**Introduction**

**Timing of the trigger**

The temporal aspect of the trigger constitutes a pivotal factor in determining the efficacy of an assisted reproductive technology (ART) cycle. It is meticulously optimized to enhance the retrieval of mature and developmentally proficient oocytes from the existing follicular cohort (1).

An efficacious trigger must guarantee adequate LH exposure to promote meiotic resumption, cytoplasmic maturation, and the attainment of oocyte competence while preserving alignment with endometrial receptivity (2-4).

Optimal triggering is characterized by a substantial yield of mature oocytes accompanied by minimal or no complications (5).

The timing of the trigger in intracytoplasmic sperm injection (ICSI) cycles is instrumental in affecting both oocyte competence and endometrial receptivity (6). Numerous factors have been explored to ascertain the optimal timing for trigger administration in ICSI cycles, which include: 1- follicular diameter 2- serum estradiol (E2) and progesterone concentrations, peak E2 levels per follicle 3- and the individual's previous response to controlled ovarian stimulation (COS).

**Timing of the trigger and Follicular Diameter:**

The timing of the trigger has been, for over three decades, contingent upon the presence of at least three follicles with a diameter of 17 mm or greater (7-10). Nonetheless, a universal consensus regarding the minimum follicular size requisite for procuring a competent oocyte remains elusive. The threshold for obtaining a mature M2 oocyte is posited to be 16 mm from one perspective (10), while follicles smaller than 12 mm yield oocytes at various stages of immaturity (8,11,12). Follicles exceeding 22 mm frequently harbor "post-mature" oocytesthat exhibit diminished fertilization rates and compromised developmental competence (10,13).

Empirical studies have indicated that follicles measuring between 16–23 mm at the time of oocyte retrieval demonstrate superior fertilization rates compared to those surpassing 23 mm (9,10). However, the proportion of oocytes with high-quality scores escalates from 55.4% in the 16–23 mm follicle cohort to 64.6% in follicles exceeding 23 mm. Consequently, the recommendations from the European Society of Human Reproduction and Embryology (ESHRE) 2020 regarding the timing of the trigger are articulated as follows: "Most frequently, final oocyte maturation is triggered at sizes of several of the leading follicles between 16–22 mm as data on specific follicle sizes that are most likely to yield a mature oocyte have predominantly been generated on the day of oocyte retrieval, at which point follicles of 16 to 22 mm are perceived to be most likely to yield oocytes." (14)

**Timing of the trigger and E2 and progesterone concentrations**

There exists no discernible correlation between E2 levels at the day of trigger and the outcomes of ICSI. Thus, the ESHRE 2020 guidelines for ovarian stimulation in IVF/ICSI do not advocate for the employment of either serum estradiol level or estradiol/follicle ratio as the exclusive criterion for determining the timing of the trigger in IVF/ICSI cycles (15). In terms of serum progesterone levels, the evidence remains insufficient to endorse the utilization of serum progesterone for ascertaining the timing of trigger administration. Furthermore, there are no unequivocal cut-off values delineating normal and elevated progesterone levels.

**Timing of the trigger and various stimulation protocols**

Postponing the administration of the HCG trigger (by 1–2 days) in agonist ICSI cycles is associated with enhanced oocyte yield, which may consequently exert a favorable influence on both the quantity of embryos produced and the rates of successful pregnancies; nonetheless, this delay could correlate with an elevated frequency of pre-ovulatory progesterone surges. (15,16)

Within the framework of antagonist protocols, it appears that the initiation of oocyte maturation should be executed with greater precision (and typically at an earlier time point) than in agonist cycles; the optimal timing for triggering should occur when a minimum of three follicles have reached a diameter of 17–18 mm (17-21), while the majority of the remaining cohort of follicles should also exhibit a considerable size (≥14 mm), taking into account the requisite serum estradiol level (100–400 pg/mL per oocyte).

**Timing of the trigger and differing ovarian reserves**

Women exhibiting normal ovarian reserve and those classified as poor responders should not be evaluated by the same parameters during ovarian stimulation, as factors such as early follicular recruitment, the rate of follicular development, endometrial receptivity, and the duration of stimulation significantly differ. A judicious duration of FSH stimulation, in conjunction with criteria based on follicular size, as well as serum estradiol and progesterone concentrations, are critical determinants in establishing trigger timing that effectively balances oocyte maturation with endometrial receptivity. In the context of PCOS, whether utilizing a GnRH agonist long protocol or a GnRH antagonist protocol, it is imperative to find an equilibrium between the risk of ovarian hyper-stimulation syndrome (OHSS) and the likelihood of clinical pregnancy when determining the timing of the trigger.

**Timing of the triggers and artificial intelligence**

Recognizing the paramount importance of accurately ascertaining the optimal timing for the trigger, artificial intelligence-driven models are being developed to enhance trigger timing by amalgamating pre-stimulation characteristics with real-time ovarian response metrics, such as follicle count and size, aimed at optimizing oocyte yield and improving procedural efficacy.

Serum estradiol concentrations and three-dimensional assessments of follicular volume via ultrasound have been utilized to ascertain the ideal trigger day and to predict the number of oocytes to be retrieved, with a focus on synchronizing this process with the peak representation of metaphase II (MII) oocytes.

Contemporary predictive models predominantly emphasize the optimization of trigger timing; however, forthcoming advancements are anticipated to incorporate additional variables, including the type and dosage of trigger, in order to further individualize and enhance ovarian stimulation protocols (22,23).

**Objective of the Study**

The objective of this study is to develop a robust predictive model utilizing Meta AI to determine the optimal timing for the administration of the ovulation trigger, with the aim of maximizing both the total number of oocytes retrieved on the day of oocyte pick-up (OPU) and the quantity of mature metaphase II (MII) oocytes. By incorporating a comprehensive set of clinical variables into the AI framework, this study endeavors to generate a decision-support tool that will assist clinicians and patients in making evidence-based decisions regarding the timing of ovulation induction without real-world data. Ultimately, this model aspires to enhance the efficiency and outcomes of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) procedures.

**Methodology**

**Problem Definition**

This study addresses a critical challenge encountered in the context of intracytoplasmic sperm injection (ICSI) - the optimization of ovulation trigger timing. The objective is to develop a predictive model that accurately forecasts the optimal timing for ovulation trigger administration to enhance the outcomes of oocyte retrieval, including maximizing the total number of oocytes and the number of mature metaphase II (MII) oocytes.

**Literature Review**

A comprehensive literature review was conducted to assess existing predictive models and to identify factors influencing the timing of ovulation trigger administration. Relevant studies were systematically reviewed, and data on various predictive factors were extracted. These included patient demographics (age and body mass index [BMI]), ovarian reserve markers (anti-Müllerian hormone [AMH] levels and antral follicle count [AFC]), gonadotropin dosing regimens, ovarian response characteristics, the number of follicles, the size of the leading follicle, stimulation duration, and hormonal parameters such as estradiol and serum progesterone levels.

**Model Selection**

Several machine learning algorithms were considered for model development, including logistic regression, decision trees, random forests, and neural networks. After a careful evaluation of the advantages and limitations of each method, logistic regression was chosen as the initial model due to its simplicity, interpretability, and efficacy in clinical prediction settings.

**Model Development**

The predictive model was developed using Meta AI and logistic regression methodology. This theoretical framework was applied in the absence of real-world patient data, facilitating the construction of a robust predictive tool for ovulation trigger timing. The model incorporated key predictive factors identified during the literature review, including age, BMI, ovarian reserve markers (AMH and AFC), gonadotropin dose, ovarian response, follicular count, the size of the leading follicle, stimulation duration, and hormonal levels (estradiol and progesterone).

**Model Inputs**

The input variables included in the model were:

* Female age
* Body mass index (BMI)
* Anti-Müllerian hormone (AMH) levels
* Antral follicle count (AFC)
* Gonadotropin dosage
* Number of follicles
* Size of the leading follicle
* Duration of ovarian stimulation
* Estradiol levels
* Progesterone levels

**Model Outputs**

The primary output of the predictive model was the estimated optimal day for ovulation trigger administration, aimed at maximizing the total oocyte yield and the number of mature MII oocytes retrieved.

**Model Evaluation**

The performance of the predictive model was evaluated through a series of theoretical scenarios, given the absence of real-world patient data. Model evaluation was based on a range of performance metrics, including accuracy, precision, recall, F1 score, and area under the curve (AUC). These metrics were employed to assess the model's ability to accurately predict the optimal day for ovulation trigger administration, in relation to the outcomes of controlled ovarian stimulation.

**Statistical Analysis**

No statistical analysis was conducted, as the model was developed using a theoretical framework and was not tested on actual patient data. Consequently, the model's evaluation is based on hypothetical data derived from simulated scenarios.

**Model Evaluation Results**

The model's performance was assessed using theoretical scenarios, with the following results presented for key evaluation metrics:

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AI-generated content may be incorrect.

It is important to note that these results are hypothetical and are based on theoretical scenarios, as the model has not been validated with real-world patient data.

**Evaluation Metrics**

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AI-generated content may be incorrect.**Accuracy**: Accuracy represents the proportion of correct predictions made by the model, and is calculated as:

where:

* + TP = True Positives (correctly predicted optimal trigger day)
  + TN = True Negatives (correctly predicted non-optimal trigger day)
  + FP = False Positives (incorrectly predicted optimal trigger day)
  + FN = False Negatives (incorrectly predicted non-optimal trigger day)

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AI-generated content may be incorrect.**Precision**: Precision measures the proportion of true positives out of all positive predictions, and is calculated as:

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AI-generated content may be incorrect.**Recall**: Recall evaluates the proportion of true positives out of all actual optimal trigger days, and is calculated as:

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AI-generated content may be incorrect.**F1 Score**: The F1 score is the harmonic mean of precision and recall, calculated as:

**Area Under the Curve (AUC)**: The AUC is derived from the Receiver Operating Characteristic (ROC) curve, which plots the true positive rate (sensitivity) against the false positive rate (1-specificity) at various thresholds. AUC quantifies the model's ability to distinguish between optimal and non-optimal trigger days, with higher values indicating better discrimination.

**Model Interpretation**

The interpretation of the predictive model's results was conducted, focusing on the estimated optimal day for ovulation trigger administration. Additionally, the relative importance of each predictive factor was analyzed to understand its contribution to the model’s performance. The clinical implications of the model’s predictions were explored, including potential applications in reproductive medicine to enhance decision-making processes related to ovulation timing and optimize IVF and ICSI outcomes.

**Results**

This study demonstrates three distinct approaches for determining the optimal timing of ovulation trigger using Follicle-Based Trigger Models (FBTM). These models integrate multiple parameters, including days of stimulation, estradiol levels, progesterone concentrations, anti-Müllerian hormone (AMH) levels, and antral follicle count (AFC), with the aim of improving the accuracy and timing of ovulation trigger during controlled ovarian hyperstimulation cycles.

The first Follicle-Based Trigger Model (FBTM) is based on the principle that ovulation trigger should be administered when multiple mature follicles are present, defined by the presence of at least two follicles measuring ≥ 18 mm and a leading follicle measuring ≥ 20 mm. The scoring system assigns points based on the number and size of follicles, duration of ovarian stimulation, and hormonal levels. Specifically, patients with fewer than four follicles ≥ 18 mm receive 10 points, those with 4-5 follicles receive 15 points, and those with ≥ 6 follicles are awarded 20 points. The size of the leading follicle is also considered, with 10 points for a lead follicle ≥ 22 mm, 5 points for a follicle measuring 20-21 mm, and 0 points for a lead follicle < 20 mm. Additionally, the duration of ovarian stimulation is evaluated, with 10 points for 8-10 days of stimulation, 5 points for 11-12 days, and 0 points for stimulation lasting ≥ 13 days. Estradiol levels ≥ 1,500 pg/mL contribute 10 points, levels between 1,000 and 1,499 pg/mL provide 5 points, and levels < 1,000 pg/mL result in 0 points. Progesterone levels are categorized as follows: values < 1.5 ng/mL receive 10 points, values between 1.5 and 2.9 ng/mL earn 5 points, and levels ≥ 3 ng/mL contribute 0 points. Based on the cumulative score, the ovulation trigger is administered immediately if the score is ≥ 55, delayed for 12-24 hours if the score is between 45 and 54, and re-evaluated if the score is < 45. While this model provides a comprehensive approach to trigger timing, it remains hypothetical and may require refinement to account for patient-specific characteristics and clinical guidelines.

The second FBTM incorporates AMH and AFC to further refine trigger timing. The model is founded on the same premise that ovulation should be triggered when multiple mature follicles are present, with the leading follicle confirmed to be ≥ 20 mm. The scoring system for follicular development, hormonal levels, and ovarian response is similar to the first model, with additional parameters for AMH and AFC, for the presumption of ovarian reserve and ultimately ovarian response. For AMH, levels ≥ 3 ng/mL indicate a high responder, earning 15 points, while levels between 1.5 and 2.9 ng/mL denote a normal responder, earning 10 points, and levels < 1.5 ng/mL indicate a low responder, awarding 5 points. AFC is also used to categorize patients into presumed low, normal, or high responders, with patients having ≥ 15 follicles receiving 15 points, those with 8-14 follicles receiving 10 points, and those with < 8 follicles receiving 5 points. The total FBTM score, which sums the points across all categories, yields a maximum score of 90 Based on the score, the timing of the ovulation trigger is determined, with scores of ≥ 65 indicating immediate trigger, scores between 55 and 64 suggesting a trigger in 12-24 hours, and scores < 55 necessitating re-evaluation. This revised model is also hypothetical and should be further validated and refined to better reflect patient-specific responses and clinical protocols.

The third model, The **Trigger Day Predictive Score (TDPS)** is a robust and multifaceted model developed to predict the optimal timing for ovulation trigger in assisted reproductive technology (ART) cycles. By incorporating a combination of patient characteristics, ovarian stimulation protocol, and follicular response, the TDPS aims to enhance the precision of timing ovulation, ultimately improving ART outcomes.

**Patient characteristics**, which contribute a total of 20 points in the model, play a crucial role in assessing the individual’s baseline ovarian reserve and general health status. Age is a key factor in predicting ovarian responsiveness, with younger women (≤ 35 years) receiving the highest score of 8 points, reflecting their generally better ovarian reserve and response to stimulation. In contrast, women aged 36-40 years are assigned 5 points, women aged 41-45 years receive 2 points, and women aged ≥ 46 years are awarded 0 points, acknowledging the diminished ovarian reserve and response associated with advancing age. Anti-Müllerian Hormone (AMH), a well-established biomarker of ovarian reserve, is scored based on its level, with values ≥ 5 ng/mL corresponding to the maximum score of 8 points, indicating a higher likelihood of favorable follicular development. AMH levels between 2.5 and 4.9 ng/mL yield 5 points, levels between 1.5 and 2.4 ng/mL result in 2 points, and levels < 1.5 ng/mL contribute 0 points, suggesting poor ovarian reserve and potentially lower follicular response. Body Mass Index (BMI), which is known to influence both ovarian function and ART outcomes, contributes 4 points for patients within the normal BMI range of 18.5-24.9 kg/m². Elevated BMI has been linked to poor ovarian response and lower implantation rates, though the model specifically considers the normal weight range as optimal.

**Stimulation characteristics**, comprising a total of 25 points, reflect the clinical aspects of ovarian stimulation, including the protocol used, gonadotropin dosage, and stimulation duration. The stimulation protocol, which is fundamental in determining the ovarian response, is assigned 8 points for GnRH agonist protocols, widely regarded as the gold standard due to their well-established effectiveness in ART cycles. GnRH antagonist protocols, often used for patients at risk of ovarian hyperstimulation syndrome (OHSS) or with poor ovarian reserve, are assigned 5 points, while other less common protocols receive 2 points. Gonadotropin dosage, which directly influences the number and quality of follicles produced, is classified into low (< 150 IU/day), medium (150-300 IU/day), and high (> 300 IU/day) dosages, with corresponding scores of 8, 5, and 2 points, respectively. Lower gonadotropin doses are generally associated with less ovarian stimulation, while higher doses may increase the risk of OHSS but may be necessary for patients with low ovarian reserve or poor response to initial stimulation. The duration of ovarian stimulation is also critical, with shorter stimulation regimens (less than 8 days) earning 4 points, reflecting the potential for quicker follicular maturation and earlier ovulation. Medium and long stimulation durations (8-12 days and > 12 days, respectively) are associated with a slower follicular growth rate and a lower risk of premature luteinization, thus contributing fewer points to the overall score.

**Follicular response**, the most influential section of the TDPS model, contributes 35 points and reflects the actual ovarian response to stimulation. The number and size of follicles are considered first, with a higher number of mature follicles (≥ 17 mm) being associated with better chances of successful ovulation and fertilization. Patients with ≥ 3 follicles ≥ 17 mm are awarded the maximum 20 points, indicating optimal follicular development, while those with 2 follicles ≥ 17 mm receive 15 points, and those with 1 follicle ≥ 17 mm are assigned 10 points. This parameter is critical for predicting the likelihood of successful egg retrieval and fertilization. Estradiol levels, which correlate with the degree of follicular development and the number of mature eggs, are categorized into three ranges: levels ≥ 2,000 pg/mL contribute 10 points, suggesting a high level of follicular maturation and readiness for ovulation; levels between 1,000 and 1,999 pg/mL yield 5 points, indicating moderate follicular development; and levels < 1,000 pg/mL result in 1 point, suggesting insufficient follicular growth. Finally, follicular growth rate, which is directly linked to the pace at which follicles mature during stimulation, is scored based on the rate of increase in follicle size per day. Fast follicular growth (> 2 mm/day) earns 5 points, indicating rapid and consistent maturation, while medium growth (1-2 mm/day) and slow growth (< 1 mm/day) are awarded 3 and 1 point(s), respectively, reflecting slower follicular development and a potentially delayed response to stimulation.

The total score, which ranges from 0 to 80 points, is the sum of the scores from each of the three categories. This score is then used to predict the optimal timing for ovulation trigger, with the following thresholds:

* A score of **75-80 points** predicts ovulation trigger on **LMP + 10-11 days**, indicating a fast ovarian response and ideal follicular maturation.
* A score of **70-74 points** suggests trigger on **LMP + 11-12 days**, reflecting a well-developed ovarian response but with slight variation in timing.
* A score of **65-69 points** corresponds to trigger on **LMP + 12-13 days**, representing a moderate ovarian response.
* A score of **60-64 points** predicts trigger on **LMP + 13-14 days**, reflecting a more prolonged response, potentially requiring closer monitoring.
* A score of **< 60 points** suggests trigger on **LMP + 14-15 days** or the consideration of alternative strategies, such as adjusting the stimulation protocol or considering egg retrieval timing adjustments.

**Discussion**

It is important to note that this section deviates from the conventional approach typically found in research papers, where the collection and analysis of real-world data are central components. In contrast, the models presented in this study was developed within a theoretical framework, with no real-world patient data utilized.

This study serves as a hypothetical example, illustrating the process of model development in reproductive medicine. The actual creation and validation of a predictive model would necessitate access to real-world clinical data, as well as specialized expertise in both machine learning and reproductive medicine. Consequently, while this theoretical model serves as a conceptual foundation, the practical implementation and refinement of such models would require empirical data to ensure their accuracy and applicability in clinical practice.

**Limitations**

The limitations of the predictive model were carefully considered, including the absence of real-world validation, which restricts its generalizability and applicability to clinical practice. Additionally, the potential for bias in the model's predictions, arising from the reliance on a theoretical framework rather than empirical data, must be acknowledged. These factors highlight the need for further validation and refinement to enhance the model’s accuracy and clinical utility.

**Future directions**

Future research should focus on the collection and analysis of real-world clinical data to rigorously validate and refine the predictive model. Additionally, further investigation into alternative machine learning algorithms and advanced computational techniques may provide opportunities for enhancing the model’s accuracy and robustness. Expanding these efforts will be crucial for ensuring the model's clinical relevance and effectiveness in guiding ovulation trigger decisions.

**Conclusion**

While the three models presented herein offer valuable theoretical frameworks for predicting the optimal timing of ovulation trigger administration, based on factors such as follicular development, hormonal profiles, and patient-specific characteristics, they remain hypothetical and necessitate further validation and refinement. To enhance the accuracy and clinical applicability of these predictive models, it is imperative to incorporate individualized patient parameters, tailored stimulation protocols, and clinic-specific guidelines. Such integrations will be crucial for optimizing the utility of these models in clinical decision-making and improving the outcomes of assisted reproductive technologies.

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