Unilateral oophorectomy results in compensatory follicular recruitment in the remaining ovary at time of ovarian stimulation for in vitro fertilization

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Objective: To assess the effect of unilateral oophorectomy (UO) by assessing ovarian reserve (OVR) and the response to gonadotropin stimulation in women with UO undergoing in vitro fertilization (IVF) compared with the response of the ipsilateral ovary of women without UO.
Design: Historical cohort study.
Setting: Academic fertility clinic.
Patient(s): Fifty-one women with single ovary compared with a referent group with both ovaries in a 1:2 fashion.
Intervention(s): None.
Main Outcome Measure(s): Day-3 follicle-stimulating hormone (FSH), estradiol, and antral follicle counts as measures of OVR, and IVF outcomes including number of follicles aspirated and oocytes retrieved.
Result(s): The baseline demographics and serum markers of OVR were not different. Referent women had greater follicular yield and oocyte numbers when compared with women with UO; however, when compared with the ipsilateral ovary of the referents, women with UO had a higher antral follicle count and greater follicle and oocyte numbers. In multivariate analyses, the ovary from women with UO was more likely to yield more than the median number of follicles and oocytes than the ipsilateral ovary in referent women. Live-birth rates in both groups were similar.
Conclusion(s): Our results suggest that the remaining ovary appears to compensate in follicular yield after UO in women, confirming the animal data. Women with UO can be reassured and appropriately counseled regarding IVF. (Fertil Steril® 2014;101:722–7. ©2014 by American Society for Reproductive Medicine.)
Key Words: Compensatory follicular recruitment, in vitro fertilization, ovarian reserve, unilateral oophorectomy

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Women with a history of unilateral oophorectomy (UO) represent a unique and challenging group presenting to fertility clinics. Most women with a single ovary have had a surgical oophorectomy for reasons that may include ovarian neoplasms, ectopic pregnancies, and advanced tubal disease (1). The true prevalence of women with a single ovary in the general population is not known. The prevalence of a single ovary in women presenting with fertility issues has been reported to range between 5.5% and 17% (2, 3).

There is an abundance of data in mice, rats, pigs, and opossums to support that compensatory hypertrophy occurs in the contralateral ovary after UO

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(4–8). An increase in ovarian weight is noted in mice after unilateral spaying (5). Increased pituitary gonadotropin secretion is the proposed mechanism of this hypertrophy (9, 10). To date, there have been no data to show such an anatomic or functional compensatory effect in women who have had one ovary removed.

Moreover, there is also evidence in many species that there are functional differences between the right and left ovary. The right ovary dominates in sheep and cows (11–13), whereas horses and camels ovulate more from the left ovary (14). In primates, the rhesus macaque ovulates from the right ovary 60% of the time (15). Limited data in humans also suggest right-sided dominance for ovulation: 64% of women ovulated from the right ovary in any single cycle, and 21% of the women consistently ovulated from the right side through 90 natural menstrual cycles (16). In women with both ovaries intact, the importance of laterality of an ovary undergoing ovarian stimulation is controversial. Some studies report similar stimulation response from each ovary (17, 18), but newer data suggest superiority of the right ovary for stimulation and pregnancy rates (19, 20).

In vitro fertilization (IVF) outcomes in women with one ovary have been studied, and most studies have shown similar pregnancy rates in women after UO compared with control women (1–3, 17, 21–26). Others have shown better pregnancy rates in women with one ovary (27, 28), although one study showed better rates in women with both ovaries intact (29). Fewer studies have examined ovarian reserve testing in women with a UO undergoing IVF. Moreover, all these studies neglect the data regarding the importance of laterality of the ovary in response and have compared follicle development and oocyte yield in women with a single ovary to the mean response of both ovaries rather than comparing it with the ipsilateral side ovary of referent women (24, 28, 30, 31).

Our study assesses the effect of UO on baseline ovarian reserve and ovarian stimulation outcomes in women undergoing IVF. The influence of laterality of the remaining ovary on ovarian stimulation outcomes in women undergoing IVF was also examined.

MATERIALS AND METHODS

Patients

This study was reviewed and approved by the Mayo Clinic institutional review board. All women undergoing IVF at the Mayo Clinic, Rochester, Minnesota, from January 1, 1996, to March 31, 2011, who gave research authorization for a review of their medical records were considered for analysis. The exposed cohort (women with history of UO) consisted of 51 women. We obtained a 1:2 matched reference group of 102 unexposed women (women with both ovaries intact) by choosing the next two age-matched (±2 years) patients who underwent oocyte retrieval to minimize the impact of changes in stimulation patterns over time. The antral follicle count (AFC) and stimulation outcomes for each woman in the exposed cohort were compared with the ipsilateral ovary of women in the referent group. Baseline demographic data as well as data from ovarian stimulation protocol and outcomes were extracted from the patients' medical records and the Mayo Clinic, Rochester, IVF database.

Treatment Protocol

Three basic ovarian stimulation regimens were employed over the study period: the long luteal gonadotropin-releasing hormone (GnRH) agonist protocol, the microdose GnRH-agonist (coflare) protocol, and the GnRH-antagonist protocol. In the long luteal GnRH-agonist protocol, ovarian down-regulation was performed by administration of GnRH-agonist (1 mg/day) starting during the midluteal phase of the preceding cycle. Controlled ovarian stimulation was achieved after down-regulation by follicle-stimulating hormone (FSH) or a combination of FSH and luteinizing hormone (LH), using individually adjusted doses depending on patient's age, ovarian reserve, monitored serum 17β-estradiol level, and follicular monitoring. In the microdose GnRH-agonist (coflare) protocol, the GnRH-agonist was started on second day of the menstrual cycle (40 μg subcutaneously twice a day from days 2 to 5, then 1 mg/day thereafter), then FSH was then started on day 3 of the menstrual cycle (again, the dose of FSH was then individualized). With the GnRH-antagonist protocol, gonadotropins were started on cycle day 3. The GnRH-antagonist (0.25 mg/day) was started on day 6 of menstrual cycle or when the lead follicle was at 14 mm. The GnRH analog in the long luteal and coflare protocols and the GnRH antagonist in the antagonist protocol were continued until the day of human chorionic gonadotropin (hCG) administration. The criteria for hCG were constant, and 10,000 U were injected intramuscularly when two or more lead follicles were noted to be greater than 18 mm and 50% of the cohort of follicles were noted to be greater than 15 mm.

Transvaginal sonographically guided oocyte retrieval was performed under monitored sedation 36 to 38 hours after hCG administration. Embryo transfer at the cleavage stage was performed 48 to 72 hours after oocyte retrieval. Progesterone, either via intramuscular injection or by vaginal suppository, was given to all patients for luteal support. Serum β-hCG measurements were obtained from all patients within 2 weeks of the embryo transfer for confirmation of biochemical pregnancy.

Outcome Measures

Ovarian reserve in all women was determined by serum FSH (immunoenzymatic assay) and estradiol (E_2) (electrochemiluminescent immunoassay) measurements on day 3 of the menstrual cycle. All tests were run by the same laboratory at Mayo Clinic, Rochester. The AFC was determined by vaginal ultrasound performed before starting ovarian stimulation. All ultrasounds were performed by the same sonographer.

The primary outcome measures in this study were achievement of greater than the median number of follicles and the median number of oocytes obtained from them, respectively. The pregnancy rate, a secondary outcome,