Increased odds of live birth in fresh in vitro fertilization cycles with shorter ovarian stimulation

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Objective: To investigate the impact of prolonged ovarian stimulation on pregnancy outcomes in IVF cycles with fresh day 3 ET.
Design: Retrospective cohort study.
Setting: University-affiliated center.
Patient(s): All patients initiating their first IVF cycle with fresh day 3 ET. Prolonged ovarian stimulation was defined as a duration of more than two standard deviations (95th percentile) for the study cohort (i.e., >13 days).
Intervention(s): None.
Main Outcome Measure(s): Live birth rate was considered the primary outcome and was compared between patients undergoing ovarian stimulation for ≤13 days and >13 days. Odds ratios (OR) with 95% confidence intervals (CI) for all pregnancy outcomes after day 3 ET were calculated. The OR for live birth was adjusted using logistic regression.
Result(s): A total of 6,410 and 339 patients underwent ovarian stimulation for ≤13 days and >13 days, respectively. There were no differences in the demographics or mean number of day 3 embryos transferred between the two groups. Ovarian stimulation ≤13 days was associated with increased odds of clinical pregnancy (OR 2.15, 95% CI 1.19–3.89) and live birth (OR 2.35, 95% CI 1.25–4.43). The increased odds for live birth in the ≤13-day group remained unchanged after logistic regression. Patients with clinical pregnancies in the >13-day group were younger (34.6 ± 4.91 years) compared with those who did not conceive (38.2 ± 4.72 years).
Conclusion(s): Our findings suggest that ovarian stimulation ≤13 days is associated with increased odds of clinical pregnancy and live birth. In patients undergoing ovarian stimulation >13 days, younger age is associated with live birth. (Fertil Steril® 2017;107: 104–9. ©2016 by American Society for Reproductive Medicine.)
Key Words: In vitro fertilization, prolonged ovarian stimulation, prolonged gonadotropin stimulation, pregnancy outcomes

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In vitro fertilization has gained popularity during the past 2 decades as a treatment modality to overcome infertility. Global data suggest that approximately 4,461,309 IVF cycles were initiated between 2008 and 2010, resulting in the birth of 1,144,858 live-born infants (1). In the United States, 160,521 IVF cycles were performed across 467 fertility clinics, contributing to 1.6% of all live births in 2013 (2). The increasing use and success of IVF worldwide has been predominantly due to the optimization of associated clinical and laboratory protocols (3). However, several patient or laboratory-related variables, either modifiable or nonmodifiable, may still impact overall IVF outcomes.

Ovarian stimulation is one such modifiable variable that has been evaluated extensively since the inception of IVF. Specifically, previous studies have investigated the effect of various ovarian stimulation protocols (step-down or step-up; long or short), gonadotropin type and combinations, and gonadotropin doses on IVF outcomes (4–8). Of these, at least two studies (6, 7) have reported a detrimental effect of prolonged ovarian stimulation on IVF outcomes. Prolonged ovarian stimulation, and therefore a higher cumulative gonadotropin dose, is thought to directly impact oocyte/embryo quality or the early implantation environment (8). For example, in vitro studies in mice have shown that exposure to high doses of

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gonadotropins can accelerate nuclear maturation and induce chromosomal abnormalities (9). Furthermore, the aneuploidy rates of luteinized human granulosa cells (GCs) were noted to be higher with increasing doses of gonadotropins (10). Prolonged ovarian stimulation is also known to induce embryo–endometrial asynchrony (8, 11), thereby decreasing the implantation potential of embryos.

Although these findings are notable, several clinical studies reporting lower pregnancy rates (PRs) and live birth rates in IVF cycles with prolonged ovarian stimulation included patients with diminished ovarian reserve (4) and polycystic ovarian syndrome (PCOS), a known risk factor for longer stimulation (6, 7). Furthermore, these studies also included a wide range of ovarian stimulation protocols (5–7). Thus, in this study, we investigate the impact of prolonged ovarian stimulation on pregnancy outcomes in patients with non-PCOS and normal responders undergoing IVF cycles with fresh day 3 ET.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

All couples initiating their first IVF cycle with fresh day 3 ET at the Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine between January 2008 and June 2015 were analyzed for potential inclusion. For the purpose of this study, only patients undergoing ovarian stimulation with GnRH antagonist (GnRH-a)-based protocols were included. Patients with known PCOS as diagnosed by the Rotterdam criteria, patients with diminished or poor ovarian reserve defined by cycle day 2/3 FSH level >12 mIU/mL or cycle day 2/3 antimüllerian hormone level <1 ng/mL, and any prior IVF-ET cycles were excluded. Also excluded from the analysis were any IVF cycles canceled before oocyte retrieval, with incomplete records, or those using surgically retrieved sperm or donor oocytes. Our analysis was also limited to patients undergoing fresh ET of cleavage-stage (day 3) embryos. The Weill Cornell Medical College institutional review board approved the retrospective study protocol.

Clinical, Laboratory, and Sperm Preparation Protocols

All patients underwent evaluation of the uterine cavity with saline infusion sonogram before ovarian stimulation (12). Ovarian stimulation, hCG trigger, oocyte retrieval, embryo culture, and ET were carried out based on previously described protocols (12). Gonadotropin dosing for ovarian stimulation was based on patient age, body mass index (BMI, in kilograms per meter squared), antral follicle count, and serum antimüllerian hormone level. Patients requiring pretreatment before ovarian stimulation were started on either 0.1-mg E_2 patches (Vivelle-Dot estradiol transdermal system, Novartis Pharmaceuticals Corporation) or oral contraceptive (OC) pills (ORTHO-NOVUM 1 mg norethindrone and 0.035 mg ethinyl estradiol, Ortho-McNeil-Janssen Pharmaceuticals, Inc.) in the preceding luteal phase. Patients received OC pills for 10–14 days for luteal pretreatment and patients on an extended course of OC pills before ovarian stimulation were excluded from the analysis.

Ovarian stimulation was performed with gonadotropins (Follistim, Merck; Gonal-F, EMD-Serono Inc.; and Menopur, Ferring Pharmaceuticals Inc.), with ovulation being suppressed with once daily 0.25 mg ganirelix acetate (Merck) injections based on a previously described flexible protocol (13). hCG (Novarel, Ferring Pharmaceuticals Inc. or Pregnyl, Merck) was used as the ovulation trigger. In general, the hCG trigger was administered when the two lead follicles attained a mean diameter >17 mm and according to a sliding scale (10,000 IU for E_2 <1,500 pg/mL, 5,000 IU for E_2 1,501–2,500 pg/mL, 4,000 IU for E_2 2,501–3,000 pg/mL, and 3,300 IU for E_2 >3,001 pg/mL). Oocyte retrieval was performed 34–35 hours after hCG administration under transvaginal ultrasound guidance with conscious sedation. Intramuscular P (50 mg daily) was begun the day after oocyte retrieval for luteal support in all patients, irrespective of the hCG trigger dose (12).

Semen samples produced on the day of oocyte retrieval were evaluated for volume, count, concentration, and motility using World Health Organization criteria (14). Fertilization of oocytes was carried out with either conventional in vitro insemination or intracytoplasmic sperm injection (ICSI), depending on the semen sample and the couple's reproductive history (15). Oocytes were examined 12–17 hours after insemination or sperm injection for fertilization and the resulting embryos were incubated in in-house culture media (15). Cleavage-stage embryos were graded based on the Veeck criteria (16). All fresh ETs were performed on day 3 with Wallace catheters (Smiths Medical Inc.). No significant changes occurred in laboratory conditions, culturing, or ET technique during the study period. Embryos that were taken to biopsy for preimplantation genetic diagnosis or screening were excluded.

Study Variables

Demographic and baseline characteristics recorded for each patient included age, gravidity, parity, BMI (in kilograms per meter squared), infertility diagnosis, cycle day 2/3 antimüllerian hormone (in nanograms per milliliter) level, and cycle day 2/3 FSH (in milliinternational units per milliliter) level. Ovarian stimulation parameters recorded were total days of ovarian stimulation, total days of GnRH-a administration, total dosage of gonadotropins administered (in international units), E_2 level (in pictograms per milliliter) on the day of trigger, peak endometrial thickness (in millimeters), total number of oocytes retrieved, and mature oocytes. The percentage of ICSI cycles, fertilization rate (%), and supernumerary embryos available for cryopreservation was also recorded. The pregnancy outcomes assessed after day 3 ET included biochemical pregnancy, clinical pregnancy, spontaneous miscarriage, and live birth rates. A biochemical pregnancy was defined as positive hCG without a gestational sac. Clinical PR was defined as the number of intrauterine gestations with fetal cardiac activity per IVF-ET cycle. Any pregnancy loss after visualization of an intrauterine gestation was considered a spontaneous miscarriage

TABLE 1

Comparison of demographic and baseline characteristics of study cohort (n = 6,749).

Parameter	≤13 days (n = 6,410)	> 13 days (n = 339)	*P* value
Age (y)	37.7 (±4.51)	37.6 (±4.78)	.69
Gravidity	1.42 (±0.32)	1.43 (±0.34)	.58
Parity	0.71 (±0.43)	0.74 (±0.51)	.29
BMI (kg/m^2)	23.3 (±6.31)	23.4 (±6.59)	.78
Infertility diagnoses			.54
Ovulatory	2,138 (33.4%)	112 (33.0%)	
Tubal	603 (9.41%)	37 (10.9%)	
Endometriosis	331 (5.16%)	23 (6.78%)	
Male factor	2,145 (33.5%)	101 (29.8%)	
Idiopathic	512 (7.99%)	40 (11.8%)	
Other	681 (10.6%)	26 (7.67%)	
Cycle day 2/3 FSH level (mIU/mL)	5.41 (±2.27)	5.58 (±2.31)	.18
Cycle day 2/3 AMH level (ng/mL)	1.89 (±0.99)	1.91 (±1.02)	.59

Note: Data are presented as mean (± SD) or n (%). AMH = antimüllerian hormone; BMI = body mass index.

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and any birth after 24 weeks of gestation was considered a live birth.

Statistical Analysis

Continuous variables were checked for normality using the Shapiro-Wilk's test, expressed as mean ± SD, with independent *t*-tests used for statistical comparisons. Categorical and nonparametric variables were expressed as number of cases with percentage of occurrence and median (interquartile range). Wilcoxon signed-rank tests, McNemar's χ^2 tests, and Kruskal-Wallis tests were used as required for these variables. Odds ratios (ORs) with 95% confidence intervals (CIs) for pregnancy outcomes after day 3 ET were calculated. Logistic regression was used to calculate the adjusted OR for live birth after controlling for the following variables: age (<35 years vs. 35–37 or 30–40 years); hCG trigger dose (10,000 IU vs. 5,000, 4,000, or 3,000 IU); starting gonadotropin dose (<150 IU vs. 150–225 or 225–300 IU); number of follicles >10 mm on cycle day 6 (<5 vs. 5–8 or >8); total gonadotropins administered (<3,000 IU vs. 3,000–4,000, 4,001–5,000, >5,000 IU); total days of GnRH-a (<4 days vs. 4–6 or >6 days); and total days of stimulation (≤13 days vs. >13 days). Statistical analyses were performed using STATA version 13 (StataCorp LP). Statistical significance was set at $P<.05$.

RESULTS

A total of 6,749 patients met inclusion criteria. The total days of ovarian stimulation of the study cohort was normally distributed. The mean duration of ovarian stimulation was 9.96 (±1.55) days, based on which >2 SD (95th percentile) for the study cohort was considered as prolonged ovarian stimulation (i.e., >13 days). Thus, 6,410 and 339 patients underwent ovarian stimulation for ≤13 days and >13 days, respectively. As evident in Table 1, there was no difference in the overall demographics and baseline characteristics of the study cohort. Table 2 summarizes the ovarian stimulation parameters of the study cohort. Of note, patients who underwent gonadotropin stimulation for >13 days had a longer duration of GnRH-a administration ($P<.001$) and more total dosage of gonadotropins administered ($P<.001$) compared with the ≤13-day group. No difference was noted in the total or mature oocytes retrieved and the fertilization rate. Patients in the ≤13-day group had more supernumerary embryos cryopreserved compared with the >13-day group ($P<.001$).

Pregnancy outcomes and the corresponding ORs after fresh day 3 ET are listed in Table 3. Ovarian stimulation ≤13 days was associated with increased odds of clinical pregnancy (OR 2.15, 95% CI 1.19–3.89) and live birth (OR 2.35, 95% CI 1.25–4.43). The adjusted OR for live birth was 2.22 (95% CI 1.38–3.57) in the ≤13-day group compared with the >13-day group, even after adjustment with logistic regression (Supplemental Table 1, available online). Supplemental Figure 1, available online, demonstrates the live birth and spontaneous miscarriage rates as a function of ovarian stimulation duration. A progressive decline in the live birth rate was noted, with no live births occurring after 20 days of gonadotropin stimulation. In contrast, the

TABLE 2

Comparison of controlled ovarian stimulation parameters of study cohort (n = 6,749).

Parameter	≤13 days (n = 6,410)	> 13 days (n = 339)	*P* value
Total days of GnRH antagonist	4.33 (±1.53)	5.89 (±2.28)	<.001
Total gonadotropins administered (IU)	3,582.8 (±1,897.7)	6,801.2 (±2,192.9)	<.001
E_2 on day of trigger (pg/mL)	1,468.2 (±686.1)	1,451.3 (±691.2)	.66
Peak endometrial thickness (mm)	10.4 (±4.82)	10.7 (±4.73)	.26
Number of oocytes retrieved	9 (6–14)	9 (7–12)	.99
Mature oocytes	8 (5–11)	8 (5–11)	.99
Gonadotropins administered per mature oocyte (IU/oocyte)	447.9	850.2	<.001
Fertilization rate (%)	82.3%	81.7%	.91
ICSI (%)	74.8%	73.7%	.86
Supernumerary embryos cryopreserved	1.11 (±0.26)	0.49 (±0.19)	<.001

Note: Data are presented as mean (± SD), median (interquartile range), or n (%). ICSI = intracytoplasmic sperm injection.

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TABLE 3

Univariate analysis of fresh day 3 IVF-ET outcomes of study cohort (n = 6,749).

Parameter	≤13 days (n = 6,410)	>13 days (n = 339)	Odds ratio (95% CI)	*P* value
Day 3 embryos transferred	2.71 (±1.01)	2.74 (±1.06)	–	.59
Biochemical pregnancy rate	628 (9.80%)	25 (7.37%)	1.37 (0.50–3.71)	.54
Clinical pregnancy rate	2,799 (43.7%)	90 (26.6%)	2.15 (1.19–3.89)	.01
Spontaneous miscarriage rate	390 (6.08%)	21 (6.19%)	0.98 (0.31–3.11)	.86
Live birth rate	2,409 (37.6%)	69 (20.4%)	2.35 (1.25–4.43)	<.001

Note: Data are presented as mean (± SD) or n (%). CI = confidence interval.

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spontaneous miscarriage rate remained relatively stable with increasing duration of ovarian stimulation. Table 4 is a subanalysis of all patients in the >13-day group to identify the characteristics associated with clinical pregnancy. Patients in the >13-day group who achieved clinical pregnancies were younger (34.6 ± 4.91 years) compared with those who did not conceive (38.2 ± 4.72 years; $P<.001$).

DISCUSSION

Our retrospective cohort study of 6,749 patients initiating their first IVF cycle with fresh day 3 ET demonstrates that ovarian stimulation ≤13 days is associated with increased odds of clinical pregnancy and live birth. Although these findings are consistent with previous studies (6, 7), the current study specifically assesses prolonged ovarian stimulation in patients with non-PCOS and normal responders undergoing IVF with GnRH-a-based protocols and fresh ET of cleavage-stage (day 3) embryos. Our findings suggest that ovarian stimulation ≤13 days is associated with 2.15 and 2.35 times greater odds of clinical pregnancy and live birth, respectively. Furthermore, roughly 28% of patients in the >13-day group achieve a clinical pregnancy, and are generally younger compared with those who do not achieve pregnancies.

Prior studies have demonstrated a detrimental impact of more ovarian stimulation requirements on fresh IVF-ET cycle outcomes. For example, Martin et al. (17) observed a significant inverse relationship between total gonadotropin requirements and PRs. Later studies ultimately revealed a relationship between duration of ovarian stimulation, independent of medication dose, and pregnancy outcomes, including that by Chuang et al. (6), who found that ≥13 days of ovarian stimulation decreased the likelihood of a live birth by 53% compared with cycles that were 10–12 days long. In addition, Royster et al. (18) compared the clinical PR and live birth rate among groups with varying stimulation lengths, and found a trend toward improved outcomes for the groups that underwent <10 days of gonadotropin administration or <4 days of GnRH-a use when compared with ≥10 days and ≥4 days, respectively. Finally, in their retrospective study of 663 fresh IVF-ET cycles, Ryan et al. (7) showed that the clinical PR was decreased when the duration of gonadotropin stimulation took ≥13 days, except in patients with PCOS.

These studies are important in that they sought to answer the question of how to best optimize IVF-ET outcomes by modifying the gonadotropin stimulation period. As postulated by these clinical studies and basic scientific investigations, prolonged ovarian stimulation can adversely impact oocyte quality (9, 10), as well as the early peri-implantation environment (10). Nonetheless, limitations to these studies exist. The population analyzed by Martin et al. (17) was composed entirely of patients undergoing GnRH-agonist-based protocols, as opposed to GnRH-a protocols used in the current study. In addition, the study compared patients based on a generic cut-off (i.e., whether they underwent ≥12 days of ovarian stimulation). The Chuang et al. (6) and Ryan et al. (7) studies included women undergoing ovarian stimulation with long luteal GnRH-agonist protocols, GnRH-agonist flare protocols, as well as GnRH-a protocols, and did not specify whether their conclusions held true

TABLE 4

Characteristics associated with clinical pregnancy after 13 days of ovarian stimulation (n = 339).

Parameter	Clinical pregnancy (n = 90)	No pregnancy (n = 249)	*P* value
Age (y)	34.6 (±4.91)	38.2 (±4.72)	<.001
Gravidity	1.49 (±0.52)	1.49 (±0.32)	.99
Parity	1.02 (±0.47)	1.05 (±0.42)	.57
BMI (kg/m^2)	23.2 (±6.36)	23.7 (±6.47)	.53
Total days of ovarian stimulation	15.1 (±1.69)	15.0 (±1.50)	.60
Total GnRH antagonist days	5.81 (±2.92)	6.01 (±2.14)	.49
Total gonadotropins administered (IU)	5,892.3 (±2,115.2)	5,812.5 (±2,152.1)	.76
E_2 on day of trigger (pg/mL)	1,436.4 (±677.1)	1,411.0 (±624.3)	.75
Peak endometrial stripe (mm)	12.2 (±2.76)	12.3 (±2.97)	.78

Note: Data are presented as mean (± SD). BMI = body mass index.

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when analyzing each subset of patients separately. Although Royster et al. (18) looked at only GnRH-a protocols, their results only showed a trend toward improved IVF-ET outcomes without reaching statistical significance.

Advantages of our study include a large sample size of 6,749 patients, all undergoing ovarian stimulation with GnRH-a protocols and fresh day 3 ET. In addition, patients with known PCOS, diminished or poor ovarian reserve, or history of poor response to gonadotropin stimulation were excluded, helping to elucidate the impact of prolonged stimulation in patients without confounding ovarian conditions. It is also important to note that the cut-off chosen for the study cohort was data specific (>2 SD or 95th percentile) and not based on post-hoc calculations. Furthermore, these data and cohort-specific cut-offs are consistent with generic cut-offs chosen in previous studies (6, 7). Given the retrospective nature of the study, we acknowledge some uncertainty in the replication of these findings in a prospective setting. However, it is worth noting that the sample sizes were adequately powered for live birth rates based on pre-existing literature (6). Specifically, post-hoc calculations suggest a sample size of 266 patients per group assuming an α-error of 5% and a power of 80% based on the Chuang et al. (6) study, which showed a 10.3% difference in live birth rates after a median duration of 11 days of ovarian stimulation (29.1%) versus >13 days of ovarian stimulation (18.8%). By study design, only normal responders receiving pure hCG triggers were included in the study cohort. Consequently, our findings may not be applicable to hyper-responders or patients with PCOS receiving pure GnRH-agonist triggers or combined GnRH-agonist and hCG triggers. Finally, we limited our analysis to patients undergoing fresh ET of day 3 embryos to avoid embryo–endometrial asynchrony as a confounder with blastocyst transfers; however, P levels were not measured on the day of hCG trigger in the current study. Therefore, it is possible that endometrial asynchrony could still contribute to the lower clinical PR and live birth rate noted in the >13-day group.

Although our retrospective analysis was not designed to address cancelation of IVF cycles in the setting of prolonged ovarian stimulation, our findings do highlight that live births may occur in patients <35 years until 19 days of ovarian stimulation. Whereas we posit that the duration of ovarian stimulation is a variable during IVF cycles that can be potentially optimized, we recognize that doing so may not be possible in all cases. Specifically, prolonged ovarian stimulation, even in the setting of normal cycle day 2/3 antimüllerian hormone and FSH levels, may indicate ovarian dysfunction in responding to exogenous gonadotropins (6, 8). Even when the oocyte yield is adequate in such situations, patients with prolonged ovarian stimulation may have compromised embryo quality, as highlighted by the lower rate of blastocyst transfers in the Chuang et al. (6) study or the lower number of supernumerary embryos cryopreserved in our study. The lower number of cryopreserved embryos also suggests that prolonged ovarian stimulation may be associated with a lower cumulative opportunity at pregnancy. The difference in rates of clinical pregnancy in patients <35 years compared with those >35 years, despite ovarian stimulation ranging between 14 and 19 days further reinforces the role of embryo quality.

In conclusion, our study emphasizes how prolonged ovarian stimulation, a potentially modifiable variable, can impact the outcomes of IVF cycles with fresh day 3 ET. Our findings highlight that patients undergoing ovarian stimulation $\leq$13 days achieve better fresh day 3 ET outcomes, with higher clinical PR and live birth rate, independent of age, hCG trigger dose, starting gonadotropin dose, and total gonadotropins administered. Patients <35 years still have a relatively good chance of clinical pregnancy despite prolonged ovarian stimulation. It is important to note that the study does not assert that a shorter duration of gonadotropin stimulation results in better IVF outcomes. However, the study's findings should be taken into consideration for normal responder patients with unsuccessful IVF cycles with fresh day 3 ET, complicated by prolonged ovarian stimulation. A shorter duration of ovarian stimulation may improve the outcomes of IVF cycles with fresh day 3 ET in such patients (8, 19, 20).

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SUPPLEMENTAL TABLE 1

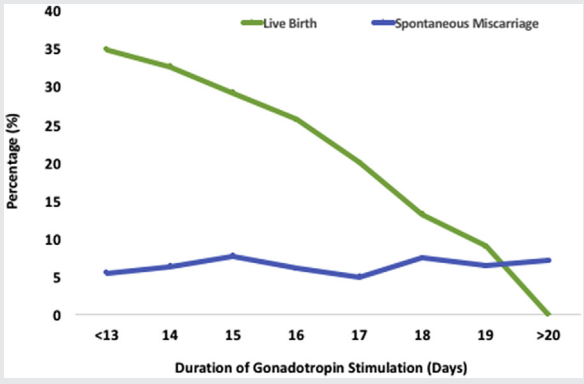
Adjusted odds ratio for live birth after logistic regression adjustment.

Parameter	Standard error	Adjusted odds ratio (95% CI)	*P* value
Age (y)[a]			
35–37	0.28	2.06 (1.58–2.69)	<.001
38–40	0.21	2.10 (1.72–2.57)	<.001
hCG trigger dose (IU)[b]			
5,000	0.23	1.91 (1.50–2.43)	<.001
4,000	0.24	1.93 (1.52–2.46)	<.001
3,300	0.24	1.95 (1.53–2.48)	<.001
Starting gonadotropin dose (U)[c]			
150–225	0.24	1.92 (1.51–2.44)	<.001
225–300	0.24	1.97 (1.55–2.51)	<.001
Number of follicles >10 mm on cycle day 6[d]			
5–8	0.23	1.92 (1.50–2.43)	<.001
>8	0.23	1.84 (1.44–2.35)	<.001
Total gonadotropin dose administered (U)[e]			
3,000–4,000	0.24	1.96 (1.54–2.50)	<.001
4,001–5,000	0.25	2.01 (1.58–2.56)	<.001
>5,000	0.36	2.25 (1.66–3.08)	<.001
Total days of GnRH antagonist[f]			
4–6	0.32	2.21 (1.67–2.94)	<.001
>6	0.34	2.11 (1.53–2.90)	<.001
Total days of stimulation[g]			
>13	0.54	2.22 (1.38–3.57)	.001

Note: Data are presented as mean ± SD. CI = confidence interval.
[a] Compared to <35 years.
[b] Compared to 10,000 IU.
[c] Compared to <150 U.
[d] Comapared to <5.
[e] Compared to <3,000 IU.
[f] Compared to <4 days.
[g] Compared to ≤13 days.

Pereira. Short ovarian stimulation and IVF outcomes. Fertil Steril 2016.

SUPPLEMENTAL FIGURE 1



Live birth and spontaneous miscarriage rates as a function of ovarian stimulation duration.

Pereira. Short ovarian stimulation and IVF outcomes. Fertil Steril 2016.