Study Title:	Comparative Efficacy of Antioxidants Alone versus Combined Therapy with SERMs or FSH in Normogonadotropic Idiopathic OAT Patients: A Randomized Controlled Trial
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1. Synopsis

Introduction
Male infertility is a growing concern, with idiopathic oligoasthenoteratozoospermia (OAT) representing a common diagnosis in men presenting with abnormal semen parameters and no identifiable cause. Despite empirical use of antioxidants, treatment outcomes vary, and optimal management remains unclear. Hormonal therapies, such as selective estrogen receptor modulators (SERMs) and follicle stimulating hormone (FSH), may enhance spermatogenesis in normogonadotropic men, yet evidence from randomized controlled trials is limited.

Objectives
This study aims to compare the efficacy of antioxidant therapy alone versus combination therapies with either SERMs or FSH in improving semen parameters in normogonadotropic men with idiopathic OAT.

Methodology
This is a prospective, randomized controlled trial to be conducted at the Ambulatory Care Center (ACC) over a 2-year period. A total of 360 male patients aged 21–50, with idiopathic OAT, FSH <8.0 IU/L, normal testosterone levels, sperm concentration > 2 million/mL, and no history of chemotherapy or undescended testis, will be enrolled. Participants will be randomized into three equal groups:

- Group 1: Antioxidants only (control)
- Group 2: Antioxidants + SERMs
- Group 3: Antioxidants + FSH

The treatments offered to participants in this study are routinely given to our patients in clinical practice and are considered standards of care. Baseline and post-treatment semen analyses and hormonal profiles will be conducted at 3 and 6 months. Data collection will involve standardized forms, and statistical comparisons between groups will assess changes in semen parameters using ANOVA and post-hoc analyses.

Outcomes
The primary outcome is the improvement in semen parameters (concentration, motility, morphology) Before and after treatment. Secondary outcomes include sperm function test (SDF , ORP) and hormonal changes. This study anticipates identifying the most effective therapeutic approach, thereby contributing to evidence-based management of idiopathic male infertility.

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2. Abbreviations and Acronyms

ACC: Ambulatory Care Center, **OAT:** Oligoasthenoteratozoospermia, **RCT:** Randomized Controlled Trial, **FSH:** Follicle Stimulating Hormone, **SERMs:** Selective Estrogen Receptor Modulators, **IU/L:** International Units per Liter , SDF : Sperm DNA Fragmentation , ORP : Oxidation Reduction Potential , **T**: Testosterone.

List abbreviations, acronyms and terms of reference used in the protocol; provide definitions for each as needed

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3. Introduction / Background

Male infertility affects up to 7% of the male population, with idiopathic Oligoozoospermia with or without, Teratozoospermia or Asthenozoospermia accounting for nearly 30–40% of these cases (Agarwal et al., 2015). Idiopathic OAT is defined by abnormal semen parameters without an identifiable cause, such as endocrine disorders, anatomical defects, or genetic abnormalities. In many of these cases, men present with normal serum gonadotropin and testosterone levels (i.e., normogonadotropic), making therapeutic decisions more complex and less evidence based.

While oxidative stress has been implicated as a contributing factor in idiopathic male infertility, and antioxidant therapy has been widely used, systematic reviews suggest that evidence of benefit remains inconclusive in terms of improving live birth rates or semen parameters (Showell et al., 2014; Tremellen, 2008). Consequently, attention has shifted toward hormonal therapy, even in the absence of overt hormonal deficiencies.

Follicle-Stimulating Hormone (FSH) in Normogonadotropic Idiopathic OAT

FSH plays a central role in initiating and maintaining spermatogenesis through its stimulation of Sertoli cells. Traditionally used in hypogonadotropic hypogonadism, exogenous FSH has shown promise in normogonadotropic idiopathic infertility. Studies demonstrate improvements in total motile sperm count, sperm DNA integrity, and even pregnancy rates (Colacurci et al., 2012; Esteves et al., 2021).

Aligned with Italian practice, the Italian Society of Andrology and Sexual Medicine (SIAMS) indicates that FSH therapy may be considered for idiopathic male infertility when basal serum FSH is <8 IU/L; however, this threshold reflects national regulatory criteria and expert consensus rather than high-quality trial-derived evidence

The 2025 European Association of Urology (EAU) Guidelines recommend considering FSH treatment in men with idiopathic infertility, particularly those with low total motile sperm counts (<10 million), regardless of baseline FSH level, provided that other causes are excluded (EAU, 2025). The American Society for Reproductive Medicine (ASRM) also notes that empirical FSH therapy may be considered in normogonadotropic men with idiopathic infertility with the aim of improving sperm concentration, pregnancy rate, and live birth rate (ASRM, 2024).

Selective Estrogen Receptor Modulators (SERMs)

SERMs such as clomiphene citrate and tamoxifen act by blocking estrogen receptors at the hypothalamic-pituitary axis, leading to an increase in endogenous gonadotropin secretion (FSH and LH) and subsequently enhancing spermatogenesis. They are often used off label in men with idiopathic infertility and normal gonadotropins.

Multiple studies have shown that SERMs can improve sperm concentration, motility, and hormonal profiles, with minimal adverse effects (Gupta et al., 2019; Taylor & Levine, 2010). A 2021 meta-analysis confirmed statistically significant improvements in sperm concentration and motility in men treated with clomiphene compared to placebo (Krzastek et al., 2021).

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According to the ASRM 2020 guideline, SERMs are listed as a viable empirical option for men with idiopathic infertility and normal FSH, particularly when treatment goals include natural conception or improvement in semen parameters before assisted reproduction (ASRM, 2020). While the EAU does not formally endorse SERMs, it acknowledges their off-label use in this population, citing the need for more standardized trials (EAU, 2023).

Problem Statement & Research Question

Despite emerging evidence and evolving guidelines, there is a lack of head-to-head comparisons between **, SERMs, and FSH** in men with **normogonadotropic** Oligoozoospermia with or without ,Teratozoospermia or Asthenozoospermia . Identifying the most effective treatment strategy remains a clinical challenge.

Research Question:

Suggested Research Question according to PICO .In normogonadotropic patients with Oligoozoospermia with or without, Teratozoospermia or Asthenozoospermia how do antioxidants (A) with selective estrogen receptor modulators (SERMs) (B) and antioxidants with exogenous follicle-stimulating hormone (FSH) (C) compared to antioxidants alone (control, A) in terms of improvement in semen parameters, and how do B and C compare to each other?

This research has significant importance for Qatar, where infertility represents a growing public health and psychosocial concern within a young and diverse population. By generating locally derived, high-quality evidence on the optimal management of idiopathic male infertility, the study directly supports evidence-based clinical practice at Hamad Medical Corporation and aligns with national priorities for advancing reproductive health services. The findings will help optimize resource utilization, reduce unnecessary treatments, and improve fertility outcomes for couples in Qatar, while positioning the country as a regional leader in male reproductive health research and guideline-driven care.

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4. Objectives

Primary Objective:

To evaluate and compare changes in semen parameters (concentration, motility, morphology) before and after intervention in the three treatment groups.

Secondary Objectives:

To assess Sperm function test , hormonal profile changes (T, Estradiol, FSH, LH, Prolactin) and patient tolerance to interventions.

5. Indicate if this is a retrospective data review

No**,** this is a Prospective randomized controlled Study

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6. Study Methodology

This research will be a Prospective randomized control, open-label clinical trial conducted at the Ambulatory Care Center (ACC) over a span of 24 months. The primary aim will be to compare the effects of three interventions on semen parameters in normogonadotropic men with idiopathic Oligoozoospermia with or without, Teratozoospermia or Asthenozoospermia The three treatment arms will include:

- **Group A (Control):** Antioxidants only
- **Group B:** Antioxidants + Selective Estrogen Receptor Modulators (SERMs)
- **Group C:** Antioxidants + Follicle-Stimulating Hormone (FSH)

The study medication are available for all potential subjects, in line with routine clinical care. No additional or special charges are levied for any of the study medication.

Participants will be advised to avoid additional antioxidant supplements, maintain stable diet, avoid high-dose vitamins, and avoid herbal fertility products. At each visit participants will report supplement intake, medication use, and dietary changes

Type and Classification of Study

We will conduct a randomized, parallel-arm intervention study. The interventions being compared will include antioxidant therapy alone versus antioxidant therapy combined with either SERMs or FSH. This is not a retrospective study, and no data will be collected from pre-existing records.

Sample Size and Justification

Based on prior studies showing an expected 50% increase in sperm concentration between treatment groups, and assuming a moderate effect size ($f = 0.25$), with $\alpha = 0.05$ and 80% power, we calculate that 98 patients per group are needed. To account for an anticipated 10% dropout rate, we will enroll 110 patients per group, totaling 390 participants across three arms.

based on 50% relative increase of sperm concentration observed in the intervention groups vs increase observed in the control

The sample size was calculated considering following assumptions:

- Study design: Three-arm, parallel-group, randomized clinical trial including one control group and two treatment groups (Treatment A and Treatment B).

- Primary endpoint: Mean sperm concentration (million/mL) from baseline to 6 months)

- Expected group means:
  - Control: 8 million/mL
  - Treatment A: 11 million/mL
  - Treatment B: 11 million/mL
- This corresponds to an expected mean difference of 3 million/mL between each treatment group and the control group, i.e., a 1.5-fold increase in sperm concentration.

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- Common standard deviation (SD): 10 million/mL
- Allocation ratio: 1:1:1 (equal randomization across the three groups)
- Stratification factor: Baseline sperm concentration (< 8 vs ≥ 8 million/mL)
- Type I error (α): 0.05 (two-sided)
- Power (1 – β): 90%
- Anticipated dropout rate: 10%

Based on a two-sample comparison between each treatment group and the control group ($\Delta = 3$, $\sigma = 10$, $\alpha = 0.05$ two-sided, power = 90%), the required number of evaluable participants per group is approximately 117.

Accounting for a 10% dropout rate, around 130 participants per group should be randomized.
Therefore, a total of 390 participants (130 per group) will be enrolled in a 1:1:1 ratio.

Blinding Procedure

This will be an **open-label study**, as blinding is not feasible due to the nature of the interventions (oral vs. injectable therapies). However, laboratory personnel conducting semen analyses and statistical analysts will remain blinded to group allocation to minimize assessment bias.

Details of Interventions

Eligible participants will be randomized into one of the three groups:

- **Group A:** Will receive a combination of antioxidants (e.g., Vitamin C 1000 mg/day, Vitamin E 400 IU/day, L. Carnitine and Zinc 25 mg/day) for 6 months.
- **Group B:** Will receive the same antioxidant regimen plus **Clomiphene Citrate 50 mg orally every other day** for 6 months.
- **Group C:** Will receive the same antioxidant regimen plus **FSH 150 IU administered subcutaneously three times weekly** for 6 months.

All interventions will begin immediately after randomization. Medication administration training will be provided for those receiving injectable FSH.

Data and Sample Collection

We will collect the following data at three key time points: baseline (pre-treatment), 3 months, and 6 months:

- **Two Semen analysis** (semen volume, sperm concentration, motility and morphology) – primary outcome
- **Advanced sperm function tests** (SDF and ORP) – secondary outcomes
- **Hormonal profile** (FSH, LH, testosterone, estradiol) – secondary outcomes

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- **Adverse events and treatment adherence reports** – for safety monitoring

Semen samples will be collected after 2–7 days of abstinence, and all laboratory testing will follow WHO 6th edition semen analysis standards. Blood samples will be drawn at fasting state in the morning.

Risk-Benefit Consideration

The risks to participants will include potential side effects of Clomiphene Citrate (e.g., mood changes, visual disturbances) and FSH (e.g., injection-site reactions). These risks are considered low and will be mitigated through clinical monitoring. Participants will have access to medical support throughout the study.

The **anticipated benefits** include potential improvement in fertility outcomes and contribution to the development of evidence-based guidelines for treating idiopathic male infertility. Given the potential to improve clinical care and reproductive success rates, the risks are justified by the expected benefits.

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7. Study Population and Study Setting/ Location

Study Population

The study population will consist of **male patients aged 21–50 years** who present with **idiopathic oligoasthenoteratozoospermia (OAT)** at the **Urology clinics** of Hamad Medical Corporation (HMC). All participants will have **normogonadotropic hormonal profiles**, including **follicle-stimulating hormone (FSH) <8.6 IU/L** and **normal serum testosterone levels**, with no identifiable cause of infertility based on standard diagnostic workup.

We will define the population using the following criteria:

Inclusion Criteria

- Male patients aged 21 to 50 years
- Diagnosed with idiopathic OAT, defined as abnormal sperm concentration, motility, and/or morphology, with no known cause (i.e., normal physical exam, hormonal profile, scrotal ultrasound, and genetic workup)
- Sperm concentration ≥ 2 million/mL on at least one semen analysis
- Normal baseline hormonal profile:
    - FSH <8.0 IU/L (HMC normal reference range 1.5–12.4 IU/L)
    - Normal serum testosterone (10.4ng\dl) (HMC normal reference range 10.4–30.0 nmol/L)
- Normal karyotype and absence of Y-chromosome microdeletions
- No varicocele or clinically insignificant Grade I varicocele only
- Ability and willingness to comply with study protocol and follow-up schedule
- Provided written informed consent

Exclusion Criteria

- History of cryptorchidism, orchidopexy, testicular torsion, or testicular trauma
- History of chemotherapy, radiotherapy, or testicular surgery
- Presence of azoospermia or severe oligospermia (less than 2 million/mL)
- Known genetic abnormalities (e.g., Klinefelter syndrome, Y-chromosome microdeletions)
- Prior hormonal treatment for infertility within the last 6 months (i.e.; any hormonal therapy intended to influence spermatogenesis or the hypothalamic–pituitary–gonadal axis within the 6 months prior to enrollment, including but not limited to gonadotropins FSH or HCG, selective estrogen receptor modulators (e.g., clomiphene citrate, tamoxifen), aromatase inhibitors (e.g., anastrozole, letrozole), testosterone or other androgen therapy, GnRH agonists or antagonists, and anti-androgen or other hormonal agents affecting fertility).
- Significant medical comorbidities (e.g., liver failure, renal disease, uncontrolled diabetes)
- Current use of medications known to affect spermatogenesis (e.g., testosterone, anabolic steroids)
- History of varicocelectomy within the past year
- Pyospermia

Study Setting / Facilities and Departments

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The study will take place at **Ambulatory Care Center (ACC)**, specifically within the following facilities and departments:

- **Ambulatory Care Center (ACC)** – primary study site
- **Male Infertility Outpatient clinic** – patient recruitment, clinical assessment, and hormonal monitoring
- **Andrology lab (ACC)** – coordination of semen analyses
- **Department of Pathology & Laboratory Medicine (ACC Lab)** – hormonal assays and blood sample processing
- **Clinical Pharmacy Services (ACC Pharmacy)** – dispensing of antioxidants, SERMs, and FSH, and patient counseling on drug use

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8. Study procedures

This study will follow a clearly defined sequence of procedures including **screening, baseline evaluation, randomization, treatment, follow-up visits, and final evaluation**. The clinical and laboratory operations will be centralized at the **Ambulatory Care Center (ACC)**.

Screening Phase

Eligible patients presenting to the Urology clinics will be screened based on clinical history, physical examination, and laboratory investigations. Screening will include:

- Semen analysis
- Hormonal profile: FSH, LH, testosterone, estradiol
- Karyotype and Y-chromosome microdeletion testing
- Scrotal ultrasound (if not already completed within past 6 months)
- Comprehensive medical and fertility history

Patients meeting the inclusion criteria will be approached for written informed consent.

Baseline Assessment (Visit 1)

Once enrolled, participants will undergo:

- Repeat semen analysis (to confirm eligibility)
- Blood tests: FSH, LH, testosterone, estradiol
- Physical examination and BMI measurement

Randomization

Participants will be randomized in a 1:1:1 ratio using a computer-generated block randomization list to one of three treatment arms:

- Group A: Antioxidants only
- Group B: Antioxidants + Clomiphene Citrate
- Group C: Antioxidants + FSH injections

Treatment Phase (6 months)

All participants will begin their allocated treatment regimen immediately after randomization. Medications will be dispensed monthly, and adherence will be monitored through pill counts and injection diaries.

Follow-up Visits

Participants will attend scheduled follow-up visits at:

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- **Visit 2 (Month 3)**:
  - Semen analysis
  - Hormonal profile
  - Review of medication adherence
  - Monitoring of adverse effects
- **Visit 3 (Month 6 – Final Visit)**:
  - Semen analysis
  - Hormonal profile
  - Final review of adverse effects and treatment experience

All semen analyses and hormonal tests will be repeated under standardized conditions.

Please provide an outline and describe in detail the processes and operations of the study, including logistics

8.1 Study Duration and Timelines

The study is expected to span **24 months**, from recruitment to final analysis.

Study Timelines

- **Months 0–3**: Ethics approval, study registration, investigator meetings
- **Months 3–15**: Participant screening, enrollment, and randomization (rolling basis)
- **Months 4–21**: Treatment and follow-up visits
- **Months 21–22**: Data cleaning and validation
- **Months 23–24**: Statistical analysis and final reporting

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- Informed Consent

This is a **prospective clinical study** involving direct participant recruitment. The informed consent process will adhere strictly to ethical research standards as per HMC and international guidelines.

a) How people will be NOTIFIED OR APPROACHED to consider being a research subject in this study

Potential participants will be notified during routine or follow-up visits at the **Urology Clinics at the Ambulatory Care Center (ACC)**. Patients who meet preliminary criteria based on their medical history and initial semen analysis will be **identified by their treating consultant**. If deemed potentially eligible, the treating physician will briefly introduce the study and refer the patient to the designated study team.

No advertising or public recruitment strategies will be used.

b) Consent Process Procedures (When, Where, How, by Whom)

- **Who**: Pi and co-investigators will obtain informed consent. All team members involved in consent will be GCP-certified.
- **Where**: The consent process will take place in a **private consultation room at the ACC clinics**.
- **When**: Consent will be sought **after screening eligibility is preliminarily confirmed** and before any study-specific procedures are conducted.
- **How**: Participants will receive a verbal and written explanation of the study objectives, procedures, potential risks and benefits, confidentiality measures, and the voluntary nature of participation. The participant will be encouraged to ask questions and will be given adequate time to consider enrollment before signing.

c) Time Given to Decide and Duration of Participation

- Participants will be given **a minimum of 48 hours** to consider their decision before signing the consent form.
- Once enrolled, participants will be followed for a total of **6 months** during the treatment and follow-up period.

d) Screening Process and Planned Screening Number

- Potential participants will undergo initial review of medical records, semen analysis, and hormonal profile as part of routine care.
- Those meeting preliminary criteria will undergo formal screening, which includes:
  - Confirmatory semen analysis
  - Blood tests (FSH, LH, testosterone, estradiol)
  - Genetic testing (karyotyping and Y-chromosome microdeletion screening)
  - Clinical assessment and medical history review

We anticipate screening approximately **450–500 patients** to enroll **390 eligible participants**, accounting for screen failures.

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e) Enrollment Procedures

- Once screening confirms eligibility and the patient has signed the consent form, they will be officially enrolled and assigned a **unique study ID**.
- Participants will then undergo **baseline evaluations** and will be randomized into one of the three intervention arms.
- The **study pharmacist** will initiate medication dispensing, and participants will receive medication counseling and follow-up schedules.

f) Participant Compensation

- **No monetary compensation** will be provided for participation.
- However, all **investigational treatments, laboratory tests, and follow-up visits will be provided as per the policy of HMC** to the participant.
    - Subject Withdrawal/ Withdrawal of Consent

Withdrawal by the Participant

Participants will be informed that **they may voluntarily withdraw from the study at any time** without providing a reason and without any impact on their current or future medical care at HMC. If a participant chooses to withdraw:

- All study-related procedures will cease immediately.
- The participant will be asked if they consent to allow **data already collected** to continue being used in the study's final analysis.
- If the participant **withdraws consent for data usage**, their identifiable data and biospecimens will be **permanently deleted or destroyed**, in accordance with HMC ethical standards.
- No further data will be collected from that participant.
- Patient will continue to receive the same standard medical care
- Patient relationship with your doctors and the hospital will not be affected
- There will be no penalty or loss of benefits

Participation is voluntary

Withdrawal by the Principal Investigator (PI)

The Principal Investigator (PI) may decide to withdraw a participant from the study for the following reasons:

- Development of a medical condition or adverse event that makes continued participation unsafe
- Non-compliance with the study protocol (e.g., repeated missed visits or refusal to take medication)
- Participant becomes lost to follow-up despite multiple documented attempts to contact
- Administrative or regulatory reasons (e.g., study suspension or termination)

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In such cases:

- The reason for withdrawal will be documented in the case report form (CRF)
- The data collected up to the point of withdrawal will be retained for analysis unless the participant requests otherwise
- No additional data will be collected following withdrawal

Participants will be offered appropriate medical advice or care if their withdrawal is due to an adverse effect or clinical concern.

8.2 Risk

The anticipated risks for study participants are minimal and primarily related to medication use which is same option of treatment to those to participate in the study with same diagnosis (Normogonadotropic Idiopathic OAT) . These include:

- **Clomiphene Citrate (SERMs):** May cause mild side effects such as mood swings, visual disturbances, gynecomastia, or headache. These effects are generally reversible and rare.
- **FSH Injections:** May cause local injection site reactions (e.g., redness, swelling), occasional gynecomastia, or testicular discomfort. Systemic effects are rare.
- **Blood Draws:** Temporary discomfort, bruising, or mild bleeding may occur.

No procedures in the study are considered high-risk. No procedures involve invasive sampling beyond routine venipuncture. No procedure is expected to cause illness, injury, or death. Adverse events will be monitored and managed promptly.

8.3 Bio-Specimens & Sample Collection

Samples Collected:

- Blood samples (for FSH, LH, testosterone, estradiol)
- Semen samples (for WHO semen analysis)

Use and Storage:
Samples will be used strictly for the proposed research. **No long-term storage** is planned unless additional consent is obtained. All samples will be destroyed following completion of analysis.

Future Use:
No specimens will be used for future research outside the current study scope.

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8.4 Admission, transfer, discharge

This study is conducted in the **ambulatory setting only**. No hospital admission, transfer, or discharge processes apply. All visits will occur at the outpatient clinics of the Ambulatory Care Center (ACC), and documentation will be maintained in research-specific case report forms (CRFs).

8.5 Outcomes

Primary Outcome:

- Change in semen parameters (concentration, motility, morphology) from baseline to 6 months.

Secondary Outcomes:

- Hormonal profile changes (FSH, LH, testosterone, estradiol)
- SDF & ORP
- Treatment tolerability and adverse events
- Medication adherence

8.6 Data Collection, Management & Confidentiality

a) Data Collection Methods

- ☑ Study Forms
- ☑ Study Database
- Data will be **de-identified** using a participant study ID. Names and HMC numbers will be replaced by codes, and DOB will be replaced by age.
- A **linking sheet** (containing the code and identifiers) will be stored in a **locked cabinet in the PI's office in Ambulatory Care Center – Urology Department** and destroyed at study completion.
- All data will be retained for **5 years** post-study completion.

b) Storage Location

- Data will be physically stored in the **Urology Department at ACC** (locked cabinet) and electronically on a **password-protected, HMC-Owned secured network drive** with access restricted to the study team.

c) Data Access Control

- The **Principal Investigator** will control all data access.

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d) Who Has Access

- Only the **authorized study team** (PI, Co-investigators) will have access to de-identified data.

e) How Data Is Accessed

- Through **encrypted HMC-owned approved systems** and physical files stored in secure cabinets.

f) External Sharing of Identifiers

- No data will be shared outside HMC.

9. Study monitoring/Data Safety Monitoring Board (DSMB)

An internal monitoring plan will be implemented.

- The study team will meet **monthly** to review adverse events and protocol compliance.
- An **independent safety monitor** (senior clinician not part of the research team) will review safety data **quarterly**.
- Serious adverse events (SAEs) will be reported to the HMC Medical Research Center and IRB within **24–72 hours**.

Stopping criteria include:

- Severe adverse reactions affecting >5% of participants
- Evidence of significant harm outweighing benefits in any arm
- DSMB recommendation to terminate

10. Statistical Consideration and Data Analysis

 Primary analysis:

The data's distribution will be assessed using the Shapiro-wilk test. Numerical values will be presented as mean +/- SD or median [IQR], while categorical values as number (%). Between group mean comparisons will be conducted using Anova or Mann-Whitney tests, while the chi-Squared test will be used for categorical variables. Changes in semen parameters, advanced sperm functions, and hormone profile will be compared with repeated measures Anova. A p value of <0.05 will be considered statistically significant. The SPSS software, version 25.0, will be used to perform the statistical analysis.

 Secondary outcomes will be analyzed using paired t-tests (within groups), chi-square or Fisher's exact test (and logistic regression (if needed).

 Software: SPSS or R

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 Analysis will be performed by: A designated **biostatistician affiliated with HMC Research Support Services**.

11. Adverse Event Reporting

 Primary analysis will compare changes in semen parameters using **one-way ANOVA** with post-hoc Tukey correction.

 Secondary outcomes will be analyzed using paired t-tests (within groups), chi-square or Fisher's exact test and logistic regression (if needed).

 Software: SPSS or R

 Analysis will be performed by: A designated **biostatistician affiliated with HMC Research Support Services**.

12. Ethical Consideration

The study will be conducted in full conformance with principles of the "Declaration of Helsinki", Good Clinical Practice (GCP) and within the laws and regulations of MOPH in Qatar. Approval of the Institutional Review Board (IRB) of Hamad Medical Corporation (HMC) will be taken to perform the study and the study will not be conducted before approval of MRC

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13. Sponsor, Funding & Collaborator Information

□ Sponsor: Hamad Medical Corporation (HMC)

□ Funding **Requested**: No

□ External **Funding**: No

14. Dissemination of Results and Publication policy

□ Results will be submitted for presentation at the:

- **Arab Association of Urology Congress**
- **ASRM**
- **ESHRE Annual Conference**

□ Manuscript will be finalized within **6 months post-study completion** and submitted to a peer-reviewed

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26. Appendices

Please list in this section all intended forms or resources that will be used in the conduct of research to collect data, interview people, recruit participants.

- Questionnaire
- Consent

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