Change in oocyte yield in repeated in vitro fertilization cycles: effect of ovarian reserve

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Objective: To examine factors that affect variability in oocyte yield between consecutive IVF cycles.
Design: Retrospective cohort study.
Setting: University-based fertility clinic.
Patient(s): A total of 292 women starting two IVF cycles within 12 months from 2005 to 2011.
Intervention(s): Variables evaluated included female age, body mass index, parity, infertility diagnosis, antral follicle count (AFC), ovarian stimulation protocol, change in stimulation protocol, total dose of gonadotropin used and change in dose between cycles. Possible associations were tested using a log linear regression model.
Main Outcome Measure(s): Change in total and mature oocyte yield between cycles and factors that predict this change.
Result(s): In cycle 1, total and mature oocyte yield were positively associated with increased AFC and negatively associated with total gonadotropin dose. In cycle 2, a significant increase was seen in both total and mature oocytes. There were no significant independent variables that predicted this change in oocyte yield. When stratified into groups based on ovarian reserve, change in oocyte yield between cycles was significant only in patients with normal ovarian reserve (AFC >10). In this group, the only independent variable associated with an increased oocyte yield was an increase in the total gonadotropin dose.
Conclusion(s): An increase in oocyte yield between cycles was found in women with normal ovarian reserve and was associated with an increased total gonadotropin dose in the second cycle. (Fertil Steril® 2014;101:399–402. ©2014 by American Society for Reproductive Medicine.)
Key Words: Oocytes, in vitro fertilization, ovarian stimulation, gonadotropin therapy, infertility

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The first cycles of IVF were performed by retrieving oocytes in the natural menstrual cycle. Although natural-cycle IVF is still performed today, a large majority of IVF is done with the use of exogenous gonadotropin stimulation in an effort to increase the number of oocytes and embryos, and ultimately the pregnancy rate, after this procedure. Pregnancy rates after IVF are highly correlated with a woman's age, but higher numbers of oocytes retrieved also are associated with higher pregnancy rates. For example, in a large series from Belgium, women with 6–10 mature oocytes had a birth rate that was 4.3% lower and women with 1–5 mature oocytes had a birth rate that was 16.4% lower than women with ≤11 metaphase II oocytes (1). The association between IVF pregnancy rate and oocyte yield is not linear, however. An analysis of more than 400,000 cycles showed that the live birth rate rose with increasing numbers of oocytes up to 15, plateaued between 15 and 20, and then declined beyond 20 (2). Oocyte efficiency in producing a live birth after gonadotropin stimulation is actually quite low. In large clinical series, only ~5% of fresh oocytes produce a baby, and the rate increases to just over 7% in the best-prognosis patients (1, 3, 4). The live birth per oocyte rate drops significantly with age, reflecting the poorer quality of oocytes because of higher aneuploidy rates in older women.

Given the importance of the number of oocytes retrieved during IVF treatment, predicting the number that

Received August 26, 2013; revised October 23, 2013; accepted October 28, 2013; published online December 12, 2013.
E.E.E. has nothing to disclose. A.E.T.S. has nothing to disclose. D.L. has nothing to disclose. B.J.V.V. has nothing to disclose.
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Fertility and Sterility® Vol. 101, No. 2, February 2014 0015-0282/$36.00
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http://dx.doi.org/10.1016/j.fertnstert.2013.10.049

one might expect to obtain in a given cycle is of value. In addition to age, the predictive value of tests of ovarian reserve has been shown by many studies. Antimüllerian hormone (AMH) levels and antral follicle counts determined by ultrasound before the first cycle of IVF have been noted to be useful for this purpose (5–8). Some studies have developed equations for predicting the oocyte yield for the purpose of counseling patients and individualizing gonadotropin dosing (7, 8). In contrast to a number of studies predicting oocyte yield after a single cycle, there are no studies looking at predicted change in oocyte yield in consecutive cycles for patients in whom the initial cycle was unsuccessful. This information is of significant value in counseling patients and planning the subsequent cycle. Our objective was to determine the cycle-to-cycle variability in oocyte yield in women undergoing controlled ovarian hyperstimulation for IVF and to determine the predictors of change in oocyte yield between consecutive IVF cycles.

METHODS

All women having two consecutive ovarian stimulation cycles leading to oocyte retrieval within 12 months from January 2006 to December 2011 were included in this study. We chose to limit the analysis to those who had stimulation within 1 year to minimize the known effect of aging on oocyte yield in IVF patients. All data were prospectively entered into our internal IVF program database, and our retrospective analysis of these data was approved by the University of Iowa Internal Review Board. Data points analyzed included the antral follicle count (AFC: follicles of 2–9 mm in diameter measured and counted in both ovaries) determined by trained sonographers at their initial IVF intake appointment within 3 months of their IVF cycle. Other variables analyzed included female age, body mass index (BMI), ethnicity, parity, smoking status, duration of infertility, infertility diagnosis, stimulation protocol, days of stimulation, and total gonadotropin dose used. To calculate the total gonadotropin dosing, we converted ampules of mixed FSH and LH products (hMG) by multiplying the number of ampules of hMG used times 150 IU and added this to the doses of pure FSH products. Days of stimulation were counted as days of gonadotropin dosing plus days of GnRH agonist for microdose flare cycles and as days of gonadotropin dosing for all other stimulation protocols.

The total number of oocytes retrieved and the number of mature oocytes retrieved (metaphase II oocytes) in each IVF cycle were recorded. To evaluate the effect of AFC on change in oocyte yield, we not only looked at AFC as a continuous variable but also divided our cohort into those with diminished ovarian reserve (defined as ≤ 10 antral follicles) and those with normal ovarian reserve (>10 antral follicles).

During the study period, our IVF program used three stimulation protocols. Nearly all cycles were preceded by 1 month of oral contraceptive pills for cycle timing purposes. Patients received either a long luteal-phase GnRH agonist protocol, a "microdose flare" protocol using a GnRH agonist, or a GnRH antagonist protocol. The choice of protocol is at the discretion of the individual physician but, in general, the long luteal protocol is used most often and the microdose flare and the GnRH antagonist protocol are reserved for older patients and poor responders (either anticipated based on ovarian reserve or observed in an earlier cycle). For gonadotropins, we use 3 days of FSH only (Follistim; Organon) followed by a mixed protocol of FSH and an LH activity–containing product (Repronex or Menopur; Ferring Pharmaceuticals). The starting gonadotropin dose is also at the discretion of the physician. This is followed by a protocol-driven step-up dosing that is the same among the three protocols and is based on adequacy of follicular response and E_2 rises. hCG (10,000 IU) is administered when there are at least two ovarian follicles with a mean diameter of ≤ 18 mm. Oocyte retrieval is performed under sedation 34.5 hours after hCG administration, and it is our practice to retrieve as many oocytes as possible by aspirating all visible follicles. Oocyte number and maturity are recorded after the embryologists spread each cumulus-oocyte complex immediately after oocyte retrieval and examine for the presence of a polar body and germinal vesicle breakdown with the use of phase-contrast microscopy at $\times$ 320 magnification. Mature oocytes are defined as metaphase II oocytes present at this time point.

Our primary outcome of interest was the change in total oocyte yield between cycles. Secondary outcomes were total and mature oocytes retrieved in cycle 1 as well as change in total and mature oocyte yields between cycles. Both total and mature oocyte yield were treated as count data, which were modeled with the use of the log-linear model. Variables potentially affecting the yield were examined by including them as explanatory variables in the log-linear model and analyzing them with a chi-square test. Variables that were found to affect change in total and mature oocyte yield between cycles were analyzed using multiple linear regression. The Wald test was used to assess the variable significance in the multiple linear regression models. For all variables, descriptive statistics were generated and tested with the use of the paired t test for paired continuous variables, the two-sample t test for independent continuous data, and the chi-square test for categoric data. Significance level of 0.05 was used for all hypothesis testings. All statistical analyses were conducted using statistical software SAS v9.2.

RESULTS

A total of 292 women met inclusion criteria for this study, 248 with normal (NOR) and 44 with diminished (DOR) ovarian reserve. Demographic and cycle stimulation data for these subjects is presented in Tables 1 and 2. The majority of women used a long luteal-phase GnRH agonist protocol in the first cycle of stimulation. Of the entire cohort, 49% had a change in protocol in cycle 2. Protocol change occurred in 65.9% of women with diminished ovarian reserve and 45.2% of women with normal ovarian reserve ($P=.018$). The ongoing pregnancy rate in cycle 2 was 45.6% for the cohort.

In cycle 1, the average total oocyte yield was 12.1 ± 6.5, and the average mature oocyte yield was 10.0 ± 5.5 (Table 2). In cycle 1, total oocyte yield was positively associated with increasing AFC ($P<.0001$) and negatively associated with total gonadotropin dose ($P=.0122$). The AFC (positive

TABLE 1

Patient demographic data.

Parameter	Value
Female age (y), mean ± SD (range)	33.9 ± 4.5 (21–43)
BMI (kg/m^2), mean ± SD (range)	27.2 ± 7.0 (17.8–51.4)
Ethnicity, %	
White	75.3
Asian	5.1
Hispanic	3.1
African American	1.0
Unknown/other	15.4
Parity, %	
0	66.8
1	25.0
≤2	8.2
Smoker, %	17.5
Duration of infertility (mo), mean ± SD	38.2 ± 29.2
Infertility diagnosis, %	
Ovulatory dysfunction	17.5
Endometriosis	13.7
Male factor	27.0
Other	41.8
Antral follicle count (mean ± SD)	20.1 ± 10.0

Note: BMI = body mass index.

Eppsteiner. Changes in IVF oocyte yield. Fertil Steril 2014.

association) and total gonadotropin dose (negative association) were also significant predictors of the number of mature oocytes retrieved in cycle 1.

In cycle 2, a small but significant increase was seen in both total oocytes (mean difference +1.8 oocytes, range −18 to +25) and mature oocytes (+1.8 oocytes, range −16 to +18) retrieved (Table 2). In analysis of the entire cohort, there were no significant independent variables that predicted a change in either mature or total oocyte yield between cycles.

When our cohort was divided into groups of DOR, defined as AFC ≤10, and NOR, defined as AFC >10, the change in oocyte yield between cycles was significant only in the group of patients with NOR (Table 3).

In those patients with NOR, multivariate analysis demonstrated that the only variable independently associated with

TABLE 2

Cycle-to-cycle variability in oocyte yield.

Stimulation protocol (%)	Cycle 1	Cycle 2
Long luteal-phase GnRH agonist	71.9%	41.8%
Flare	21.9%	39.0%
GnRH antagonist	6.2%	19.2%
Change in protocol	N/A	49%
Clinical pregnancy rate	13.7%	60.6%
Delivery rate	0	45.6%
Days of stimulation, mean ± SD	10.9 ± 0.2	11.2 ± 0.2
Total gonadotropin dose (IU), mean ± SE	3,594.9 ± 84.3	4,093.0 ± 90.2[a]
Total oocytes	12.1 ± 6.5	14.0 ± 7.2[a]
Mature oocytes	10.0 ± 5.5	11.8 ± 6.3[a]

[a] $P<.05$.

Eppsteiner. Changes in IVF oocyte yield. Fertil Steril 2014.

TABLE 3

Change in oocyte yield by antral follicle count (AFC).

	AFC ≤10	AFC ≥10
n	44	248
Total oocytes, cycle 1	9.2 ± 6.9	12.7 ± 7.6
Total oocytes, cycle 2	9.7 ± 7.4	14.8 ± 8.1
Difference in oocyte yield between cycles	0.49 ± 4.3	2.0 ± 0.6[a]

[a] $P<.05$.

Eppsteiner. Changes in IVF oocyte yield. Fertil Steril 2014.

an increased oocyte yield was an increase in the total gonadotropin dose from cycle 1 to cycle 2. On average, the total increase in dose was ~500 IU of medication (3,420.4 ± 87.6 to 3,926.3 ± 96.7; $P=.009$). This increase in total dose was due to an increase in the daily dosage of medication, because there was no difference in the total days of stimulation between cycle 1 and cycle 2 (10.6 ± 0.1 days vs. 11.0 ± 0.1 days). Change in stimulation protocol, though performed frequently, was not associated with a change in oocyte yield.

DISCUSSION

In the cohort of women undergoing two consecutive IVF cycles within one year, we found a relatively small increase in the average number of oocytes retrieved. However, this average increase of two oocytes may be clinically relevant for women who fail an initial cycle, given the delivery rate of 5% per oocyte with IVF (3, 4). Unfortunately, our data indicate that women with DOR are less likely to have an increase in oocyte yield than women with NOR. Thus, ovarian reserve as estimated by the AFC can be used not only to predict the number of oocytes that are expected in the first IVF cycle, but also to counsel couples regarding expectations for a second cycle, if this is necessary.

The only variable we identified as significant in predicting an increase in oocyte yield (total gonadotropin dose) was found only among women with NOR. Furthermore, it appears that an increase in the average daily dose is what leads to an increased oocyte yield, because the total number of days of stimulation did not differ. There have been limited studies on the optimal daily dose of gonadotropin medications in IVF cycles. A recent meta-analysis found that, among presumed normal responders <39 years old, daily doses of gonadotropins of >200 IU/d resulted in more oocytes and a higher risk of ovarian hyperstimulation syndrome but no change in pregnancy rates compared with women using 100–150 IU/d (9). Those authors concluded that a starting dose of 150 IU/d was likely to result in optimal pregnancy and ovarian hyperstimulation syndrome rates for normal responders, though oocyte yield would be slightly compromised. We found that, among women with NOR, an increase in the gonadotropin dose led to a higher oocyte yield if a second cycle is necessary.

Whether an increase in dosing in the second cycle makes a difference likely depends on the dosing used in the first cycle. In younger women with normal ovarian reserve, we

generally start with 150 IU/d FSH. Our average daily gonadotropin dose was in fact 330 IU/d in the first cycle using our step-up dosing regimens. Under these conditions (NOR and relatively low starting gonadotropin doses in the first cycle), increased gonadotropin dosing was associated with a higher oocyte yield in the second cycle. These findings are consistent with a prospective randomized trial of normal responders <37 years old in which a starting gonadotropin dose of 200 IU/d resulted in a significantly higher oocyte yield compared with a starting dose of 100 IU (12.0 oocytes vs. 5.7 oocytes, respectively) (10). In a prospective randomized trial of women aged 30–39 years, increasing the starting gonadotropin dose from 150 IU/d to 250 IU/d resulted in no significant difference in oocyte yield in the entire group. However, the subset of women aged 30–33 years, with presumably a higher ovarian reserve, had ~4 more oocytes retrieved with higher gonadotropin doses, whereas no difference in egg yield was seen in women aged 34–39 years (11).

In contrast to women with NOR, we found little change in oocyte yield in women with DOR as defined by AFC. This information may prove to be helpful in counseling couples regarding their prospects for a second IVF cycle. Our findings support a prospective randomized trial that found no benefit to higher starting doses of gonadotropins (300 IU/d vs. 150 IU/d) among women with DOR (12).

One weakness of the present study is that we studied a select group of patients with a poor outcome (no ongoing pregnancy) in their first cycle of treatment, which may not be representative of all patients that we treat. In addition, although the relatively high ongoing pregnancy rate and greater oocyte yield (among women with NOR) in cycle 2 are encouraging, this could represent a regression to the mean. However, the lack of improvement in oocyte yield among DOR patients suggests that it is a clinically relevant predictive variable.

After a failed cycle, physicians review the cycle and often change the stimulation protocol or gonadotropin dosing in the hopes of improving the outcome. We found that increasing doses are not associated with any improvement in oocyte yield in women with DOR. In contrast, in women with NOR, an increase dose of medications was associated with higher oocyte yield. AFC has previously been considered to be a useful tool in predicting oocyte yield in an initial IVF cycle. For the first time, the present study suggests that the utility of the AFC can be extended to predict variability between ovarian stimulation cycles and to help create reasonable expectations for patients undergoing additional treatments with IVF.

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