Sonography in Comparison to Urinary Kit in Intra-Uterine Insemination Timing

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Citation

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Abstract: Background: Despite all attempts to increase pregnancy rates, overall success rate of Intrauterine Insemination (IUI) is still not acceptable. Proof of ovulation is an important indicator to determine the time of IUI, but to date there is no test proving that the ovulation has definitely occurred. Objective: This study was aimed to compare the efficiency of ultrasound in measuring the size of follicles and urinary Luteinizing Hormone (uLH) kit in determining LH surge for IUI timing. Method: In this comparative, nonrandomized, not blinded clinical trial, 311 IUI cycles in 262 infertile couples who were candidate of IUI were assigned into two groups of ultrasound (n=100 cycles) and uLH kit (n=211 cycles) for IUI timing. Two weeks after doing the IUI, the βHCG was checked, and chemical pregnancy was confirmed. Four weeks after positive chemical pregnancy test, the fetal heart activity was confirmed by pelvic ultrasonography to confirm clinical pregnancy. Results: Chemical pregnancy rate was lower in ultrasonography group but not significant in comparison to LH kit (14.3% and 18.4%, respectively (P= 0.11)). Clinical pregnancy rate in the groups of ultrasonography and LH kit was respectively 10.3% and 10.3% which did not differ significantly (P= 0.3). Conclusion: Considering that the use of uLH kit is a simple and low cost way and can be done at home by the patients, so the patients can have an active participation in their treatment process.

Key Words: Intra uterine insemination, Urinary luteinizing hormone, Pregnancy rate

Introduction:
Despite all attempts to increase the pregnancy rates, overall success rate of Intrauterine Insemination (IUI) is still not acceptable [1]. In addition, pregnancy rates vary widely among centers, but a successful rate of 10% is reasonable for an IUI therapy combined with controlled ovarian stimulation [2]. Proper timing of IUI still is a controversial aspect of IUI cycles in partners receiving infertility treatment and it is extremely important to achieve pregnancy [2].

Proof of ovulation is an important indicator to determine the time of IUI, but to date there is no test proving that the ovulation has definitely occurred. The only definitive evidence of ovulation is the pregnancy [3]. Finding reliable methods to predict occurrence of ovulation is a critical task in human reproductive medicine such as artificial insemination [4]. The traditional methods of IUI timing were based on a chart of basal body temperature or cervical mucus evaluation [5]. There are two common methods for ensuring the correct time of IUI including serial ultrasound to monitor follicular growth and urinary luteinizing hormone (uLH) tests for detecting urinary luteinizing hormone surge [6]. Transvaginal ultrasonography is not only impractical means of monitoring the follicle size for individual cycles, it also leads to a spontaneous premature LH increase which makes the administration of human chorionic gonadotropin (hCG) impossible before LH surge. Moreover, premature LH surge due to follicular growth monitoring can happen before the prevailing follicle reaches 18 mm in mean diameter. On the other hand, a World Health Organization (WHO) Task Force has shown that LH surge is the best marker of predicting ovulation. The sudden LH level surge and then its mid-cycle peak cause rupturing of the dominant follicle and releasing a mature ovum. Ovulation usually occurs about 28-48 hours after the beginning of the LH surge and approximately 12 hours after the peak in LH levels. Determination of peak LH in blood is easy. Urinary LH reaches to its peak level coinciding with or after ovulation, while urinary LH surge day provides 24-36 hours warning of happening ovulation, hence making it a perfect factor to provide ovulation information [4,7,8]. uLH kit can help to detect the occurrence or non-occurrence of ovulation, the time of ovulation, and to determine the luteal phase [9]. The comparison of ultrasound and uLH kit in timing of IUI and its outcome for improving pregnancy rate was not studied before. This clinical trial was aimed to compare the efficiency of transvaginal ultrasonography with uLH kit in determining...
the proper time of IUI and consequently improving the chance of pregnancy.

Materials and Methods
This was a comparative, nonrandomized, not blinded clinical trial conducted on 262 infertile couples attending our infertility clinic at Imam Khomeini Hospital between February 2013 and February 2014 in Ahvaz, Iran. The study was approved by ethic committee of Ahvaz Jundishapur University of Medical Sciences (Ethic Code: ajums.REC.1392.82). The trial was registered with Iranian Registry of Clinical trials at www.irct.ir (Identifier: IRCT2014121720358N1). All patients signed the informed consent.

The inclusion criteria were history of infertility for at least one year and those partners who were candidates for IUI. Exclusion criterion was not at age limit for IUI in both groups. The ovarian stimulation protocols were the same in both groups. All participants underwent infertility evaluations such as thyroid function test (TFT), prolactin and semen analysis, and hysterosalpingogram (HSG). Also, transvaginal ultrasonography was performed on the third day of menstruation in order to check the possible pathologies and ovarian cysts. Then ovulation induction was done with 50-100 mg of clomiphene citrate or 5-2.5mg Letrozole during third to seventh day of menstruation.

The second ultrasound procedure was done on the eleventh day of menstrual cycle in order to determine the follicle size. According to patient’s preference, volunteers were divided into two groups monitored either by uLH kit (87 couples) or by ultrasound (175 couples) for IUI timing. The group of uLH kit used the kit for two or three days before the probable date of the LH surge which determined based on the length of the menstrual cycle and if the size of follicles was 14-15 mm, it was used daily in hours between 16 to 22 (for example the uLH kit was used in the 28-day menstrual cycle from the eleventh day of cycle), as long as the test is to be positive (positive test means the occurrence of two crisp lines on the uLH kit). Then the patient was requested to attend the infertility clinic to perform the IUI just 24 hours after getting a positive test. Subjects were excluded from the analysis if the urinary LH test was clearly not positive or if urine sample was clearly negative. The ultrasound group underwent transvaginal ultrasonography at seventh day of menstrual cycle. In the ultrasound group, this procedure was performed two times in which follicle size was recorded. In addition, the second ultrasound procedure time was determined based on the follicle size at first ultrasound. In ultrasound group when 1 to 2 follicles with 16-18 mm in mean diameter were seen, then 10000 units hCG was injected musculary and the patient was requested to attend our Infertility Clinic in next 36-40 hours to undergo IUI. After performing IUI, the patient was placed in supine position for twenty minutes and no drugs were administered to support the luteal phase. Participants were monitored for maximum three consecutive cycles. Two weeks after performing the IUI, hCG was checked for confirming chemical pregnancy; monitoring of fetal heart activity by pelvic ultrasound was done for confirming the clinical pregnancy at fourth week after the positive pregnancy test. If the pregnancy did not occur, cycles were repeated. In order to perform IUI in the laboratory of our Infertility Clinic at Imam Khomeini Hospital, the semen sample of 2 or 4 days after sexual abstinence was collected by masturbating, and then a routine method of swim up was used for washing and separating sperm from the seminal fluid.

SPSS software version 19 (SPSS, Inc., IBM, Chicago) was used for data entering and analysis. The continuous variables were summarized as mean ± SD and categorical variables were summarized as frequency (percentage). Statistical significance of difference between qualitative variables was found using chi-square test and between quantitative variables was detected by Student’s t-test. P value less than 0.05 was considered statistically significant.

Results
In this study, 262 infertile couples were evaluated in two groups of uLH kit (87 couples with 100 IUI cycles) and ultrasound (175 couples with 211 IUI cycles). The LH time in two groups of ultrasonography and uLH kit was determined based on the follicle size on ultrasound evaluations and time of becoming positive uLH kit, respectively. The causes of infertility are listed in Table 1. The most prevalent cause of infertility was male factor in uLH kit (38.5%) and also in sonography group (51.4%).

<table>
<thead>
<tr>
<th>Cause</th>
<th>uLH kit group</th>
<th>Ultrasound group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male factor</td>
<td>30</td>
<td>54</td>
<td>0.3</td>
</tr>
<tr>
<td>Unexplained infertility</td>
<td>20</td>
<td>40</td>
<td>0.6</td>
</tr>
<tr>
<td>Hypothalamic amenorrea</td>
<td>15</td>
<td>37</td>
<td>0.76</td>
</tr>
<tr>
<td>Tubal factor</td>
<td>10</td>
<td>20</td>
<td>0.76</td>
</tr>
</tbody>
</table>

*The values are presented as mean±SD or n(%).

There was no significant difference in terms of abortion, ectopic and twin pregnancies between two groups (Table 2). Most of the patients underwent one IUI cycle attempt (71.4%). The rate of chemical pregnancy according to number of IUI attempts did not significantly differ (P value= 0.07). In addition, the IUI attempts did not differ significantly between two groups (P value= 0.06) (Table 3).
Discussion
In this trial, comparing the efficacy of uLH kit and ultrasonography in timing of IUI, the rates of chemical pregnancy and also clinical pregnancy were similar between uLH kit and ultrasound groups (18.4% vs 14.3% and 10.3% vs 10.3%, respectively). Moreover, there was no statistically significant difference in terms of the number of attempts for IUI cycles between the two groups. Three common causes of infertility in these cycles included male factor, unexplained infertility and PCOS.

The routine method of IUI timing in our department is monitoring of follicle size using ultrasonography. To date, there is no clear advantage of ultrasound over uLH kit or vice versa in terms of pregnancy rates [6]. However, there is some feasibility in using of urinary LH kit over ultrasonography for IUI timing. In a study by Robinson el al., has been shown the considerable reduction of the number of patients visiting per cycle of IUI in users of uLH kit [10]. In the study by Federman et al., the other benefits of using uLH kit reported are the reduced costs and time spent. Other applications of uLH kit are to use it in the detection of the premature LH surge that happens in 24% of the IUI cycles [5].

In a meta-analysis of four randomized controlled trials in 1997 by Flierman et al., it has been shown that the use of the uLH kit in the IUI cycles does not affect the pregnancy rate [11]. In a study conducted by Awoonga et al.[9] the rate of pregnancy in cycles in which hCG had been prescribed were compared with the cycles that the uLH kit had been used to determine the time of IUI, and there was no difference between the two groups. These studies are consistent with our study.

In a study by Arici A et al., it has been noted that if the peak level of LH is lower than 40 IU/L, it causes the false negative results of uLH kit, as happened in 35% of the cycles [12]. Lloyd et al., in their study, also stated that uLH kit may show the time of IUI incorrectly in more than one-third of cycles if the uLH kit has been used alone to determine the time of the LH [13].

In some conditions uLH kit method is not useful in comparison to ultrasonography. Ovulation in some women may occur before the detection of the LH in the urine. In some other patients, the urinary LH surge is not detectable, therefore the vaginal ultrasound can be used to provide the required information and finally the selected method must be planned and implemented in accordance to the needs of each individual [14].

It is suggested that to find more robust comparison between ultrasound and uLH kit in timing of IUI, the studies with larger sample size than our study needs to be conducted.

Table 3. Comparing between chemical pregnancy rates in the two groups based on the numbers of IUI cycles attempt

<table>
<thead>
<tr>
<th>No. IUI attempt</th>
<th>No. couples</th>
<th>Group</th>
<th>No. cycles</th>
<th>P value</th>
<th>Chemical pregnancy (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>187</td>
<td>uLH kit</td>
<td>70/187 (37.4%)</td>
<td>10/70 (14.3%)</td>
<td>117/187 (62.6%)</td>
<td>16/117 (13.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ultrasound</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>uLH kit</td>
<td>12/57 (21.1%)</td>
<td>0.06</td>
<td>4/12 (33.3%)</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ultrasound</td>
<td>45/57 (78.9%)</td>
<td>6/45 (13.3.52%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>uLH kit</td>
<td>5/18 (27.7%)</td>
<td>2/5 (40%)</td>
<td>13/18 (72.3%)</td>
<td>3/13 (23.1%)</td>
</tr>
</tbody>
</table>

Conclusion
The use of the uLH kit is very easy and frugal in terms of cost and is more acceptable to the patient and the physician, which can reduce the cost of the patient and the number of ultrasound. Considering that the use of uLH kit is a simple and low cost way and can be done at home by the patients, the patients can have an active participation in their treatment process.

Conflict of Interest
The authors declare no conflict of interest.

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