

Infertility patient clinical journey outcome depends on initial treatment, starting with ovulation induction versus *in vitro* fertilization: results from a large real-world database

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INTRODUCTION

- Infertility affects 10–15% of couples.¹
 - This makes it one of the most common diseases for people aged 20–45 years.¹
 - Infertility is attributed equally (1/3 of cases) to male factors, female factors, or a combination of factors in both partners.²
- Infertility can result from multiple causes in both female and male partners, and the cause(s) of infertility may remain unknown despite a complete medical evaluation.^{3,4}
 - Diagnostic evaluation includes assessment of ovulatory function (eg, follicle-stimulating hormone [FSH] level), ovarian reserve (eg, antral follicle count [AFC], anti-Müllerian hormone [AMH] level), and gynecologic structure (eg, tubal patency), in conjunction with medical history and a general physical exam.^{3,4}
- The fertility treatment journey is individualized to the patient and depends in part on the cause of infertility, diagnosis, and age of the patient.⁵
 - Surgery may be used to correct structural causes of infertility (eg, for tubal obstruction),⁶ and clinical fertility treatment may include ovulation induction (OI) with oral medications, OI with gonadotropins (Gn), and assisted reproductive technologies (ARTs), including *in vitro* fertilization (IVF).^{5,7}
 - Many patients begin their clinical treatment journey with OI Oral. If pregnancy is not achieved, success rates are higher and the time to pregnancy is shorter if patients escalate to OI Gn or IVF.⁸
 - Unfortunately, many patients discontinue treatment before achieving pregnancy or live birth. Common reasons for treatment discontinuation include financial concerns, emotional stress, and perceived medical futility. Discontinuation rates are also higher among older patients.⁹
 - How the treatment journey is navigated by the patient, with guidance from their clinical care team, is determined by the effectiveness of different treatment modalities.

OBJECTIVE

- To analyze a large US real-world database to delineate the paths that treatment-naïve infertility patients take through their clinical treatment journey.
- To provide observed cumulative clinical pregnancy rates and patient-centric outcomes (time to pregnancy and treatment discontinuation rates) depending on initial fertility treatment and prognosis.

METHODS

Study design

- This was a non-randomized, observational, retrospective analysis that utilized a large, real-world database comprising patient- and cycle-level data on OI Oral and/or OI Gn and/or IVF cycles.

Patient population

- Details of initial treatment were analyzed from deidentified electronic medical records collected from 78,958 treatment-naïve infertile patients who started treatment between July 2009 and September 2015. The three treatment types were:
 - OI Oral, with or without intrauterine insemination [IUI] with oral medication (clomiphene or letrozole)
 - OI Gn, with or without oral medication and with or without IUI
 - IVF/ART (ovarian stimulation with fresh or cryopreserved embryo transfer).
- Treatment-naïve patients were identified as those who had no previous clinical infertility treatment with OI Oral, OI Gn, or IVF/ART, either with their current or previous physician.

- The overall population and prognosis subgroups were studied and stratified by initial treatment type.
- To compare outcomes by prognosis, analyses were conducted on three example populations consisting of common infertility diagnoses and age stratifications:
 - poor prognosis: diminished ovarian reserve, age ≥35 years
 - intermediate prognosis: unexplained infertility, all ages
 - best prognosis: ovulatory disorder or polycystic ovary syndrome, age <35 years.

Statistical methods

- Clinical pregnancy was defined as clinical intrauterine gestation or later evidence of pregnancy (ie, ongoing pregnancy or live birth).
- Descriptive statistics were calculated for the overall population and within each example prognosis subgroup.
- Analyses were stratified by initial treatment (OI Oral, OI Gn, IVF/ART).

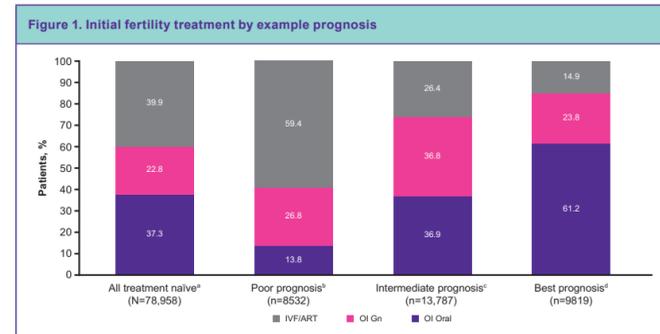
RESULTS

Patient population

- A total of 78,958 patients who were naïve to fertility treatment were included in this analysis (Table 1, Figure 1).
 - 32,138 patients were included in the analysis by example diagnosis- and age-related prognoses.
 - Among all treatment-naïve patients, those patients who initiated treatment with IVF/ART were older (35.4 vs 32.5 years), had a lower mean AFC (14.6 vs 18.7), and had lower AMH levels (2.78 vs 4.33 ng/mL) than patients who initiated treatment with OI Oral (Table 1).
 - Baseline demographics and clinical characteristics were similar between treatment paths within each prognosis category; however, patient age, AFC, and AMH were markedly different between prognoses (Table 1).

Patient group	Characteristic	Initial fertility treatment		
		OI Oral	OI Gn	IVF/ART
All treatment naïve (N=78,958)	Patients, n (%)	29,450 (37.3)	18,015 (22.8)	31,493 (39.9)
	Age (years)	32.5 (4.68)	34.7 (5.09)	35.4 (5.12)
	BMI (kg/m ²)	26.5 (6.71)	26.3 (8.04)	25.5 (5.29)
	Day 3 FSH (mIU/mL)	7.31 (4.68)	6.07 (6.06)	8.31 (7.28)
	AFC	18.7 (10.51)	15.0 (9.37)	14.6 (8.95)
	AMH (ng/mL)	4.33 (4.94)	3.32 (4.43)	2.78 (3.28)
Poor prognosis: DOR, ≥35 years (n=8532)	Patients, n (%)	1179 (13.8)	2286 (26.8)	5067 (59.4)
	Age (years)	40.0 (2.88)	40.5 (2.73)	41.0 (3.40)
	BMI (kg/m ²)	25.8 (5.92)	26.1 (8.19)	25.2 (5.10)
	Day 3 FSH (mIU/mL)	11.1 (11.00)	10.8 (10.29)	11.7 (13.74)
	AFC	9.2 (6.00)	8.7 (5.17)	8.6 (5.17)
	AMH (ng/mL)	1.20 (2.08)	0.97 (1.40)	1.11 (1.54)
Intermediate prognosis: unexplained infertility, all ages (n=13,787)	Patients, n (%)	5085 (36.9)	5068 (36.8)	3634 (26.4)
	Age (years)	32.9 (3.85)	34.4 (4.29)	35.3 (4.11)
	BMI (kg/m ²)	24.7 (5.18)	25.3 (6.68)	24.9 (4.99)
	Day 3 FSH (mIU/mL)	7.18 (2.69)	7.60 (3.55)	7.64 (3.57)
	AFC	17.3 (8.53)	14.7 (7.63)	14.8 (7.81)
	AMH (ng/mL)	3.48 (3.15)	3.14 (3.11)	2.70 (2.79)
Best prognosis: OD/PCOS, <35 years (n=9819)	Patients, n (%)	6013 (61.2)	2340 (23.8)	1466 (14.9)
	Age (years)	29.3 (3.02)	29.6 (2.88)	30.3 (2.66)
	BMI (kg/m ²)	28.0 (7.31)	27.7 (7.19)	27.0 (6.12)
	Day 3 FSH (mIU/mL)	6.11 (2.152)	6.08 (3.195)	6.19 (2.308)
	AFC	25.9 (11.28)	25.5 (11.36)	24.6 (11.43)
	AMH (ng/mL)	8.08 (6.88)	7.93 (7.17)	6.73 (5.90)

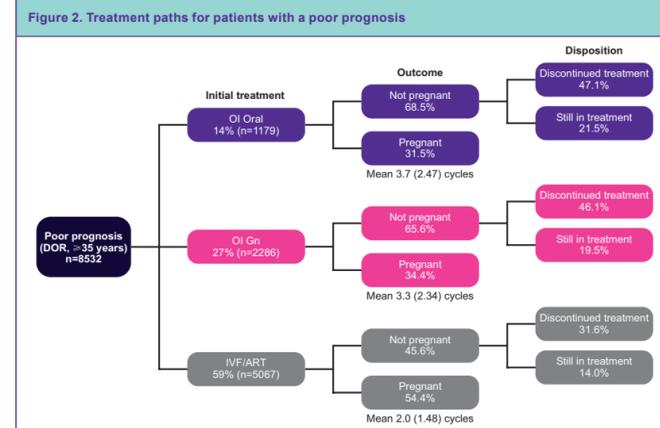
Data reported as mean (SD) unless otherwise specified. AFC, antral follicle count; AMH, anti-Müllerian hormone; ART, assisted reproductive technology; BMI, body mass index; DOR, diminished ovarian reserve; FSH, follicle-stimulating hormone; Gn, gonadotropin; IVF, in vitro fertilization; OD, ovulatory disorder; OI, ovulation induction; PCOS, polycystic ovary syndrome.



Percentages may not add up to 100 due to rounding. *All treatment-naïve patients of all diagnoses and ages, included patients that were not part of the example prognoses: *Patients with DOR (≥35 years); *Patients with unexplained infertility of all ages; *Patients with ovulatory disorders or PCOS (<35 years). ART, assisted reproductive technology; DOR, diminished ovarian reserve; Gn, gonadotropin; IVF, in vitro fertilization; OI, ovulation induction; PCOS, polycystic ovary syndrome.

Fertility treatment paths

- A depiction of the patient journey taken through clinical treatment is provided for the subgroup of patients with a poor prognosis (DOR, age ≥35 years; Figure 2). These older patients most often began their treatment with IVF/ART.

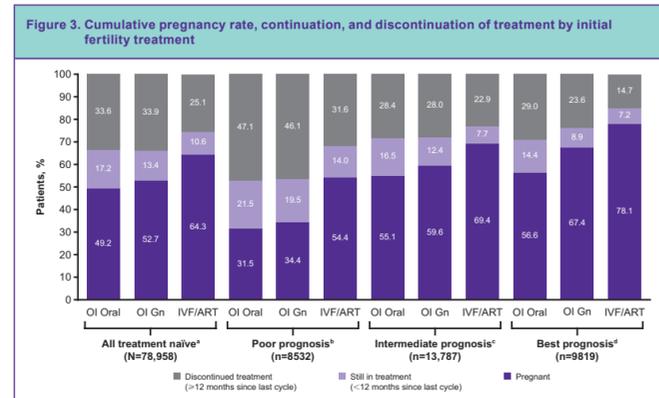


Percentages may not add up to 100 due to rounding. Number of cycles reported as mean (standard deviation). Discontinued treatment defined as not pregnant and >12 months since last cycle; still in treatment, not pregnant and <12 months since last cycle. ART, assisted reproductive technology; DOR, diminished ovarian reserve; Gn, gonadotropin; IVF, in vitro fertilization; OI, ovulation induction.

- Patients with best or intermediate prognoses were more likely to start their clinical journey with OI Oral or OI Gn (Figure 1).
- Conversely, patients with poor prognosis were more likely to start directly with IVF/ART (Figure 1).

Pregnancy outcomes

- Cumulative pregnancy rates were higher in patients with best or intermediate prognoses compared with patients with poor prognosis, irrespective of the treatment initiated (Figure 3).
- The proportion of patients who achieved a pregnancy was highest among those who initiated treatment with IVF/ART, regardless of prognosis (Figure 3).



Percentages may not add up to 100 due to rounding. *All treatment-naïve patients of all diagnoses and ages, included patients that were not part of the example prognoses: *Patients with DOR (≥35 years); *Patients with unexplained infertility of all ages; *Patients with ovulatory disorders or PCOS (<35 years). ART, assisted reproductive technology; DOR, diminished ovarian reserve; Gn, gonadotropin; IVF, in vitro fertilization; OI, ovulation induction; PCOS, polycystic ovary syndrome.

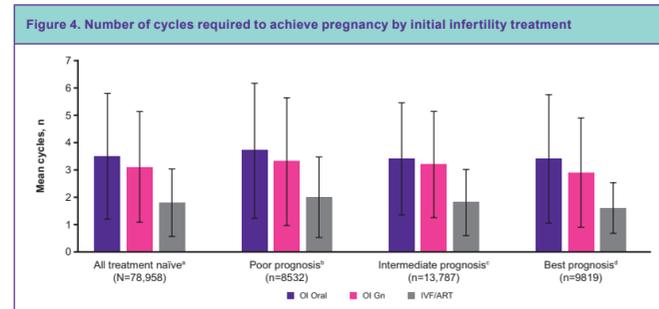
- Among patients who start treatment with OI Oral or OI Gn, a large percentage (26–48%) of pregnancies resulted from IVF/ART after OI failed (Table 2).

Patient group	Initial treatment	Proportion of pregnancies from IVF/ART (%)
All treatment naïve* (N=78,958)	OI Oral	36.4
	OI Gn	42.7
Poor prognosis: DOR, ≥35 years (n=8532)	OI Oral	41.8
	OI Gn	47.6
Intermediate prognosis: unexplained infertility, all ages (n=13,787)	OI Oral	46.2
	OI Gn	46.6
Best prognosis: OD/PCOS, <35 years (n=9819)	OI Oral	26.1
	OI Gn	34.5

*All treatment-naïve patients of all diagnoses and ages, included patients that were not part of the example prognoses. ART, assisted reproductive technology; DOR, diminished ovarian reserve; Gn, gonadotropin; IVF, in vitro fertilization; OI, ovulation induction; PCOS, polycystic ovary syndrome.

Time to pregnancy

- Patients who started treatment with OI Oral required more cycles to achieve pregnancy than those who started with IVF/ART (mean 3.5 vs 1.8 cycles) (Figure 4).



Data are presented as mean number of cycles to achieve pregnancy ± standard deviation. *All treatment-naïve patients of all diagnoses and ages, included patients that were not part of the example prognoses: *Patients with DOR (≥35 years); *Patients with unexplained infertility of all ages; *Patients with ovulatory disorders or PCOS (<35 years). ART, assisted reproductive technology; DOR, diminished ovarian reserve; Gn, gonadotropin; IVF, in vitro fertilization; OI, ovulation induction; PCOS, polycystic ovary syndrome.

Treatment discontinuation

- A higher percentage of patients who started their treatment journey with OI Oral or OI Gn discontinued fertility treatment without a pregnancy (ie, were not pregnant ≥12 months since the last treatment cycle) compared with those who started with IVF/ART (Figure 3).
- Similarly, a greater proportion of patients treated with OI Oral or OI Gn did not achieve pregnancy and were still on their fertility treatment journey (ie, <12 months since the last treatment cycle, as of December 31, 2015 [last available data]) compared with patients who were treated with IVF/ART (Figure 3).

CONCLUSIONS

- The path that infertility patients took through clinical treatment was impacted by their diagnosis- and age-based prognosis
- Beginning their treatment with IVF/ART rather than OI resulted in higher cumulative pregnancy rates, fewer total treatment cycles (ie, shorter time to pregnancy), and lower rates of treatment discontinuation without a pregnancy.
- The advantage of IVF/ART was greatest among patients with poorer prognosis.
- These results favor initiating treatment with IVF/ART to provide a more patient-centric approach to treatment—offering a higher likelihood of pregnancy, shorter time to pregnancy, and less potential for discontinuation without a positive outcome—unless a patient has a strong personal preference for less invasive approaches.

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ACKNOWLEDGMENTS

The authors thank Joanna Rakoczy, PhD, of Caudex, Oxford, UK (supported by EMD Serono, Inc.,* Rockland, MA, USA) for editorial assistance in drafting the poster, collating the comments of authors, and assembling tables and figures. Study supported by EMD Serono, Inc.,* Rockland, MA, USA.

DISCLOSURES

MCM and BH are employees of EMD Serono, Inc.,* Rockland, MA, USA. GLM is an employee of Shady Grove Fertility Center, Annapolis, MD, USA. KSR is an employee of Fertility Science Consulting, Silver Spring, MD, USA. GDB has consulted for EMD Serono, Inc.* SA is a former employee of Prometrika, LLC, which received funding from EMD Serono, Inc.* to run the analyses.

*A business of Merck KGaA, Darmstadt, Germany.



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