Estimating the Incidence and Severity of Ovarian Hyperstimulation Syndrome (OHSS) After Solitary Gonadotropin-Releasing Hormone Agonist (GnRH-a) Trigger

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1) Introduction

Assisted reproductive technology (ART), particularly in vitro fertilization (IVF), relies on an ovulatory trigger to achieve oocyte maturation. Traditionally, a bolus of human chorionic gonadotropin (hCG) has been used as the gold standard for this purpose. However, hCG triggers are associated with an increased risk of ovarian hyperstimulation syndrome (OHSS), one of the most serious complications of IVF. Recent evidence indicates that gonadotropin-releasing hormone agonist (GnRH-a) triggers are superior to hCG in reducing OHSS risk. Nevertheless, the use of solitary GnRH-a triggers does not fully eliminate the risk, highlighting the need to better understand their incidence and severity.

2) Objectives and Goals

- Estimate the incidence and severity of OHSS after GnRH-a trigger in ART.
- Identify patient characteristics and ovarian stimulation parameters that are associated with OHSS after GnRH-a trigger in ART.

3) Current Progress and Milestones Achieved

- **Data Collection Initiated:** Gathered clinical records of **252 patients** undergoing ART cycles at Mount Sinai Fertility.
- **Variable Identification:** Established key data points for analysis, including patient demographics, ovarian reserve markers (AMH, AFC), stimulation details, trigger type, and OHSS outcomes.
- **Preliminary Cohort Formation:** Began structuring a retrospective dataset spanning January 2020–December 2024.

4) Methodology and Approach

This retrospective cohort study was conducted using clinical data from Mount Sinai Fertility (MSF). All patients who underwent assisted reproductive technology (ART) including in vitro fertilization (IVF), oocyte cryopreservation, or embryo cryopreservation between January 1, 2020, and December 20, 2024, were assessed for inclusion. Data collected included type of stimulation protocol, medication used for controlled ovarian stimulation (COS), trigger type, blind trigger (yes/no), number

of days of gonadotropin administration, total dose of follicle-stimulating hormone (FSH, IU), and OHSS classification (no OHSS, mild, moderate, or severe).

Patients were stratified into two groups based on the presence or absence of ovarian hyperstimulation syndrome (OHSS) following a gonadotropin-releasing hormone agonist (GnRH-a) trigger.

Comparisons of ART parameters between groups were performed, and variables meeting statistical significance were further analysed using machine learning models and receiver operating characteristic (ROC) curves to assess their association with OHSS. The incidence of OHSS was calculated as:

$$Incidence\ of\ OHSS = \frac{Number\ of\ patients\ with\ OHSS}{Number\ of\ patients\ undergoing\ ovarian\ retrieval\ for\ ART\ during\ the\ study\ period} \times 100$$

Severity was classified according to clinical symptoms and laboratory findings. Additionally, keyword extraction and term frequency–inverse document frequency (TF-IDF) vectorization were applied to transform text data into numerical features, and SHapley Additive exPlanations (SHAP) values were used to identify the most influential predictors. Data collection is currently ongoing, and upon completion, a machine learning model will be developed to predict OHSS risk using the finalized dataset.

5) Preliminary Results

A total of 252 patients were included – 200 hCG trigger and 52 GnRH-a trigger. The overall incidence of severe OHSS was 0.8% - 1 in each group.

6) Challenges and obstacles encountered

- **Data Collection Limitations:** Patient recruitment and record retrieval are ongoing, with only 252 patients collected so far; reaching the full cohort requires additional time and resources.

- **Data Completeness and Consistency:** Some patient records contain missing or incomplete information (e.g., hormone levels, medication details), requiring manual verification and cleaning.
- **Model Development Deferred:** Predictive modeling is currently on hold until the dataset is complete and validated, delaying the ability to generate early results.

7) Next steps and future work

- **Complete Data Collection:** Expand the cohort to include all eligible ART cycles (Jan 2020–Dec 2024) to strengthen statistical power.
- **Incidence & Severity Analysis:** Finalize OHSS incidence rates and stratify outcomes by severity (mild, moderate, severe).
- **Model Development:** Build predictive models (e.g., logistic regression, machine learning with SHAP interpretability) to identify key risk factors for OHSS after GnRH-a triggers.

8) Conclusion

In this preliminary analysis, OHSS occurred across both GnRH-a and hCG trigger groups. GnRH-a triggers demonstrated a relatively higher proportion of mild OHSS cases, underscoring that the risk is not completely eliminated with this approach. These findings highlight the need for individualized stimulation protocols and careful patient monitoring, regardless of trigger type. Completion of data collection and subsequent machine learning modelling will allow for a more comprehensive risk prediction framework to optimize safety in ART cycles.