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Are intra follicular estradiol and oocytes quality in women undergoing assisted reproductive technology different between the right and left ovaries? An observational study



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ABSTRACT

Objective: Controlled Ovarian Stimulation (COS) for In-Vitro Fertilization (IVF) or Intracytoplasmic Sperm Injection (ICSI) is considered as an assisted reproduction technology. There are established structural and biological differences between both ovaries which may affect their responsiveness to COS. Whether the right or the left ovary responds superior to COS is a question which is unresolved in the literature.

Study design: The present study was conducted as a prospective observational to make a comparison between right and left ovaries' oocytes based on oocyte quality and follicular fluid estradiol level. A total of 100 infertile women who had referred to Infertility and Reproductive Health Research center at Shahid Beheshti University of Medical Sciences, Tehran, Iran, were investigated.

Results: The total number of very good and good oocytes were 63.01% vs. 50.3%, and immature and interstitial oocytes were 36.99% vs. 49.6% in the right and the left ovaries, respectively. There were no significant differences between oocyte rates between the two ovaries ($P > 0.05$).

Conclusion: Good and very good quality oocytes and fertilization rate ($P < 0.001$) are higher in the right ovary compared with the left ovary; however, no significant difference was observed between the right and the left ovaries in oocyte yields and cleavage rates. Moreover, despite higher follicular estradiol levels in the left ovary, there was no relationship noticed between follicular fluid estradiol and oocyte quality among oocytes of each ovary.

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Introduction

Various studies have been conducted on the effects of oocyte quality on fertility effectiveness. According to previous studies, in

human females, ovulation in the right ovary is significantly more often than in the left ovary [1,3]. (64% vs. 36%). This could be happening due to hormonal and anatomical changes in the ovaries.

Primary endocrine circumstances are identical in both ovaries, but there are some physiological differences within and between ovaries that determine the growing procedure of follicles and also the site of ovulation in each cycle [1,4]. It is suggested that side of ovulation is related to the previous menstrual cycle length. In each cycle, formation of the dominant follicle and subsequent ovulation are likely to occur in the ovary with lower progesterone level during the follicular phase [5].

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Ovulation occurs alternately in each ovary during every short follicular phase. However, during long cycles, ovulation occurs randomly. Therefore, prediction of ovulation side will be difficult [6]. In addition, the fertility potential of oocytes in the right and the left ovaries is still ambiguous.

Fertilization rate is defined as the ratio between the number of zygotes with two pronucleus and the injected oocytes and cleavage rate is defined as the ratio of the number of 4–6 cells embryos to two PN zygotes.

Generally, follicular progesterone and androstenedione are both lower in immature follicles compared to mature ones [7]. According to Anderson's finding, higher estradiol to testosterone ratio as well as higher size and volume of follicle have a direct positive impact on pregnancy efficiency rate [8].

It seems that the levels of steroids in follicular fluid can play a significant role in preparing a good endocrine milieu in induced cycles.

Using different protocols that are available for induction of ovulation can lead to variable hormonal situation of follicular fluid in IVF and ICSI cycles. Exogenous FSH administration eliminates internal regular processes and negative feedback mechanisms on folliculogenesis. Therefore, many follicles begin to grow. Yet, a question remains to be answered: which one of the right or the left ovaries responds better to superovulation, and correspondingly has better fertilizing ability.

Some previous studies have compared the right and the left ovaries during IVF cycles in women with two healthy ovaries [9]. Whether the right or the left ovary responds superior to controlled ovarian stimulation is a question which remains unresolved in the literature. Therefore, physicians may believe that oocyte recovery is more effective from one side rather than the other, but these ideas are subjective. Physiological mechanism of ovulation is different between the two ovaries, and all women ovulate considerably more often from the right ovary than from the left ovary and thus the pregnancy from the right ovary is more likely than from the left one. The variation in biochemical profile of follicular fluid between the two ovaries in response to ovarian stimulation in IVF protocols was already demonstrated in 10 patients [10]. Yet, the higher action of the right ovary is less investigated.

For this purpose, we decided to examine whether the right and the left ovaries respond differently in IVF cycles. At the same time, in the study reported previously [10], the authors did not evaluate estradiol or any hormonal assay or any relationship between hormonal levels and oocyte quality. Therefore, another aim of the present study was to find the possible relationship between estradiol level and its effect on ovum quality in each ovary. In other word, we made an attempt figure out whether higher estradiol level has a positive effect on ovum quality for further cell division or leads the ovaries to senescence.

Materials and methods

The present prospective cross-sectional observational study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran and the informed consent was obtained from all patients. A total of 118 infertile women aged 20–40 years who had referred to Infertility and Reproductive Health Research center were investigated in a 12-month period between January and December 2016. Because of their high age, above 40 ($n=3$), ovulation disorder ($n=6$), Male factor infertility ($n=4$), and endometrioma ($n=5$), 18 participants were excluded. All participants who had two intact ovaries and underwent one cycle of ovulation induction and had no ovulatory infertility were included. Patients more than 40 years old or those with diminished ovarian reserve, women with severe male factor that required PESA and TESE or any other ovarian factor, and those

with endometrioma were excluded. Moreover, patients who did not undergo oocyte pick-up were excluded from the study.

GnRH agonist method or antagonist protocol was used for ovarian stimulation. Primarily, the long protocol with GnRH agonist was performed for induction of ovulation [11]. GnRH agonist injection was launched from the previous mid luteal phase. Then, on the second day of cycle, 150–225 IU of gonadotropins (rFSH, Gonal-F; Merck Serono SA, Geneva, Switzerland) were injected based on age range (participants aged 20–30 years used 150 IU gonadotropins and those aged 30–40 years used 225 IU). The patients were followed until three of follicles with about 17 mm diameter were observed on vaginal ultrasound. Then, 10'000 units of Human Chorionic Gonadotropins (HCG) were injected. The oocyte pick-up was done 34–36 hour after injection of HCG under general anesthesia by one physician. Also, the oocytes quality was assessed by an embryologist. In women who underwent GnRH antagonist protocol, ovarian stimulation started using recombinant FSH (rFSH, Gonal-F; Merck Serono SA, Geneva, Switzerland) 225–400 IU/day for the first five days. Subsequently, the gonadotrophin dose was changed along with ovarian response every other day [12]. The rest of the method is like an agonist protocol.

Follicular fluids were stored together after separating oocytes from them. After operation, the puncture needle of one ovary was removed and apparatus was washed using the Hams-F10 media.

Oocytes of each ovary were put in separate dishes for monitoring their growth stages. Oocyte assessment continued until injection. Thereafter, two or three embryos on day 3 were transferred into the uterus guided via ultrasonography by one gynecologist. Follicles fluids were centrifuged for 3 min at 2000 xG at room temperature to eliminate blood and other debris and then supernatant fluids were used to measure estradiol level by micro partial enzyme immunoassay.

The samples were frozen in -70 in order to emit the inter-assay bias. Approximately, 2 or 3 embryos were transferred to the uterus considering the female age. Luteal phase support was done by the injection of 100 mg intramuscular progesterone from the day of pick-up until 14 days when the patients did the B-HCG tests.

The primary objective was to evaluate oocyte quality differences and intra follicular estradiol levels between the two ovaries and the secondary objectives were studying the relationship between follicular fluid estradiol levels and oocyte quality as well as the differences in fertilization and cleavage rates between the two ovaries. Fertilization rate is defined as the ratio between the number of zygotes with two pronucleus and the injected oocytes. Cleavage rate is defined as the ratio of the number of 4–6 cells embryos to two PN zygotes. Therefore, it was calculated at the end of the study by an embryologist.

Oocyte quality was assessed using Trounson and Bongco criteria. According to these morphological criteria, human oocytes are classified into: 1. Germinal oocytes (Grade 1 or Immature), 2. metaphase I (Grade 2 or Interstitial), 3. Metaphase II (Grade 3 or good), 4. Metaphase II and well matured stage (Grade 4 or Very good), and 5. Late stage (grade 5 or late) (Table 1).

T test was run using SPSS, v. 16.0, for data analysis (SPSS, Chicago, IL., USA). Descriptive analyses were carried out as mean

Table 1
Trounson and Bongco criteria for determination of embryo and oocyte quality.

Stage	Grade number
Germinal vesicle stage	1 (Immature)
Metaphase I stage	2 (Interstitial)
Metaphase II stage	3 (Good)
Metaphase II and well matured stage	4 (Very good)
Late stage	5 (Late)

plus standard deviation (SD). Statistical significance was set at $p < 0.05$.

Results

A total of 100 infertile women participated in the present study. The participants' mean age was 32.2 ± 3.6 year. The main causes of infertility are given in Table 2. Six patients were excluded from the study, because their serum level of follicular estradiol was significantly out of the range in comparison with that of the other ones.

The total number of retrieval oocytes was 730 among which 404 were collected from the right ovary (mean 4.45 ± 1.23) and 326 were collected from the left ovary (mean 3.46 ± 1.09). There was no significant difference between the two ovaries in terms of oocytes retrieval rates ($P > 0.05$).

Cumulative percentage of good and very good quality oocytes were 63.01% and 50.4% in right and left ovaries, respectively ($P < 0.05$).

In the rest of the samples, mean estradiol levels in follicular fluid of the right ovary and left ovary were $428,427 \pm 14,271$ pg/ml and $441,586 \pm 17,993$ pg/ml, respectively, which shows a statistically significant difference ($P < 0.0001$) (Table 3).

Moreover, a significant correlation was observed between mean follicular estradiol levels and oocyte qualities of the two ovaries. In addition, no relationship was found between the oocyte qualities and estradiol levels more than 800,000 pg/ml.

On the other hand, we could not find any positive correlation between follicular estradiol levels and both very good and good quality oocytes of the left and right ovaries (Table 3).

The results showed more fertilization rate in the right ovary compared to the left ovary ($p = 0.0001$), but no significant differences were observed in cleavage rate of the two ovaries ($P = 0.4$) (Table 4). Fertilization and cleavage rates and embryos parameters among the ovaries was shown in Table 4. On the appointed day for transferring embryos, the numbers of embryos were 217 and 108 for the right and left ovaries, respectively. Approximately, 31.3% of the injected oocytes formed embryo in the left ovaries versus 49.8% in the right ovaries, which does not show a statistically significant difference ($p = 0.4$) (Data was not shown).

Discussion

We found that the right ovary releases more numbers of oocytes in comparison with the left ovary. In the present study, we tried to find a relationship between right and left ovaries regarding good quality oocytes and fertilization, but in spite of different oocytes qualities and fertilization rates, we found difference in estradiol level concentrations but not in general oocytes quality (very good,

Table 2

Demographic characteristics of the study participants and infertility causes.

Variable	Mean (SD) (n = 100)
Age	32.2 ± 3.6
Duration of infertility	9.34 ± 2.9
Cause of infertility	N (%)
Tubal infertility (%)	22(22%)
Male infertility (%)	39(39%)
Ovarian factor (%)	29(29%)
Unknown cause (%)	10(10%)

good and, interstitial and immature oocytes) in follicular fluids, which may be due to lower number of follicle that punctured in the current study. Yet, we found better quality oocytes in the right ovary in spite of the same general oocytes quality in both ovaries, which could be validated in future research.

There are just a few numbers of papers such as an article by Lass [22] and another by Thomson [9] that have worked on the oocyte quality and follicular fluid estradiol levels. Lass observed no difference between the left and right ovarian responses in IVF cycles of patients with the history of single ovary [22]. The reason for this difference in findings could be due to lateral oophorectomy or other iatrogenic and congenital anomaly in our patients. However, Thomson used long GnRH agonist protocol for IVF in females with unexplained or tubal factor infertility, which could have induced different results.

In one observational study on 10 unexplained infertile women, aspirated follicular fluids were investigated in both ovaries in terms of estradiol, calcium, phosphorus, uric acid, urea, total protein, AST, ALT, glucose, sodium, potassium, and creatinine. These parameters were not different between the two ovaries [10]. These opposite results could be due to the lower number of recruited women and use of GnRH agonist or antagonist protocol for IVF. Nevertheless, they did not evaluate oocyte quality in their research.

In another investigation, Thomson et al found no significant differences in oocytes number, fertilization, and cleavage rate between the right and left ovaries [13]. However, these researchers investigated 84 women with two ovaries and 7 with one ovary in their retrospective study, which could explain the contrary results.

Unequal ovulation frequency between the right and left ovaries has not strongly been confirmed yet. Furthermore, the accurate mechanisms of folliculogenesis process are unclear and no study has been performed on finding different response of the left or right ovarian to gonadotropin as well as the number of oocytes. Many anatomical, physiological, and endocrine differences are present between the two ovaries and from each cycle to the next that may affect ovarian response to gonadotropins.

Table 3

Comparison between right and left ovaries regarding oocytes quality and follicular estradiol levels.

Variable	Right ovary (n = 404)	Left ovary (n = 326)	df	t	%95,CI	P value*
Mean number of retrieved oocytes (Mean \pm SD)* *	4.45 ± 1.23	3.46 ± 1.09	728	-11.370	-1.1609 to -0.8191	0.00 ^a
Mean follicular estradiol levels (pg/ml) (Mean \pm SD)* *	$428,427 \pm 14271$	441586 ± 17993	728	11.020	10814.6171 to 15503.3829	0.00 ^a
Oocyte quality			df	Chi 2		P value*
Grade 4	60 (14.32%)	40 (12.26%)	1	0.659		0.41 ^b
Grade 3	194 (48.69%)	124 (38.03%)	1	8.312		0.00 ^b
Grade 2	46 (10.98%)	61 (18.71%)	1	8.718		0.00 ^b
Grade 1	104 (26.01%)	101 (30.98%)	1	2.197		0.13 ^b
Grade 3 plus Grade 4	254 (63.01%)	164 (50.3%)	1	11.898		0.00 ^b
Grade 1 plus Grade 2	150 (36.99%)	162 (49.6%)	1	11.715		0.00 ^b

* P value < 0.05 significant ** data shown as Mean \pm SD ^a independent t-test, ^bchi-square test.

Grade 4=Very good quality oocytes Grade 3= Good quality oocytes Grade 2= Interstitial oocytes Grade 1= Immature oocytes. Grade 3 plus Grade 4 were defined as good quality oocytes. Grade 1 plus Grade 2 were defined as bad quality oocytes.

Table 4
Fertilization and cleavage rates and embryos parameters among the ovaries.

Variables	Right ovary	Left ovary	df	Chi 2	P value ^c
Number of oocytes	404	326			
Fertilization rate ^a (%)	258(67.7%)	129(46.26%)	1	34.026	0.00**
Cleavage rate ^b (%)	237 (93%)	127(96.8)	1	5.181	0.02**
Total available embryos for transfer	217	108			
embryo / oocyte ratio	54.43	34.08			
Total transferred embryos (no)	195	89			

^aP value < 0.05. Significant. ^bchi-square test, ^cFertilization rate was defined as total number of fertilized oocytes by total number of mature oocytes retrieved. ^dCleavage rate was defined as total number of da 3 embryos by total number of fertilized oocytes.

No special pattern exists for normal ovulation in ovulatory cycles. Although ovulation occurs randomly, some evidences suggest that ovulation in each cycle is more frequent in contralateral ovary than in ipsilateral ovary that ovulation has been occurred in the previous cycle [9,14–18].

It seems that ovulation side selection is related to the hormonal changes of follicular fluid [6].

Some explanations have been proposed for this, such as anatomical differences of ovaries that cause faster drainage secretion of the right ovary in comparison with the left ovary.

Also, some studies have indicated that the formation of dominant follicles is under the control of Inhibin and Activin as paracrine messengers [28]. As a point, increase in FSH level, similar to the decrease in the level of Inhibin A, leads in formation of dominant follicle [19,20].

It has been observed that oophorectomy has no significant effect on ovarian responses to stimulation in IVF cycles and pregnancy rate [13,21–24]. On the contrary, some investigations have showed that ovarians with complicated disorders have lower response to ovarian stimulation and consequently lower amounts of follicles and oocytes [19].

In healthy fertile women, growth of dominant follicles are similar in both ovaries and do not depend on corpus luteum of the previous cycle of the same ovary [1]. However, oocytes of contralateral ovulation in infertile women have better quality compared with those of ipsilateral ovulated ovaries [25]. It seems that luteal phase corpus luteum has effects on the follicular diameter of the ipsilateral ovary [2]. In one animal study, ALSAFY reported that, the medium number of large follicles and recovered Compact cumulus oocyte Complexes (COCs) was significantly more in the right ovary than in the left ovary. The corpus luteum-absent ovaries deliver great numbers as well as high quality of COCs as compared with the corpus luteum-present ovaries [29]. However, we did not evaluate corpus luteum due to the use of agonist and antagonist protocol in the corpus luteum-absent ovaries.

Follicular fluid analysis before IVF, during natural cycles, and also stimulation by clomiphene demonstrated that fertilization, cleavage, transfer rate, and pregnancy outcomes are better if the next cycle ovulation occurs in contralateral ovary [1].

Pampiniform Plexus and venous drainage of this network is discharged into the ovaries and uterus. Anastomosis between uterus [25,26] and ovaries vein causes higher hormonal concentration and endometrial thickness in uterine [27], especially induced by the left ovary and accordingly better pregnancy outcome [3].

We found that, implantation rate of pre-embryo derived from the right ovarian oocytes is higher than that of pre-embryo derived from the left ovarian oocytes ($P < 0.05$). In line with the present investigation is Fukuda et al who reported that the percentage of pregnancies from right-sided ovulation per total number of pregnancies was higher than that of left-sided ovulation throughout non-pregnant cycles ($P < 0.05$). The implantation rate in right-sided ovulation seemed to be higher than that in left-sided

ovulation; however, they showed that formation of embryos is more likely to occur in the left ovary due to higher androgen to estrogen ratio [1]. They concluded that these different results may be due to anatomical and vascular predominance in the right ovary rather than in the left ovary similar to other organs like kidney and adrenal glands.

Limitations of the current study include using agonist and antagonist protocols for controlled ovarian stimulation, which could affect the results. In future research, it is suggested that effects of agonist and antagonist protocols be compared in ovarian environment and oocyte quality between the right and the left ovaries.

In the current study, we found that although the right ovary has more and better ovum than those obtained from the left ovary, there was no significant difference among each set of ovaries. Mainly, the current study provides a backbone in investigation of estradiol level of follicles and oocyte number and efficiency in ovaries. In the current research, we evaluated follicular estradiol level in both ovaries and its correlation with oocyte quality. Although the results were not significant, this finding could be helpful for future research for more and detailed hormonal investigation.

Declaration of interest

All authors declare that there is no potential conflict of interests.

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