Title page

Is it possible to apply trial outcomes to a real world population? A novel approach to external validity analysis

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RF is an employee of Ferring Pharmaceuticals Pty Ltd. AP is a member of the Medical Advisory Board for Ferring Pharmaceuticals, however, there has been no significant financial support for this work that could influence its outcome. The remaining authors have no conflicts of interest relevant to this article.

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Abstract (Limit 250 words; currently 200 words)

Background: Translation of findings from Randomised Controlled Trials (RCT), the foundation of evidence-based medicine, into clinical practice requires an understanding of relationships between patient characteristics, treatment practices and outcomes. We propose a novel technique, External Validity Analysis (EVA), to evaluate applicability of findings from a large RCT, comparing baseline characteristics, interventions and outcomes between the RCT and a large clinical database.

Aim: To perform EVA of the findings of a randomised controlled trial (ESTHER-1) to a population in an Australian clinic setting. To demonstrate this method, we evaluated the discordance in first cycle follicle stimulating hormone (FSH) exposure and outcomes between the two populations, to inform clinical practice.

Materials and Methods: In this retrospective, descriptive analysis, we compared practices and outcomes between the follitropin alfa 'conventional' dosing arm of the ESTHER-1 trial and a selected comparable clinic subpopulation of patients who underwent controlled ovarian stimulation (COS) using FSH.

Results: Mean FSH exposure was 34% higher in the *clinic subpopulation* than in the *trial subpopulation*, resulting in higher average ovarian response without improving the likelihood of clinical pregnancy or live birth.

Conclusions: EVA allowed for the comparison of a trial population with a selected clinic population with similar characteristics. With respect to FSH consumption, this analysis revealed higher exposure to FSH in the clinic setting without a corresponding benefit. The comparison reveals population differences as well as the potential to improve clinical outcomes through a reappraisal of current practices and objectives in gonadotropin dose selection.

Introduction

Reproductive medicine has advanced significantly over the past four decades.¹ While there is increasing interest in evidence-based practice protocols, the management of infertility with assisted reproductive technology (ART) among clinicians remains very diverse.² For example, a retrospective analysis of more than 650,000 autologous cycles of *in vitro*

fertilisation (IVF) in the United States found that the daily dose of gonadotropin prescribed ranged from 25 IU to more than 450 IU of FSH, even within subpopulations of similar age.³

While many clinicians adopt various approaches to individualising dose selection based on patient characteristics and treatment objectives, there remains a paucity of prospectively-developed, evidence-based protocols for individualising COS based on established pharmacological principles.² A recently published randomised controlled trial (RCT; ESTHER-1) validated an individualised dosing algorithm that was developed using a pharmacokinetic-pharmacodynamic modelling approach for follitropin delta by comparing its use with a 'conventional' dosing regimen using follitropin alfa.⁴

Extrapolating the findings of controlled clinical trials to a real-world population is challenging due to the heterogeneity in patient populations and clinical practices in the real-world setting.⁵ Understanding the external validity of trial findings and whether they may potentially impact current clinical practice requires a formal approach to characterising the relationships between patient characteristics, treatment practices and relevant clinical outcomes (Figure 1).

In the current study, we compared findings from the ESTHER-1 trial against routinely-collected, local population clinical data to understand the clinical relevance of the trial findings and whether they can be viewed as externally valid (or generalisable). We were particularly interested in answering the following questions:

1. How comparable are the trial and clinic populations?
2. Are FSH doses selected for comparable patients in the clinic setting different from the trial setting?
3. If FSH doses are different in the clinic setting are they associated with better outcomes for our patients?

Exploring these questions can potentially inform further prospective research and improve practice in the clinic.

Materials and Methods

Study design and patient populations

This retrospective, observational, comparative analysis of fresh cycle data were derived from two sources: (i) an international, multicentre, RCT (ESTHER-1)⁴ and (ii) a large dataset collected from a single Australian IVF clinic.

Comparison between the trial and clinic settings of treatments and outcomes can be confounded by differences in patient characteristics for the respective populations.⁶ To minimise the potential for confounding due to differences in patient characteristics, a subset of the clinic population was selected for this analysis (Figure 2), using relevant criteria for inclusion, exclusion and treatment (with the exception of the dosage regimen) that were applied in the ESTHER-1 trial.⁴

Patient characteristics (age, body weight, body mass index (BMI), serum AMH level), treatments and outcomes were described and compared for two populations:

- i. ESTHER-1 trial population treated with follitropin alfa (*trial subpopulation*) included premenopausal women aged 18 to 40 years undergoing their first COS cycle for IVF/intracytoplasmic sperm injection. Additional inclusion criteria were BMI between 17.5 and 32.0 kg/m², gonadotropin releasing hormone (GnRH)-antagonist protocol, COS for less than 20 days and blastocyst transfer. There was no restriction on AMH level.⁴
- ii. The clinic population data included de-identified individual patient data from fresh cycles performed from January 2012 to December 2016, extracted from the clinic's electronic patient records system. A subset of the clinic population undergoing their first ART cycle was selected based on criteria described above for the ESTHER-1 trial (*clinic subpopulation*). Data for other inclusion or exclusion criteria used in the ESTHER-1 trial were not included in the clinic dataset (e.g. there were no restrictions related to underlying diagnosis, ovulatory status or BMI in the clinic population). AMH concentration was measured using the Roche Elecsys® AMH immunoassay from April 2015. Prior to this date, AMH was measured by the clinic's Diagnostics laboratory using the Gen-II (Beckman Coulter) or Ansh manual assays and for this study those values were normalised to Roche Elecsys® AMH values using the validated correlation provided by the laboratory. Both assays were performed in a single laboratory using standard operating procedures. Serum AMH concentration was not measured for all

patients as this was not considered routine practice during the nominated study period.

The study protocol was submitted and approved by the Melbourne IVF Ethics Committee (December 2016, Approval number 51/16) and access was provided to de-identified individual patient data from the clinic's database.

Treatments

The ESTHER-1 trial was a large phase 3 registration study that compared individualised follitropin delta (REKOVELLE®, Ferring Pharmaceuticals) and conventional follitropin alfa (Gonal-f, EMD Serono) treatment regimens.⁴ Treatment was initiated on day 2 or 3 of the menstrual cycle and the dosing regimen (chosen to be consistent with the product label [EMD Serono] and international recommendations aimed at achieving a balance between efficacy and safety⁷ included a daily standard SC dose of 150 IU for the first 5 days; thereafter the dose could be adjusted up or down according to follicular response, up to 450 IU per day. Data from this arm of the ESTHER-1 trial was chosen as the comparator for the current study (*trial subpopulation*).

For the ESTHER-1 trial, a GnRH antagonist (cetorelix acetate, Cetrotide, EMD Serono) was administered from stimulation Day 6 onwards to prevent a premature endogenous luteinising hormone (LH) surge. Embryos were transferred at blastocyst stage.⁴

The *clinic subpopulation* received either follitropin alfa, follitropin beta or highly purified human menopausal gonadotrophin (HP-hMG). Dosing was based on clinician discretion with consideration of each patient's clinical profile, including age, AMH, BMI and reproductive history. Decision-making in relation to FSH dose was not restricted in any way and was based on individual clinician preference at the time of cycle commencement. The day of GnRH antagonist administration was not protocolised, but generally it commenced on Day 6 of stimulation.

Outcomes

The following treatment parameters and clinical outcomes were determined for patients in the *clinic subpopulation* and compared with the *trial subpopulation*: FSH exposure data (starting and total FSH dose and duration of exposure); numbers of oocytes collected; numbers of 2 pronuclear-stage embryos; numbers of cleavage or blastocyst-stage embryos transferred and/or frozen; administration of GnRH agonist trigger (as a preventative

intervention for those at risk of developing OHSS) , hospital admission for OHSS, clinical pregnancy and live birth.

In both groups clinical pregnancy was defined as “*at least one gestational sac five to six weeks after transfer*”.⁴

Statistical analyses

Continuous variables are presented as means and standard deviations (SD) (SAS 9.4 statistical software; SAS Institute INC., Cary, NC, USA). Dichotomous outcomes are presented as proportions (%). Differences between independent sample population means and proportions were calculated using MedCalc (MedCalc Software, Ostend, Belgium) by applying the relevant statistical test (t test or chi-square test), with a statistical significance limit set at $p < 0.05$. Since this observational study is for the purpose of generating hypotheses, no correction for multiple testing was applied.

Missing data for patient weight in the clinic dataset (671 of 11,275 cycles) were imputed based on population average.

Results

Patient characteristics

A total of 661 patients from the ESTHER-1 trial were treated with follitropin-alfa (*trial subpopulation*). Over the study period, a total of 6,818 patients from the Australian clinic were treated in fresh cycles of COS (representing 11,275 fresh cycles). Of the total clinic fresh cycle population, a subpopulation of 1,692 patients met the ESTHER-1 criteria (*clinic subpopulation*). The *clinic subpopulation* was slightly older than the *trial subpopulation* (34.3 ± 3.9 vs 33.2 ± 3.9 years; $p < 0.0001$), with a higher proportion of patients in the 38 to 40 years age group (20.0% vs 15.4%; $p < 0.05$; Table 1). Within the *clinic subpopulation*, AMH values were recorded in 617 patients (*clinic AMH subpopulation*) and the mean AMH values for this group (18.8 ± 17.3 pmol/L) were comparable to those of the *trial subpopulation* (19.4 ± 14.8 pmol/L, Table 1).

FSH exposure

For the *clinic subpopulation*, 94.5% of cycles involved recombinant FSH as either follitropin alfa or follitropin beta. The remaining 5.5% of cycles involved HP-hMG, either alone or in combination with follitropin alfa or follitropin beta.

The ESTHER-1 trial had a fixed starting dose of follitropin alfa of 150 IU. The *clinic subpopulation* was treated with significantly ($p < 0.0001$) higher average FSH starting doses (195 ± 71 IU) and for longer durations (9.2 ± 1.8 days versus 8.6 ± 1.7 days) than the *trial subpopulation*. Consequently, the total exposure to FSH in the *clinic subpopulation* (1896 ± 826 IU) was approximately 34% higher than in the *trial subpopulation* (1414 ± 458 IU, $p < 0.0001$; Table 2).

Clinical outcomes

A significantly higher number of oocytes were retrieved (Table 2; $p < 0.0001$) in the *clinic subpopulation*, at the expense of higher rates of extreme (< 4 or ≥ 15 oocytes, and < 4 or ≥ 20 oocytes) or excessive (≥ 15 oocytes in those with high AMH levels ≥ 15 pmol/L) response when compared with the *trial subpopulation* (Table 2; $p < 0.05$).

The higher rate of oocyte retrieval in the *clinic subpopulation* did not translate to higher numbers of useable blastocysts, nor to higher rates of clinical pregnancy or live birth following fresh transfer (Table 2).

Safety outcomes

Although not statistically significant, the rate of OHSS requiring hospitalisation in the *clinic subpopulation* was more than double the rate reported in the *trial subpopulation* (2.01% vs 0.90%; OR: 2.24, 95% CI: 0.93–5.35, $p = 0.0703$; Table 2). The use of GnRH agonist trigger to reduce the OHSS risk was significantly higher in the *clinic subpopulation* than in the *trial subpopulation* (5.67% vs 3.50%; OR: 1.67, 95% CI: 1.04–2.65, $p = 0.0306$; Table 2).

Discussion

In this study, we report that patients in a comparable first ART cycle population in an Australian clinic setting are exposed to significantly higher doses of FSH than patients in the ESTHER-1 trial.⁴ These higher FSH doses were associated with a significantly higher ovarian response in terms of numbers of oocytes collected and a higher (albeit low) rate of excessive response and risk of OHSS. These observations suggest that clinicians targeted a higher ovarian response than in the ESTHER-1 trial.⁴

While the higher doses used in the clinic setting were associated with a higher number of oocytes retrieved and fertilised, this did not translate to an increased likelihood of pregnancy

or live birth following a fresh embryo transfer. It should also be noted that the mean number of useable embryos was not significantly different and so cumulative pregnancy rates would be expected to be similar between the trial and clinic settings.

However, we acknowledge that comparing results between settings is difficult and a number of potential confounding factors may have contributed to the differences in clinical outcomes. First, the *clinic subpopulation* had a higher proportion of older patients (38 to 40 years age group) than the *trial subpopulation* (20.0% vs 15.4%, $p < 0.05$). Second, not all selection criteria used in the ESTHER-1 trial were applied to the clinic population, largely because the data were not available (e.g. underlying diagnoses, regularity of menstrual cycles, etc.). Third, the data were not selected solely from follitropin alfa-treated patients. All recombinant FSH products were coded identically in the clinic dataset and all doses were treated as equivalent across products. However, we do not consider this a weakness of the study as the aim was to capture real-world treatment practices and the uniform coding reflects the clinical equivalence of these preparations.⁸ Other potential confounders include differences in the distribution of aetiologies, clinical definitions, AMH test methods, GnRH-antagonist protocol scheduling, and criteria for cancelling cycles as well as differences in embryology laboratory practices. We also acknowledge that the differences in clinical pregnancy and live birth rates between settings apply to fresh cycles and that cumulative pregnancy rates are not likely to differ significantly, based on comparable useable embryo numbers between the settings. Also, It is important to note that the identification of patients as undergoing their first cycle of ART in the *clinic population* is in relation to treatment undertaken at the Australian clinic and it is conceivable that some of these patients may have received treatment at other clinics before seeking assistance from this clinic, while the *trial subpopulation* was naïve to ART.

These confounding factors are important, and may limit the generalisability of the RCT findings to the real world population. Nevertheless, the current findings add to the growing body of evidence that there is a limit to which the extent of increasing the dose of gonadotropin improves the likelihood of pregnancy in fresh cycles.^{3,9} Our observations are consistent with those made in other studies, which suggest that the likelihood of pregnancy reaches a plateau after retrieval of approximately 15 oocytes, but the risk of OHSS increases significantly with ovarian responses above this threshold.^{10,11} Other observational studies have also demonstrated that increasing doses of gonadotropin are associated with reduced rates of pregnancy or live birth,^{3,12} and have inferred that high FSH doses may have a direct effect on oocytes or an indirect effect via a rise in follicular-phase progesterone on endometrial receptivity.³

Our study has a number of strengths and a number of limitations. We have presented an approach to external validation of a large phase 3 trial by analysing data from a subpopulation of a large clinical dataset that was selected using clinical trial criteria. If the approach demonstrates better outcomes in the trial when compared with a similar population from the clinic, as is the case in the current study, then this approach would suggest that clinical practices may warrant reappraisal with a view towards adopting practices from the trial, followed by an evaluation of the impact of the practice changes. Such an approach of comparing trial and real-world data may be utilised across therapeutic areas. We term this novel technique External Validity Analysis.

The analysis is not without limitations. Due to the observational nature of the study, our approach should be considered hypothesis-generating. While this approach sought to identify and reduce the degree of confounding and bias between the settings, by applying the patient selection criteria and treatments used in the trial protocol, other confounding factors may exist.

In conclusion, our study showed a unique approach to perform External Validity Analysis, in order to evaluate clinical trials against real-world data, to understand the influence of patient characteristics and variations in practice. Patients in a comparable first ART cycle population in an Australian clinic setting are exposed to, on-average, 34% higher FSH doses than patients in a large phase 3 trial, without improvement in pregnancy rates. Since EVA is envisaged to be a hypothesis generating exercise, further prospective research should focus on evaluating FSH dose influence on clinical outcomes.

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Table 1. Characteristics of patients in the ESTHER-1 trial treated with follitropin-alfa and the clinic subpopulation treated with FSH in fresh cycles

Parameter	Trial	Clinic	P value
Patients (n)	661	1692	-
Patients with AMH values (n)	661	617	-
Age (years)	33.2 ± 3.9	34.3 ± 3.9	< 0.0001
Age strata			
<35 years (%)	59.3	55.3	0.0787
35-37 years (%)	25.3	24.7	0.7622
38-40 years (%)	15.4	20	0.0101
>40 years (%)	-	-	
BMI (kg/m ²)	23.3 ± 3.3	23.8 ± 3.2	0.0007
Weight (kg)	63.4 ± 10.4	64.2 ± 10.1	0.0869
AMH (pmol/L) ^a	19.4 ± 14.8	18.8 ± 17.3	0.5045
AMH <15.0 pmol/L (%) ^a	46.3	51.2	0.0800
AMH ≥ 15.0 pmol/L (%) ^a	53.7	48.8	0.0800

Values are numbers, mean ± standard deviation or percent

^a AMH statistics relate to the populations of patients for whom AMH values were recorded

Table 2. Treatments and outcomes for patients in the ESTHER-1 trial treated with follitropin alfa and Clinic subpopulation treated with FSH in fresh cycles

PARAMETER	Trial subpopulation	Clinic subpopulation	Odds ratio (95% CI)	P value
Patients (n)	661	1692	-	-
FSH starting dose (IU)	150	195 ± 71	-	< 0.0001
FSH duration (days)	8.6 ± 1.7	9.2 ± 1.8	-	< 0.0001
FSH total dose (IU)	1414 ± 458	1896 ± 826	-	< 0.0001
Number of oocytes	10.4 ± 6.5	12.6 ± 7.9	-	< 0.0001
Extreme response (<4 or ≥15 oocytes) (%)	31.3	44.9	-	< 0.0001
Extreme response (<4 or ≥20 oocytes) (%)	18.4	27.6	-	<0.0001
Excessive response (≥15 oocytes) in high AMH stratum (AHM ≥ 15 pmol/L) (%)	35.1	47.8	-	0.0010
Excessive response (≥20 oocytes) in high AMH stratum (AHM ≥ 15 pmol/L) (%)	15.6	23.3	-	0.0127
Number of fertilised oocytes 2PN	5.9 ± 4.4	7.7 ± 5.3	-	< 0.0001
Number of blastocysts	3.5 ± 3.2	3.3 ± 3.1	-	0.1635
Clinical pregnancy (%)	36.5	30.5	0.76 (0.62)	0.0075

			- 0.93)	
			0.73	
Live birth (%)	30.7	24.4	(0.59 - 0.89)	0.0029
OHSS monitoring (%)	-	27.3		
			2.24	
OHSS - hospital admission (%)	0.90	2.01	(0.93 - 5.35)	0.0703
			1.67	
GnRH agonist trigger (%)	3.50	5.67	(1.04 - 2.65)	0.0306

Values are numbers, mean $\pm$ standard deviation or percent

Calculations for clinical pregnancy and live birth are per initiated cycle and excluded 2016 data as live birth outcomes were not known for all 2016 cycles.

2PN: numbers of 2 pronuclear-stage embryos; AMH: anti-Müllerian hormone; GnRH: gonadotropin releasing hormone OHSS: ovarian hyperstimulation syndrome.

FIGURE 1

** While the clinic data was selected based on a number of patient and treatment characteristics applied in the trial, potential confounding factors for which data was not available may also have influenced differences in outcomes among the populations.*

Figure 1: Concept model for evaluating current practice versus trial protocols by considering relationships between patient characteristics, treatment features and outcomes.

FIGURE 2 **Figure 2:** Overall study design and analysis strategy.

HP-hMG: highly purified human menopausal gonadotropin; MIVF: Melbourne IVF

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