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Prediction of ovarian hyperstimulation syndrome in women undergoing *in vitro* fertilization: A systematic review

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Abstract

Background: Ovarian hyperstimulation syndrome (OHSS) is a significant complication of controlled ovarian stimulation in assisted reproductive technologies (ART). Identifying predictors of OHSS is important to optimize patient outcomes and prevent severe complications. This systematic review aimed to discuss evidence on predictive markers of OHSS in women undergoing *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycles.

Methods: Following the PRISMA guidelines, electronic searches conducted in PubMed, Scopus, Web of Science, and Google Scholar databases. Keywords related to OHSS prediction and IVF were used, restricted to English-language full-text articles published between 2009 and 2024. Eligible studies included original prospective, retrospective, observational, or cohort studies investigating predictors of OHSS. Twelve studies were included in the qualitative synthesis.

Results: Antral follicle count (AFC), anti-Müllerian hormone (AMH) levels, serum estradiol (E2) concentrations on the day of hCG administration, number of follicles, and number of retrieved oocytes emerged as the most evaluated predictors. High AFC, elevated AMH, and increased E2 levels were associated with development of OHSS. Several studies developed predictive models, including nomograms, with good discriminatory performance (AUC 0.70–0.85). Intrafollicular melatonin concentrations and coagulation factors were also studied.

Conclusion: AFC, AMH, and E2 levels are reliable predictors of OHSS risk in IVF/ICSI cycles. Integrating traditional markers with emerging predictive tools allow earlier identification of high-risk patients, and enable stimulation protocols and improved clinical outcomes.

Keywords: Ovarian hyperstimulation syndrome; OHSS prediction; IVF; Antral follicle count Anti-Müllerian hormone; Assisted reproductive technologies

1. Introduction

Ovarian hyperstimulation syndrome (OHSS) is iatrogenic complication of controlled ovarian stimulation (COS) in assisted reproductive technologies (ART), mainly *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI)

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(1). It is characterized by increased vascular permeability, leading to fluid shifts into the third space and associated with morbidity, and in severe cases, mortality (2). The pathophysiology of OHSS is complex and driven by the upregulation of vascular endothelial growth factor (VEGF) in the ovaries, resulting in capillary leakage (3).

The incidence of OHSS differ depending on patient populations and stimulation protocols. Mild to moderate OHSS occurs in 20–33% of IVF cycles, and severe OHSS is reported in 0.1–2% of cycles (2). Including the introduction of GnRH antagonist cycles and safer ovulation trigger alternatives, OHSS is a major concern in ART programs (4).

Identifying patients at increased risk is important to prevent the occurrence of OHSS. Several predictors have been initiated, with antral follicle count (AFC), anti-Müllerian hormone (AMH) levels, serum estradiol concentrations, and the number of growing follicles is the most significant markers (3). The presence of ≥15 follicles ≥10 mm on the day of hCG administration associated with the development of moderate to severe OHSS (3).

AMH is independent predictor of ovarian response, with high AMH levels correlating with an increased risk of OHSS (5). AMH measurement allows for the adjustment of stimulation protocols to reduce the risk of excessive response. GnRH agonist triggers in antagonist cycles and embryo cryopreservation, were efficient in reducing OHSS incidence without compromising pregnancy rates (6).

This systematic review aims to find evidence about the predictive markers for OHSS in IVF/ICSI cycles. A better understanding of these predictors facilitate individualized ovarian stimulation protocols, minimize the incidence of OHSS, and improve patient safety and ART outcomes.

2. Methodology

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We aimed to identify, and evaluate original research studies focused on predicting the risk of OHSS in women undergoing *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI).

2.1. Search Strategy

An electronic search was performed in PubMed, Web of science, Scopus and Google scholar.. Keywords include: ovarian hyperstimulation syndrome, OHSS prediction, *in vitro* fertilization, IVF, risk factors, and predictive models. The search was restricted to full-text original articles published in English in the period from 2009 to 2024.

2.2. Eligibility and exclusion Criteria

We include, original research articles (prospective, retrospective, observational, or cohort studies); investigated predictors or developed models for OHSS risk in IVF/ICSI patients; reported specific predictive factors (estradiol levels, antral follicle count, oocyte retrieval numbers, hormonal markers, or clinical scores); and provided sufficient methodological details for data extraction. We exclude reviews, case reports, conference abstracts, editorials, expert opinions, studies focusing exclusively on OHSS treatment without predictive assessment, and non-English language publications. We include 12 articles in the qualitative analysis (Fig1).

2.3. Study Selection

Two reviewers screened titles and abstracts. Full-text articles were retrieved for eligible studies and assessed against the inclusion and exclusion criteria. Discrepancies resolved through discussion with a third reviewer.

2.4. Data Extraction

A data extraction form was developed to collect the important information from each study which include, citation details, study design and duration, population characteristics, predictive factors and methods used, main findings, and outcomes. Qualitative data synthesis was performed to find predictive factors, and outcome definitions. Results were grouped and compared based on predictors evaluated.

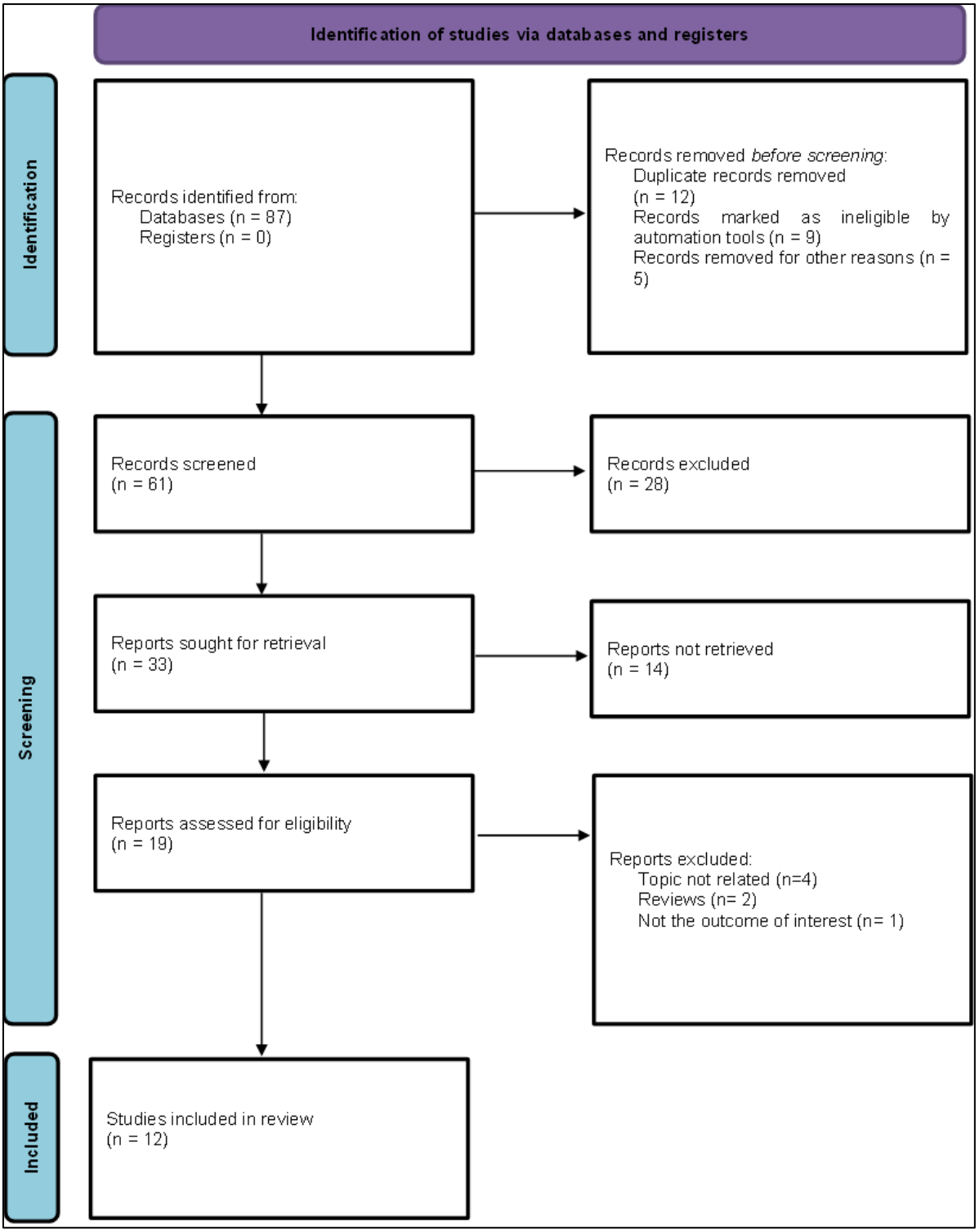

Figure 1 PRISMA consort chart of study selection

3. Results

A total of twelve original studies were included in this systematic review, which analyze predictive methods for OHSS risk in women undergoing *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI). The studies include different populations and clinical settings, varied predictive markers and statistical approaches (Table 1).

The included studies evaluated diverse patient groups, rang from general IVF populations to high-risk groups such as patients with polycystic ovary syndrome (PCOS). Age distribution differ but included women of reproductive age (20–

40 years). Two studies targeted PCOS populations (Li et al., 2021; Zheng et al., 2019), while others assessed broader IVF cohorts.

Antral follicle count (AFC), serum anti-Müllerian hormone (AMH) levels, estradiol (E2) levels on the day of human chorionic gonadotropin (hCG) administration, number of follicles, and number of retrieved oocytes were the most common evaluated indicators. Five studies indictaed that AFC and AMH were strong predictors of OHSS (Tan et al., 2021; Li et al., 2021; Zheng et al., 2019; Madrazo et al., 2020; Griesinger et al., 2016). E2 levels on the day of hCG were investigated in six studies, with varying cutoffs proposed for risk stratification (Table 1).

Several studies developed predictive models. Nomograms were used by Li et al. (2021) and Tan et al. (2021) to facilitate clinical application. Logistic regression and receiver operating characteristic (ROC) curve analyses were used to evaluate predictive performance, with area under the curve (AUC) values rang between 0.70 and 0.85, which indicate good discriminatory capacity. Madrazo et al. (2020) reported an AUC of 0.85 for number of ova collected predicting severe OHSS.

Some studies examined novel predictors: Zheng et al. (2019) show intrafollicular melatonin levels as a new biomarker, which had a strong correlation with traditional risk factors and IVF outcomes. Abbara et al. (2018) compared the incidence of OHSS between different ovulation triggers, and indicate kisspeptin as a safer alternative. Outcomes differ but show the importance of early risk prediction to guide preventive strategies, trigger modification, cycle cancellation, or embryo freezing (Table 2).

Table 1 Characteristics of the studies included

Citation	Study Design	Study Duration	Inclusion Criteria	Prediction Method Used	Study Aim	Methodology
Aljawoan et al., 2012 (7)	Retrospective study	2004–2007	Coasted patients in IVF/ICSI cycles	Serum E2 and number of oocytes	Identify predictors of OHSS in coasted patients	Manual review of coasted patient records
Kaur et al., 2015 (8)	Retrospective observational study	2012–2014	Women undergoing IVF at risk of OHSS	Hematocrit levels	Evaluate hematocrit as a predictor of OHSS	Review of hematocrit at OPU and ET days
Kahnberg et al., 2009 (9)	Prospective observational study	2003–2005	First IVF/ICSI cycle with oocyte retrieval	Number of follicles, oocytes retrieved	Identify independent predictors of severe OHSS	Univariate and multivariate analyses
Grynnerup et al., 2022 (10)	Secondary analysis of RCT	2022	Women undergoing ART, examined at OPU and 5 days later	Peritoneal fluid measurement on day 5	Evaluate peritoneal fluid as predictor for severe late OHSS	Logistic regression and ROC analysis
Madrazo et al., 2020 (11)	Retrospective study	2008–2017	Women undergoing IVF between 2008-2017	Estradiol levels, AFC, number of ova collected	Assess estradiol, follicle count, ova in predicting OHSS	ROC analysis of E2, AFC, ova collected
Tarlatzi et al., 2017 (12)	Retrospective cohort study	2009–2014	Fresh IVF cycles using gonadotropins and GnRH analogues	Follicle count ≥10 mm	Identify best predictor of severe OHSS	GEE modeling for multiple IVF cycles

Shields et al., 2016 (13)	Case-control study	2008–2013	Women admitted with OHSS diagnosis after IVF	Risk score based on multiple risk factors	Identify risk factors and create a risk score	Multivariate Poisson regression to create risk score
Abbara et al., 2018 (14)	Retrospective cohort study	2013–2016	Women at high risk of OHSS undergoing IVF	Comparison of hormonal triggers (hCG, GnRHa, kisspeptin)	Compare OHSS symptoms after different triggers	Comparison across three hormonal trigger groups
Tan et al., 2021 (15)	Longitudinal study	2018–2019	Women undergoing IVF-ET with specific eligibility criteria	AFC, AMH, and progesterone levels	Develop prediction model for high ovarian response	Logistic regression and internal validation
Li et al., 2021 (16)	Retrospective analysis	Not explicitly stated (based on retrospective IVF cycles)	PCOS patients undergoing IVF/ICSI	Nomogram based on AMH, FSH, E2, Gn dose, follicles	Develop a nomogram predicting OHSS risk in PCOS patients	Logistic regression and nomogram creation
Griesinger et al., 2016 (17)	Retrospective analysis of RCT data	Data from Engage, Ensure, Trust trials (RCTs completed previously)	Women treated with corifollitropin alfa or rFSH in GnRH antagonist protocols	Number of follicles ≥11 mm and E2 levels on hCG day	Identify threshold for predicting OHSS using follicles and E2 levels	ROC analysis, logistic regression on pooled RCT data
Zheng et al., 2019 (18)	Prospective observational study	April 2016 to May 2016	Women undergoing IVF-ET, 20 OHSS and 23 non-OHSS women	Intrafollicular melatonin concentration measurement	Assess intrafollicular melatonin as a predictor for OHSS	Measurement of follicular fluid melatonin and correlation analysis

Table 2 Main findings of the studies included

Citation	**Demographic Characteristics**	**Main Findings**	**Outcome**
Aljawoan et al., 2012	IVF coasted patients, age range not reported	High estradiol and oocyte numbers linked to OHSS risk	Serum E2 and oocyte retrieval numbers valuable for OHSS risk stratification
Kaur et al., 2015	Women at high risk of OHSS, various ages	Hematocrit is a simple predictor for OHSS	Simple blood test (hematocrit) aids early OHSS detection
Kahnberg et al., 2009	First IVF cycle patients, mainly young women	Follicle count and oocytes best predicted severe OHSS	Ultrasound and retrieval data useful for predicting severe OHSS
Grynnerup et al., 2022	Women undergoing ART with variable risk	Peritoneal fluid volume predicts late OHSS severity	New predictor for late OHSS cases identified

Madrazo et al., 2020 (11)	Women undergoing IVF, control and OHSS groups matched	Ova number and E2 levels predict OHSS and culdocentesis need	Early intervention strategies possible with E2, AFC, ova collected
Tarlatzi et al., 2017 (12)	Women in IVF cycles, follicle monitoring	Follicle count ≥15 on trigger day best predicts severe OHSS	Follicle monitoring key to prevent severe OHSS
Shields et al., 2016 (13)	Women hospitalized for OHSS post IVF	Risk score including multiple factors predicts OHSS hospitalization	Risk score enables proactive OHSS management
Abbara et al., 2018	Women triggered with hCG, GnRHa, or kisspeptin	Kisspeptin trigger associated with lowest OHSS risk	Kisspeptin may be preferred for high-risk patients
Tan et al., 2021 (15)	Women aged 20–40 years undergoing IVF-ET	AFC, AMH, and progesterone predict high ovarian response	Model accurately identifies high responders
Li et al., 2021 (16)	PCOS patients undergoing IVF/ICSI	Nomogram model predicts OHSS risk in PCOS patients	Tool improves patient-specific risk management
Griesinger et al., 2016	Women aged 18–36 years in GnRH antagonist protocol	≥19 follicles ≥11 mm predicts moderate/severe OHSS	Follicle count better than E2 for OHSS risk prediction
Zheng et al., 2019	Women undergoing IVF aged 20–35 years	Intrafollicular melatonin higher in OHSS patients	Melatonin may be used as a novel OHSS biomarker

4. Discussion

This systematic review include twelve original studies to assess predictors of OHSS in patients undergoing in IVF or ICSI. Elevated antral follicle count (AFC), high anti-Müllerian hormone (AMH) levels, and elevated serum estradiol (E2) levels at the time of human chorionic gonadotropin (hCG) administration were reported. These markers are included in assessment of patient's risk profile before oocyte retrieval and have been widely used in clinical decision-making (19).

Metabolomic profiling of follicular fluid show that elevated concentrations of deoxyinosine, L-isoleucine, and pyruvic acid, are correlated with the number of retrieved oocytes and serum E2 levels, which give potential as a predictors of OHSS (19). This biochemical approach supplement traditional markers and give earlier, and more accurate indication of OHSS risk.

In vitro maturation (IVM) represents one such alternative, eliminate the risk of OHSS while permitting oocyte retrieval without full ovarian stimulation (20). IVM is associated with lower cumulative live birth rates compared to conventional IVF, but it give a compelling option for OHSS-prone patients and accent the importance of individualized therapy.

Predictive modeling also gained prominence as method to optimize patient-specific risk assessment. Recent developments through a nomogram model incorporates patient characteristics (age, BMI, baseline hormone levels, and ovarian response parameters) to predict the moderate to severe OHSS (21). These models assist clinicians in risk stratification and enable preemptive adjustments to treatment plans, minimizing complications. The follicle count remains is a powerful and simple predictor for severe OHSS. Studies indicate that having 15 or more follicles ≥10 mm on the day of hCG administration is associated with increased risk (22). This obtainable ultrasonographic marker is valuable in guiding trigger strategies and considering a freeze-all approach to mitigate OHSS risk.

Coagulation and fibrinolysis markers are emerging as predictive biomarkers in addition to hormonal and ultrasound parameters. Elevated levels of thrombin-antithrombin complex and plasmin-α2-plasmin inhibitor complex (PIC) correlate with OHSS severity, which suggest that vascular permeability changes integral to OHSS pathophysiology is detectable through simple blood tests (23). The integration of such laboratory biomarkers into predictive algorithms improve early preventive measures.

List of Abbreviations

OHSS, Ovarian Hyperstimulation Syndrome; IVF, *In vitro* Fertilization; ICSI, Intracytoplasmic Sperm Injection; COS, Controlled Ovarian Stimulation; ART, Assisted Reproductive Technologies; hCG, Human Chorionic Gonadotropin; GnRH, Gonadotropin-Releasing Hormone; AFC, Antral Follicle Count; AMH, Anti-Müllerian Hormone; VEGF, Vascular

Endothelial Growth Factor; E2, Estradiol; IVM, *In vitro* Maturation; TAT, Thrombin-Antithrombin Complex; PIC, Plasmin-α2-Plasmin Inhibitor Complex; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; AUC, Area Under the Curve.

5. Conclusion

AFC, AMH, and E2 levels were a reliable and practical predictors to assess OHSS risk in IVF/ICSI patients. Early identification of high-risk patients through predictive models allow for safer treatment protocols, reduced complications, and improved reproductive outcomes.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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