Single versus double intrauterine insemination in multi-follicular ovarian hyperstimulation cycles: a randomized trial

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BACKGROUND: The rationale for double insemination is to create the opportunity for a longer fertilization period as follicle rupture may occur over a wide interval (∼22–47 h) after hCG administration in ovarian hyperstimulation (OH) with intrauterine insemination (IUI) cycles. This randomized study evaluates the effectiveness of single versus double IUI in only OH cycles with multi-follicular development.

METHODS: We conducted a single center trial, 228 eligible patients were randomized for this study on the day of hCG. Only cycles with multi-follicular development without premature luteinization (progesterone levels >1 ng/ml on the day of hCG), were included in the study. Multi-follicular development has been defined as at least two dominant follicles reaching minimum ≥15 mm diameter in which one of them is >17 mm. OH cycles with more than five dominant follicles (>15 mm in diameter) were excluded from the study. In the single IUI group (Group 1 = 112 patients) IUI was applied 36 h after the hCG injection and in the double IUI group (Group 2 = 114 patients) the first IUI was performed 18 h after hCG administration and the second IUI was performed 40 h after hCG administration. The primary end-point is to compare live birth rates (LBRs) between single and double IUI arms.

RESULTS: LBRs were 10.7% (12/112 patients) in the single IUI group and 12.3% (14/114) in the double IUI group and the difference was not statistically significant (P = 0.835, OR = 1.16, 95% CI: 0.51–2.64). In the unexplained infertility group the LBR was 11.1% (5/45 patients) with single IUI and 18.4% (9/49) with double IUI (P = 0.393). In the mild male factor group this rate was 10.4% (7/67) and 7.7% (5/65) in the single and double IUI groups, respectively (P = 0.764).

CONCLUSION: Our study did not find any difference in LBRs between single and double IUI groups in OH cycles with multi-follicular development. To the best of our knowledge this is the first report with this kind of study design.

The study was registered at clinicaltrials.gov: NCT 00993902.

Key words: intrauterine insemination / ovarian hyperstimulation / live birth rate / randomized clinical trial

Introduction

Ovarian hyperstimulation (OH) with intrauterine insemination (IUI) is an evidence-based, first-step approach for the management of patients with unexplained infertility (Verhulst et al., 2006), and it is a generally preferred treatment for mild male factor infertility, ovulatory dysfunction, cervical factor infertility and endometriosis (Duran et al., 2002). However, there is still debate about the effects of addition OH to IUI in isolated cervical factor infertility (Steures et al., 2007) and there is no clear evidence for the additive effect of IUI to the ovulation induction in ovulatory dysfunction group.

Prediction of pregnancies in OH/IUI cycles is very important and selection of the most suitable patients for this treatment modality will probably increase its cost effectiveness. The success of OH/IUI has been attributed to a number prognostic factors including duration of infertility, follicle number, female age, numbers of sperm inseminated, progressive motile sperm count, sperm morphology, endometrial thickness and infertility etiology, with a wide range of results.
(Tomlinson et al., 1996; Nuojua-Huttunen et al., 1999; Khalil et al., 2001; Houmard et al., 2002; Ghosh et al., 2003; Ibércico et al., 2004; Steures et al., 2004; Barros Delgadillo et al., 2006; Guven et al., 2008). Two further important factors that could be associated with success rates are the timing and frequency of insemination.

The rationale for double insemination is to create the opportunity for a longer fertilization period as follicle rupture may occur over a wide interval (~22–47 h) after hCG administration in OH/IUI cycles (Testart and Frydman, 1982). It has been also demonstrated that multiple ovulations occur sequentially in human menopausal gonadotrophin cycles after hCG (Abbasi et al. 1987). However, the debate about the effectiveness of double IUI is still continuing. A recent meta-analysis published in the Cochrane Library investigated the efficiency of double IUI in stimulated cycles (Cantineau et al., 2003). The authors updated their previous meta-analysis and they found a statistically significant difference in favor of double insemination (OR 1.8, CI: 95% 1.4–2.4) in contrast to their previous report. This difference is largely due to the contribution of the new study by Liu et al. (2006) to the meta-analysis, which includes a large number of cycles (1257 cycles).

In this meta-analysis, one of the most important observations was that the mean number of follicles larger than 15 mm was greater in the studies that favor double insemination (mean 3 follicles and 1.7 follicles). They conclude that ‘double insemination seems to be more effective for couples suffering from mild male subfertility and when more dominant follicles are available. To offer advice regarding clinical practice, further research is warranted’. However, to the best of our knowledge, no prospective randomized study has compared double and single IUI by exclusion of the cycles with mono-follicular development and we think that this can affect the results considerably.

In this pilot study, we aimed to demonstrate the effectiveness of double IUI in only OH cycles with multi-follicular development. The study included only patients with unexplained infertility and mild male factor infertility. The primary end-point is to compare live birth rates (LBRs) between single and double IUI arms.

**Materials and Methods**

This study was a randomized trial conducted at Baskent University, Obstetrics and Gynecology Department, Division of Reproductive and Endocrinology and IVF Unit, from February 2008 to January 2009. The study was approved by the Ethical Committee of Baskent University. Informed consent was obtained from each patient at the day of hCG just before IUI procedure.

The eligibility criteria were as follows: the couple had not conceived after at least 1 year of unprotected intercourse; the women were younger than 37 years, with basal FSH levels <12 mIU/l and total antral follicle count (AFC) on Day 3 of the menstrual cycle greater than six; and a diagnosis of unexplained or mild male factor infertility. Each woman only received one cycle of treatment during the study.

All couples had undergone a fertility workup consisting of medical history, confirmation of an ovulatory cycle by mid-luteal serum progesterone and semen analysis (abnormal results confirmed by a second or third spermogram). Tubal patency of at least one tube was confirmed by laparoscopy and/or hysterosalpingography. All patients underwent sonohysterography to rule out pathology of the endometrial cavity before the IUI cycle.

The couples with normal sperm parameters, normal tubal patency and confirmed ovulation were classified as having unexplained infertility. We defined male factor infertility based on sperm concentration and progressive motility in which reference values were determined according to the World Health Organization criteria (semen with concentration >20 million/ml, >50% progressive motile spermatozoa within 1 h of ejaculation). Presence of oligospermia or asthenospermia or both but with total progressive motile sperm count ≥10 million was regarded as mild male factor infertility.

During the OH cycle, baseline transvaginal sonography was done on Day 3 of menstruation to exclude ovarian cysts larger than 15 mm. Women with ovarian cysts were rested for one cycle. Clomiphene citrate (CC) or recombinant FSH (rec-FSH) preparations—folitropin alfa (Gonal-F; Serono-Turkey, Istanbul) or follitropin beta (Puregon; Organon-Turkey, Istanbul) or both (CC and rec-FSH) were used for OH. CC was started on Day 3–5 of the cycle. The starting dose of CC was 100 mg/day for 5 days. In some patients 75 IU rec-FSH was added to the CC on the fourth day of the regimen. In women in the rec-FSH group the starting dose, administered sub-cutaneously, was between 50 and 150 IU/day according to the body weight and AFC, and was begun on Day 3 of menstruation and continued until follicle maturation. The serial estradiol (E2), LH and progesterone measurements were performed in all cycles to rule out premature luteinization.

Patients were selected for this study on the day of hCG administration. Only the cycles with multi-follicular development without premature luteinization (progesterone levels >1 ng/ml on the day of hCG) were included in the study. Multi-follicular development has been defined as at least two dominant follicles reaching minimum ≥15 mm diameter in which one of them is >17 mm. OH cycles with more than five dominant follicles (≥15 mm in diameter) were excluded from the study.

The 228 eligible patients were randomized into two groups by an allocation sequence generated from a random numbers table and assigned using consecutively numbered opaque, sealed envelopes on the day of hCG (Fig. 1). The envelopes were opened by a person (generally the responsible nurse) independent of the study. Accordingly, the patient was included in the single or double IUI group. Two patients in the single IUI group were lost to follow-up and the results were compared among 226 patients. In the single IUI group (Group 1; n = 112 patients) IUI was applied 36 h after the hCG injection (Pregnyl® 5000 IU, Organon, Turkey) and in the double IUI group (Group 2; n = 114 patients) the first IUI was performed 18 h after hCG administration and the second IUI was performed 40 h after hCG administration. hCG was administered at 12.00 p.m in single IUI group and 07.00 p.m in the double IUI group.

Semen specimens were produced by masturbation and collected for insemination within 1 h of production. Sperm washing was carried out by the gradient method with supra-sperm medium (Medicult®, sperm wash medium, Turkey) for 20 min, and then supra-sperm medium (Medicult-IVF®, sperm wash medium, Turkey) for 10 min.

All IUI procedures were performed by the same three authors. Insemination with a sterile catheter (Wallace® artificial insemination catheter, Smiths Medical International Ltd, UK) was performed with a 1- or 2-ml syringe in all patients. The catheter was gently passed through the cervical canal and the sperm suspension expelled into the uterine cavity slowly. Insemination volumes were 0.6 ml in all cycles. The women remained supine for 10–15 min after IUI. To eliminate the possible positive effect, especially in the single IUI group, intercourse after the procedure was forbidden for the rest of the cycle. The luteal phase was not supported by any medication.

The primary end-point of the study was LBR. Miscarriage was defined as non-vital pregnancy or loss of a previously visible pregnancy.

**Statistical analysis**

The data are expressed as means ± SD. The baseline differences between the two groups were analyzed by Student’s t-test. Pearson’s χ² test and
Baseline characteristics of the patients are given in Table I. The mean age of patients, duration of infertility and Day 3 FSH, LH and E2 levels, sperm concentration, mean percentage of progressive motile sperm count and percentage of women with a previous pregnancy (secondary infertile women) were not significantly different between the groups. Forty-five patients (40.2%) in Group I and 49 patients (43%) in Group II were in the ‘unexplained infertility’ diagnosis group ($P = 0.688$).
Primary outcome of the study

LBRs were 10.7% (12/112 patients) in the single IUI group and 12.3% (14/114) in the double IUI group and the difference was not statistically significant (P = 0.835, OR = 1.16 95% CI: 0.51–2.64; Table III). The data demonstrates that double IUI instead of single IUI increases success of LBRs 14.9%. Estimated number needed to treat (NNT) is 62. This means 62 cycles of double IUI instead of single IUI should be done for one additional live birth.

Other comparisons

Although power of our study protocol is not sufficient, the results were also compared according to the diagnostic subgroups. In the unexplained infertility group the LBRs was 11.1% (5/45 patients) with single IUI and 18.4% (9/49) with double IUI (P = 0.393). In the mild male factor group this rate was 10.4% (7/67) and 7.7% (5/65) in the single and double IUI groups, respectively (P = 0.764).

Table III shows LBRs in CC, FSH and CC/FSH cycles. Miscarriage rates were 25% (4/16) and 30% (6/20) in the single and double IUI groups, respectively (P = 0.52). There were four multiple pregnancies among the 36 pregnancies, all of which were twins. Three of them were in the single IUI group. None of the patients in this study had ovarian hyperstimulation syndrome or ectopic pregnancy.

We compared LBRs according to follicle number in Groups I and II. The LBRs were 6.7% (8/120), 17.8% (13/73) and 15.2% (5/33) when there were two, three or more than three dominant follicles on the day of hCG. The difference between two and three follicles were statistically significant (P = 0.03). However, LBRs in groups according to follicle number were not significantly different in either group (Fig. 2). The mean number of follicles did not differ between pregnant and non-pregnant women (2.86 ± 0.79 and 2.6 ± 0.78, P = 0.07).

We also compared the results according to duration of infertility. In women with a duration of infertility ≤ 3 years LBRs were 8.7% (4/46) and 21.1% (8/38) in the single and double IUI groups, respectively (P = 0.128). In women with a duration of infertility > 3 years LBRs were 12.1% (8/66) and 7.9% (6/76), respectively (P = 0.415).

Discussion

In this study, we aimed to compare single or double IUI in only cycles with multi-follicular development. We hypothesized that cycles with a single dominant follicle could reduce the success of double IUI and elimination of these cycles may improve LBR by extending the fertilization period. At the end of the study, we demonstrated that double IUI was of no value in patients with unexplained infertility or mild male factor infertility in multi-follicular OH/IUI cycles.

The value of double IUI is still a subject of debate in the literature. Three meta-analyses have been published recently on this topic. Osuna et al. (2004), in their meta-analysis, found no significant difference between single and double IUI, but with a trend towards better results with double IUI (RR = 1.31; 95% CI: 0.99–1.73, P = 0.06). In another meta-analysis (Polyzos et al., 2009), the two procedures were compared only in unexplained infertility patients and it was reported that there was no difference between the single and double IUI groups (OR = 0.92; 95% CI: 0.59–1.45, P = 0.715). In a third analysis (Cantineau et al., 2003), the results favored double IUI (OR = 1.8, 95% CI: 1.4–2.4). The main contributor to this difference was the

**OH cycle characteristics**

The OH agent was rec-FSH in 72.3% (81/112 patients) and 77.2% (88/114 patients) of cycles in Group I and Group II, respectively. The distribution of OH agents (CC, rec-FSH or CC/rec-FSH) did not differ significantly between the groups (P = 0.257, Table I). The OH agent was rec-FSH in 72.3% (81/112 patients) and 77.2% (88/114 patients) in Group I and Group II, respectively (Fig. 2). The mean number of follicles did not differ between pregnant and non-pregnant women (2.86 ± 0.79 and 2.6 ± 0.78, P = 0.07).

**Table I** Baseline characteristics of the patients.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
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<tbody>
<tr>
<td>Female age</td>
<td>29.57 ± 4.27</td>
<td>29.03 ± 4.55</td>
<td>0.398</td>
</tr>
<tr>
<td>Body mass index</td>
<td>25.01 ± 4.18</td>
<td>25.01 ± 3.91</td>
<td>0.992</td>
</tr>
<tr>
<td>Duration of infertility (years)</td>
<td>4.9 ± 3.3</td>
<td>5.3 ± 3.3</td>
<td>0.069</td>
</tr>
<tr>
<td>Day 3 FSH</td>
<td>5.66 ± 1.89</td>
<td>5.96 ± 2.05</td>
<td>0.198</td>
</tr>
<tr>
<td>Day 3 LH</td>
<td>4.84 ± 6.04</td>
<td>4.70 ± 3.19</td>
<td>0.853</td>
</tr>
<tr>
<td>Day 3 E2</td>
<td>47.61 ± 42.70</td>
<td>47.24 ± 47.64</td>
<td>0.851</td>
</tr>
<tr>
<td>Sperm concentration</td>
<td>74.44 ± 54.45</td>
<td>68.84 ± 51.62</td>
<td>0.523</td>
</tr>
<tr>
<td>% progressive motile sperm</td>
<td>47.17 ± 16.87</td>
<td>47.48 ± 14.58</td>
<td>0.852</td>
</tr>
</tbody>
</table>

Table I: Single IUI group (N:112), Group 2: Double IUI group (N:114).

**Table II** COH cycle characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>COH agent</td>
<td></td>
<td></td>
<td>0.257</td>
</tr>
<tr>
<td>CC</td>
<td>17 (15.2%)</td>
<td>19 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>FSH</td>
<td>81 (72.3%)</td>
<td>88 (77.2%)</td>
<td></td>
</tr>
<tr>
<td>CC + FSH</td>
<td>14 (12.5%)</td>
<td>7 (6.1%)</td>
<td></td>
</tr>
<tr>
<td>Follicle no &gt; 15 mm</td>
<td>2.6 ± 0.78</td>
<td>2.64 ± 0.81</td>
<td>0.981</td>
</tr>
<tr>
<td>HCG day E2</td>
<td>613.94 ± 339.97</td>
<td>661.23 ± 356.94</td>
<td>0.314</td>
</tr>
<tr>
<td>HCG day P</td>
<td>0.338 ± 0.20</td>
<td>0.366 ± 0.24</td>
<td>0.362</td>
</tr>
<tr>
<td>HCG day endometrial thickness</td>
<td>9.59 ± 2.16</td>
<td>10.5 ± 2.16</td>
<td>0.002</td>
</tr>
<tr>
<td>Day of HCG administration</td>
<td>8.29 ± 3.04</td>
<td>8.17 ± 3.42</td>
<td>0.767</td>
</tr>
</tbody>
</table>

Table II: Single IUI group (N:112), Group 2: Double IUI group (N:114). Parametric values are expressed as mean ± standard deviation (SD).
inclusion of a study by Liu et al. (2006), which included 1257 patients with, as in our study, unexplained and mild male factor infertility. Their results were surprising because the overall pregnancy rate in the mild male factor infertility group was 18.1% (139/767 patients), which was greater than that in the unexplained infertility group (11.2%, 55/490 patients). Although it can be speculated that a second sperm sample with inferior quality might not improve the pregnancy rates with second IUI (Osuna et al., 2004), higher pregnancy rates in the mild male factor infertility group were achieved by double IUI (unexplained and male factor, single IUI, pregnancy rates, 10.53 and 11.34%, double IUI, pregnancy rates, 11.83 and 24.93%, respectively, P-value was only significant in male factor infertility group P = 0.000001). In our study, LBR did not differ between the single and double IUI groups (10.7 and 12.3%) in the mild male factor infertility group (single and double IUI, LBRs, 10.4 and 7.7%) or in the unexplained infertility group (11.1 and 18.4%, P = 0.393). Although the reason for the discrepancy between our results and those of Liu et al. is not clear, it is probable that differences in ovarian stimulation protocols and elimination of cycles with single dominant follicles in our study could have affected the results.

We used gonadotrophins for ovarian stimulation in the majority of our study cycles (72.3 and 77.2%). There was no difference between the single and double IUI groups in only gonadotrophin cycles (LBR 8.6% in the single IUI group and 13.6% in the double IUI group, Table III). Osuna et al. found that double IUI increases pregnancy rates in cycles when ovarian stimulation was performed with CC or CC/gonadotrophins (RR = 1.59, 95% CI: 1.04–2.45). They speculated that the lower pregnancy rate in insemination cycles in which CC was used, with or without gonadotrophins, could be related to a reduced number of available mature oocytes at the moment of insemination. According to this speculation, the presence of fewer oocytes guarantees a greater exposure to sperm, and this could increase pregnancy rates in double IUI cycles. The mean number of follicles >15 mm in our study was 2.44 ± 0.69, 2.61 ± 0.78 and 3.19 ± 0.81 in CC, gonadotrophin and CC/gonadotrophin cycles, respectively (P = 0.002). Thus, we disagree with the speculation of Osuna.

### Table III LBR in single and double IUI groups.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBRs (Per protocol)</td>
<td>10.7% (12/112)</td>
<td>12.3% (14/114)</td>
<td>1.16 (0.51–2.64)</td>
<td>0.835</td>
</tr>
<tr>
<td>LBRs (Intention to treat)</td>
<td>10.5% (12/114)</td>
<td>12.3% (14/114)</td>
<td>1.19 (0.52–2.69)</td>
<td>0.835</td>
</tr>
<tr>
<td>LBR in unexplained group</td>
<td>11.1% (5/45)</td>
<td>18.4% (9/49)</td>
<td>1.80 (0.55–5.84)</td>
<td>0.393</td>
</tr>
<tr>
<td>LBR in male infertility group</td>
<td>10.4% (7/67)</td>
<td>7.7% (5/65)</td>
<td>0.71 (0.21–2.37)</td>
<td>0.764</td>
</tr>
<tr>
<td>LBR in CC cycles</td>
<td>11.8% (2/17)</td>
<td>5.3% (1/19)</td>
<td>0.41 (0.03–5.05)</td>
<td>0.593</td>
</tr>
<tr>
<td>LBR in FSH cycles</td>
<td>8.6% (7/81)</td>
<td>13.6% (12/88)</td>
<td>1.66 (0.62–4.47)</td>
<td>0.339</td>
</tr>
<tr>
<td>LBR in CC + FSH cycles</td>
<td>21.4% (3/14)</td>
<td>14.3% (1/7)</td>
<td>0.61 (0.05–7.24)</td>
<td>0.999</td>
</tr>
<tr>
<td>Miscarriage rates</td>
<td>25% (4/16)</td>
<td>30% (6/20)</td>
<td>1.28 (0.29–5.67)</td>
<td>0.52</td>
</tr>
<tr>
<td>Multiple pregnancy rates</td>
<td>25% (3/12)</td>
<td>7.1% (1/14)</td>
<td>0.23 (0.02–2.58)</td>
<td>0.208</td>
</tr>
</tbody>
</table>

Group 1: Single IUI group (N:112), Group 2: Double IUI group (N:114).

![Figure 2](https://example.com/figure2.png)

**Figure 2** LBRs according to dominant follicle number in single and double IUI groups.

LBRs are not statistically different in either group when there is two, three or greater than three dominant follicles.
as we observed higher follicle numbers in CC/gonadotrophin cycles, however, the results of our study should be interpreted with caution due to the small number of cases in CC and CC/gonadotrophin cycles.

A recently published meta-analysis of the influence of number of follicles on pregnancy rates in OH/IUI cycles (van Rumste et al., 2008) has demonstrated that multi-follicular growth is associated with increased pregnancy rates. The authors suggest that to achieve one additional pregnancy, 16 cycles of multi-follicular growth instead of mono-follicular growth are necessary at the cost of two additional multiple pregnancies. They concluded that three or four follicles instead of two follicles do not add any advantage in achieving further pregnancies. Therefore, we were also interested in the influence of follicle numbers on pregnancy rates in this study. Overall LBRs were 6.7% (8/120 patients) in cycles with two dominant follicles and 17.8% (13/73 patients) in cycles with three dominant follicles ($P=0.03$; RR $=3.03$, 95% CI: 1.19–7.72). The estimated NNT is nine according to these results, which favors three follicles instead of two. There was no advantage of more than three follicles in achieving pregnancy in this study. We agree with the ESHRE Capri Workshop Group (2009) that the success of multi-follicular cycles could be related to better ovarian reserve and perhaps better oocyte quality, rather than number of follicles as we did not find any difference in the mean number of follicles in cycles that resulted in pregnancy or not (2.86 ± 0.79 and 2.6 ± 0.78, $P=0.07$). Additionally, there were four twin pregnancies in our study (11.1%, 4/36 pregnant patients, all of whom delivered healthy babies), two of which were in the two follicle group (2/8 pregnant patients), whereas one was in the three follicle group (1/13 pregnant patients) and other was in the four follicle group (1/4 pregnant patients).

The recent ESHRE Capri Workshop Group report suggested that IUI in stimulated cycles is effective only in patients with more than 3 years' duration of infertility, but is associated with a significant rate of higher-order multiple births. The reason for this conclusion was two randomized studies (Guizzik et al., 1999; Steures et al., 2006), in one of them duration of infertility was 2 years and the pregnancy rate was 4.3% with FSH/IUI treatment (Steures et al., 2006). Therefore, we eliminated CC and CC/gonadotrophin cycles from our study population and we compared the overall pregnancy rates according to infertility duration. There were 64 cycles with infertility duration ≤3 years and 105 cycles with infertility duration >3 years. LBRs were 15.6% in the first group and 8.6% in the second group ($P=0.209$). The mean female age was 33 years with 4.3% pregnancy in the former study (Steures et al., 2006) and thus the mean age of patients in our study could have affected these results (mean age 29.3 ± 4.4 years). We also believe that calculation of spontaneous pregnancy rates of patients (Steures et al., 2004) and replicating this kind of study with some prognostic groups will give more useful information for the effects of OH/IUI (calculations of spontaneous pregnancy rates: http://www.freyar.probability.php.).

Our results also revealed a pregnancy rate and multiple pregnancy rate similar to those of the European IVF Monitoring Programme in 2004, which reported 98 388 IUI cycles from 19 countries leading to 12 081 births (12.3% per cycle), of which 87% were singleton and 13% were multiple births (Andersen et al., 2008).

In conclusion, our study did not find any difference in LBRs between single and double IUI groups in OH cycles with multi-follicular development. To the best of our knowledge this is the first report with this kind of study design. Inclusion of good prognosis patients and exclusion of cycles with a single dominant follicle, cycles with pre-mature luteinization and patients with potential poor ovarian reserve could have positively affected our LBRs. Our power analysis is not sufficient to demonstrate small differences in pregnancy rates and this is the main limitation factor of our study. To demonstrate the absolute difference that we have found, of 1.6% between groups, a total sample size of more than 4000 patients would be required (two-tailed, $P=0.05$). The clinical significance of a 1.6% improvement is debatable, but a sample size of >4000 is clearly not feasible with single center studies.

The disadvantage of double IUI is the increase in the cost and burden to both the health provider and the couple. These considerations should be taken into account by health care providers before offering double IUI in clinical practice. Whether double IUI increases pregnancy rates in a subgroup of patients should be determined in further large randomized trials.

References


