450 IU versus 600 IU gonadotropin for controlled ovarian stimulation in poor responders: a randomized controlled trial

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Objective: To compare the outcomes of controlled ovarian stimulation/in vitro fertilization cycles using 450 IU and 600 IU gonadotropin per day in women at risk of poor ovarian response.
Design: Prospective randomized controlled nonblinded study.
Setting: University-affiliated private IVF center.
Patient(s): Women considered to be at risk of poor ovarian response: aged <41 years with basal FSH >10 IU/L, antimüllerian hormone <1 ng/mL, antral follicle count ≤8, or a previous IVF cycle with ≥300 IU/d gonadotropin that resulted in a cancellation, <8 follicles, or <5 oocytes.
Intervention(s): A total of 356 patients underwent a microdose GnRH agonist flare-up IVF/intracytoplasmic sperm injection protocol with a fixed daily dose of either 450 IU FSH (n = 176) or 600 IU FSH (n = 180) equally divided between Menopur and Bravelle.
Main Outcome Measure(s): Number of mature oocytes retrieved.
Result(s): The two groups were similar in terms of age, ovarian reserve, cause of infertility, duration of stimulation, and cycle cancellation rate. There were no significant differences in the number of metaphase II oocytes retrieved (4 [range 0–6] vs. 4 [range 2–7]), fertilization rate (62.4% vs. 57.0%), biochemical pregnancy rate (20.5% vs. 22.9%), clinical pregnancy rate (16.4% vs. 18.3%), and implantation rate (29.8% vs. 30.4%) between the 450 IU and 600 IU groups, respectively.
Conclusion(s): Gonadotropin of 600 IU/d does not improve outcome of IVF cycles compared with 450 IU/d in women at risk of poor ovarian response.
Clinical Trial Registration Number: NCT00971152. (Fertil Steril® 2015;104:1419–25. ©2015 by American Society for Reproductive Medicine.)
Key Words: In vitro fertilization, poor ovarian responder, controlled ovarian hyperstimulation, flare-up protocol, gonadotropin dose

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Poor ovarian response (POR) has always been a challenge for clinicians and accounts for 9%–24% of all patients undergoing controlled ovarian stimulation (COS)/in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycles (1). A lower number of follicles and mature oocytes are expected after ovarian stimulation with gonadotropins (2), and pregnancy rates are reduced in POR patients compared with normal responders (3). Several treatment strategies have been proposed to increase ovarian response in this population but, to date, there is insufficient evidence to support the routine use of any particular protocol (4–6). For years, one of the major difficulties in evaluating POR

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treatment was the variability in the definitions of POR used in different studies (7, 8).

In our department, the microdose GnRH agonist (GnRH-a) flare-up protocol was one of the approaches used in the management of poor responders (9, 10), with a daily dose of 450 IU or 600 IU exogenous gonadotropin. We based our approach on a 1998 study that compared a GnRH-a microdose regimen with the standard GnRH-a long-protocol COS regimen and showed decreased cycle cancellation and increased pregnancy rates (11). In the microdose protocol, the initial release (flare-up) of endogenous gonadotropins induced by the administration of low-dose GnRH-a in the early follicular phase helps to enhance the response to the subsequent administration of exogenous gonadotropins, without the risk of concomitant corpus luteum rescue or a rise in circulating LH, T, or P levels (11–13). This short GnRH-a regimen also avoids excessive pituitary suppression compared with the long GnRH-a regimen (12). However, after the beginning of our trial, several studies and reviews failed to confirm the improved outcomes with a GnRH-a flare-up protocol (5, 6). Moreover, a 2014 randomized controlled trial (RCT) in a POR population indicated that the GnRH-a flare-up protocol could even be less effective because of fewer eggs retrieved (14).

The ideal daily dose of gonadotropins for COS has been the subject of much discussion in the treatment of POR. In IVF in general, the use of the lowest dose possible of FSH that would optimize the number of eggs retrieved, maximize live birth rates and minimize the risk of cycle cancellation, is recommended. In POR, the use of high doses of gonadotropins is common practice among clinicians. However, few randomized studies have evaluated different high gonadotropin doses with the use of the same treatment protocol in POR (14–18). In 2003, a systematic review on the management of POR in IVF concluded that high gonadotropin doses were used in the majority of studies but that the results were still controversial (19). The 2013 National Institute for Health and Care Excellence guideline on fertility recommends a maximum daily dose of 450 IU gonadotropin for COS (20).

In North America, the daily gonadotropin doses prescribed for POR often range from 450 IU to 600 IU. According to a recent survey conducted in 196 centers from 45 countries, 23.7% of patients defined as POR received daily doses from 450 IU to 600 IU gonadotropin (FSH or FSH/hMG) (21).

The aim of the present RCT was to determine, in a population of PORs undergoing COS with a microdose agonist flare-up IVF/ICSI protocol, the optimal daily gonadotropin dose. We chose to compare 450 IU/d and 600 IU/d because these two doses are the most commonly used in North American clinics in POR. The primary outcome was the number of mature (metaphase II [MII]) oocytes, because it has previously been shown that IVF success is related to the number of mature oocytes retrieved (22–24).

MATERIALS AND METHODS

Patients and Protocols

This was a prospective randomized controlled nonblinded study, conducted from October 2009 to September 2013 at the OVO clinic, a university-affiliated private IVF center in Montreal, Quebec, Canada. The study was approved by the independent Institutional Ethics Committee, and all patients gave written informed consents. The study was registered with clinical trial reference number NCT00971152. Randomization was done by means of sequential study numbers (ratio 1:1) for the two groups of intervention (450 IU/d and 600 IU/d gonadotropin).

Patients included were aged <41 years old with a body mass index (BMI) <35 kg/m^2, had a basal FSH <20 IU/L, and had a history of primary or secondary infertility with an indication of IVF/ICSI. The risk of POR was defined as <5 oocytes, <8 follicles, or cancellation in a previous IVF cycle with ≥300 IU/d, basal FSH >10 IU/L, antimüllerian hormone (AMH) <1 ng/mL, or antral follicle count (AFC) ≤8.

We excluded all patients participating in other clinical trials, patients with FSH level >20 IU/mL, patients using or having used an investigational drugs in the 3 months preceding the trial, patients tested positive for human immunodeficiency virus or hepatitis B or C antibodies, and patients unwilling or unable to give written informed consent.

All ultrasound measurements were performed with the use of a 9.1-MHZ vaginal probe on a GE Voluson E8. AFC and serum AMH, FSH, and E_2 levels were measured on days 2–4 of the cycle preceding the initiation of the stimulation protocol. Response to ovarian stimulation was monitored with the use of transvaginal ultrasound (US) to determine the diameter (mm) and number of follicles as well as with serum E_2 (pmol/L) and P (nmol/L) levels.

Stimulation Protocol

All participants were primed with 4 mg 17β-E_2 tablets (Estrace), started on day 20 of the cycle preceding ovarian stimulation and continued up to the beginning of COS. Stimulation was achieved with 225 IU/d Menopur and 225 IU/d Bravelle in the 450 group and 300 IU/d Menopur and 300 IU/d Bravelle in the 600 group (Ferring Pharmaceuticals Canada). Buserelin (Suprefact; Sanofi-Avantis) at 0.05 mg subcutaneously, administered twice daily, was started simultaneously. The first US was performed on day 9 of stimulation combined with serum hormonal measurements and then repeated as needed. Final follicular maturation was induced with 5,000 IU of hCG (Pharmaceutical Partners of Canada) when at least two follicles were ≥18 mm. Oocyte retrieval was carried out 36 hours after administration of hCG. Luteal phase support was achieved with intramuscular P in oil (Cytex Pharmaceuticals) and 17β-E_2 patches (100 μg Climara; Bayer Canada). Acetylsalicylic acid tablets (80 mg; Asaphen EC; Pharmascience) were given until the 12th week of pregnancy, and ciprofloxacin was given for 5 days after oocyte collection. Embryo transfer was usually performed on day 3 with the use of a Wallace catheter. A serum β-hCG test was performed 15 days after oocyte retrieval (biochemical pregnancy) and a transvaginal ultrasound at 7 weeks for the detection of an intrauterine fetal heart beat (clinical pregnancy).

The primary outcome measure was the number of mature (MII) oocytes retrieved. Secondary outcomes were: duration of stimulation, FSH dosage, number of mature follicles, total

number of oocytes retrieved, number of available embryos, fertilization and implantation rates, and biochemical pregnancy and clinical pregnancy rates.

Disclosure

Ferring Pharmaceuticals Canada contributed to the study by supplying part of the medication used by the patients at no charge, but they had no involvement in the analysis of the results. Ferring also assumed the costs of the statistician involved in designing the initial protocol and of the Ethics Committee fees. There was no financial remuneration to any member of the research team by the aforementioned company.

Statistical Analysis

The calculation of the sample size required to demonstrate a clinically relevant minimally important difference for the number of mature oocytes (primary outcome) retrieved was based on the observed differences in existing literature as well as the results from our clinic. With the use of the two-group *t* test model, the tolerance margin was set at 1.6 mature oocytes, the power to 90%, and the alpha error to 0.025 to provide a 95% two-sided confidence interval (CI). These results indicated that 164 subjects were required in each treatment group. Factoring in a dropout rate of 10%, 183 subjects were required for each treatment group, giving a total of 366 patients.

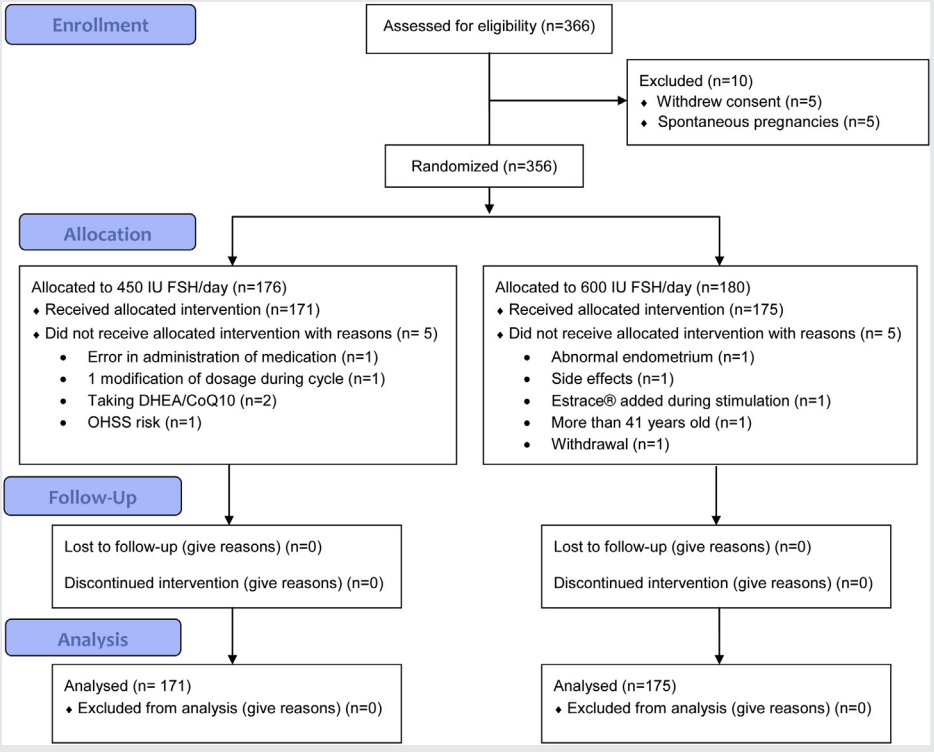
Analyses were performed by intention to treat per started cycle. The baseline data and outcome data were summarized separately. For continuous variables, data were reported as median values and interquartile ranges according to the Wilcoxon test. Discrete variables were reported as percentages with respective *P* values reported according to the χ^2 test. A secondary analysis with the use of logistic regression and permutation tests was performed to evaluate if the women's age (<38 vs. ≥ 38 years) made a difference in IVF/ICSI outcomes.

RESULTS

A total of 366 women were recruited for the study. Five withdrew after consenting, and five had a spontaneous pregnancy. Finally, 356 subjects were randomized between the two groups, 176 patients in the 450 group, with five being excluded after randomization, and 180 patients in the 600 group, with five being excluded after randomization. No patients were lost to follow-up, and there was an adherence rate of 97.2%. This resulted in 346 patients receiving the intervention protocol that they were assigned to (Fig. 1).

The two groups were similar regarding age, AFC, basal FSH (IU) and AMH (ng/mL) levels, duration of infertility, and indication for IVF/ICSI. BMI (kg/m^2) was significantly lower in the 600 group (24.2 vs. 25.5; $P=.01$). There was no

FIGURE 1



CONSORT flow diagram.

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TABLE 1

Demographic parameters.

Characteristic	450 IU/d FSH (n = 171)	600 IU/d FSH (n = 175)	*P* value
Baseline characteristics[a]			
Age (y)	37.9 (35.0–39.5)	37.8 (34.6–39.5)	.91
BMI (kg/m^2)	25.5 (22.4–28.9)	24.2 (21.3–27.5)	.01
Antral follicle count	8 (6–11)	9 (7–11)	.52
Basal FSH (IU)	8.7 (6.9–10.5)	8.0 (6.5–10.0)	.16
AMH (ng/mL)	0.42 (0.21–0.74)	0.44 (0.22–0.70)	1.00
Infertility duration (mo)	48.0 (27.0–83.8)	55 (36.0–86.3)	.06
ICSI cycles, n (%)[b]	72 (42.1)	74 (42.3)	1.00
IVF/ICSI indication, n (%)[b]			
Male factor	62 (36.3)	72 (41.1)	.41
Tubal or peritoneal factor	13 (7.6)	17 (9.7)	.61
Endometriosis	15 (8.8)	19 (10.9)	.64
Unexplained infertility	61 (35.7)	53 (30.2)	.34
Multiple factors	20 (11.7)	14 (8)	.33
Stimulation characteristics[a]			
Duration of stimulation (d)	12 (10–13)	11 (11–13)	.96
Total dose of FSH (IU)	5,400 (4,500–5,850)	6,600 (6,600–7,800)	< .0001
E_2 at last US (pmol/L)	5,509 (3,655–7,092)	5,464 (3,904–7,966)	.32
P at last US (nmol/L)	2.1 (1.6–2.8)	2.3 (1.9–2.9)	.02
Endometrial thickness at last US (mm)	9.8 (8.0–11.9)	10.2 (8.6–11.6)	.21

Note: Data are presented as median (interquartile range) or n (%). AMH = antimüllerian hormone; BMI = body mass index; ICSI = intracytoplasmic sperm injection; US = ultrasound.
[a] Wilcoxon test.
[b] χ^2 test.

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difference in number of cycles, duration of stimulation (days), E_2 levels (pmol/L), and endometrial thickness (mm) at last US. The total FSH dose (IU; $P<.0001$) and the P level at last US (nmol/L; $P=.02$) were significantly higher in the 600 group than in the 450 group. The difference in P level was not deemed to be clinically significant, because levels were low in both groups: 2.1 and 2.3 nmol/L (25) (Table 1).

Cycle outcomes are listed in Table 2. Our primary outcome, the number of mature (MII) oocytes retrieved, was similar between the two groups: 4 (range 0–6) in the 450 group versus 4 (range 2–7) in the 600 group ($P=.17$). There were no significant differences in number of follicles at last US, number of oocytes retrieved, fertilization rate, number of normally developing embryos on day 2, and number of

TABLE 2

Cycle outcomes.

Characteristic	450 IU/d FSH (n = 171)	600 IU/d FSH (n = 175)	*P* value
Cancelled before egg retrieval, n (%)[b]	45 (26.3)	34 (19.4)	.16
No. of cancelled cycles, n (%)[b]	32 (18.7)	29 (16.5)	.70
No. of cycles converted to IUI, n (%)[b]	13 (7.6)	5 (2.9)	.08
No. of cycles with no egg retrieved, n (%)[b]	1 (0.6)	1 (0.6)	NA
Stimulation characteristics[a]			
No. of follicles at last US	7.0 (4.0–10.5)	8.0 (5.0–11.0)	.3
No. of oocytes retrieved	5 (0–8)	5 (3–9)	.15
No. of mature (MII) oocytes	4 (0–6)	4 (2–7)	.17
Fertilization rate	0.67 (0.50–0.86)	0.61 (0.33–0.80)	.22
No. of normally day 2 embryos	1 (0–3)	1 (0–3)	.54
No. of embryos (day of transfer)	1 (0–2)	1 (0–2)	.60
No. of transferred embryos	1 (0–1)	1 (0–1)	.91
No. of vitrified embryos	0 (0–1)	0 (0–1)	.26
Cycle outcome, %[b]			
Cycles with embryo transfer	56.7	60.0	.61
Biochemical pregnancy rate[c]	20.5	22.9	.68
Clinical pregnancy rate[c]	16.4	18.3	.74
Implantation rate[d]	29.8	30.4	1.00

Note: Data are presented as median (interquartile range) or n (%). IUI = intrauterine insemination; MII = metaphase II; US = ultrasound.
[a] Wilcoxon test.
[b] χ^2 test.
[c] Pregnancy rate per started cycle.
[d] Number of gestational sacs divided by the number of embryos transferred.

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vitrified embryos between the two groups, and the number of cycles converted to intrauterine insemination (7.6% vs. 2.9%; $P=.08$), percentage of cycles reaching embryo transfer (56.7% vs. 60.0%; $P=.61$), and implantation rates (29.8% vs. 30.4%; $P=1$) were similar in the 450 and 600 groups, respectively (Table 2).

A subanalysis of the two study groups was performed according to the patient's age. Patients <38 years old represented 51.2% of the population. The age groups were similar for BMI, FSH, AMH, duration of infertility, days of stimulation, and cancellation rate. The AFC was higher in the 450 group, but there was no difference in the number of MII oocytes retrieved. There were no significant differences in the fertilization rates, biochemical pregnancy rates, clinical pregnancy rates, and implantation rates (Table 3).

DISCUSSION

Our randomized controlled trial showed that in POR, a microdose GnRH-a flare-up protocol with a daily dose of 600 IU gonadotropin does not significantly increase the number of mature (MII) oocytes compared with 450 IU/d. To our knowledge, this is the largest RCT comparing daily doses of 450 IU versus 600 IU gonadotropin in a microdose GnRH-a protocol. We also demonstrated that the dose increase to 600 IU/d did not shorten the duration of stimulation and did not improve total number of oocytes retrieved, number of embryos available for transfer, fertilization and implantation rates, number of cancelled cycles, and biochemical or clinical pregnancy rates.

Our findings are consistent with earlier studies demonstrating that increases in the daily dose of gonadotropins above a certain level of FSH does not increase the number of mature oocytes or pregnancy rates (15, 17, 18, 26–28). A recent randomized study assessing IVF outcomes in 119 patients with the use of a microdose GnRH-a protocol showed no significant differences in number of mature oocytes retrieved or pregnancy rates when comparing three different high rFSH doses (300 IU, 450 IU, and 600 IU) with the same duration of stimulation (15). Dilbaz et al. compared COS with the use of 375 IU/d gonadotropin or 450 IU/d in 91 POR women and showed that embryologic and pregnancy outcomes were similar in both groups, but costs were lower with the use of 375 UI/d (27). Previously, a randomized study with a GnRH-a microdose flare protocol comparing high fixed-dose (450 IU/d) with a decremental-dose regimen (450 IU/d to 300 IU/d) had shown similar pregnancy rates but increased cancellation rates with the decremental-dose regimen (18). Moreover, a systematic review of the literature determined that studies reporting on COS with high gonadotropin doses in POR had inconsistent conclusions and that prospective studies had demonstrated either minimal or lack of benefit (19). According to Pellicer et al., the most plausible explanation for low response is decreased ovarian reserve (29). Klinkert et al. reported that patients with decreased ovarian reserve respond poorly to aggressive doses of gonadotropins because the number of FSH-sensitive follicles is very limited and is not increased with higher doses (16). Other theories for POR have been proposed and include a decreased number of FSH receptors available in granulosa cells, a defect in signal transduction after FSH receptor binding, presence of an FSH receptor–binding inhibitor with FSH agonist activity in human follicular fluid, an abnormal follicular blood flow impedance, and antiovarian autoantibodies directed against the β-subunit of FSH (27, 29–32). Some reports even suggest that higher doses of gonadotropins may have a negative effect on oocyte quality, with more perivitelline space granularity and atretic follicles (33, 34).

TABLE 3

Cycle outcomes with different age groups.

	< 38 years			38–40 years	
Characteristic	**450 IU/d**	**600 IU/d**	***P* value (between age groups)**	**450 IU/d**	**600 IU/d**
Baseline characteristics					
BMI	25.4	23.7	.09	25.5	25.1
Antral follicle count	8	10	.001	9	8
Basal FSH (IU)	8.9	7.9	.07	8.5	8.1
AMH (ng/mL)	0.5	0.5	.83	0.4	0.4
Infertility duration (mo)	53	54	.43	47	58
Duration of stimulation (d)	11	11	.64	12	12
Total dose of FSH (IU)	4,950	6,600	.58	5,400	7,200
E_2 at last US (pmol/L)	5,692	5,929	.60	5,370	4,960
Cycle outcomes					
% of cancelled cycles	18.6	11.0	.14	18.8	22.6
% of cycles converted to IUI	8.1	2.2	.55	7.1	3.6
No. of mature (MII) oocytes	4	5	.37	4	3
Fertilization rate	0.67	0.58	.87	0.57	0.67
No. of transferred embryos	1	1	.76	1	1
No. of cycles with transfer	58.1	63.7	.56	55.3	54.8
Biochemical pregnancy rate (%)	20.9	26.4	.49	20	19
Clinical pregnancy rate (%)	17.4	24.2	.23	15.3	11.9
Implantation rate (%)	30.7	38.8	.17	28.9	21.7

Note: Tests: logistic regression and permutation tests. Abbreviations as in Tables 1 and 2.

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The cost of treatment is another important factor that should be taken into account when choosing gonadotropin doses for COS. We have shown that an additional 1,200 IU gonadotropin was required for the 600 IU/d regimen compared with 450 IU/d. This would obviously result in a higher cost for the patient without any improvement in IVF outcome or even a reduced duration of stimulation. Our findings are similar to many earlier reports that failed to show significant benefits despite a significantly higher total dose (15, 27).

On the other hand, data on the ideal COS protocol for POR are scarce and heterogenous. Kahraman et al. (35) found that cycle outcomes in POR are similar when comparing a microdose GnRH-a flare-up protocol and a multiple-dose GnRH antagonist protocol (35), whereas Akman et al. did not report any difference in implantation and pregnancy rates when comparing a GnRH antagonist protocol with simple COS with gonadotropins (36). More recently, Sunkara et al. (14), in a randomized study comparing different treatment regimens with 450 IU/d in 111 POR patients, concluded that the long GnRH-a protocol resulted in a significantly higher number of oocytes retrieved compared with the GnRH-a short regimen (14). That study was not powered enough to detect significant differences in pregnancy outcomes, but there was a trend in favor of a higher ongoing pregnancy rate in the GnRH antagonist group (16.2%) compared with 8.1% with long and short agonist regimens. Finally, a recent meta-analysis concluded that there is insufficient evidence to support the routine use of any particular intervention in the management of POR in IVF (5).

For years, the main reason behind the heterogeneity of data comparing different COS protocols in POR was the difference in definition of POR. In 2011, the European Society of Human Reproduction and Embryology, in an attempt to standardize the definition of POR in a simple and reproducible manner, published the Bologna criteria (37). This definition of POR has since been uniformly adapted by reproductive centers worldwide. Unfortunately, we did not use the Bologna criteria for the definition of POR, because our study had already started 2 years before its first publication. We used criteria from the literature available at the time (2009) to define patients at high risk of POR. Kailasam et al. had found that cancellation of an IVF cycle following COS with $\geq$300 IU/d FSH was associated with a significantly worse prognosis and could define poor response (37). Furthermore, a recent meta-analysis indicated that as standalone tests, AFC and AMH can both predict POR and that a higher FSH level was associated with higher chances of a poor response (38). The age limit was set at $<$41 years based on the evidence that older women differ in their rate of poor response and embryo quality compared with younger women (39).

Female age is strongly related to IVF outcomes (38) and is the best predictor of the probability of achieving a live birth (40). To assess the impact of age on IVF outcomes, we performed a secondary analysis of our study groups. We evaluated cycles from women $<$38 years compared with women aged 38–40 years in both groups. Even for women $<$38 years, there were no significant differences in the number of mature oocytes and IVF outcomes between 450 IU/d and 600 IU/d. Therefore, a higher dose of gonadotropin does not seem to have any benefit on IVF outcomes in POR, even at a younger age.

Finally, one of the major weaknesses of our study was the difference in BMI between the two groups: BMI was significantly lower in the 600 group (24.2 vs. 25.5; P=.01). However, we do not think that this difference had any impact on cycle outcomes. If anything, a lower BMI would be expected to improve the ovarian response to stimulation, which was not the case in our study.

CONCLUSION

In conclusion, our study demonstrated that a microdose agonist flare-up IVF/ICSI regimen with a daily dose of 600 IU gonadotropin does not improve cycle outcomes in POR compared with 450 IU/d. Therefore, clinicians should not use more than a daily dose of 450 IU in POR.

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