J Assist Reprod Genet (2009) 26:335–339
DOI 10.1007/s10815-009-9323-9

ASSISTED REPRODUCTION

Follicle curetting at the time of oocyte retrieval increases the oocyte yield

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Received: 4 January 2009 / Accepted: 18 May 2009 / Published online: 23 June 2009

Abstract
Purpose To determine whether follicle curetting at the time of oocyte retrieval increases oocyte yield.
Methods Retrospective review of all patients who underwent oocyte retrieval from July 1, 2003 to June 30, 2005.
Main outcome measure Number of oocytes retrieved. Secondary outcome measures: retrieval time, number of cryopreserved embryos, pregnancy rates, and incidence of ovarian hyperstimulation syndrome.
Results There were no differences in patient demographics, antral follicle count, cycle stimulation characteristics, fertilization rates, embryo quantity or quality, embryo cryopreservation rates, clinical pregnancy rates, live birth rates, or ovarian hyperstimulation syndrome between the groups. Retrievals that utilized curetting took three minutes longer. Follicle curetting significantly increased the number of oocytes retrieved, 13.9±0.6 compared to 11.4±0.6 oocytes without curetting (P=0.003). The quantity of mature oocytes was also increased with curetting (10.3± 0.5 versus 8.4±0.5, P=0.006).
Conclusions This study demonstrated that follicle curetting significantly increased oocyte yield. While it did not increase live birth rates, this increase in oocyte yield should lead to increased numbers of embryos for selection at transfer and increased embryos for cryopreservation.

Keywords Curetting · Egg retrieval · Follicle curetting · In vitro fertilization · Oocyte yield

Capsule Patients undergoing follicle curetting at the time of oocyte retrieval had a 22% increase in oocyte yield which was significant.

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Introduction

Follicle curetting is a technique frequently used during IVF oocyte retrieval. This technique involves gently and rapidly rotating the needle in a clockwise and counter- clockwise fashion inside the follicle after complete aspiration of the follicular fluid [1]. Proponents of this technique report an increased likelihood of aspirating all oocytes and a decreased risk of ovarian hyperstimulation syndrome (OHSS) secondary to removal of a greater number of granulosa cells. Other physicians do not curette during oocyte retrieval and cite an increased length of the procedure and no proven benefits. No studies reported in the literature have evaluated this retrieval technique.

Studies have evaluated other aspects of oocyte retrieval techniques. Follicle flushing after aspiration of the follicular fluid has not been shown to increase the number of oocytes retrieved by most studies [2-5]. The type and caliber of the needle used during oocyte retrieval was also examined and, while pain was directly associated with needle caliber, there were no significant differences in pregnancy outcomes [6-8].

A Medline search from January1980 to October 2008, using the keywords “in vitro fertilization”, “oocyte”, “retrieval technique”, and “follicle curetting” did not yield any previous studies that evaluated the impact of follicle curetting at oocyte retrieval. This study was undertaken to determine if there is any advantage to curetting the follicles

at the time of oocyte retrieval and if curetting increases the procedure time. We hypothesized that follicle curetting would increase the oocyte yield while decreasing the rate of OHSS.

Materials and methods

Approval for this retrospective chart review was obtained from the Institutional Review Board at Christ Hospital and the University of Cincinnati Medical Center in Cincinnati, Ohio. Patients who underwent oocyte retrieval from July 1, 2003 to June 30, 2005 at the Center for Reproductive Health at Christ Hospital were included in the study. At our center, two physicians routinely utilize follicle curetting during oocyte retrieval while a third physician dos not curette. Oocyte retrievals were performed by these physicians on a rotating basis without patient selection. Patients were excluded from the study if their cycle was cancelled prior to oocyte retrieval.

All patients underwent standard stimulation protocols with either a long agonist or flare protocol. Ovulation was triggered with hCG (10,000 IU IM or 250 mcg SC) when maximal oocyte recruitment was achieved and transvaginal oocyte retrieval was performed using conscious sedation 35.5 h later. The luteal phase was supplemented with IM Progesterone in oil and all patients received aspirin 81 mg daily starting on the day of transfer. All patients received doxycycline 100 mg on the day of transfer. Embryo transfer was performed by 1 of 3 physicians who use the same transfer techniques. Embryo transfer was performed on day 3 after retrieval in all but 2 patients. One patient in each group underwent embryo transfer on day 5 after retrieval (blast stage).

Excess embryos are routinely cryopreserved at the 2PN stage and at the blast stage at our center. By protocol, if greater than 6 embryos are present at the 2PN stage, the excess embryos are cryopreserved. The remaining 6 embryos are kept in culture and the best quality embryos are transferred on day 3. Embryos that are not cryopreserved at the 2PN stage or transferred are maintained in culture and frozen if they progress to the blastocyst stage.

We recorded patient demographics including gravidity, parity, and infertility diagnosis. The following were also recorded: cycle characteristics, embryo quality, pregnancy, and OHSS outcomes.

Cycle characteristics

Type of cycle (long agonist or flare protocol); baseline antral follicle count; ampules of gonadotropin used; quantity of follicles stratified by diameter on the day of HCG; oocytes retrieved; oocytes with fractured zonas; number and quality of embryos transferred; estradiol on day of hCG; oocyte maturity; fertilization rate; duration of retrieval (minutes from insertion of retrieval needle to completion of procedure); pain score as reported by the patient on a scale of 1(least) to 10 (most) after the procedure.

Embryo quality

Cell number and grade of embryos transferred; number of frozen 2 PN and number of blastocyst embryos.

Pregnancy and ovarian hyperstimulation outcomes

Rates of clinical pregnancy (fetal heart motion by sonogram at 6.5 weeks gestation); live birth; and moderate or severe OHSS. Moderate OHSS was defined as symptoms that required office consultation such as increasing abdominal girth, abdominal discomfort and nausea. OHSS was considered severe if patients required medical intervention such as hospitalization or paracentesis [9].

Statistical analysis

The independent variable was the performance or omission of follicular curetting during oocyte retrieval and the primary outcome was the number of oocytes retrieved. Secondary outcomes included the number of embryos cryopreserved, length of procedure, clinical pregnancy rates, live birth rates, and rates of moderate and severe OHSS. Chi square analysis and t-tests were performed on the categorical and continuous data, respectively using SPSS, (Chicago, IL) Data are presented as mean number± SEM and statistical significance was assessed at a 2-tailed t-test $P<0.05$. Post hoc power analysis revealed effect size of $d=0.36$ with power=96%. A power analysis revealed we would need 9,000 patients in each arm of the study to detect a difference of OHSS between groups.

Results

220 women of reproductive age underwent 281 consecutive in vitro fertilization cycles. Six cycles were cancelled prior to oocyte retrieval which resulted in 275 IVF cycles that were included in the analysis. Indications for IVF-ET included male factor infertility, diminished ovarian reserve, endometriosis, tubal factor infertility, and oocyte donation. There were no differences in patient demographics between

Table 1 Patient demographics and cycle characteristics

	Follicle curetting N=186	No curetting N=89	P value
Female age	33.8±0.4	34.7±0.7	0.25
Gravidity	1.2±0.1	1.3±0.2	0.47
Parity	0.5±0.1	0.6±0.1	0.41
Male age	34.8±0.5	36.7±1.1	0.13
Male factor infertility diagnosis	62.4%	52.9%	0.15
Female infertility diagnosis			
Ovulatory dysfunction	11.3%	6.7%	0.28
Donor egg recipient	14.0%	16.9%	0.59
Tubal factor	24.7%	24.7%	1.0
Diminished ovarian reserve	26.3%	29.2%	0.67
Endometriosis	15.1%	15.7%	0.86
PCOS	9.1%	9.0%	1.0
Adhesions	6.5%	7.9%	0.8
Unexplained	5.4%	4.5%	1.0
Other	17.2%	24.7%	0.15
Number antral follicles	17.4±0.8	16.1±1.0	0.33
Follicles≥16 mm	8.5±0.3	8.5±0.5	0.99
Follicles 12 – 15.5 mm	6.2±0.4	5.4±0.4	0.24
Follicles<12 mm	2.4±0.2	2.1±0.2	0.40
Mean ampules of medication	32.5±1.1	34.5±1.7	0.33
Peak estrogen level	2454.2±147.5	2401.8±81.5	0.74

Data presented as mean number ± SEM or as percentage

*denotes statistical significance

the groups of women who underwent follicle curetting during oocyte retrieval compared to the group that did not undergo follicle curetting. The basal antral follicle count and size of follicles on the day of hCG were also similar between groups (Table 1).

There was a significant increase in the number of oocytes retrieved in the curetting group 13.9±0.6 compared to the no-curetting group 11.4±0.6 (P=.003, CI 0.9 – 4.1). There were also more metaphase II oocytes (MII) 10.3±0.5 retrieved in the curetting group compared to 8.4±0.5 MII oocytes retrieved in the no-curetting group

(P=.006, CI 0.5 – 3.2). This was a twenty-two percent increase in number of oocytes retrieved with follicle curetting. There were no differences in the stimulation protocols or method of fertilization. More embryos were frozen at the 2 PN stage with follicle curetting compared to

Table 2 Retrieval characteristics and cycle outcomes

	Follicle curetting N=186	No curetting N=89	P value
Oocytes retrieved	**13.9±0.6**	**11.4±0.6**	**0.003***
Metaphase II oocytes	**10.3±0.5**	**8.4±0.5**	**0.006***
Length of retrieval in minutes	**27.2±0.9**	**24.3±1.0**	**0.040***
Germinal vesicles	1.7±0.1	1.1±0.2	0.07
Fractured zonas	0.1±0.03	0.1±0.1	0.6
Pain score	3.9±0.2	3.3±0.3	0.10
Percent of cycles using ICSI	55.9%	51.7%	0.51
Percentage oocytes fertilized	53.2%	55.2%	0.78
Embryos transferred	2.4±0.1	2.5±0.1	0.32
Mean embryo grade	2.1±0.1	2.0±0.1	0.9
Mean cell number	6.5±0.1	6.8±0.2	0.22
Ovarian hyperstimulation	3.8%	4.5%	0.75
Embryos cryopreserved at 2PN	1.9±0.3	1.2±0.3	0.05
Embryos frozen at blast	0.5±0.1	0.5±0.1	0.78
Clinical pregnancy rate	57%	55%	0.83
Live births	41%	49%	0.41

Data presented as percentage or as mean number ± SEM

*denotes statistical significance

the no- curetting group (1.9±0.3, 1.2±0.23 respectively) but this did not reach statistical significance (P=.05). No other differences in embryo characteristics or pregnancy outcomes were observed (Table 2).

The overall incidence of OHSS was less than 5% in both groups (Table 2). The duration of the retrieval procedure was 27.2±0.9 min in the curetting group and 24.3±1.0 minutes in the non-curetting group which was significant (P=.040, CI 0.1 –5.8). Pain scores were at the low range of the scale and similar between groups (Table 2).

Discussion

We demonstrated that follicle curetting during in vitro fertilization oocyte retrieval resulted in a 22% increase in the total number of oocytes and the number of mature oocytes (MII) obtained. This increased yield was achieved without any evidence of oocyte damage.

Although there were more patients in the curetting group, there were no differences with respect to patient demographics or cycle characteristics. It is also important to note that there were no differences between the groups in the number of antral follicles or in the size of follicles on the day of hCG which are both major factors predicting oocyte yield [10] and maturity [11]. There was no difference in the number of germinal vesicles (immature oocytes) between the groups which we may expect to see with an increase total number of oocytes retrieved. No other oocyte retrieval techniques, including follicle flushing and altering needle characteristics have been associated with increased oocyte yield [2-8]. This benefit would appear to outweigh the three extra minutes required to implement curetting during the retrieval procedure.

Ovarian hyperstimulation syndrome has been shown to increase the risk of adverse perinatal outcomes and factors that may decrease this syndrome are important to identify [12]. Vascular endothelial growth factor is thought to be involved of the pathophysiology of OHSS [13]. Therefore, the rationale for curetting the follicle to remove increased numbers of granulosa cells during retrieval to decrease the amount of VEGF release. The OHSS rate in our population was within previously reported ranges of moderate to severe OHSS of 2–5% [11, 14, 15]. Given these overall low OHSS rates, our study was insufficiently powered to detect a difference in the incidence of OHSS.

This study did not determine if there was a difference in the numbers of embryos available for embryo selection at the day of transfer because we routinely freeze excess embryos (greater than 6 embryos) at the 2PN stage. There was a nonsignificant (P=.05) trend toward increased numbers of embryos cryopreserved at the 2PN stage with follicle curetting. This study may be even more relevant to programs that culture all embryos to either the day 3 or to the blast stage (i.e. do not cryopreserve at the 2PN stage). It is interesting to speculate that in those programs, follicle curetting may increase the number of embryos available for selection purposes at the time of transfer.

The findings from this study are limited by the non-randomized approach and retrospective design. The results from this study should be confirmed with a future prospective randomized controlled trial.

Conclusions

Follicular curettage during oocyte retrieval is a technique that aids to increase mature oocyte yield without sacrificing oocyte quality, or integrity. While it increases the length of the oocyte retrieval, this increase is minimal. Despite the fact that pregnancy rates between the two groups were not different, follicle curetting should be strongly considered as a means to increase the number of oocytes in all women undergoing in vitro fertilization. We believe this is particularly relevant to increase the oocyte yield in women who have responded poorly to gonadotropin stimulation.

Acknowledgements We would like to thank Dr. Rose Maxwell and the in vitro fertilization nurses at our center, Judy Eckert, Brenda Huber, and Terry Anderson for their assistance with this study

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