Original Article

Effect of lower than expected number of oocyte on the IVF results after oocyte-pickup

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Abstract: Objectives: To investigate whether a lower than expected number of oocyte after ≥14 mm follicle aspiration during OPU has any effect on pregnancy outcomes. Methods: This is a retrospective study done between 2010 and 2013 at the IVF Unit of the Zeynep Kamil Women and Children Diseases Education and Research Hospital, dealing with the medical records of infertile patients who underwent IVF cycle and controlled ovarian stimulation with long agonist or fix antagonist protocol. The patients included into the study were those diagnosed with a primary infertility, aged between 23 and 39, at a BMI of 22-28 kg/m² and having received the first or second IVF treatment. Male factor, presence of uterine anomaly, patients with serious endometriosis and patients with low ovarian reserve were all excluded from the study. Typically, oocyte pick-up was performed in all the patients 35.5 hours after the hCG implementation. Single or double embryo transfer was performed, where available. Patients were classified into two groups. Group 1 consisted of those with no difference between ≥14 mm aspirated follicle number and expected number of oocyte or with 1 missing number of oocyte at the most. Group 2 consisted of those with at least ≥2 missing number of oocyte between aspirated follicle number and expected number of oocyte. Statistical analysis was performed using Student’s t test for continuous variables and chi-square test for categorical variables. Additionally, a Linear regression analysis was conducted between the total number of oocyte and pregnancy. Results: In total, 387 treatment cycles were included into the study. Group 1 consisted of 134 patients and Group 2 consisted of 252 patients. Antral follicle number (12.8 ± 4.3 and 14.5 ± 4.1, P = 0.0007), hCG day E2 value (1990.7 ± 1056.4 and 2515.2 ± 1332.7, P < 0.0001) and the number of aspirated follicle during OPU (9.1 ± 4.4 and 13.7 ± 5.5, P < 0.0001) were significantly higher in Group 2; whereas on the other hand, daily gonadotropin dose (290.9 ± 79.9 and 273.4 ± 74.4, P = 0.034) and total gonadotropin doses (2545 ± 1031.8 and 2247.7 ± 901.9, P = 0.004) were significantly higher in Group 1. The pregnancy rate was significantly higher in Group 1 (29.1% and 19.4%, P = 0.041). No correlation was observed between the number of oocyte and pregnancy (r = 0.082, P = 0.107). Conclusions: The number of aspirated follicles during IVF treatment being higher than the collected number of oocyte leads to a statistically significant fall in the pregnancy rates. There is no correlation between the number of oocyte and pregnancy.

Keywords: Follicle/egg numbers, oocyte pickup, IVF-ICSI outcome, infertility, ovarian stimulation

Introduction

Today almost 15% of people receive treatment in in vitro fertilization units (IVF) with a diagnosis of infertility [1, 2]. Even though there has been a progress in the pregnancy rates over the last two decades, live birth rates have not still reached the desired levels. Some researchers examine the reasons underlying infertility and some others try to find ways to have more success in treatment and to increase live birth rates. Nevertheless, there are still problems waiting to be resolved [3]. There are various factors involved in the formation of pregnancy, ranging from the age of the woman in question to the selected treatment protocol and even the reasons of infertility. Today, a couple of endocrine biochemical markers and ultrasonographic signs are used, which are influential in predicting in vitro fertilization (IVF) outcomes and determining the gonadotropin doses to be used in ovarian stimulation (OS) [4]. Among them, the
ones which are used most in practice, having maximum reliability, are the ultrasonographic assessment of the primordial antral follicle pool in the early follicular phase and ovarian volume [5, 6]. Nonetheless, ovarian reserve tests are still inadequate in predicting live birth rates [7, 8].

The primary aim of IVF treatment is to achieve a term live birth. The main component of assisted reproduction treatment is OS. To know the factors influencing the success of IVF is crucial not only for the decision of the patient to begin treatment, but also for the determination of the treatment protocol to be selected by the doctor. If the ovarian reserve is sufficient, the collected number of oocyte is largely dependent on the OS protocol to be implemented [9]. Thus, a series of OS procedures have been implemented until today. Recently, the most frequently used stimulation protocols have been the combination of long-term GnRH agonists with pituitary suppression and exogen FSH or the combination of exogen FSH and GnRH antagonist with pituitary suppression [10]. In many studies, no difference was observed between GnRH agonist and GnRH antagonist protocols in terms of pregnancy rates [11, 12].

Follicle or oocyte are parameters which have been frequently studied to achieve success for IVF treatment. Lan et al. reported that in IVF patients the right ovarian response was better [13], Choe et al. reported that there was an equivalence between the total number of oocyte collected from both ovaries and the IVF success [14] and Knopman et al. reported that large dimensions of follicles extended the duration of treatment, even if they do not change live birth rates [15]. In a recent study concerning the number of oocyte and live birth, it was argued that there is a non-linear increase between the number of oocyte and live birth [16]; and additionally, that a high number of oocyte presence leads to high estrogen values, thus decreasing implantation rates [17-19]. Consequently, it seems that the success of IVF treatment depends upon a number of factors. A survey of relevant literature reveals that there has been multiple studies on this topic, ranging from IVF treatment protocols to the number of oocyte and the quality of embryo. It appears that no study conducted until today has dealt with the effects of the synchronization between the number of stimulated follicles after OS and (≥14 mm) the collected number of oocyte on pregnancy rates.

The primary aim of this study is to investigate whether a lower than expected number of oocyte after follicle aspiration ≥14 mm during oocyte pickup (OPU) has any effect on pregnancy outcomes in IVF patients who received OS. The secondary aim of this study is to investigate whether there is a correlation between the total number of oocyte and the obtained rates of pregnancy.

Material and methods

This is a retrospective single-centered study which was conducted between January 2010 and September 2013 over the medical records of patients who applied to the IVF Unit of the Zeynep Kamil Women and Children Diseases Education and Research Hospital. The patients included into the study were those diagnosed with a primary infertility, aged between 23 and 39, at a BMI of 22-28 kg/m² and having received the first or second IVF treatment. Male factor (according to the World Health Organization’s the 2010 criteria), presence of uterine anomaly, patients with severe endometriosis and patients with low ovarian reserve (FSH>10 or unresponsive in spite of maximum dose) were all excluded from the study.

Patients received ovulation induction with either long protocol or antagonist protocol. With the beginning of the protocol, all patients received a 100 mg daily dose of baby aspirin and were reinforced with a 400 mcg of folic acid. Gonadotropin doses were ascertained in accordance with the age of the patient, BMI, follicle number in the early follicular phase, basal FSH level and the response given to the previous treatment. During the treatment, ovarian response was assessed with vaginal ultrasound guided monitoring of follicle growth and measurement of serum estradiol (E2) levels. When the dominant follicle reached a diameter of 18 mm or in the presence of two follicles with a diameter of >16 mm, 10,000 IU human chorionic gonadotropin (hCG) were implemented to all patients. OPU was performed 35.5 hour after the hCG implementation, under intravenous (iv) sedation and with the guidance of transvaginal ultrasonography. During OPU procedure, all patients received a 1 gr single dose of cefazolin IV (Cefamezin 1000 mg IM/IV
Lower than expected number of oocyte and IVF results

Table 1. Demographic characteristics of patients and IVF outcomes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>31.1 ± 4.0</td>
<td>30.9 ± 4.0</td>
<td>0.614a</td>
</tr>
<tr>
<td>Duration of infertility, year</td>
<td>7.5 ± 3.7</td>
<td>7.1 ± 3.9</td>
<td>0.306a</td>
</tr>
<tr>
<td>Basal FSH, IU/L</td>
<td>6.7 ± 1.4</td>
<td>6.4 ± 1.5</td>
<td>0.161a</td>
</tr>
<tr>
<td>Basal E2, pg/ml</td>
<td>49.5 ± 17.6</td>
<td>51.5 ± 16.9</td>
<td>0.330a</td>
</tr>
<tr>
<td>Basal AFS, n</td>
<td>12.8 ± 4.3</td>
<td>14.5 ± 4.1</td>
<td>0.0007a</td>
</tr>
<tr>
<td>Daily dose/day, IU</td>
<td>290.9 ± 79.9</td>
<td>273.4 ± 74.4</td>
<td>0.034a</td>
</tr>
<tr>
<td>Daily usage time, day</td>
<td>8.9 ± 1.6</td>
<td>8.7 ± 1.4</td>
<td>0.397a</td>
</tr>
<tr>
<td>Total daily dose, IU</td>
<td>2545 ± 1031.8</td>
<td>2247.7 ± 901.9</td>
<td>0.004a</td>
</tr>
<tr>
<td>hCG day E2, pg/ml</td>
<td>1990.7 ± 1056.4</td>
<td>2515.2 ± 1332.7</td>
<td>&lt; 0.0001a</td>
</tr>
<tr>
<td>hCG day endometrial eco, mm</td>
<td>9.9 ± 1.7</td>
<td>10.1 ± 1.7</td>
<td>0.505a</td>
</tr>
<tr>
<td>Number of follicles during OPU, n</td>
<td>9.1 ± 4.4</td>
<td>13.7 ± 5.5</td>
<td>&lt; 0.0001a</td>
</tr>
<tr>
<td>Total oocyte, n</td>
<td>8.5 ± 4.4</td>
<td>8.3 ± 4.5</td>
<td>0.695a</td>
</tr>
<tr>
<td>MII oocyte, n</td>
<td>7.1 ± 4.4</td>
<td>6.9 ± 4.3</td>
<td>0.694a</td>
</tr>
<tr>
<td>Cycle cancellation rate, n (%)</td>
<td>11/134 (8.2%)</td>
<td>14/253 (5.5%)</td>
<td>0.423a</td>
</tr>
<tr>
<td>ET day</td>
<td></td>
<td>0.092a</td>
<td></td>
</tr>
<tr>
<td>3rd day</td>
<td>55.1%</td>
<td>56.7%</td>
<td></td>
</tr>
<tr>
<td>2nd day</td>
<td>30.8%</td>
<td>30.5%</td>
<td></td>
</tr>
<tr>
<td>Pregnancy rate, n (%)</td>
<td>39/134 (29.1%)</td>
<td>49/253 (19.4%)</td>
<td>0.041b</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD and number (percent). *Student t test. †Chi-square test.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows 15.0 software (SPSS, Chicago, IL, USA). Descriptive statistics were given as mean, standard deviation, frequency and percentage. Statistical analysis was performed using Student’s t test for continuous variables and chi-square test for categorical variables. When there was a need for a non-parametric test, Mann Whitney U and Kruskal-wallis tests were performed. In addition, a Linear regression analysis was conducted between the total number of oocyte and pregnancy. Statistical significance was defined as p < 0.05. A nominal two-sided P-value was considered for all comparisons.

Results

Between January 2010 and September 2013, at the IVF Unit of the Zeynep Kamil Women and Children Diseases Education and Research...
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Hospital, a total of 3379 files containing IVF cycle information were surveyed. 387 treatment cycles were included into the study. There were 134 patients in Group 1 and 253 patients in Group 2. Demographic characters, basal hormone values, IVF treatment values and IVF treatment results are shown in Table 1. In terms of demographic characters such as age, BMI and duration of infertility, there was no difference between the groups. Additionally, basal FSH and E2 levels were similar. However, even if it has not a clinical significance, the number of antral follicles were significantly higher in Group 2 (12.8 ± 4.3 and 14.5 ± 4.1, p = 0.0007). Daily gonadotropin dose (290.9 ± 79.9 and 273.4 ± 74.4, p = 0.034) and total gonadotropin doses (2545 ± 1031.8 and 2247.7 ± 901.9, p = 0.004) were significantly higher in Group 1 than in Group 2. hCG day E2 value (1990.7 ± 1056.4 and 2515.2 ± 1332.7, p < 0.0001) and the number of aspirated follicles during OPU (9.1 ± 4.4 and 13.7 ± 5.5, p < 0.0001) were significantly higher in Group 2 than in Group 1. In terms of the total number of oocyte (8.5 ± 4.4 ve 8.3 ± 4.5, p = 0.695) and the number of MI oocyte (7.1 ± 4.4 and 6.9 ± 4.3, p = 0.694), there was no difference between the groups. Nevertheless, pregnancy rate were significantly higher in Group 1 (29.1%) than in Group 2 (19.4%) (p = 0.041). No correlation was observed between the number of oocyte and pregnancy (r = 0.082, p = 0.107).

Discussion

Despite technological advances, assisted reproduction methods are not only still expensive, but also tiresome and arduous for patients on account of the medical effects of the treatment and the ensuing emotional stresses. Therefore, knowledge of the factors that would help predicting the success of IVF is very crucial not only for the decision to begin IVF, but also for the determination of the suitable OS method in the process of treatment. Up to the present, many studies have been done in order to increase success in IVF, but one of the most researched structures has been follicle or oocyte. With respect to the issue at hand, Lan et al, reported in their studies that in IVF treatment both ovaries do not have an identical response and that the right ovary generally has a better response [13]. These data comply with the data of the study by Fukuda et al. which investigated the characteristic of ovulation in natural cycle [20]. In their study on the dimension of oocyte, Knopman et al. reported that the postponement of ovulation induction in order to enhance the dimension of oocyte leads to financial cost increase and extends the duration of treatment, without increasing the number of embryos and live birth rates [15]. Choe et al. reported that there is an equivalence between the total number of oocyte collected from both ovaries and the IVF success [14], that the rate of pregnancy increases as the difference decreases, and finally, that the rate of difference between the total number of oocyte collected from both ovaries has a predictive value on IVF cycles. In addition, it was emphasized that the difference between the total number of oocyte collected from both ovaries is inversely proportional to the total number of collected oocyte [14]. In the animal study conducted by Falconer et al. there was a counter argument that there is a direct proportion between the difference and total number [21]. And in our study, too, what was investigated was whether a difference between the number of aspirated follicle and expected number of oocyte had any effect on pregnancy outcomes. It was seen that in case of a difference between the number of follicles aspirated independently of the total number of oocyte and the number of collected oocyte, pregnant rates tend to decrease (29.1% to 19.4%, p = 0.041). Additionally, the number of follicles aspirated during OPU appeared to be higher in the group where the number of pregnancy was lesser (p < 0.0001). In other words, the fact that the number of oocyte per follicle is higher in Group 1 and that the pregnancy rate is higher in this group, supports the data provided by previous literature, which argued that increases in the number of oocytes to certain limits also lead to an increase in the rate of pregnancy[16, 22-24].
obtainment of a few number of oocyte despite OS represent weak clinical pregnancy outcomes and ovarian aging [25, 26]. There are also some publications which argue the opposite, i.e., which claim that there is an equivalence between a low number of oocyte presence and high rates of pregnancy [9, 27], or that there is no correlation between the number of collected oocyte and pregnancy outcomes [28] or that there is no explicit relation between the two [29]. However, there is no explicit data about the optimum number of oocyte in IVF treatment today. The most comprehensive study on this topic is the study done by Sunkara et al. [16], where they examined the results of 400,135 IVF cycles and assessed the relationship with live birth rates. In accordance with these data, it was reported that the increase in the number of collected oocyte up to 15 accompanies an increase in the rate of live birth rates, plateaued between 15 and 20 eggs, and finally declined beyond 20 eggs. Other studies conducted with similar methods also reported that there is a correlation between the number of oocyte and the pregnancy rates. Nevertheless, these were small-scale studies and there were discordances between the data. For example, van der Gaast et al. reported the optimum collected oocyte as 9 [24] whereas Ji et al. as between 6 and 15 [22], and Kably Ambe et al. as 10-15 [30]. Even though it seems that the main aim of in these treatments is to obtain a maximum number of oocyte, the fact that usage of a high dose of gonadotropin may effectively damage the morphology of oocyte and also damage the embryo transfer by way of increasing the likelihood of chromosomal anomaly should always kept in mind [31]. In addition, some studies highlighted that high E2 levels might have negative effects on implantation and development potential [17-19]. In our study, lower pregnancy rates in Group 2, might be attributed to the negative effects of high serum estradiol levels (1990.7 ± 1056.4 to 2515.2 ± 1332.7, p < 0.0001) arising from a higher number of follicle (9.1 ± 4.4 to 13.7 ± 5.5, p < 0.0001) upon embryo implantation.

There are some weaknesses of our study. First, although all OPU procedures were conducted in a single center, the implementation was done by different doctors. Even if these operations were standardized by our center as far as possible, there might have been individual differences. Second, on account of the density of volume of work, the information about the operation could not always be recorded on the spur of the moment and these records were kept by different doctors. And this might have led to a decrease in the accuracy of the recorded data.

Consequently, we are not still at the desired levels with regard to IVF treatment. Therefore, it is crucial to know all the factors that might influence IVF success. Follicular development and oocyte complex during the IVF treatment is a complicated process and even if less compared to the past, it still retains its mystery. In the context of patients receiving IVF treatment, the number of follicles aspired during OPU being higher that the total number of collected oocytes leads to a statistically significant decrease in pregnancy rates. There is no correlation between the number of oocyte and pregnancy. There is a need for larger controlled studies to analyze how the factor that damages synchronization leads to a decrease in pregnancy rates.

Disclosure of conflict of interest

None.

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