

# The causal effect of dynamic fertility treatment strategies on the probability of pregnancy: a novel application of marginal structural models (MSMs)

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## INTRODUCTION

- Infertility is a complex, multifactorial disorder. Although fertility treatments are increasingly accessible in many countries, there is still wide variation in the probability of pregnancy in couples experiencing infertility.<sup>1,2</sup>
  - Pregnancy rates vary across age, infertility diagnosis, type of treatment, and history of previous treatments.<sup>1,2</sup>
- With increasing data on various treatment strategies, clinicians will be better able to counsel their patients, guide them to the best treatment decisions, and set realistic expectations.

## OBJECTIVE

- To estimate the probability of clinical pregnancy, had all patients or subgroups of patients (<35 years old or ≥35 years old) followed 1 specific treatment strategy (Figure 1).

## METHODS

### Challenges

- Confounding by indication: observed covariates during each treatment cycle, such as the number of oocytes retrieved in an *in vitro* fertilization (IVF) cycle, can affect both the probability of pregnancy and the choice of subsequent treatment.<sup>2</sup>
- Censoring/dropout: many patients experiencing infertility discontinue treatment before achieving a pregnancy. Among patients who did not have a live birth after their first treatment cycle, 34% discontinued treatment.<sup>3</sup>
- The gold standard for assessing pregnancy outcomes is a randomized, controlled trial (RCT), but few studies have been conducted.<sup>4</sup>
  - In RCTs, randomization balances measured and unmeasured covariates among all treatment groups. However, in an observational study, patients following a particular treatment strategy may have different characteristics than the overall study population.
    - For example, older female patients and patients with poorer prognoses (eg, patients with diminished ovarian reserve) are more likely to undergo IVF or other assisted reproductive technology (ART) earlier than younger patients with better prognoses.<sup>5</sup>

### Study design and statistical analyses

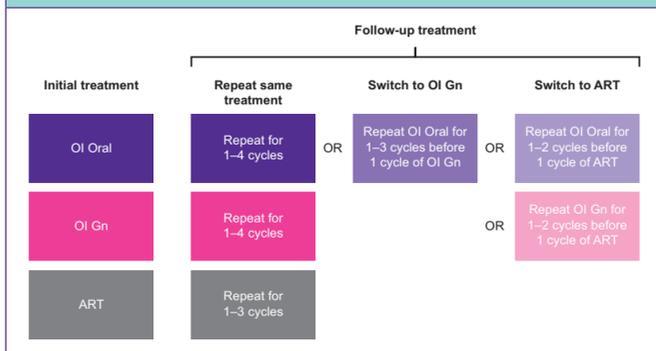
- Patient- and cycle-level data from electronic medical records (EMRs) in a large, retrospective, observational cohort were used to emulate an RCT.<sup>6</sup>
  - Analyses used EMR data from female patients treated in a network of fertility clinics across the US over 7 years (May 1, 2009 to December 31, 2016).
    - Patients included were initially treatment naïve.
    - Patients were excluded if their initial diagnosis was infertility of their male partner, or if they used donor eggs.
    - If a patient had multiple pregnancies, only treatment cycles up to the first pregnancy were included.
  - Patients were followed for up to 4 treatment cycles.
  - All database records were de-identified and fully compliant with US patient confidentiality requirements.

- Marginal structural models (MSMs)<sup>7,8</sup> were used to estimate the probability of pregnancy, had everyone followed 1 particular treatment strategy.
- Inverse probability (IP) weighting creates a pseudo-population in which all patients follow the treatment strategy of interest.
  - IP of censoring weighting adjusted for stopping treatment before getting pregnant.
    - Patients were censored from the analyses when they no longer followed the selected treatment strategy or had a gap between 2 consecutive treatments that was >12 months (censored at start of gap).
  - IP of treatment weighting adjusted for patient characteristics (eg, diminished ovarian reserve) that made some infertility patients more likely to choose a treatment strategy (eg, 1 ART over 4 ovulation induction [OI] cycles).
    - Covariates for initial treatment included age, primary infertility diagnosis, antral follicle count, follicle-stimulating hormone level on Day 3 of the menstrual cycle, ovarian reserve, insurance status, and residency in a state that mandates coverage for fertility treatment.
    - Covariates for subsequent cycles depended on treatment type.
    - The different "trial" treatment arms are shown in Figure 1.

### Clinical endpoint

- The probability of clinical pregnancy for each of the different "trial" treatment arms.
- Clinical pregnancy was defined as clinical intrauterine gestation or later evidence of pregnancy (ie, ongoing pregnancy or live birth).

Figure 1. Treatment patterns selected for MSM analysis



ART, assisted reproductive technology, including *in vitro* fertilization or intracytoplasmic sperm injection, with fresh or cryopreserved embryo transfer; MSM, marginal structural model; OI Gn, ovulation induction with gonadotropins (with/without oral medications), with timed intercourse or intrauterine insemination; OI Oral, ovulation induction by oral medications (clomiphene or letrozole), with timed intercourse or intrauterine insemination.

## RESULTS

### Patient population

- There were 84,301 patients who had undergone multiple treatments (219,925 cycles).
- Included in the analyses were 31,943 patients who started with OI with oral medication (OI Oral), 19,500 who started with OI with gonadotropins (OI Gn), 24,693 who started with ART, and 8165 who started with other OI treatments.

### Estimated probability of clinical pregnancy

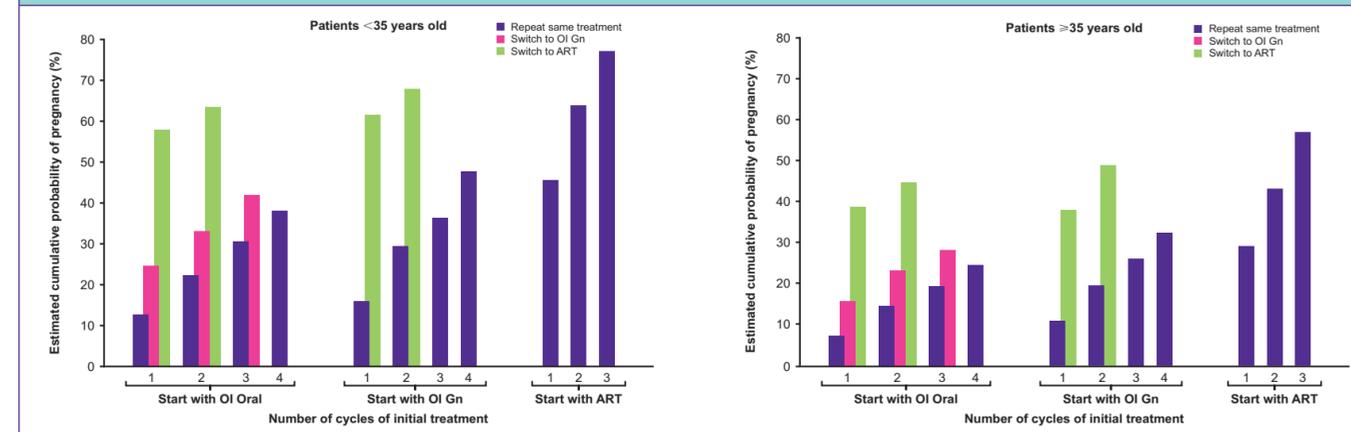
- Irrespective of the number of cycles of initial treatment and patient age, a greater estimated probability of pregnancy was observed when treatment was escalated from OI Oral to OI Gn or ART, or OI Gn to ART, compared with repeating the same treatment (Table 1; Figure 2).
  - This difference was more pronounced when patients switched to ART.

- Across all treatment strategies, patients <35 years old would have a higher probability of pregnancy than patients aged ≥35 years when following the same treatment strategy (Table 1; Figure 2).
- The estimated probability of pregnancy was below 50% had all patients undergone 4-cycle treatment strategies with <1 ART cycle (Table 1; Figure 2).

Table 1. Estimated cumulative probability of pregnancy									
Estimated cumulative clinical pregnancy rate, % (95% confidence interval)									
Initial treatment	Cycles, n	Repeat same treatment		Switch to OI Gn			Switch to ART		
		Age group		Age group			Age group		
		<35 years	≥35 years	<35 years	≥35 years	<35 years	≥35 years		
OI Oral	1	12.6 (12.1, 13.0)	7.8 (7.3, 8.4)	1 then 1 OI Gn	24.8 (23.5, 26.1)	16.1 (14.5, 17.7)	1 then 1 ART	58.1 (56.4, 59.8)	39.1 (36.5, 41.8)
	2	22.4 (21.8, 23.1)	14.8 (14.0, 15.6)	2 then 1 OI Gn	33.3 (32.1, 34.5)	23.6 (21.9, 25.4)	2 then 1 ART	63.7 (62.4, 65.0)	45.2 (42.9, 47.4)
	3	30.7 (29.9, 31.5)	19.6 (18.5, 20.7)	3 then 1 OI Gn	42.1 (40.9, 43.4)	28.5 (26.6, 30.4)			
	4	38.1 (37.1, 39.2)	25.0 (23.5, 25.4)						
OI Gn	1	16.5 (15.7, 17.3)	11.1 (10.5, 11.7)				1 then 1 ART	62.0 (59.9, 64.0)	38.3 (36.2, 40.4)
	2	29.8 (28.8, 30.9)	19.8 (18.9, 20.7)				2 then 1 ART	68.3 (66.7, 70.0)	49.4 (47.5, 51.4)
	3	36.6 (35.3, 37.9)	26.5 (25.3, 27.8)						
	4	48.2 (46.7, 49.7)	33.0 (31.5, 34.6)						
ART	1	45.8 (44.8, 46.8)	29.7 (29.0, 30.5)						
	2	64.1 (63.1, 65.1)	43.7 (42.8, 44.7)						
	3	77.6 (76.7, 78.6)	57.4 (56.3, 58.5)						

ART, assisted reproductive technology; OI Gn, ovulation induction with gonadotropins (with/without oral medications); OI Oral, ovulation induction by oral medications.

Figure 2. Estimated cumulative probability of pregnancy



ART, assisted reproductive technology; OI Gn, ovulation induction with gonadotropins (with/without oral medications); OI Oral, ovulation induction by oral medications.

## LIMITATIONS

- When applying MSMs, the models for the IP weights are assumed to be correctly specified.
- Factors were selected that contribute to the decision to use a particular fertility treatment. However, other factors not captured in the data may exist that influence dropout and treatment selection.

## CONCLUSIONS

- MSMs can account for both treatment discontinuation and the observed covariates at each treatment cycle, such as the number of oocytes retrieved in an IVF cycle, that can affect both the choice of subsequent treatment and the probability of pregnancy.<sup>2</sup>
- Patients starting treatment with OI could benefit by switching to ART rather than repeating OI multiple times.
- The probability of pregnancy within 4 cycles is not the only concern when deciding about fertility treatment; costs and invasiveness of therapy are other important considerations.
- Analyses based on MSMs may help inform the difficult decisions that physicians and their patients must often consider.

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## DISCLOSURES

SA is a former employee of Prometrika, LLC, which received funding from EMD Serono, Inc.\* to run the analysis. MPL and SL have nothing to disclose. BH and MCM are employees of EMD Serono, Inc. GLM is an employee of Shady Grove Fertility Center. JLL has received research funding from Merck Serono, Inc.

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