**Cover page**

**Official Title:**

Effect of Albumin and Furosemide Combination for Prevention of Severe Ovarian Hyperstimulation Syndrome in Hyper-Responders Undergoing Intracytoplasmic Sperm Injection Cycles: A Randomized Controlled Trial

**NCT Number:**

Not yet assigned

**Document Type:**

Study Protocol

**Version:**
Version 1.0

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## Study protocol

### Background and Rationale:

Ovarian Hyperstimulation Syndrome (OHSS) is a potentially serious iatrogenic complication of controlled ovarian stimulation during assisted reproductive techniques, particularly in patients undergoing intracytoplasmic sperm injection (ICSI). It is characterized by increased vascular permeability, fluid shift into third spaces, hemoconcentration, and in severe cases, thromboembolic events and organ dysfunction.

Hyper-responders, especially those with elevated serum estradiol levels and high oocyte yield, are at increased risk of developing OHSS. Preventive strategies remain critical in minimizing morbidity.

Human albumin has been proposed to reduce the incidence of OHSS by increasing plasma oncotic pressure and reducing fluid extravasation. Furosemide, a loop diuretic, promotes diuresis and may help prevent fluid accumulation. The combination of both agents may provide a synergistic effect in reducing OHSS severity.

### Study Objectives:

- **Primary Objective:**

To evaluate the effectiveness of combined albumin and furosemide in preventing moderate and severe OHSS in hyper-responders undergoing ICSI cycles.

- **Secondary Objectives**

- To assess incidence of mild OHSS
- To evaluate changes in ovarian volume
- To measure serum estradiol levels on trigger day
- To assess hematocrit changes post oocyte retrieval
- To evaluate endometrial thickness and vascularity
- To determine hospital admission rate
- To assess clinical pregnancy rate

### Study Design:

- Prospective randomized controlled trial
- Parallel-group design
- Single-blinded (outcome assessor)
- Allocation ratio 1:1

### Study Setting

The study was conducted at the Assisted Reproduction Unit, at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies.

**Study Population:**

- **Inclusion Criteria**

- Women aged 20–40 years
- Undergoing ICSI cycles
- Hyper-responders (≥15 oocytes retrieved or estradiol >3000 pg/mL)
- At risk for OHSS
- Provide written informed consent

- **Exclusion Criteria**

- Severe systemic disease (renal, hepatic, cardiovascular)
- Uncontrolled diabetes mellitus
- Known hypersensitivity to albumin or furosemide
- Autoimmune disorders
- Patients planned for freeze-all strategy

**Randomization and Blinding:**

Participants were randomly allocated into two groups using a computer-generated randomization sequence. Allocation concealment were ensured using sealed opaque envelopes. Outcome assessors were blinded to group allocation.

**Interventions:**

**Intervention Group**

- Intravenous Human Albumin (20%, 100 ml) administered after oocyte retrieval
- Intravenous Furosemide (20 mg) administered post-retrieval
- Standard luteal phase support

**Control Group:**

- Standard luteal phase support only

**Outcome Measures:**

**Primary Outcome:**

- Incidence of moderate and severe OHSS within 14 days post oocyte retrieval

**Secondary Outcomes:**

- Incidence of mild OHSS
- Ovarian volume changes
- Serum estradiol levels on trigger day
- Hematocrit levels post retrieval

- Endometrial thickness and vascularity indices
- Hospital admission rate
- Clinical pregnancy rate

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**Statistical Analysis Plan (SAP)**

- Data were analyzed using SPSS version 27
- Continuous variables were expressed as mean ± standard deviation
- Categorical variables were expressed as frequency and percentage

**Statistical Tests:**

- Independent t-test for continuous variables
- Chi-square test for categorical variables
- Fisher's exact test when appropriate

**Significance Level:**

- P-value < 0.05 considered statistically significant

**Sample Size**

Sample size were calculated based on expected reduction in OHSS incidence, with power of 80% and significance level of 5%.

**Ethical Considerations**

- Ethical approval were obtained from the Institutional Review Board
- Written informed consent were obtained from all participants
- The study followed the principles of the Declaration of Helsinki

**Study Timeline:**

- Recruitment period: 2 years
- Follow-up: 14 days post oocyte retrieval

**Data Management:**

All patient data were anonymized and stored securely. Only authorized personnel will have access.

**Dissemination of Results**

Results will be published in peer-reviewed journals and presented at scientific conferences.

## *INFORMED CONSENT FORM*

*Study Title*

*Effect of Albumin and Furosemide Combination for Prevention of Ovarian Hyperstimulation Syndrome in Hyper-Responders Undergoing Intracytoplasmic Sperm Injection Cycles: A Randomized Controlled Trial*

*Investigator Information*


*• Principal Investigator: Dr. Mufeda Ali Jwad*

*• Institution: high institute for infertility diagnosis and assisted reproductive technologies*

*• Contact Number: 07822651332*

*• Email: dr.mufedaali@st.nahrainuniv.edu.iq*


*Invitation to Participate*

*You are invited to participate in a research study because you are undergoing intracytoplasmic sperm injection (ICSI) treatment and are at increased risk of developing ovarian hyperstimulation syndrome (OHSS). Before you decide, it is important to understand why the research is being done and what it will involve.*

*Purpose of the Study*

*The purpose of this study is to evaluate whether the combination of albumin and furosemide can reduce the risk and severity of ovarian hyperstimulation syndrome (OHSS) in women undergoing ICSI treatment.*

*Study Procedures*

*If you agree to participate:*

*• You will undergo standard ICSI treatment.*

*• You will be randomly assigned into one of two groups:*

*o Intervention Group: You will receive intravenous albumin and furosemide after oocyte retrieval.*

*o Control Group: You will receive standard care without these medications.*

*• You will be monitored for signs and symptoms of OHSS for approximately 14 days after oocyte retrieval.*

*• Blood tests and ultrasound examinations will be performed as part of routine care.*

*Risks and Discomforts*

*• Albumin and furosemide are generally safe but may cause:*

*o Allergic reactions (rare)*

*o Fluid imbalance*

*o Electrolyte disturbances*

*• There is a risk of developing OHSS as part of ovarian stimulation.*

*• All procedures will be conducted under medical supervision to minimize risks.*

*Benefits*

*• You may benefit from a reduced risk of OHSS.*

*• Your participation may help improve future treatment strategies for patients undergoing ICSI.*

*Voluntary Participation*

*Your participation is entirely voluntary. You may refuse to participate or withdraw at any time without affecting your medical care.*

*Confidentiality*

*All personal and medical information will be kept confidential. Your data will be coded and stored securely. Results may be published, but your identity will not be revealed.*

*Compensation*

*There is no financial compensation for participation. No additional costs will be imposed on you beyond standard treatment.*

*Alternatives*

*You may choose not to participate and still receive standard ICSI treatment without any penalty.*

*Contact for Questions*

*If you have any questions about the study, please contact:*

- *Dr. Mufeda Ali Jwad*
- *Phone: 0782265332*
- *Email: dr.mufedaali@st.nahrainuniv.edu.iq*
- *For ethical concerns, you may contact: Dr.Ula Muhammad Alkwas*

*Consent Statement*

*I have read and understood the information provided above. I have had the opportunity to ask questions and received satisfactory answers. I voluntarily agree to participate in this study.*

*Participant Information*

- *Name:* _____
- *Signature:* _____
- *Date:* _____

*Investigator Statement*

*I confirm that I have explained the nature and purpose of the study to the participant.*

- *Investigator Name:* _____
- *Signature:* _____
- *Date:* _____