; (2) long-term radiation work, prolonged sitting or standing, and other similar activities can cause symptoms such varicocele, blockage of the vas deferens, low or absent sperm count, normal testicular morphology, or mild shrinkage; abnormal feeling in the vas deferens or epididymis; (3) hormone treatment within the last three months; (4) concomitant erectile dysfunction; (5) concomitant with other forms of sexual dysfunction, such as anorexia, retrograde ejaculation, low desire, etc.; accompanied by conditions like thyroid disorders that could be the reason for early ejaculation; (6) mental and neurological disorders, inability to express personal will, inability to cooperate, and poor compliance.

2.4. Normal liquefaction group inclusion and exclusion criteria

Inclusion Criteria: (1) males aged 20 to 40 years; (2) sperm liquefaction time of ≤60 min as measured during clinical evaluation at the time of hospital admission; (3) males presenting with male-related health issues (e.g. infertility, reproductive health concerns) who do not exhibit any sperm liquefaction delays (normal liquefaction time); (4) Patients who are conscious and capable of understanding and agreeing to participate in the study (i.e. signed informed consent); (5) patients who sought medical attention at the Maternal and Child Health Hospital of Hubei Province during the study period (January 2021 to January 2023) for male reproductive health issues; (6) no history of severe systemic or metabolic diseases (e.g. cancer, diabetes, major cardiovascular diseases) that could influence sperm liquefaction or fertility.

Exclusion Criteria: (1) individuals with known conditions affecting male fertility or semen quality (e.g. varicocele, azoospermia, oligospermia, hormonal imbalances) that may alter sperm liquefaction time; (2) patients who recently had ejaculation or sexual activity that could influence the quality of the semen sample (e.g. within the last 24–48 h); (3) individuals currently using medications (e.g. hormone treatments, chemotherapy, medications known to affect sperm quality) or illicit drugs that could alter semen liquefaction; (4) patients with active genital infections (e.g. prostatitis, epididymitis, orchitis) or any inflammatory conditions affecting the reproductive organs; (5) individuals with health conditions known to interfere with normal sperm production and liquefaction, such as autoimmune diseases or genetic disorders (e.g. Klinefelter syndrome).

2.5. Semen parameter analysis

Semen liquefaction time: Semen liquefaction refers to the thinning of newly ejaculated semen in a gelatinous form after 10–20 min under the action of fibrinolytic enzymes, allowing the sperm to move fully. Patients collected semen through masturbation. The collected semen was placed on a 37 °C warming plate for natural liquefaction. Patients whose semen completely liquefied within 30–60 min were assigned to the normal liquefaction group, while those with non liquefaction time of more than 60 min or incomplete liquefaction were included in the abnormal liquefaction group.

Sperm morphology analysis: The Israeli SQA-V sperm routine automated analysis system was used to

measure semen concentration, liquefaction status, and normal morphology rate. Duplicate determinations were carried out for each sample by two examiners, and corrective measures were taken if necessary. Normal sperm criteria: Sperm are 2–3μm wide and 3–5μm long; the head is smooth and elliptical, with the acrosome accounting for 40%-70% of the head; the head width is 2/3 to 3/5 of the head length; the midpiece aligns with the longitudinal axis of the head and must be slender; the midpiece width is ≤1μm, which is similar to half of the head width; the tail is 45 μm long, must be straight without curling, regular, and slightly thinner than the midpiece. Cytoplasmic droplets, exceeding half the head size, critical form sperm, vacuolated head, irregular head shape, pear-shaped head, round head, elongated head, overly large or small acrosome, abnormal tail connection, bending, and curling were considered as abnormalities. In this study, SQA-V sperm routine automated analysis system was used with reference to the findings of Lammers et al. [15], who compared the SQA-V GOLD and CEROS and CASA systems with the standardized manual assessment based on the fifth edition of WHO in 2014. The main outcome indicators of the three methods were sperm concentration, total sperm count, total viability, forward motility, non-forward motility, morphology, motile sperm concentration and forward motile sperm concentration.

2.6. Reproductive hormone levels

The reproductive hormone assay kits were produced by Siemens Healthineers Diagnostics Products (Shanghai) Co., Ltd. The Bayer ADVIA Centaur fully automated chemiluminescence immunoassay system was employed for measurement. Fasting venous blood samples were collected from all patients on the morning after admission, and the reproductive hormone levels, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone (T), estradiol (E2), and prolactin (PRL), were measured using the assay kits according to the specific kit instructions. A flowchart illustrating patient selection for analysis in Figure 1.

2.7. Statistical analysis

The SPSS 22.0 software was used for statistical analysis of the data, and GraphPad Prism 9.0 software was employed to visualize the data into required images. Normally distributed measurement data were presented as mean ± standard deviation ($\bar{x}\pm s$) and analyzed using t-tests. Count data were presented as percentages (%) and analyzed using the chi-square test. Pearson's correlation analysis was used to explore the relationship between reproductive hormones and semen liquefaction time. The effectiveness of biomarkers in predicting delayed semen liquefaction time was assessed using receiver operating characteristic (ROC) curves. The significance level was set at $p < 0.05$.

3 Results

3.1. Semen parameter comparison

The incidence of liquefaction defects is 26.09% (36/138). A comparison of semen parameters between the two patient groups is presented in Table 2. In the delayed liquefaction group, the mean values for normal morphology sperm rate, forward progressive motility rate, and sperm concentration were 14.25 ± 2.61%, 30.22 ± 5.69%, and 17.22 ± 5.26 × 10^6/mL, respectively. In the normal liquefaction group, the mean values for normal morphology sperm rate, forward progressive motility rate, and sperm concentration were 19.26 ± 3.48%, 37.26 ± 6.14%, and 21.02 ± 6.01 × 10^6/mL, respectively. Patients with delayed semen liquefaction had significantly lower rates of normal morphology sperm, forward progressive motility,

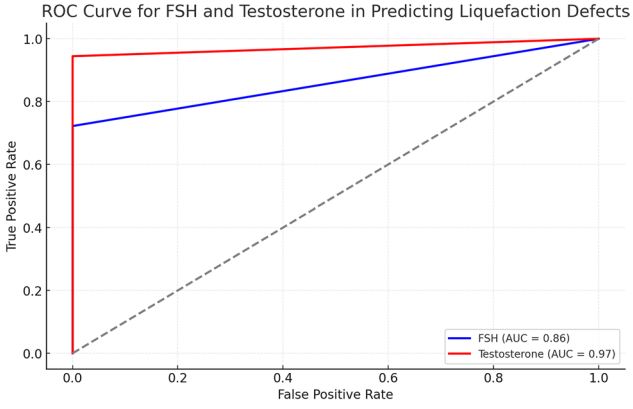

Figure 1. Scatter plot of correlation between semen liquefaction time and reproductive hormones.
*Represents P < 0.05, *** Represents P < 0.001; the red line represents a trend chart

Table 2. Semen parameter comparison ($\bar{x}\pm s$).

	n	Normal morphological rate (%)	Forward progressive sperm motility rate (%)	Sperm density ($\times 10^6$ /ml)
Delayed liquefaction	36	14.25 ± 2.61	30.22 ± 5.69	17.22 ± 5.26
Normal liquefaction	138	19.26 ± 3.48	37.26 ± 6.14	21.02 ± 6.01
t		8.060	6.217	3.462
P		<0.001	<0.001	<0.001

Table 3. Hormone level comparison ($\bar{x}\pm s$).

	n	FSH(U/L)	LH(U/L)	PRL (mIU/L)	PRL (pmol/L)	PRL (nmol/L)
Delayed liquefaction	36	4.26 ± 1.11	3.82 ± 0.85	170.22 ± 30.25	131.56 ± 28.36	12.26 ± 2.85
Normal liquefaction	138	4.92 ± 1.25	4.63 ± 1.14	174.85 ± 34.25	140.25 ± 30.21	17.63 ± 3.29
t		2.884	3.981	0.739	1.556	8.952
P		0.004	<0.001	0.461	0.122	<0.001

and sperm concentration when compared to patients with normal liquefaction ($p < 0.05$).

3.2. Hormone level comparison

As depicted in Table 3, in the delayed liquefaction group, the mean levels of FSH, LH, PRL, E2, and T were 4.26 ± 1.11 U/L, 3.82 ± 0.85 U/L, 170.22 ± 30.25 mIU/L, 131.56 ± 28.36 pmol/L, and 12.26 ± 2.85 nmol/L, respectively. In the normal liquefaction group, the mean levels of FSH, LH, PRL, E2, and T were 4.92 ± 1.25 U/L, 4.63 ± 1.14 U/L, 174.85 ± 34.25 mIU/L, 140.25 ± 30.21 pmol/L, and 17.63 ± 3.29 nmol/L, respectively. Patients with delayed semen liquefaction exhibited significantly lower FSH, LH, and T levels than patients with normal semen liquefaction ($p < 0.05$).

3.3. Correlation analysis between semen liquefaction time and reproductive hormones

The results are presented in Table 4. The Pearson correlation analysis revealed that semen liquefaction time was negatively correlated with FSH and T concentrations ($p < 0.05$). The correlation coefficient between semen liquefaction time and FSH was −0.175 (95%CI: −0.316, −0.028), indicating a weak correlation. The correlation coefficient between semen liquefaction time and T was −0.453 (95%CI: −0.563, −0.326), suggesting a moderate correlation. There were no significant correlations between semen liquefaction time and LH, PRL, and E2 concentrations ($p > 0.05$). The scatter plots depicting the correlations are shown in Figure 2.

3.4. The sensitivity of FSH and testosterone in predicting cases of liquefaction defects

The sensitivity of FSH for predicting semen liquefaction defects is 72.2%, whereas testosterone exhibits a sensitivity of 94.4%. This suggests that testosterone serves as a more sensitive marker than FSH for identifying delayed semen liquefaction, as illustrated in Figure 3.

4. Discussion

Male with abnormal semen liquefaction time accounts for approximately 30–40% of fertility issues in infertile couples and is considered the sole cause in 20% of cases [16]. Known causes of abnormal semen liquefaction time include oxidative stress, reactive oxygen species, leukocytospermia, varicocele, and unexplained infertility, which lead to abnormal sperm characteristics and DNA damage [17,18]. Additionally, infections, inflammation, and functional disorders are also contributing factors to decreased sperm vitality and elevated white blood cell levels [19,20]. Semen is composed of fluids secreted by male accessory glands, containing proteins crucial for semen coagulation and liquefaction [21]. Semen liquefaction is vital for reproduction, as abnormal sperm liquefaction restricts sperm motility and impedes or inhibits sperm's entry into the uterine cavity for fertilization, compromising conception and fertility [22]. Secretions from the prostate and seminal vesicles participate in the processes of semen coagulation and liquefaction. The coagulation factors produced by the seminal vesicles induce semen coagulation, while the liquefaction factors produced by the prostate, such as proteases and fibrinolytic enzymes, facilitate semen liquefaction [23]. Inflammation-induced dysfunction of the seminal vesicles or prostate can lead to abnormalities in the secretion of these factors, causing increased levels of coagulation factors or decreased liquefaction factors, thereby resulting in non-liquefying semen [24]. Reproductive hormones play a crucial role in initiating and maintaining male reproductive function. Spermatogenesis in the testes is regulated by the hypothalamic-pituitary-testicular axis, with the anterior pituitary responding to hypothalamic GnRH by secreting LH and FSH. LH stimulates testosterone and other hormone production in the testicular interstitial cells [25].

The results of the correlation analysis between semen liquefaction time and reproductive hormones showed that it is negatively connected with the

Table 4. Correlation analysis between semen liquefaction time and reproductive hormones.

	r	95% CI (upper, lower)	p-value
FSH	−0.175	−0.316, −0.028	0.021
LH	−0.113	−0.257, 0.036	0.137
PRL	−0.103	−0.248, 0.047	0.178
E2	−0.124	−0.268, 0.025	0.102
T	−0.453	−0.563, −0.326	<0.001

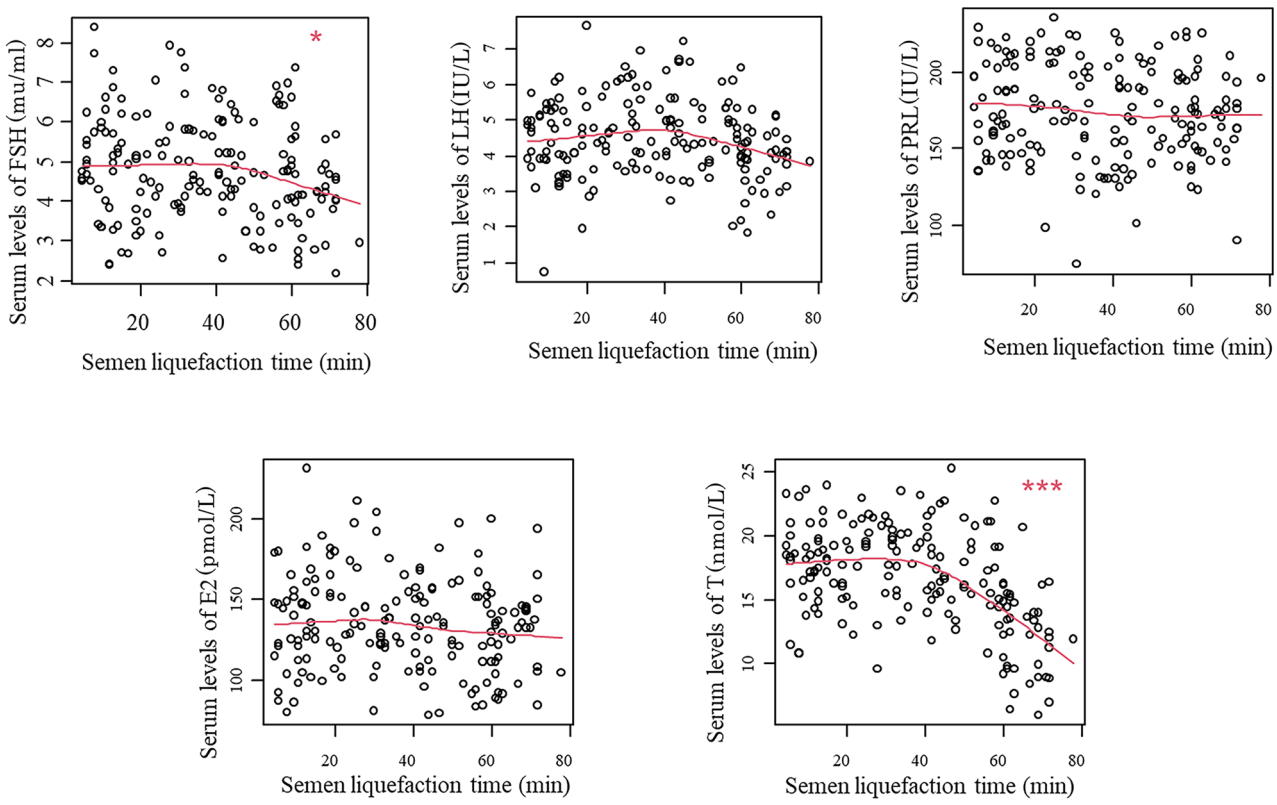

Figure 2. Receiver operating characteristic curve for FSH and testosterone in predicting liquefaction defects.
Blue line: ROC curve for FSH with its Area under the Curve (AUC) value.
Red line: ROC curve for testosterone with its AUC value.

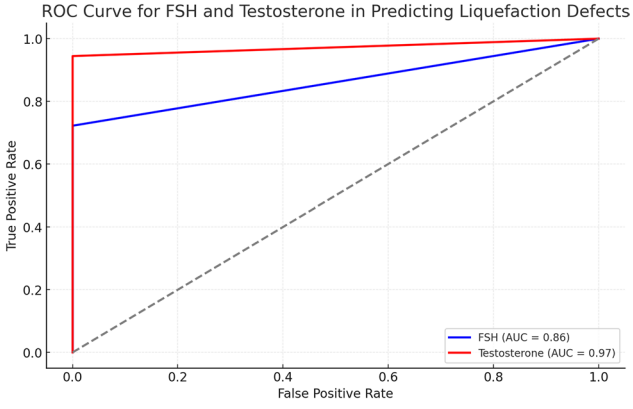

Figure 3. ROC curve for FSH and testosterone in predicting liquefaction defects.

concentrations of FSH and T, but not with the concentrations of LH, PRL, or E2. The diagnostic effectiveness of FSH and testosterone as prognostic biomarkers for delayed semen liquefaction time is further confirmed by using the ROC curve. FSH and T as predictive biomarkers, these hormones are important regulators of male reproductive function, with FSH playing a key role in spermatogenesis and testosterone influencing various aspects of sperm quality and motility. It is plausible that the study hypothesized that abnormal levels of these hormones could be associated with delayed sperm liquefaction.

The current study demonstrates that delayed semen liquefaction is associated with significantly lower rates of normal sperm morphology and forward motility, as well as a lower sperm concentration compared to normal liquefaction. Moreover, patients with delayed semen liquefaction exhibited significantly lower FSH, LH, and T levels than patients with normal semen liquefaction. Furthermore, the serum levels of FSH and T in male patients with abnormal semen liquefaction time demonstrate a negative correlation with semen liquefaction time. These findings align with existing research results, indicating a certain impact of delayed semen liquefaction on sperm viability, velocity, and directionality [26]. Currently, little knowledge is available related to the relationship between reproductive hormone levels and semen parameters, as well as semen liquefaction. FSH, a gonadotropin synthesized and released by the anterior pituitary gland, holds a fundamental significance in reproduction. Within the male reproductive context, FSH assumes a pivotal role in orchestrating testicular maturation, the development of seminiferous tubules, and the process of

sperm production [27]. In mature gonads, FSH acts on Sertoli cells, spermatogonia, primary and secondary spermatocytes, and cells in the seminiferous tubules, initiating spermatogenesis [28]. Prior investigations substantiate the functions of FSH and T in the maturation and operation of sperm, wherein FSH and T exert an impact on sperm motility. Evidence proved that T facilitates the adherence and specialization of spermatogenic cells to Sertoli cells, thereby contributing to the initiation of GnRH and LH secretion. Alterations in sperm characteristics, including increased vigor attributed to T and reduced levels of concentration, vitality, and morphology linked with LH, are connected to the perturbations and adaptive reactions within the hypothalamic-pituitary-gonadal axis [29]. The correlation between FSH and semen liquefaction time might be associated with the Epididymal Protease Inhibitor (Eppin). It is known that Eppin is a key component of the protein mixture on the sperm surface that tightly binds with coagulation factors in semen and is time- and dose-dependent during the liquefaction process [30]. The supporting cells of the testes participate in Eppin synthesis and are regulated by FSH [31].

The results showed that the advantages of using automated semen analyzers are: standardization, speed (shorter turnaround time), accuracy, reduced possibility of human error, automated data logging, and less need for highly skilled professionals to run the system.The SQA-V sperm routine automated analysis system demonstrated better consistency than the manual method. In conclusion, automated semen analyzers can be used for routine semen analysis to rapidly provide clinically acceptable results with greater precision and positively impact laboratory standardization.

Currently, WHO shows semen liquefaction time in intervals, because this study is more innovative, the patients with delayed semen liquefaction were included in the correlation analysis, but only men with semen that had not liquefied for more than 60 min were included, and there was no comparison of liquefaction time in the gradient, which is a limitation of the present study, and the gradient will be carried out in the future in order to obtain more accurate research data.

A prior study evaluated the impact of testosterone supplementation on sperm vitality in oligoasthenospermic males and found that testosterone supplementation maintains optimal sperm vitality [32]. This study corroborates the correlation between T and semen liquefaction time. However, further research is required to elucidate the precise mechanisms involved.

5. Conclusion

The semen liquefaction time of male infertility patients is closely correlated with semen parameters and reproductive hormone levels. Specifically, FSH and T exhibit a negative correlation with semen liquefaction time.

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Ethics approval

This study was conducted in accordance with the ethical regulations of the Declaration of Helsinki. The experiments were admitted to Maternal and Child Health Hospital of Hubei Province. The number of the Ethics Committee's acceptance is:2023IEC108.

Informed consent

All patients signed the informed consent form.

Authors contributions

Guoqiong Zhang and Xingxing Wang conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.Guoqiong Zhang, Jie Zheng, and Lian He designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.Xingxing Wang coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Disclosure statement

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Data availability and materials statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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