



Real-World Insights on Controlled Ovarian Stimulation for IVF/ICSI: Data from a Large Fertility EMR Database in the US (2010 - 2024)



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OBJECTIVE

To characterize real-world ovarian stimulation patterns across 42 fertility clinics in the US from 2010 to 2024.

KEY TAKEAWAYS

- Mixed protocols combining rFSH and HP-hMG were the predominant stimulation protocol in our US cohort, with most patients starting at 300 IU rFSH and 150 IU HP-hMG per day (3:1 FSH to LH bioactivity ratio).
- Starting doses of rFSH and HP-hMG increased with age and decreased with baseline AMH level.
- Dose adjustments were made frequently during stimulation, suggesting a high degree of individualization by physicians.
- Overall variability in gonadotropin dosing patterns and frequent dose adjustments in our study suggest that administration of gonadotropins as a fixed-dose ratio may not be compatible with current practice focused on individualization of treatment.

Abbreviations

ART, assisted reproductive technology; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; rFSH, recombinant follicle-stimulating hormone; HP-hMG, highly purified-human menopausal gonadotropin; LH, luteinizing hormone; BMI, body mass index; IU, international unit.

References

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Disclosures

MY and DB are employees of Ferring Pharmaceuticals Ltd., West Drayton, UK
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BACKGROUND

- In the United States, the use of assisted reproductive technology (ART) continues to increase and is influenced by multiple factors, including variations in clinical practice, patient preferences, insurance coverage, and patient demographics^{1,2}.
- Ovarian stimulation practices for IVF/ICSI cycles vary widely across clinics, with clinicians tailoring gonadotropin selection, dosing, dosage adjustments, and the balance of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) bioactivity to individual patients.
- Though these clinical decisions are central to treatment effectiveness and patient outcomes, large-scale real-world evidence describing ovarian stimulation treatment patterns and bioactivity ratios in routine practice remains limited in the US³.
- This study aims to characterize real-world ovarian stimulation patterns across 42 fertility clinics in the US from 2010 to 2024.

METHODS

- Study design:** Retrospective observational study using de-identified EMR data on IVF/ICSI cycles starting from January 1, 2010 to December 31, 2024 in 42 U.S. fertility clinics.
- Data source:** Cercle database, a large-scale harmonized and curated multi-center EMR dataset integrated via Cercle's Biomedical Graph™, with rigorous de-identification (Safe Harbor Method) and quality assurance/validation processes.
- Study population:** Autologous, non-donor IVF/ICSI cycles reaching oocyte retrieval; exclusions applied for social-freezing cycles, cancelled cycles, missing key variables, or biologically implausible values.
- Variables and outcomes:** Baseline patient characteristics (age, BMI, AMH, infertility diagnosis, etc.) and stimulation treatment patterns (protocol type, gonadotropin dosage, dose adjustments, stimulation duration, and FSH:LH bioactivity ratios, etc.) were described.
- Statistical analysis:** Descriptive analyses of patient characteristics and treatment patterns, with subgroup analyses by age, BMI, and AMH; analyses conducted in R (v4.5.2).

RESULTS

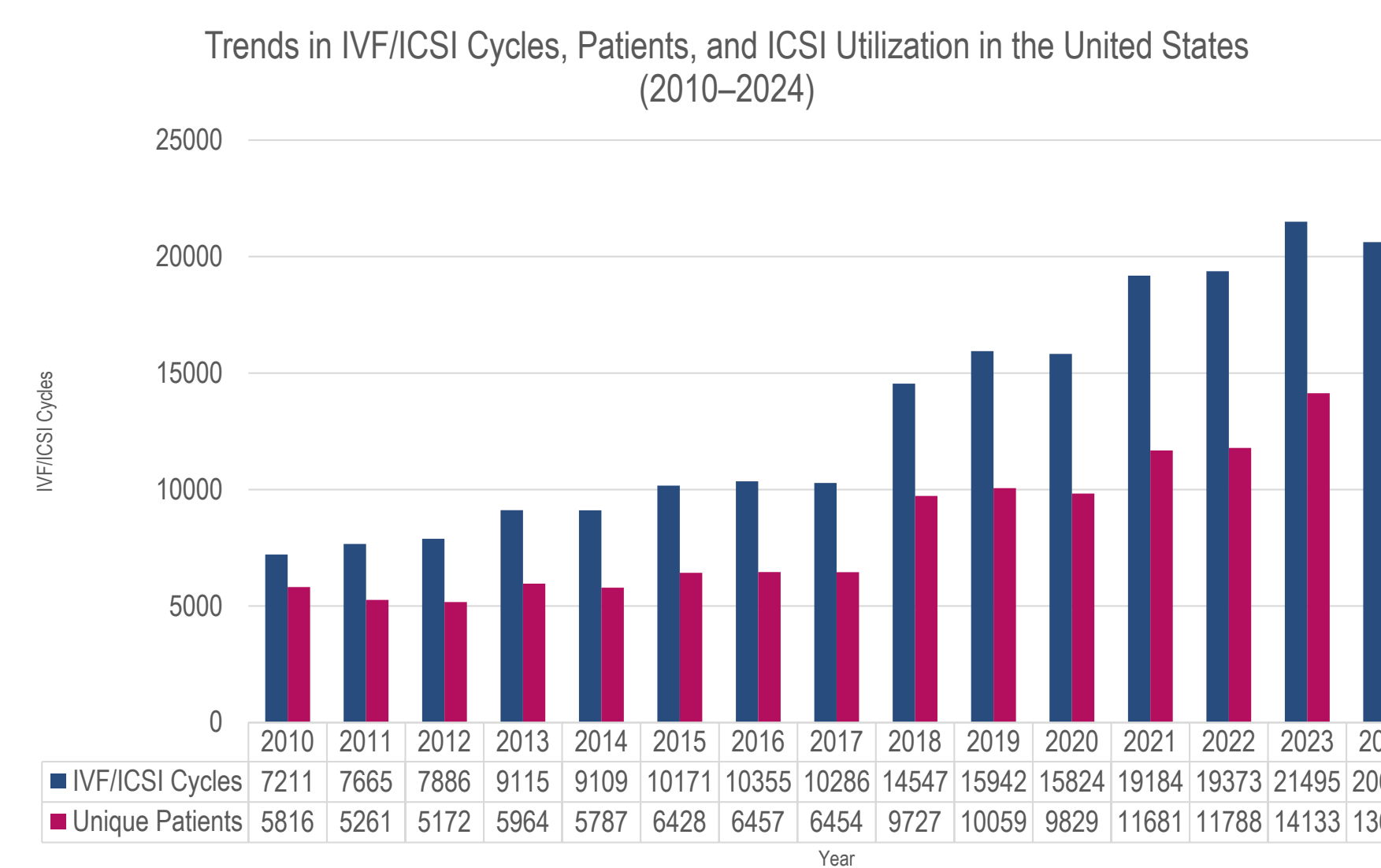
- A total of 223,639 cycles were available for analysis in the Cercle dataset. After applying the pre-specified inclusion and exclusion criteria, a total of 198,782 cycles from 128,166 patients were included in the final analyses.

TABLE 1 Baseline Patient Clinical and Demographic Characteristics at the Index Cycle (N=128,166)

Variable	n	%
Age: Mean age= 36 [IQR=33-39]		
Age <35	49,704	38.8
Age 35-38	42,514	33.2
Age ≥ 39	35,948	28.0
BMI (kg/m²): Mean BMI = 25.1 kg/m² [IQR: 21.5-28.7]		
Underweight BMI <18.5	2253	1.8
Normal BMI 18.5 - <25	58,018	45.3
Overweight BMI 25 - <30	35,329	27.6
Obese BMI ≥30	28,130	21.9
Missing BMI ^a	4436	3.5
AMH (ng/mL): Median AMH = 2.2 ng/mL [IQR: 0.7-3.7]		
Low AMH <1	18,342	14.3
Normal AMH 1 - <5	50,078	39.1
High AMH ≥5	14,764	11.5
Missing AMH	44,982	35.1
Race/ethnicity		
White	45,422	35.4
Asian	14,123	11.0
Black or African American	8484	6.6
Hispanic or Latino	6324	4.9
Native Hawaiian or Other Pacific Islander	217	0.2
American Indian or Alaska Native	201	0.2
Other	906	0.7
Missing race/ethnicity	52,489	41.0
Infertility diagnosis^b		
Male infertility factor	25,899	20.2
Diminished ovarian reserve	21,201	16.5
Age	12,724	9.9
Polycystic ovary syndrome	12,222	9.5
Tubal factor	6245	4.9
Endometriosis	4987	3.9
Other	21,996	17.2
Missing or unknown	62,497	48.8

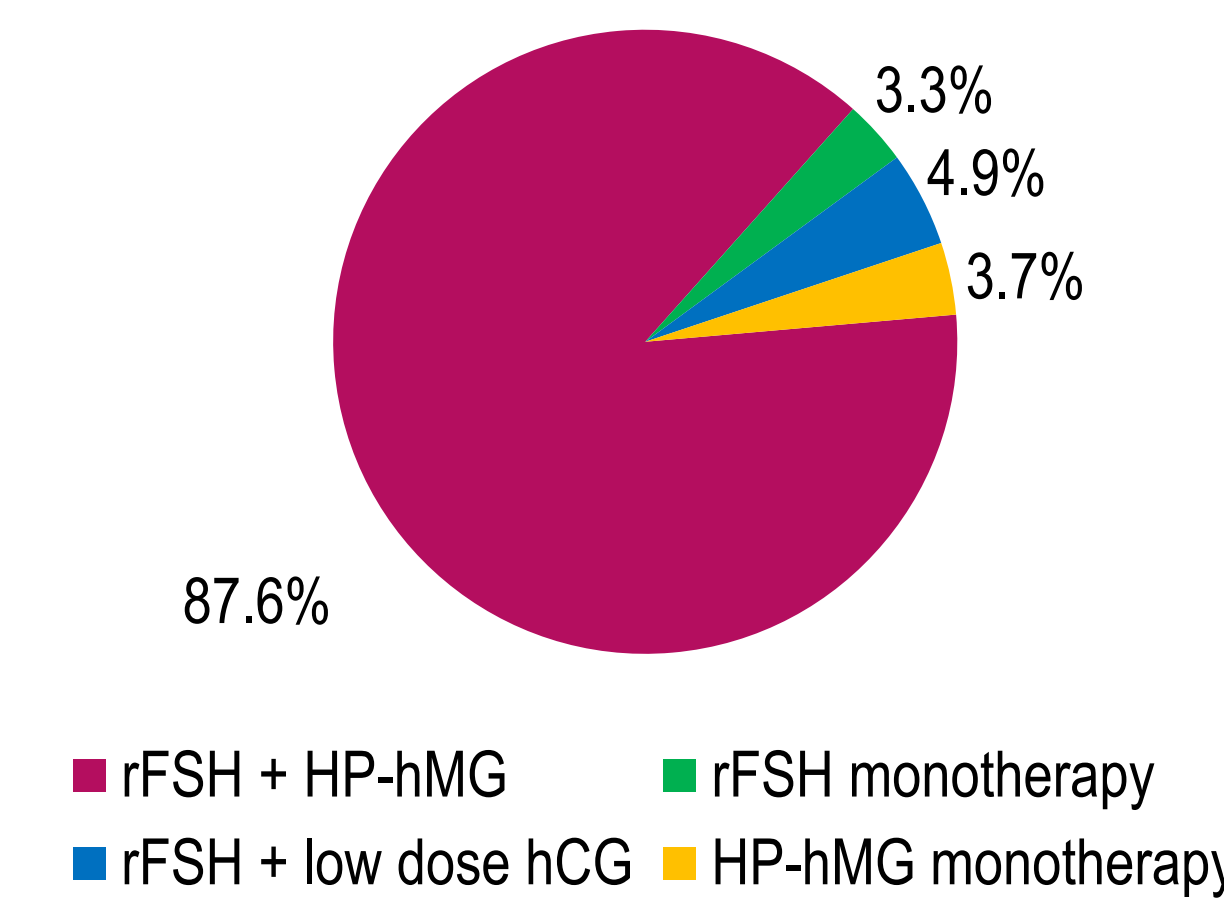
^aMissing AMH data may partially reflect gradual uptake of AMH testing in the early years of the dataset.
^bPatients may have more than one infertility diagnosis recorded.

FIGURE 1 Overall ART Utilization



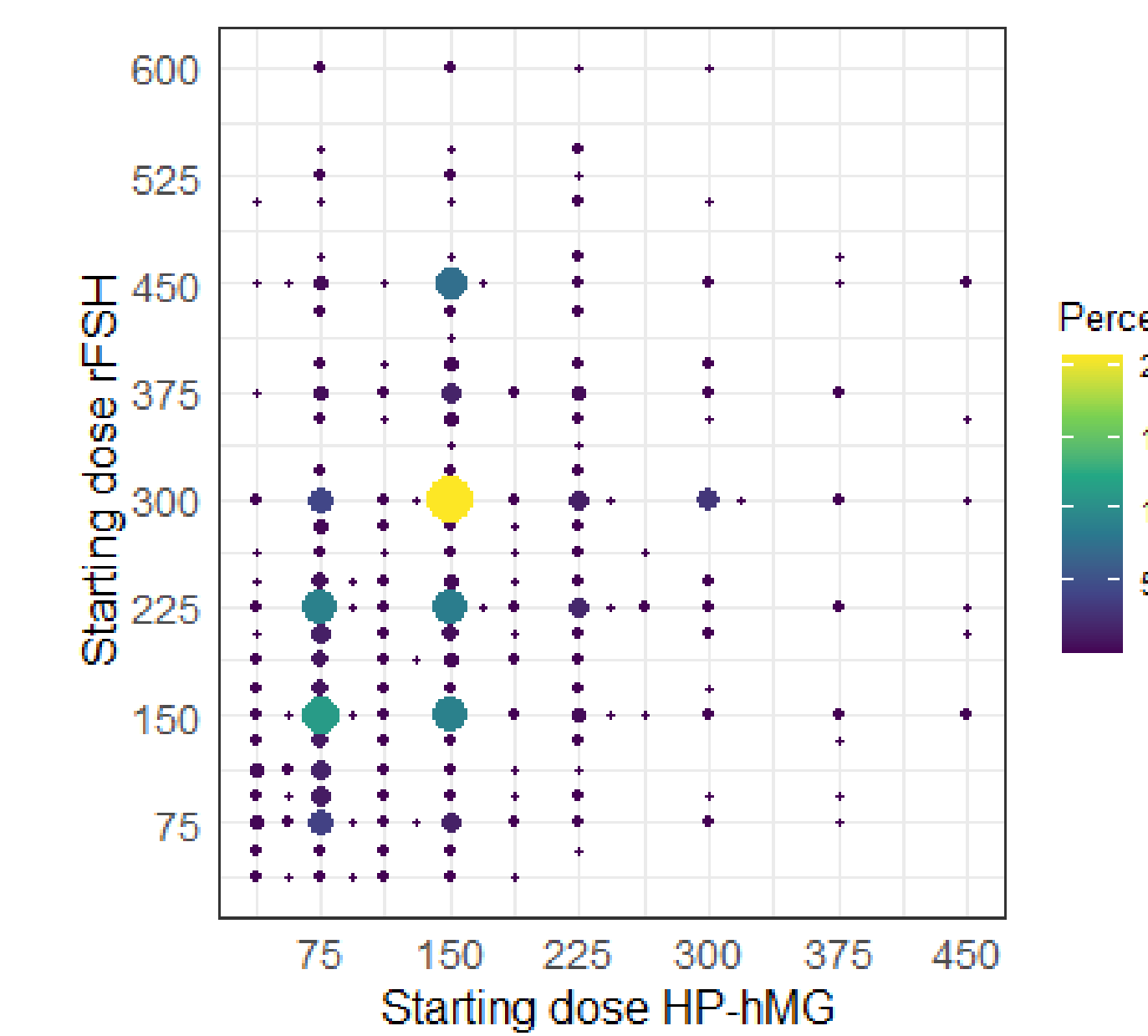
- IVF/ICSI volume increased substantially across the study period (Figure 1). The total number of cycles rose from 7,211 in 2010 to 20,619 in 2024, with particularly pronounced growth observed after 2018. The number of unique patients increased from 5,816 in 2010 to 13,610 in 2024.
- The proportion of cycles utilizing ICSI remained relatively stable over time, ranging between 70% and 80% (data not shown).

FIGURE 2 Stimulation Protocols



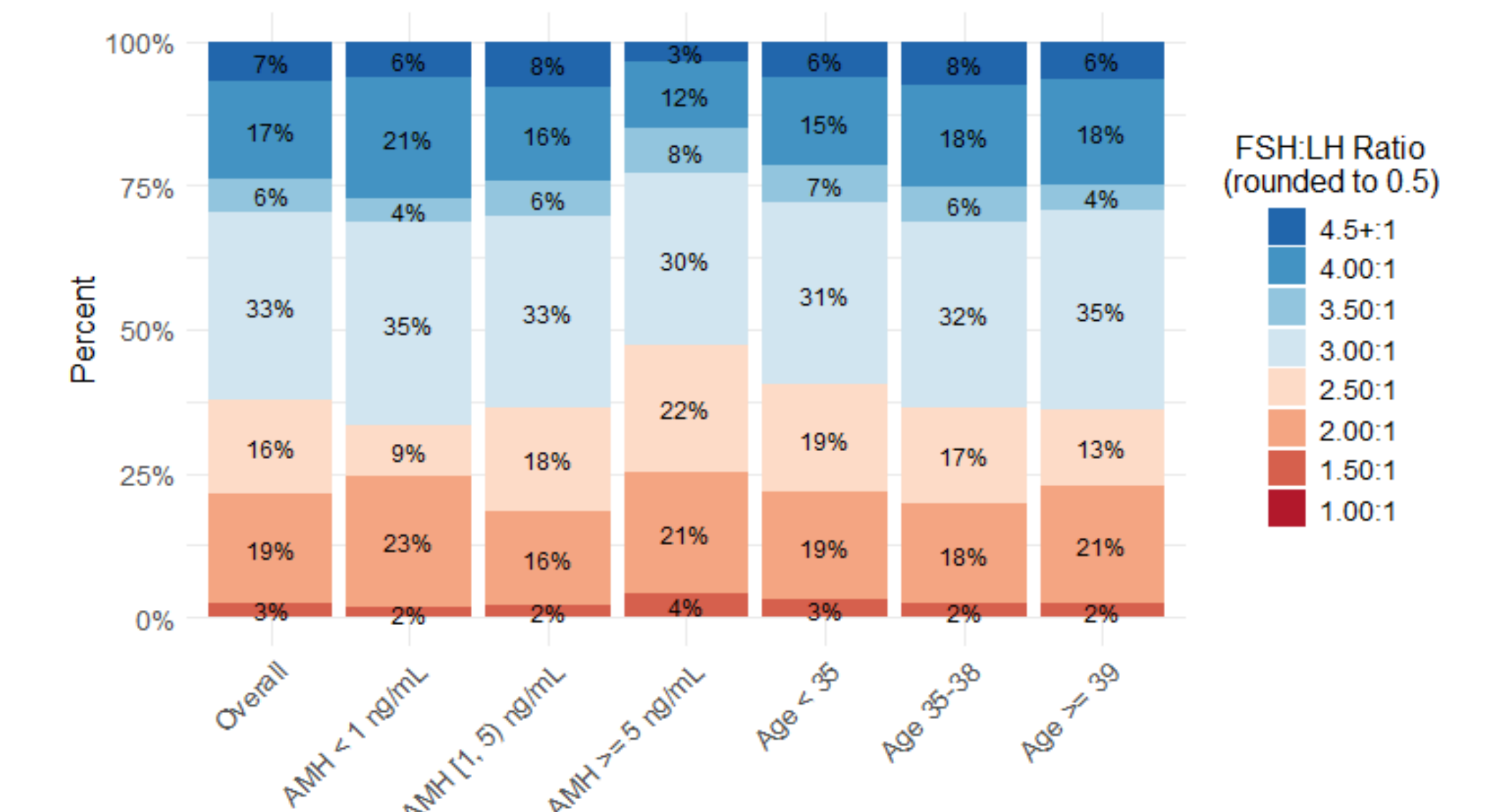
- 77.5% of cycles (n=153,540) used antagonist down-regulation protocols.
- Mixed protocols combining rFSH with HP-hMG was the predominant stimulation protocol, used in 87.6% of all cycles (Figure 2).
- Among mixed protocol cycles, 94.9% started rFSH and HP-hMG concurrently on day 1 of stimulation; 5.1% started on different days.
- The use of mixed protocols (rFSH + HP-hMG) increased over time, rising from approximately 34,181 cycles (83.4%) in 2010-2014 to 84,548 cycles (87.6%) in 2020-2024.
- The median duration from stimulation start to trigger was 10.0 days (IQR: 8.5-11.5), with a mean of 10.6 days (SD 1.9).

FIGURE 3 Gonadotropin Dosage in Mixed Protocols



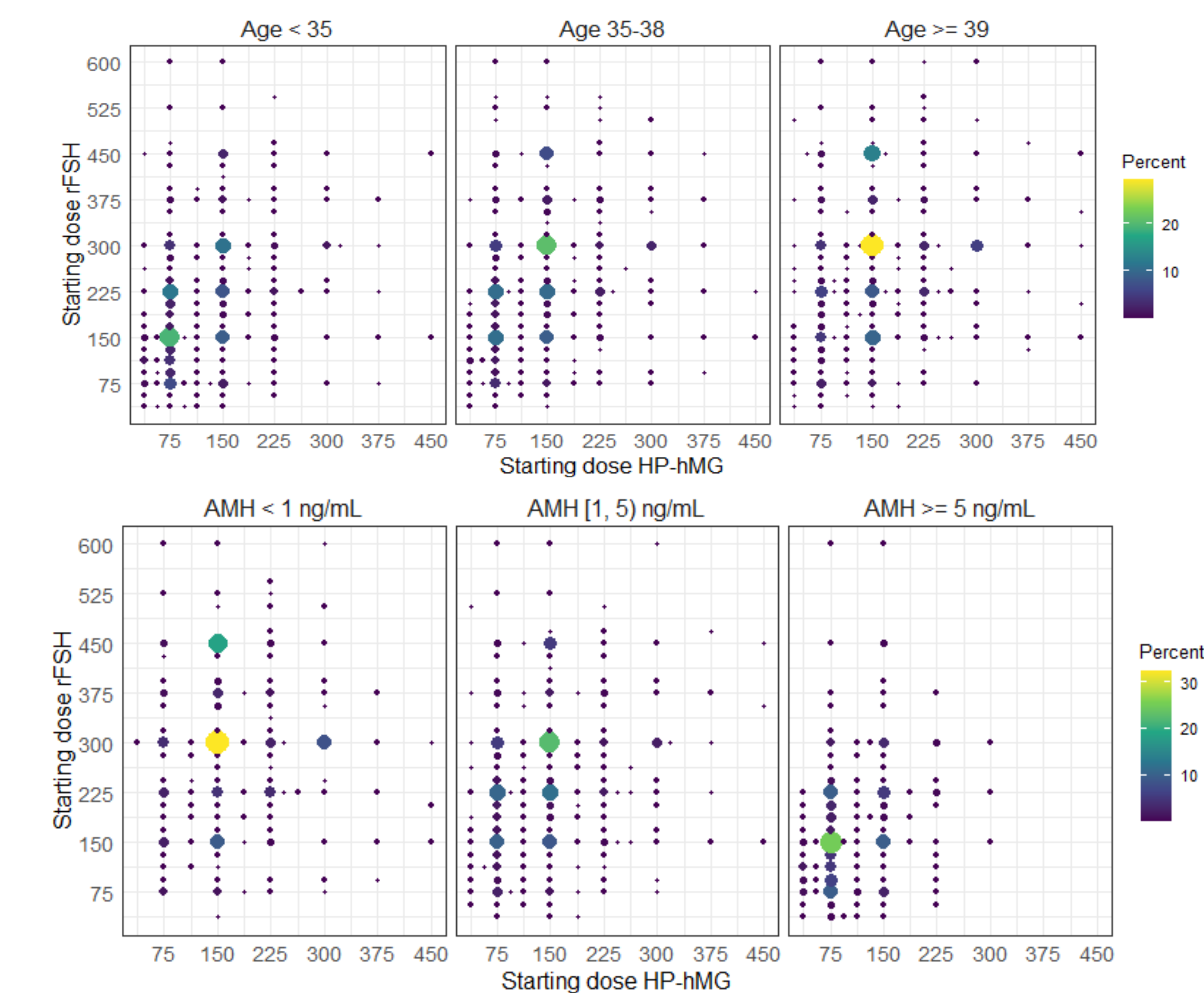
- Overall, the most common starting doses used in mixed protocols were 150 IU HP-hMG and 300 IU rFSH per day (Figure 3). They were also the most common average daily doses of HP-hMG and rFSH.
- For rFSH, 38.9% of cycles had at least one dose increase and 38.4% had at least one dose decrease during stimulation, with a median dose adjustment of +/-150 IU.
- For HP-hMG, 48.1% of cycles had at least one dose increase and 13.0% had at least one dose decrease during a stimulation cycle, with a median dose adjustment of +/-75 IU.

FIGURE 4 FSH:LH Bioactivity Ratio in Mixed Protocols



- The most common FSH:LH bioactivity ratio was 3:1, accounting for over 30% of all mixed-protocol cycles (Figure 4). **Note:** HP-hMG provides 1:1 ratio of FSH:LH.
- Mixed-protocol cycles with an FSH:LH bioactivity ratio of 3:1 or higher comprised approximately 62.1% of all mixed-protocol cycles, reflecting the predominant practice pattern.

FIGURE 5 Gonadotropin Exposure by Age, AMH and BMI



- Higher gonadotropin doses were observed in older patients and patients with lower AMH levels (Figure 5).
- Differences in gonadotropin dosing patterns across BMI categories were less pronounced (data not shown).