Microdose flare protocol with interrupted follicle stimulating hormone and added androgen for poor responders—an observational pilot study

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Objective: To investigate whether temporarily withholding FSH and adding androgen could improve follicular response during a microdose flare protocol in women with slow follicular growth or asynchronous follicular development.
Design: Observational pilot study.
Setting: University-affiliated private fertility center.
Patient(s): Twenty-six women aged 34–47 years with poor response to stimulation or a previous cancelled IVF cycle and with slow or asynchronous follicular growth during a microdose flare cycle.
Intervention(s): For 13 women, after initiation of ovarian stimulation using the microdose flare protocol, gonadotropin administration was interrupted and transdermal testosterone gel was added for several days (4.4 ± 1.2 d) starting after cycle day 7 (mean cycle day 10 ± 2.6).
Main Outcome Measure(s): FSH, E_2, follicular growth, and total number of mature oocytes retrieved were determined for all of the patients. Cycle cancellation rate as well as pregnancy rate following embryo transfer were also documented when applicable.
Result(s): FSH levels declined (25.2 ± 6.5 to 6.8 ± 3.2 IU/L), E_2 levels increased (896 ± 687 to 2,163 ± 1,667 pmol/L), and follicular growth improved significantly during gonadotropin interruption and were tracked for 2 days during this time frame. The average number of oocytes retrieved was 5.3 ± 2.6, and the ratio of mature to total oocytes was 4:5. Four of the 13 women in the interruption group conceived following frozen embryo transfer, whereas none in the control group did.
Conclusion(s): The androgen–interrupted FSH protocol may improve follicular response to gonadotropins in cycles that might otherwise be cancelled. (Fertil Steril® 2016;105:100–5. ©2016 by American Society for Reproductive Medicine.)
Key Words: Androgen, gonadotropin resistance, interrupted protocol, microdose flare, poor responder

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Poor responders comprise a broad category of patients that respond suboptimally to ovarian stimulation. A unanimous consensus regarding the precise description of poor responders is lacking and >35 definitions are currently available (1). According to the Bologna definition, two of three criteria should be met for the diagnosis to be made (1). These include advanced maternal age (≥40 years) or another risk factor, an earlier poor response cycle (≤3 oocytes with the use of conventional stimulation), and an abnormal ovarian reserve test (antral follicle count <5–7 or antimüllerian hormone <0.5–1.1 ng/mL). Two previous poor response cycles after maximal stimulation are

Received February 26, 2015; revised September 27, 2015; accepted September 28, 2015; published online October 20, 2015.
F.M. has nothing to disclose. L.A.B. has nothing to disclose. C.A.M. has nothing to disclose. A.H.-K. has nothing to disclose. R.F.C. has nothing to disclose. Y.B. has nothing to disclose.
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Fertility and Sterility® Vol. 105, No. 1, January 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.09.038

considered to be sufficient for making a diagnosis. Poor responders are a challenging category of patients to treat, primarily because of the low number of oocytes and embryos obtained following ovarian stimulation.

Over the years, numerous adjunctive treatments have been proposed, but few seemed to add much benefit to the outcome (2). Recently, a meta-analysis, based on limited data, concluded that transdermal testosterone may improve clinical pregnancy and live birth rates in poor responders. Lower doses of gonadotropin and significantly fewer days of stimulation were also observed (3). The rationale for this treatment is based on primate studies showing that increasing intrafollicular androgen levels may up-regulate FSH receptors on granulosa cells, enhance response to gonadotropins, and augment follicular growth (4).

Poor responders are given large quantities of gonadotropin to improve follicular response. Unfortunately, administering ever-increasing quantities of gonadotropin in this category of women very often does not improve follicular response, oocyte yield, or overall outcome (5, 6). In fact, maximal dosage requirements are unclear and poor responders often purchase excessive quantities of expensive gonadotropins with cycles often culminating in high costs, poor response, and cancellation. Maximum gonadotropin dosage for optimal response often relies on arbitrary rules or habits. We recently demonstrated that response to gonadotropins may be predicted and titrated based on fluctuating serum levels of FSH (7). Serum FSH levels of >20 IU/L on cycle day 7 (day 4 of stimulation) may indicate FSH receptor saturation in the granulosa cells, and therefore the addition of more exogenous FSH would not result in increased follicular response.

Antral follicles express a wide spectrum of sensitivities to FSH, especially in poor responders. This phenomenon may account for the asynchronous and occasional monofollicular growth despite a larger cohort of small antral follicles seen earlier in the cycle (8). The exposure of a cohort of follicles with a differential sensitivity to extremely high serum concentrations of FSH may result in the rapid development of one or two follicles that are more sensitive while not allowing enough time for the remaining follicles to develop and mature. This result may be even more frequent in short microdose flare protocols, where GnRH agonist stimulates pituitary secretion of FSH and LH during the first week of administration and augments the ovarian stimulation of exogenously administered FSH.

We present here a pilot study of poor responder stimulation cycles that began with slow follicular growth or asynchronous follicular development. The objective of this preliminary observational study was to determine if withdrawal of the gonadotropins and supplementation of transdermal testosterone, once poor response was observed, could sensitize as well as synchronize follicular growth.

MATERIALS AND METHODS

Study Population

This observational pilot study included a total of 13 women who had at least one previous failed or cancelled IVF cycle with suspected gonadotropin resistance (serum FSH ≥20 mIU/L on day 7, as we have previously described [7], in conjunction with absent or minimal follicular growth) during the current cycle. Follicles that grew <0.5 mm per day (average diameter) after 5–8 days of high-dose stimulation were considered to be slow growing. IVF treatments including ultrasound monitoring, and follow-up was carried out at TCART Fertility Partners (Toronto, Ontario, Canada) from October 2013 to December 2014. Institutional Review Board approval (protocol no. 15-0013-C) was obtained from the Mount Sinai Research Ethics Board on February 6, 2015. Six of these patients were confirmed poor responders based on the Bologna criteria. The remaining women had earlier failed IVF cycles, and some of them were expected to be poor responders (Table 1).

Control Group

To compare the effect of gonadotropin interruption and addition of topical androgens to common practice we assembled a control group. A medical student (C.A.M.), masked to the purpose of the study, was instructed to search for records of IVF cycles stimulated with an uninterupted microdose flare protocol that showed either poor or no synchronous follicular development. These cycles were conducted in 2011 and earlier, before the use of topical testosterone gel began in our clinic. Chosen cases had to include a complete data set and show a serum FSH level suggestive of gonadotropin resistance. The 13 patients' stimulation cycles that fulfilled the above criteria took place from April 2006 to November 2011.

Ovarian Stimulation Protocol

The microdose flare protocol was used for ovarian stimulation. After confirming normal baseline blood levels and excluding any functional ovarian cysts, gonadotropin treatment was initiated on the 3rd day of menses with the use of recombinant FSH (Gonal F, EMD Serono; or Puregon, Merck). Serum concentrations of FSH and E_2 were measured by means of immunoassay with the use of the Vitros ECiQ Immunodiagnostic System (Ortho-Clinical Diagnostics, Johnson and Johnson). Baseline FSH levels ≤15 IU/L and E_2 levels <200 pmol/L were necessary for starting stimulation; otherwise the cycle was cancelled.

TABLE 1

Patient characteristics (average values for each group of 13 patients).

Characteristic	Study group	Control group	*P* value
Age (y)	37.53 ± 4.4	39.85	NS
Basal FSH (IU/L)	7.8 ± 3.66	9.36 ± 6.48	NS
Basal E_2 (pmol/L)	106 ± 41	133 ± 55	NS
Basal AFC	6.9 ± 2.84	4.57 ± 2.06	<.05
AMH (ng/mL)	0.8 ± 1.2	NA	
No. of cancelled cycles for women with history of cycle cancellation	2 ± 1	1.9 ± 1.3	NS

Note: AFC = antral follicle count; AMH = antimüllerian hormone.

Mitri. Androgen–interrupted FSH protocol. Fertil Steril 2016.

The GnRH agonist buserelin acetate (Suprefact; Sanofi-Aventis) was administered at a dose of 50 μg subcutaneously twice daily beginning on cycle day 3. Five women were given 150 IU and eight women 200 IU recombinant FSH twice daily starting on cycle day 3. Serum FSH, LH, P, and E_2 levels were measured at baseline and at every visit for all patients.

When serum FSH levels exceeded 20 IU/L on cycle day 7 or any time thereafter and follicular growth was considered to be slow or asynchronous, gonadotropins were discontinued for 4–7 days. Patients were given the option to come back to the clinic at any point during this time frame and gonadotropins were immediately restarted at the same dose. In addition, 25 mg of daily transdermal testosterone (2.5 g 1% Androgel; Abbott) was administered from the day FSH injections were interrupted until the day of the ovulation trigger. This is one of the standard treatments offered at TCART to patients that respond in the manner described above. Follicular growth was considered to be asynchronous when one or two leading follicles were ≥4 mm larger (average diameter) than the rest of the cohort. The stimulation protocol for patients that were included in the control group did not include withholding of gonadotropin treatment or use of topical testosterone. When at least three dominant follicles were noted and at least two had attained a size of ≥18 mm, 10,000 IU hCG (Pregnyl; Merck) was administered subcutaneously for ovulation trigger. Thirty-six hours later, the oocytes were retrieved by means of ultrasound-guided transvaginal needle aspiration. Following egg retrieval, intracytoplasmic sperm injection was performed for 12 patients, conventional IVF for one, and egg freezing for three (13 intracytoplasmic sperm injection, 1 conventional IVF, 3 egg freezing, and 9 converted to intrauterine insemination—a total of 26 for the 2 groups). All embryos were transferred at the cleavage or blastocyst stage at the discretion of the physician and patient, and some embryos were vitrified (Table 2).

Statistical Analysis

Statistical analysis was performed with the use of Graphpad Prism version 5.02. The distribution of the data was first analyzed, and both the Wilcoxon matched-pairs test and paired *t* test were used to compare necessary parameters.

RESULTS

All of the 13 patients completed one cycle of ovarian stimulation with the use of the interrupted microdose flare protocol, and the 13 patients in the control group completed a conventional microdose flare protocol. Nine of the 13 patients in the control group were converted to intrauterine insemination instead of IVF owing to an unsatisfactory number of mature follicles (Table 2). Baseline characteristics and gonadotropin levels were recorded (Table 1). The two groups were of similar age, BMI, and basal serum FSH and E_2. There was a difference in basal antral follicle count between the groups that may have been partially the result of a lower resolution of the ultrasound machines used in the earlier years. Antimüllerian hormone measurement was not done in our clinic before 2012. For the interruption group, gonadotropins were withdrawn on cycle day 10 ± 2.6 (Supplemental Fig. 1, available online at www.fertstert.org). The duration of gonadotropin withdrawal was determined by the attending physician and varied between 3 to 7 days (mean 4.4 ± 1.2 d). FSH, E_2, and follicle sizes were recorded on the first day of gonadotropin interruption and on the day of resumption for all participants (Supplemental Table 1, available online at www.fertstert.org). These values were also determined at every visit (Supplemental Fig. 1). When gonadotropin stimulation was resumed, FSH levels had significantly declined, approximating baseline (mean 25.2 ± 6.5 IU/L to 6.8 ± 3.2 IU/L; Fig. 1). Surprisingly, estrogen levels and the number of follicles >1 cm increased dramatically during the interval of gonadotropin withdrawal (Supplemental Table 1; Supplemental Fig. 1). The average number of oocytes obtained closely resembled the average number of follicles >1.6 cm measured at the time of ovulation trigger (5.9 ± 4.1 vs. 4.9 ± 2.7; Table 2). For the majority of patients, the total number of oocytes obtained correlated with the basal antral follicle count (Supplemental Fig. 2, available online at www.fertstert.org). A reasonable proportion of

TABLE 2

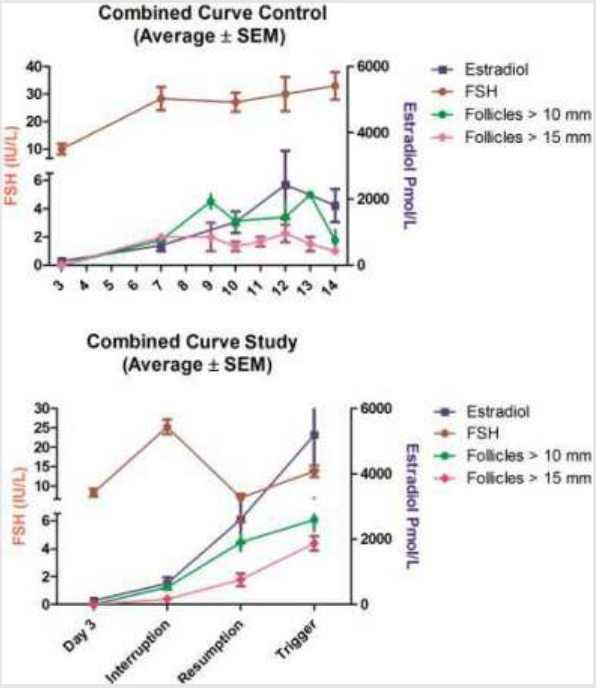
Cycle characteristics and outcomes for each group of patients.

	Interrupted group	n	Control group	n	*P* value
Duration of gonadotropin withdrawal (d)	4.4 ± 1.2	13	NA	13	
First day of gonadotropin withdrawal (cycle day)	10 ± 2.6	13	NA	13	
No. of follicles ≥1.6 cm (at ovulation trigger)	4.92 ± 2.73	13	1.69 ± 0.85	13	<.001
Ovulation trigger injection (cycle day)	17.7 ± 1.07	13	12.46 ± 0.5	13	<.05
Total dose of FSH	3,407 ± 580.7	13	3,685 ± 1,113.6	13	NS
Serum E_2 on trigger day	5,802 ± 3,765.7	13	2,222.84 ± 1,748.49	13	<.01
Serum FSH on trigger day	15.46 ± 5.96	13	28.13 ± 10.17	6	<.01
No. converted to IUI	0		9		
No. of oocytes	5.92 ± 4.11	13	4.25 ± 2.06	4	NS
No. of MII oocytes	4.53 ± 2.98	13	2.75 ± 1.3	4	NS
No. of cleavage embryos	3.46 ± 2.81	11	3.33 ± 2.08	3	NS
No. of pregnancies	4		0		

Note: IUI = intrauterine insemination; MII = metaphase II.

Mitri. Androgen–interrupted FSH protocol. Fertil Steril 2016.

FIGURE 1

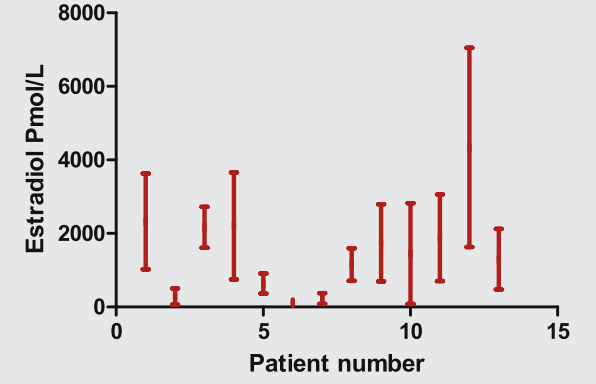


Combined data for study and control groups. Error bars indicate ±SEM.

Mitri. Androgen–interrupted FSH protocol. Fertil Steril 2016.

mature to total oocytes was obtained, and a total of four pregnancies, including a twin gestation, was noted among the ten women who had embryo transfers (Table 2). On trigger day, the control group (Fig. 1; Table 2) had a significantly lower number of mature follicles (≥1.6 cm) and serum E_2 levels, whereas serum FSH levels were significantly higher and the total dose of FSH consumption in both groups was similar. None of the control cycles resulted in a pregnancy.

FIGURE 2



Change in serum estradiol levels during the gonadotropin withdrawal for all 13 patients. Each line represents a patient.

Mitri. Androgen–interrupted FSH protocol. Fertil Steril 2016.

DISCUSSION

Poor responders are resistant to gonadotropin stimulation and have inadequate follicular growth. Some of these patients have a very low number of small antral follicles at the beginning of the cycle. Others may have more antral follicles during the early follicular phase but fail to respond to gonadotropin stimulation, resulting in a small oocyte yield. The problem is further aggravated by the fact that most of these patients are relatively older and have previously produced embryos of poor quality. The objective in either case is to obtain a sufficient number of oocytes and embryos to improve pregnancy rates.

On the other end of the spectrum, hyperresponders exhibit a high level of sensitivity to gonadotropin stimulation and are at risk of developing ovarian hyperstimulation syndrome (OHSS). Before the discovery of GnRH antagonists, the use of GnRH agonists to trigger ovulation and minimize the risk of OHSS was not possible. Consequently, the long protocol was widely used for high-risk patients, and "coasting" was implemented as a safeguard against OHSS. Coasting involves withholding gonadotropin stimulation following rapid follicular growth and significantly rising E_2 levels (9). During coasting, E_2 levels usually continue to rise for 1 or 2 days after withdrawal of gonadotropins, before declining abruptly (10, 11). Follicles >1.5 cm normally continue to grow and may survive for several days in the absence of gonadotropin support (12). Granulosa cells within the smaller follicles, however, undergo apoptosis, resulting in follicular atresia (13).

In the present study, gonadotropins were withheld in a manner similar to coasting. The outcome, however, was clearly different, because E_2 levels continued to rise and follicles kept growing even after 1 week of gonadotropin cessation (Fig. 2). A large proportion of the follicles ≤1 cm continued to grow steadily while maintaining significantly lower serum FSH levels compared with the preinterruption period and the control group. This highlights differences in the effect of gonadotropin withdrawal between women with poor response compared with those with hyperresponse.

Perhaps the most plausible factor to explain the difference between these two groups is the difference in gonadotropin "utilization rates." Compared with urinary gonadotropins, recombinant FSH is more acidic and therefore has a shorter half-life and higher bioactivity. The half-life of recombinant FSH is estimated to range between 24 and 40 hours, and steady state levels are achieved after 3–5 days of treatment (14). It is known that clearance of FSH from the serum involves FSH receptor binding (7). Therefore, hyperresponders with a large cohort of large and small follicles, and consequently with a large number of FSH receptors, rapidly remove FSH from the serum. Withholding gonadotropins would result in a rapid FSH withdrawal leading to follicular atresia. Coasting therefore results in a sharp decline in E_2 levels and apoptosis of the smaller follicles which are unable to sustain growth following gonadotropin withdrawal. On the other hand, poor responders have a much lower number of growing

follicles with fewer FSH receptors and utilize gonadotropins in a much slower, more delayed manner. This is reflected by the high serum level of FSH after administration of a standard dose of FSH and by an average of 5 days required for serum FSH to decline back to prestimulation levels (7) (Supplemental Fig. 1). The slowly declining FSH levels were associated with follicular growth and rising E_2 levels during this interval. Remarkably, growth of follicles ≤ 1 cm continued even in the presence of larger follicles and declining FSH levels. A similar growth of the smaller follicles did not take place in the control group, in which gonadotropins were not discontinued (Fig. 1). Smaller ovarian follicles contain fewer FSH receptors, have higher FSH thresholds, and require greater levels of gonadotropin to respond, yet they continued to grow despite declining FSH levels. This suggests that these follicles may have also become "more efficient" in utilizing gonadotropins, possibly as a result of the added androgen coincident with the interruption of FSH. Maximum FSH levels before gonadotropin withdrawal remained higher than maximum FSH levels after resumption of gonadotropin treatment for all of the patients (Supplemental Fig. 3), suggesting improved follicular sensitization and gonadotropin utilization.

The second factor is related to the stimulation protocol used. The microdose flare protocol is generally reserved for suspected or confirmed poor responders. Compared with a long luteal protocol, there is likely a milder degree of pituitary suppression, reflected in more sustained follicular growth when coasting occurs during flare cycles to prevent hyperstimulation (15–17). Thus, interrupting gonadotropins in the present study may have resulted in some residual endogenous gonadotropin that facilitated the growth of small antral follicles.

The third factor involves a possible direct stimulatory effect of GnRH agonists on the ovaries. E_2 levels decline more abruptly during coasting when both GnRH agonist and gonadotropins are concomitantly withdrawn than when GnRH agonist is maintained and only FSH is withdrawn (18, 19). In addition, the fall in E_2 is quicker and the duration of coasting generally shorter for antagonist cycles compared with GnRH agonist–based cycles (19). It is possible that GnRH agonists may bind to ovarian GnRH receptors to stimulate follicular growth directly (20). Local intraovarian factors also regulate ovarian function. FSH induces the expression and secretion of FSH-binding inhibitor (FSHBI) from granulosa cells. This inhibitory peptide blocks the binding of FSH to its receptor (21). Therefore, administering excessive doses of exogenous FSH may increase the production of FSHBI and other local inhibitory factors suppressing follicular growth and development.

Finally, transdermal testosterone was used during gonadotropin interruption. The use of transdermal androgen therapy during infertility is still controversial. Adverse effects of androgen supplementation include oily skin, acne, excess hair, skin irritation, and possibly deepening of the voice, especially after long-term treatment. The patients in the present study received transdermal testosterone over a short period of time and reported minimal side effects. Androgens are crucial for granulosa cell differentiation and signaling, particularly during the early stages of follicular development. Excessive intraovarian androgen levels may be detrimental to follicles and may result in apoptosis, whereas insufficient levels of androgen may impair follicular growth and development. Androgens have been shown to up-regulate FSH receptor expression (4, 22). Therefore, androgen induction of FSH receptors along with declining serum FSH levels resulting from withdrawal of recombinant FSH may add together to sensitize growing follicles to gonadotropins and increase gonadotropin utilization "efficiency." Androgens also provide a substrate for FSH-induced aromatization, possibly contributing to increased E_2 levels during the gonadotropin interruption.

This observational pilot study included a small group of gonadotropin-resistant patients with elevated serum FSH levels and minimal follicular growth after gonadotropin administration. More than one-half of these women were already confirmed poor responders and some of the rest may have been "delayed" or normal responders. Although a head-to-head comparison between current and previous cancelled cycles was not conducted, these patients seem to have had improved overall response during the current cycles, all of which progressed to oocyte retrieval. E_2 levels and the number of follicles >1 cm almost tripled during the short interval of gonadotropin interruption (Supplemental Fig. 1) and were significantly higher compared with the control group. This is suggestive of improved gonadotropin utilization after the intervention. To some extent, the total number of oocytes retrieved correlated with the basal antral follicle count (Supplemental Fig. 2). The number of dominant follicles (≥ 1.4 cm) at the time of the ovulation trigger also correlated with the number of mature oocytes retrieved, suggesting optimal stimulation of the antral follicles present.

During gonadotropin interruption, serum FSH consumption was maintained, as indicated by the declining FSH levels and simultaneous follicular growth that occurred, resulting in the production of higher estrogen levels. Furthermore, the addition of transdermal testosterone likely contributed to the significantly higher peak serum E_2 both as a substrate for the aromatase enzyme and as an FSH sensitizer leading to induction of more aromatase in granulosa cells.

The emotional and psychologic burden of having cancelled stimulation cycles can not be underestimated, particularly in patients who have already received a large number of injections and incurred high medication costs (23). A certain level of depression or anxiety may be noted in these women (24). Better outcomes in future stimulation cycles can not be guaranteed, either. Temporarily interrupting gonadotropin and supplementing with transdermal testosterone seems to be a simple cost-effective alternative to cycle cancellation. This strategy can be used to sensitize and synchronize the growth of follicles and may help rescue cycles that would otherwise be cancelled. If, after gonadotropin interruption, response is subsequently deemed to be suboptimal, the cycle can still be cancelled with no added expense. Patients that require large doses of gonadotropins or have elevated FSH levels (>20 IU/L) during stimulation in conjunction with minimal or asynchronous follicular growth may benefit the most from this strategy. Higher basal antral follicle

counts seem to correlate with better outcome. Interestingly, follicular growth persisted even after 7 days of withholding gonadotropins, although earlier studies suggests that interrupting gonadotropins for >5 days is not recommended and may be detrimental to oocytes (25).

Limitations to our study include the small sample size, retrospective nature, and multiple interventions used. To reduce bias, all of the patients who underwent intervention with the use of this protocol were included in the study. Larger randomized studies are necessary to support and validate our findings, determine the quality of oocytes and embryos obtained with the use of our interrupted gonadotropin–androgen strategy, and elucidate the underlying receptor dynamics.

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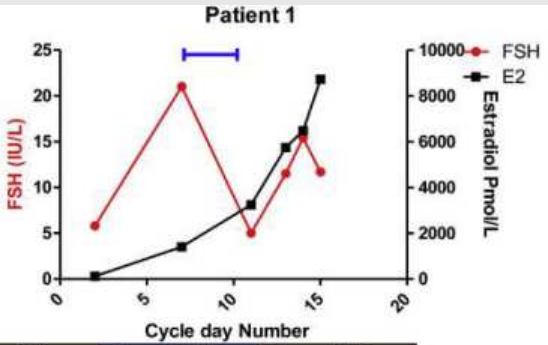
SUPPLEMENTAL FIGURE 1



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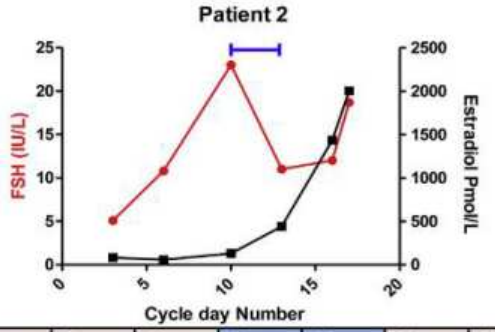
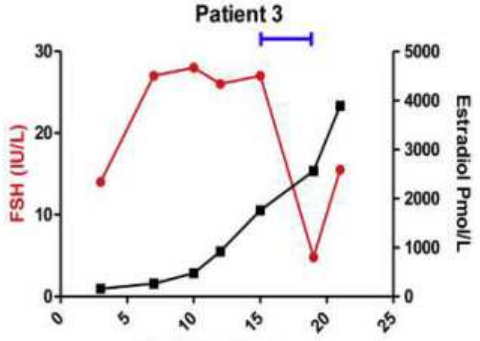
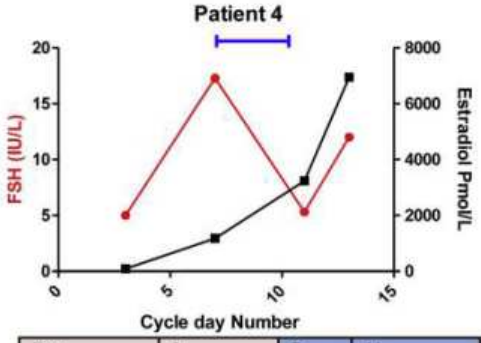


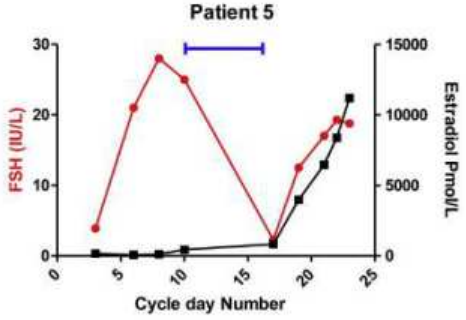
Day	3	6	10	13	16	17
Left	2AF		12	12,10	21,15 15,14	22,17 16,14
Right	3AF		12	12,11 10	21,19 16,11	20,19 17,12



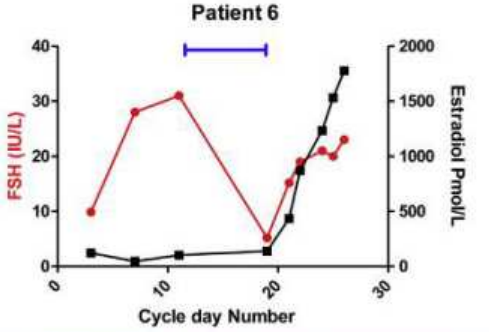
Day	3	12	15	19	21
Left	4AF			18,17	23,19
Right	4AF		11,10	15,11	16,11



Day	3	7	11	15
Left	3AF		17,14 13	22,19,19,15 13,10
Right	3 AF	13	20	25



Day	3	6	8	10	17	19	23
Left	0 AF				16	16	20
Right	12 AF	11,10	11,10	12,11	15,14 12,11 11	17,14 12,12 12	28,23 23,23 18,17 16,15

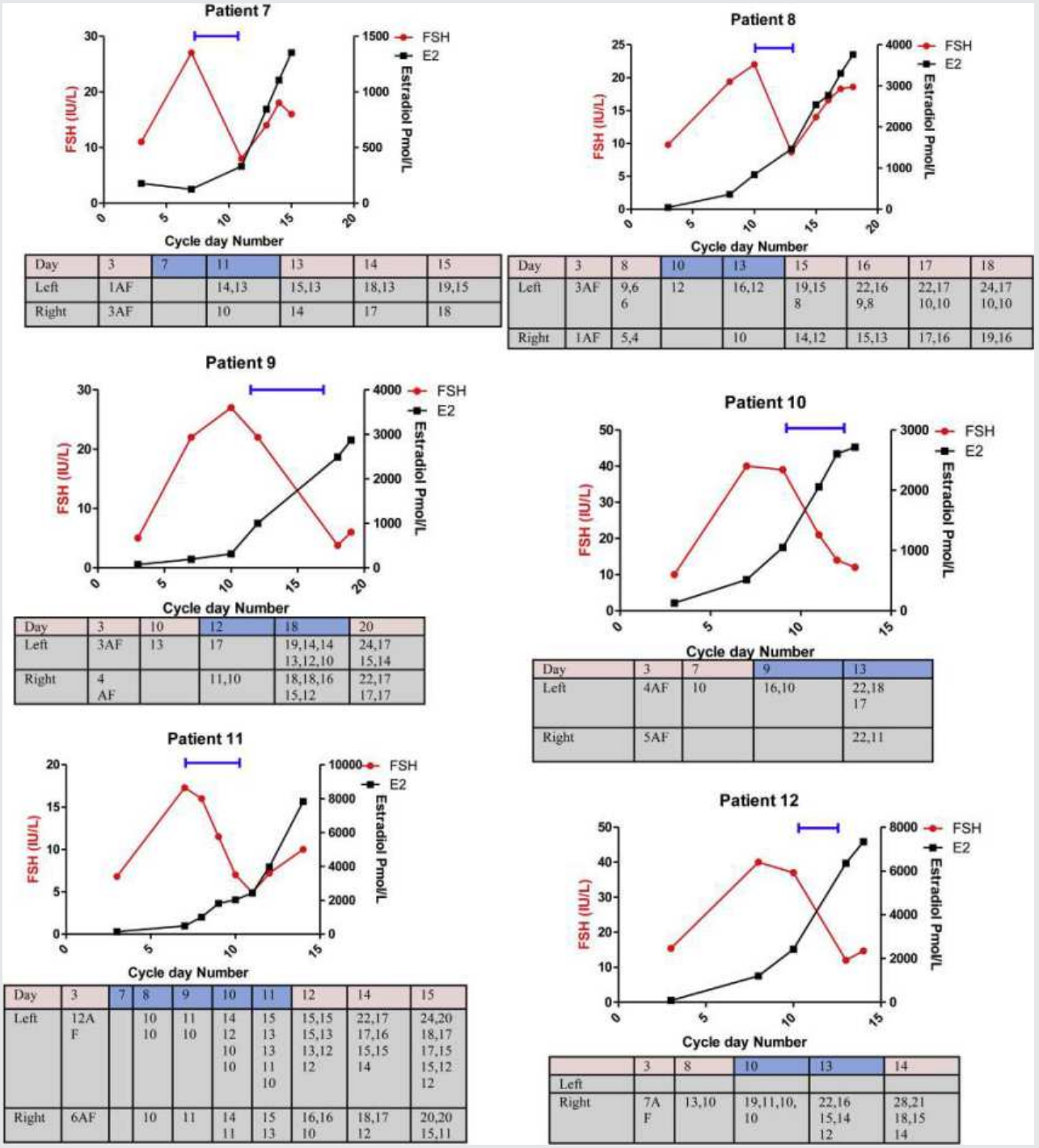


Day	3	12	19	22	24	25	26
Left	0AF						
Right	3 AF		13,12	14,13 12	16,15 12	17,17 13	20,19 18

Combined figures and tables portraying serum E_2 and FSH and follicle size in relation to cycle day number. Interrupted intervals are highlighted in *blue* on both graphs and tables. The first highlighted day indicates gonadotropin withdrawal and the subsequent highlighted day indicates gonadotropin resumption. Only follicles >10 mm and baseline antral follicle (AF) counts are represented.

Mitri. Androgen–interrupted FSH protocol. Fertil Steril 2016.

SUPPLEMENTAL FIGURE 1 Continued



Day	3	7	11	13	14	15
Left	1AF		14,13	15,13	18,13	19,15
Right	3AF		10	14	17	18

Day	3	8	10	13	15	16	17	18
Left	3AF	9,6 6	12	16,12	19,15 8	22,16 9,8	22,17 10,10	24,17 10,10
Right	1AF	5,4		10	14,12	15,13	17,16	19,16

Day	3	10	12	18	20
Left	3AF	13	17	19,14,14 13,12,10	24,17 15,14
Right	4 AF		11,10	18,18,16 15,12	22,17 17,17

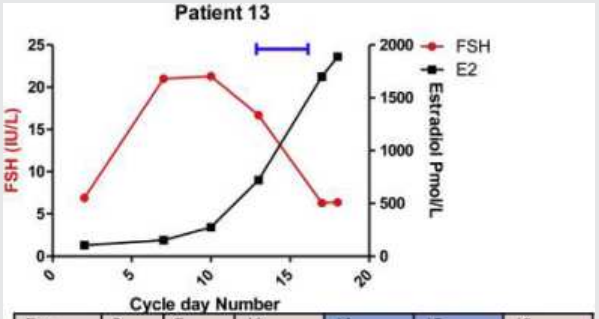
Day	3	7	9	13
Left	4AF	10	16,10	22,18 17
Right	5AF			22,11

Day	3	7	8	9	10	11	12	14	15
Left	12A F		10 10	11 10	14 12 10 10	15 13 13 11 10	15,15 15,13 13,12 12	22,17 17,16 15,15 14	24,20 18,17 17,15 15,12 12
Right	6AF		10	11	14 11	15 13	16,16 10	18,17 12	20,20 15,11

	3	8	10	13	14
Left					
Right	7A F	13,10	19,11,10, 10	22,16 15,14 12	28,21 18,15 14

Mitri. Androgen–interrupted FSH protocol. Fertil Steril 2016.

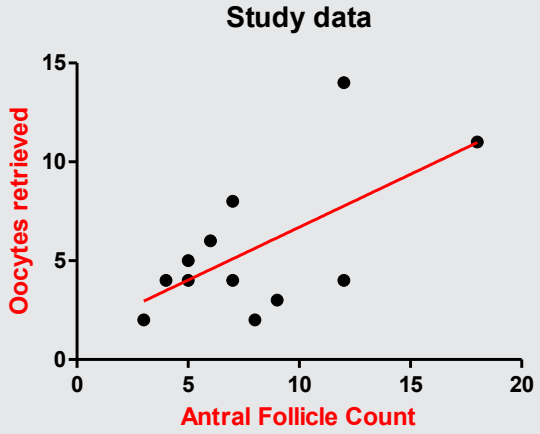
SUPPLEMENTAL FIGURE 1 Continued



Day	2	7	10	13	17	18
Left	2AF					
Right	3AF		11	17	22,15 13	25,17 14

Mitri. Androgen–interrupted FSH protocol. Fertil Steril 2016.

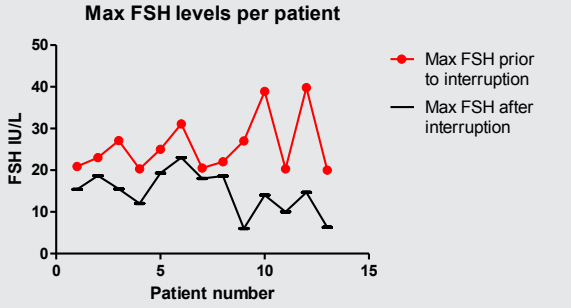
SUPPLEMENTAL FIGURE 2



Baseline antral follicle count plotted against the total number of oocytes retrieved for all 13 patients. Each dot represents a patient.

Mitri. Androgen–interrupted FSH protocol. Fertil Steril 2016.

SUPPLEMENTAL FIGURE 3



Maximum serum FSH levels (pmol/L) before and after gonadotropin withdrawal and resumption for all 13 patients.

Mitri. Androgen–interrupted FSH protocol. Fertil Steril 2016.

SUPPLEMENTAL TABLE 1

Hormone levels and follicular growth before and after gonadotropin interruption.

Variable (average values)	First day of gonadotropin interruption	First day of gonadotropin resumption (after interruption)	*P* value
FSH (IU/L)	25.2 ± 6.5	6.8 ± 3.2	< .05
E_2 (pmol/L)	896 ± 687	2163 ± 1667	< .05
No. of follicles ≥ 1 cm (ultrasound)	1.5 ± 1.2	4.9 ± 2.3	< .05

Mitri. Androgen–interrupted FSH protocol. Fertil Steril 2016.