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RESEARCH

A new decision-support tool in a multi-center randomized trial for personalized, optimized, and simplified fertility treatment in non-PCOS patients

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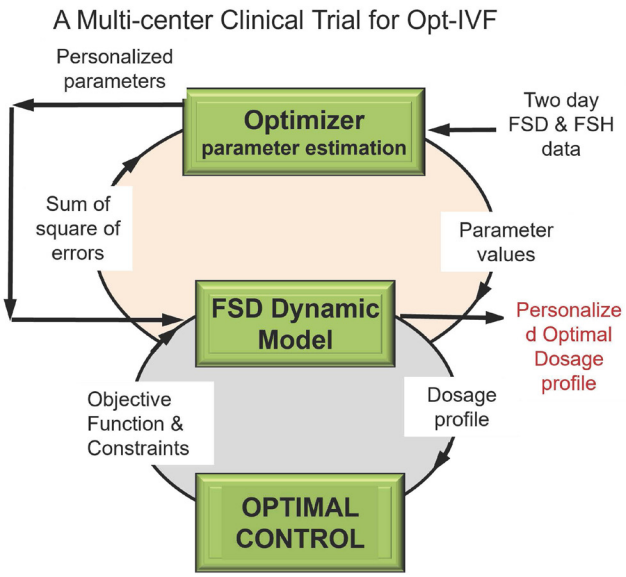
Graphical abstract



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Abstract

This study aimed to evaluate the effectiveness of a clinical decision support tool, Opt-IVF, in achieving the following outcomes: reducing the total cumulative dosage of Gonadotropins (Gns) used during controlled ovarian stimulation cycles and reducing the repeated ultrasonograms (USG) for monitoring follicular growth without compromising the number of good quality blastocysts obtained. The study design employed a multi-center randomized trial. The study enrolled 115 women aged 25–45 years undergoing IVF. Among the participants, 55 were randomly assigned to the intervention group (Opt-IVF), and 60 were randomly assigned to the control group. The intervention involved using a clinical decision support tool, Opt-IVF, to guide Gn dosing and trigger dates. The participants in the intervention group required significantly lower cumulative Gn dosage. The intervention group had higher numbers of oocytes retrieved and M2 retrieved than the control group. The number of good-quality blastocysts, the good-quality blastocyst rate, the ovarian sensitivity index (OSI), and the pregnancy rate in the intervention group were significantly higher than in the control group. The utilization of the clinical decision support tool led to several positive outcomes, including eliminating the need for ultrasound exams after day 5, reducing the dosage of Gn required, and yielding significantly higher numbers of high-quality blastocysts and higher pregnancy rates. Thus, Opt-IVF can successfully provide a personalized, optimized, and simplified approach to superovulation. Opt-IVF consistently outperformed the clinical teams in most of the outcomes.

Clinical trials registration: ClinicalTrials.gov (ID - NCT05811065). Date of Registration: 15 March 2023. Date of enrollment of the first subject: 20 March 2023.

Lay Summary

The high cost of IVF is a result of costly drugs, fixed prices for infrastructure, extensive testing required, and labor costs for physicians and other healthcare personnel. Superovulation, which involves the drug-induced release of multiple eggs needed for IVF, accounts for a significant share of these costs. Current approaches to superovulation involve almost daily monitoring of follicle development using ultrasound and/or blood tests. The daily dosage of stimulatory hormones is then prescribed by physicians based on empirical data and clinical experience. However, the dose is not optimized for each patient, and overstimulation complications can occur. The cost of testing and drugs makes this stage very expensive. To overcome the shortcomings of this system, we have developed a decision support tool (Opt-IVF) that can provide a personalized model-optimized dosage profile for each patient. The clinical results show that Opt-IVF optimizes and personalizes dosage, reduces testing, and provides better outcomes for patients.

Keywords: clinical decision support tool for controlled ovarian stimulation; Opt-IVF; optimal control

Introduction

Infertility is a widespread issue affecting millions of people of reproductive age worldwide, with significant consequences for families and communities. Global estimates suggest that up to 186 million individuals grapple with infertility (www.who.int/news-room/fact-sheets/detail/infertility). According to a 2022 WHO report on infertility, approximately one in six people have experienced infertility at some stage in their lives globally (WHO 2022). Assisted reproductive technology relies heavily on in-vitro fertilization (IVF), the most commonly used technique. IVF has proven effective in addressing infertility. To enhance the chances of success in IVF, controlled ovarian stimulation is employed, a drug-induced method that encourages multiple follicles per menstrual cycle. The effectiveness of IVF hinges on successful controlled ovarian stimulation, which is determined by the number and quality of oocytes retrieved in each cycle.

Despite its benefits, controlled ovarian stimulation presents challenges, including the high cost of gonadotropins (Gns) and the need for frequent monitoring of follicular development through ultrasound and blood tests (Conrad & Grifo, 2023). Determining the hormone dosage for each patient relies on physician experience and general guidelines, often leading to suboptimal outcomes and potential overstimulation complications (Klemetti *et al.* 2005).

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In 2021, Leahy and co-workers showed that ovarian stimulation drugs used in IVF are usually administered at a saturating or slightly higher dosage, suggesting the potential scope for dose reduction (Leahy *et al.* 2021). Additionally, the future of IVF treatment is predicted to involve personalized approaches based on modeling (Simopoulou *et al.* 2018).

Based on our earlier theoretical work, we developed a unique decision support tool, Opt-IVF, to address the current system's limitations (Nisal *et al.* 2020, 2021). First, principles-based models are often engineering design models that reflect physical laws such as thermodynamics and kinetics. In contrast, data-driven models use regressions and neural networks to connect inputs and outputs. We used a hybrid approach (Nisal *et al.* 2020, 2021), integrating first principles concepts with data-driven techniques to develop a model that describes follicle maturation using theory derived from particulate growth in nature.

Optimal control theory, which provides a mathematical procedure for optimizing a particular performance index (in this case to maximize mature follicles at the end of the cycle) by manipulating time-dependent variables (dosage in this case), is then used to determine the optimal dosage profile for each patient. This tool provides personalized and optimal dosage profiles for controlled ovarian stimulation cycles. In comparison to our approach (Nisal *et al.* 2020, 2021, Diwekar *et al.* 2022, 2023), machine learning models have been proposed to decide the initial dose for superovulation (Curchoe *et al.* 2020, Correa *et al.* 2022, Fanton *et al.* 2022*a*,*b*, Hariton *et al.* 2023) and trigger day (Hariton *et al.* 2021). Still, these models do not offer guidance with daily dosage for the remaining days of the cycle, nor have the models been evaluated in clinical trials.

Initial dose

Opt-IVF determines the initial Gn dosage either based on the nomogram proposed by La Marca & Sunkara (2014), which takes into account age, day 3 serum FSH, and AMH, or based on heuristics utilizing age, AMH, and AFC values as shown in Table 1 below. In our study, we used Table 1 for both arms.

Table 1 Heuristics to determine initial Gn dosage. The dosages are a combination of rFSH (Gonal-F/Folisurge) and HMG only.

		Age in years		
AFC	**AMH** (ng/dL)	**21–30**	**31–35**	**>35**
<6	<0.8	MSP*	MSP*	MSP*
6–10	0.8–1.4	150 + 75	150 + 75	150 + 75
10–20	1.5–4.0	150 + 75	150 + 75	225 + 75
21–30	4.1–7.0	187.5	150 + 75	150 + 75
>30†	>7.0	187.5	187.5	150 + 75

*MSP= Clomiphene citrate + HMG (Menopur/Menotas); †If BMI >30 add FSH75 IU to the standalone dose.
MSP, minimum stimulation protocol.

Profile for the rest of the cycle

While there are general guidelines for Gn dosage, individualization of hormone dosage is primarily based on clinical experience and judgment. To overcome this limitation, a mathematical procedure was developed, which incorporates the change in follicle size distribution during days 1 to 5 and the Gn dose used on days 1 to 4. The D-1 and D-5 follicular size distribution (FSD) data are obtained through ultrasound. The algorithm uses optimal control theory to determine hormone dosage on each subsequent day to maximize the number of mature follicles (18–22 mm) (Nisal *et al.* 2020, 2021) The Opt-IVF algorithm also forecasts the best timing for antagonist administration and the optimal trigger day to optimize the retrieval of mature oocytes. The model was validated using data from 150 patients from various IVF centers in India and the United States (Nisal *et al.* 2020, 2021). Two single-center clinical trials have demonstrated the success of the Opt-IVF tool in practice (Diwekar *et al.* 2022, 2023). On average, participants in both clinical trials required approximately 30% lower cumulative Gn dosage, and controlled ovarian stimulation cycles yielded more high-quality embryos.

This paper presents findings from a prospective multi-center randomized controlled clinical trial where the clinical decision support tool was utilized to guide controlled ovarian stimulation, further validating its effectiveness as a valuable tool in IVF treatment. PCOS patients were not included in this trial.

Materials and methods

Clinical work for this study was conducted at four centers of Indira IVF, India. The institutional review board at the Indira IVF Ethics Committee, India, approved the protocol and consent forms (IIHPL-UDR/RCT/004_2022). All participants provided written informed consent, and clinical investigators continuously monitored patient safety throughout the study.

The clinical trial

This is a multi-center prospective randomized control trial. The clinical trial was registered on ClinicalTrials.gov (ID NCT05811065). It is a parallel trial with a 1:1 allocation. A simple randomization method was used to assign patients to the intervention and control groups using a lottery method. The patients were separately registered and assigned to different groups

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at each of the four centers. Power analyses were conducted using previous trials (Diwekar *et al.* 2022, 2023) for key outcomes, including total dosage and the number of high-quality embryos. To achieve a power of 0.95 with a significance level of 0.05 for an average total dosage to be 20% lower and for the grade A embryos to be 60% higher in the intervention group than the control group, we required 38 subjects in each arm. We registered 60 patients for each arm of the trial. Five patients out of the 60 randomized to the intervention group dropped out before starting treatment and were excluded. Neither the investigators nor the patients were blinded regarding gonadotropin dosage. As a routine practice, we used recombinant gonadotropin (Follisurge, by Intas Pharmaceuticals, India). The initial dose of Gn was decided, as shown in Table 2. PCOS patients were excluded from this trial.

All patients underwent transvaginal ultrasound exams on D-1 and D-5 of the cycle to determine the number and size of follicles present. For the intervention group, this data was used in the Opt-IVF decision support tool to suggest gonadotropin dosage for D-5 and beyond and to recommend the antagonist start day and trigger day. Clinical investigators did not override the Opt-IVF recommended dosage in any patients, although the study protocol allowed them to do so if warranted in their clinical judgment. All patients underwent an antagonist protocol. Control group participants received hormone dosage based on the clinical investigators' clinical judgment and frequent ultrasound exams. The frequency of ultrasonography depended on the initial size of the follicular cohort and the response to the gonadotropin stimulation; however, usually, the first monitoring scan was planned on the 4th or 5th day after the start of

Table 2 Results and analysis of outcomes.

	All patients		Normal responder only	
	Intervention	**Control**	**Intervention**	**Control**
Patients	55	60	46	57
Age (years)				
Average	31.8	32.3	31.5	32.4
SD	4.0	3.8	3.8	3.8
P (*t*-test)	0.24		0.484	
Cumulative gonadotropin dose (IU)				
Average	2099	2947	2084	2993
SD	262	935	271	932
95% CI	2028–2170	2705–3189	2004–2165	2746–3240
P (*t*-test)	<0.001		<0.001	
Oocytes retrieved				
Average	10.9	8.5	11.5	8.7
SD	4.5	4,4	4,3	4.4
95% CI	9.7–12.1	7.3–9.6	10.2–12.8	7.5–9.8
P (*t*-test)	0.004		0.001	
M2 oocytes				
Average	7.5	5.8	8	5.9
SD	3.3	3.1	3.2	3.1
95% CI	6.6–8.4	5.0–6.6	7.0–8.9	5.1–6.8
P (*t*-test)	0.005		0.002	
OSI				
Average	5.3	3.1	5.6	3.2
SD	2.5	1.9	2.4	2
95% CI	4.7–6.0	2.6–3.6	4.9–6.3	2.7–3.7
P (*t*-test)	<0.001		<0.001	
Embryos				
Average	4.2	4.8	4.4	4.9
SD	2.8	2.8	2.8	2.9
95% CI	3.5–5.0	4.0–5.5	3.6–5.2	4.1–5.6
P (*t*-test)	NS		NS	
Good quality blastocysts				
Average	2.2	1.2	2.3	1.2
SD	1.7	1.4	1.6	1.4
95% CI	1.8–2.7	0.8–1.6	1.8–2.7	0.8–1.6
P (*t*-test)	0.001		0.001	

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stimulation. Opt-IVF recommended the trigger day for the intervention participants. For control patients, the trigger day was chosen by the clinical investigator. M2 oocytes were considered mature if they had at least one polar body present.

The primary outcomes measured included cumulative gonadotropin dosage, the number of M2 oocytes retrieved, the ovarian sensitivity index (OSI) defined below, the total number of embryos, and the number of high-quality blastocysts obtained after in-vitro fertilization. The embryo grading was done as per Gardner's embryo grading system. OSI is an independent predictor of the clinical pregnancy rate. High OSI is associated with high pregnancy rates (Revelli *et al.* 2020).

$$OSI = \frac{number\,of\,oocytes\,retrieved}{total\,gonadotropin\,dose} \times 1000$$

Statistical analyses

Statistical analyses were performed using Microsoft Excel. Confidence intervals shown are based on the *t* distribution. Two-tailed *t*-tests and chi-square tests were performed using the statistical functions in Microsoft Excel. The significance level was set at $P < 0.05$ for all analyses.

Results

Intervention and control participant groups were similar in age, as shown in Table 2. All except 12 patients in the trial were predicted normal responders, based on the Bologna classification, except nine patients in the intervention group and three patients in the control group who were considered predicted poor responders. Results shown include the normal responders and the total, which includes the predicted poor responders. Table 3 shows that the cumulative total Gn dosage received by intervention participants was significantly lower than that of control participants. On average, the cumulative FSH dose in the intervention group was 29% lower than in the control group.

Table 2 also shows the numbers of oocytes and M2 retrieved, and the Ovarian Sensitivity Index (OSI) defined earlier. The intervention group outperformed the control group across all three metrics, with statistically significant differences observed in each case. Table 2 also displays the results for total embryos and good-quality blastocysts. While comparable numbers of embryos were harvested in both groups, the intervention group yielded significantly more good-quality blastocysts.

Table 3 describes the progression of patients through various stages. Nearly all patients in both cohorts exhibited a satisfactory count of M2 oocytes, with 100% in the intervention group and over 90% in the control group. Most patients with at least one M2 oocyte successfully formed embryos after in vitro fertilization. Overall, 46 out of 55 patients in the intervention group obtained at least one good-quality blastocyst, whereas the success rate in the control group was lower, with only 33 out of 60 patients reaching this stage ($P < 0.001$, chi-square test).

Among the patients who reached the embryo formation stage, only 33 out of 54 in the control group developed one or more good-quality blastocysts. In contrast, 46 out of 52 intervention group patients progressed from embryo formation to the good-quality blastocyst stage ($P < 0.001$, chi-square test). Patients in the intervention group also had higher proportions of cycles with multiple good-quality blastocysts than control group patients.

Focusing on normal responders exclusively, over 90% (40 out of 44) of intervention group patients with embryos formed in vitro produced at least one good blastocyst, as opposed to only 31 of 51 control group patients ($P < 0.001$, chi-square test). Patients in the intervention group also had higher proportions of cycles with multiple good-quality blastocysts.

Table 4 shows the pregnancy data for patients for this cycle. The clinical pregnancy rate (including cancellations) is significantly higher with Opt-IVF than control patients.

Table 3 Analysis of M2, embryos, and good quality blastocysts.

	All patients			Normal responder only		
	Intervention	**Control**	***P*** (chi-square)	**Intervention**	**Control**	***P*** (chi-square)
Patients	55	60	–*	46	57	–*
1 or >1 M2 oocytes	55 (100%)	57 (95%)	–*	46 (100%)	54 (95%)	–*
1 or >1 embryos	52 (95%)	54 (95%)	–*	44 (96%)	51 (94%)	–*
1 or >1 good d5 blastocysts	46 (89%)	33 (61%)	0.0009	40 (91%)	31 (60%)	0.0004
2 or >2 good d5 blastocysts	35 (67%)	22 (41%)	0.0061	31 (70%)	21 (41%)	0.0021
3 or >3 good d5 blastocyst	20 (38%)	10 (19%)	0.016	17 (39%)	9 (17%)	0.0139
4 or >4 good d5 blastocyst	11 (21%)	5 (9%)	0.0709	8 (18%)	5 (10%)	0.1930

*Chi-square testing could not be done as the numbers in at least one of the categories were less than 5.

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Table 4 Clinical pregnancy data.

Category	Opt-IVF	Non Opt-IVF	*P* (chi-square)
Pregnant	30	23	0.0407
Not pregnant	22	37	
Remaining	3	0	Not applicable
Pregnancy rate %	58	38	0.005

Discussion

This study presents the outcomes of a multi-center trial of a clinical decision support tool for predicting personalized dosage profiles from D-1 to the end of the controlled ovarian stimulation cycle. The tool is based on a physics-based model (Nisal *et al.* 2020, 2021) that utilizes follicle size distribution data from D-1 and D-5 to tailor the dosage for each patient. The use of optimal control theory allows for the prediction of an optimal dosage profile, minimizing variance in follicle sizes at the end of the cycle. This study is a multi-center randomized trial with non-PCOS patients to assess the effectiveness of the decision support tool Opt-IVF.

The results obtained in this trial confirm and extend the results recently reported in previous trials (Diwekar *et al.* 2022, 2023). Importantly, this is a multi-center trial compared to earlier studies from a single center. Opt-IVF-recommended trigger days were used in this trial, unlike previous trials where the clinical investigator determined the trigger day. Unlike in the previous trials, we focused on predicted normal responders. PCOS patients were excluded, and only a small number of poor responders were included. As the intervention group contained a higher proportion of predicted poor responders, we analyzed data for all patients and the normal responders separately. Despite the intervention group having more poor responders than the control group, the intervention group had significantly better outcomes on all metrics except in the average number of embryos, which were similar in the two groups. A possible explanation for this discrepancy is seen in Table 4. In the case of many control patients, embryos were obtained, but in many cases, these embryos did not develop to the stage of good-quality blastocysts, the endpoint in this study. Even among the patients that had at least one good D-5 blastocyst, a higher proportion of the intervention group had multiple good-quality blastocysts, as shown in Table 4. These results suggest that using the decision support tool can increase both the number and the proportion of oocytes capable of maturing after fertilization to a good-quality blastocyst resulting in higher pregnancy rates (Table 4).

Unlike previous studies, where the investigators determined the trigger day based on clinical judgment, we used an Opt-IVF predicted trigger day for all patients in the intervention group in this clinical trial. This may have contributed to the fact that intervention group patients had significantly higher numbers of M2 oocytes than the control group, which was not seen in the earlier trials.

Our results show that using the clinical decision support tool significantly reduced Gn dosage compared to the control. Eliminating the need for ultrasound exams after D-5 of the start of stimulation is also significant. This reduction in testing could lower treatment costs, especially in resource-limited settings, and reduce the logistical and emotional burdens associated with ultrasound testing on patients undergoing controlled ovarian stimulation. None of the participants in the trial experienced OHSS or significant side effects.

One limitation of the study is that we studied mostly normal responders, excluding patients with PCOS and including only a small number of poor responders. In other reported clinical trials (Diwekar *et al.* 2022, 2023), poor responders and PCOS patients were included in sufficient numbers to show that using the clinical decision support tool resulted in higher numbers of oocytes and high-quality embryos with lower dosages of gonadotropins. Another limitation is that we studied patients from a specific ethnic background (Indian), which might impact the generalizability of the results. However, the follicle development model underlying Opt-IVF was validated in patients from India and the USA (Nisal *et al.* 2020, 2021). The clinical decision support tool also creates an ovarian follicle development model for a particular controlled ovarian stimulation cycle in an individual patient based on the observed follicular response from D-1 through D-5. This personalized approach essentially eliminates the effects of confounding factors, including age, ethnic background, BMI, and individual variation in ovarian responsiveness to hormones.

Conclusion

The clinical trial demonstrates that with non-PCOS patients, using the Opt-IVF clinical decision support tool for hormone dosing during controlled ovarian stimulation leads to lower overall hormone dosage and eliminates the need for ultrasound testing after D-5 of the cycle. This approach resulted in increased high-quality blastocysts and higher pregnancy rates compared to control patients. Opt-IVF shows promise as a valuable tool for personalized and optimized IVF treatment for patients.

Declaration of interest

Urmila Diwekar and Sanjay Joag have an ownership interest in Stochastic Research Technologies LLC, USA, which owns and markets Opt-IVF. Shyam

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Data availability
The data underlying this article can be obtained by contacting the corresponding author.

Author contribution statement
UD, SJ, and NB conceptualized the study and developed the protocol. UD and SJ conducted the literature review. SG, AG, SH, KM, NM, VC and NB carried out the clinical work. UD and SJ extracted data, assessed data quality, analyzed the data, and interpreted the data. All authors reviewed, edited, and approved the final manuscript.

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