Luteal phase support in normo-ovulatory women stimulated with clomiphene citrate for intrauterine insemination: need or habit?

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BACKGROUND: Limited data exist concerning the need for luteal support in clomiphene citrate-stimulated intrauterine insemination (IUI) cycles. The addition of progesterone became an established clinical practice, despite the absence of evidence of effectiveness.

METHODS: A prospective randomized controlled trial was performed in a tertiary referral centre to assess the effect of intravaginal micronized progesterone as luteal support on the probability of ongoing pregnancy in patients stimulated with clomiphene citrate for IUI. Normo-ovulatory women, ≤36 years of age, undergoing ovarian stimulation with clomiphene citrate (50 mg) for IUI (n = 468) were randomized during the period from September 2008 to December 2009. Patients were randomized, either to receive luteal phase support (n = 243) in the form of vaginal micronized progesterone in three separate doses (200 mg, 3 times a day), or to the control group who did not receive luteal phase support (n = 225).

RESULTS: Data from 400 women were analysed. Following the first interim analysis, the study was prematurely cancelled as an extremely low total pregnancy rate was found. No difference was observed in ongoing pregnancy between patients who did, or did not, receive vaginal progesterone as luteal support [8.7% (17/196) versus 9.3% (19/204), respectively, P = 0.82; difference −0.6%, 95% confidence interval (CI): −6.4, 5.2]. Additionally, the early pregnancy loss rate did not differ between groups (1.5% progesterone group versus 2% no progesterone group, P = 0.78; difference −0.5%, 95% CI: −3.6, 2.7).

CONCLUSIONS: Routine supplementation of the luteal phase with vaginal progesterone does not seem to improve pregnancy rates in normo-ovulatory women stimulated with clomiphene citrate for IUI.

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Key words: clomiphene citrate / progesterone / intrauterine insemination / luteal support / normo-ovulatory women

Introduction

Luteal phase defects have been attributed principally to inadequate production of progesterone, the major product of the corpus luteum, which is absolutely essential for the establishment and maintenance of early pregnancy (Csapo et al., 1972). Progesterone improves endometrial receptivity by inducing secretory changes of the endometrium in the luteal phase (Bourgain et al., 1990).

The objective of superovulation is to achieve the development of multiple follicles. As a result, multiple follicles and corpora lutea secrete supraphysiological concentrations of progesterone and estrogen in the luteal phase. These high concentrations of steroids result in a negative feedback on the pituitary–hypothalamic axis, and thus inhibit the production of luteal LH, mandatory for luteal progesterone production (Fauser and Devroey, 2003). Although the benefit of progesterone administration has been well documented in IVF (Fatemi et al., 2007), the question remains whether it is really necessary in mildly stimulated IUI cycles, in which 1–2 follicles have developed.

In IVF or gamete intra-Fallopian transfer, the absence of a beneficial effect of luteal support in cycles stimulated with clomiphene citrate has already been demonstrated (Van Steirteghem et al., 1988). However, there is lack of evidence in the literature that could give us an answer regarding the need for luteal phase support in clomiphene citrate-stimulated IUI cycles. The prospective randomized study by Erdem et al. described a beneficial effect of progesterone administration on pregnancy rates in IUI cycles stimulated with gonadotrophins in couples with unexplained infertility (Erdem et al., 2009). Montville et al. strongly recommended luteal supplementation with...
progesterone in women with polycystic ovary syndrome (PCOS) using letrozole for ovulation induction, while no positive effect of progesterone on those stimulated with clomiphene citrate was detected (Montville et al., 2009).

In patients with unexplained infertility, the beneficial role of ovulation induction in IUI has been established (NICE, 2004; Verhulst et al., 2006). Although FSH or hMG is far more efficient in improving pregnancy rates than anti-estrogens (Cantineau et al., 2007), clomiphene citrate remains one of the most popular drugs for stimulating women undergoing IUI for various indications, such as male factor infertility, in lesbian couples or for single parents who request donor artificial insemination.

The addition of progesterone has become a well-established clinical practice, yet there is no prospective trial investigating the need for progesterone administration in the widely used stimulation protocol involving clomiphene citrate for IUI in normo-ovulatory patients.

**Materials and Methods**

**Patient population**

Four hundred and sixty-eight women undergoing ovarian stimulation with clomiphene citrate for their first IUI attempt, from September 2008 to December 2009, were randomized at the outpatient clinic. The randomization was performed on the basis of a computer-generated list that was not concealed from the physicians, identifying the treatment strategies only as ‘A’ or ‘B’. The patients were assigned either to receive luteal phase support in the form of intravaginal progesterone (progesterone group), or not to receive luteal support (no progesterone group); see patient flowchart (Fig. 1). Patients could participate only for one cycle.

Inclusion criteria were: age ≤36 years, BMI of 18–29 kg/m², regular menstrual cycles, no PCOS (Rotterdam criteria), no endometriosis (≥American Fertility Society grade III), basal levels of FSH (<12 IU/l), estradiol (E₂, <80 pg/ml) and progesterone (<1.6 ng/ml) at the initiation of stimulation. All women had bilateral tubal patency confirmed by hysterosalpingography performed a maximum of 3 months before starting the stimulation. The use of donor sperm was also accepted as an inclusion criterion.

The research project was approved by the Institutional Review Board, and written informed consent was obtained from the participating women.

**Ovarian stimulation, sperm preparation and IUI**

All patients underwent transvaginal ultrasonography on Day 3 of the menstrual cycle to confirm that the ovaries appeared to be normal, while basal hormonal values were controlled the same day. Clomiphene citrate (Clomid®; Sanofi-Aventis, Brussels, Belgium) was administrated from Day 3 to Day 7 of the cycle at a fixed dose of 50 mg. Ovulation was triggered with hCG 5000 IU as soon as ≥1 follicle of ≥17 mm was present at ultrasound. Sperm preparation and IUI procedure have been described previously in detail (Dellaert et al., 1993). IUI was performed 36 h after hCG administration. Patients were randomized, either to receive luteal phase support in the form of vaginal micronized progesterone in three separate doses (Utrogestan® 200 mg) starting 1 day after IUI and continuing until 7 weeks of gestation if pregnancy is achieved, or in the second group not to receive luteal phase support.
Pregnancy testing was performed by measuring serum hCG level at 14 days after the IUI.

**Outcome measures**

The outcome measures were ongoing pregnancy and early pregnancy loss. Ongoing pregnancy was defined as pregnancy developing beyond 12 weeks, while early pregnancy loss was defined as the proportion of patients with initially positive hCG in whom pregnancy failed to develop by 12 weeks of gestation.

**Statistical analysis**

**Power analysis**

A power analysis showed that in order to detect a difference of 5% in ongoing pregnancy rates between the two groups, assuming a baseline ongoing pregnancy of 15% at an α level of 0.05 and β of 0.2, 906 patients should be included in each group. As this was the first randomized controlled trial (RCT) to test the necessity of luteal support in IUI cycles stimulated with clomiphene citrate, we were ethically obliged to be sure that our treatment (no progesterone) was not harmful for the participating patients. At the first interim analysis, planned to take place after the enrolment of ~25% of the projected 1812 patients, the pregnancy rate of the two groups was lower than expected for our centre and therefore the study was cancelled prematurely.

As (to the best of our knowledge) this is the first RCT to evaluate the beneficial effect of luteal phase support in regular cycles stimulated with clomiphene citrate for IUI, the data we provide here on a reasonably large patient population could be included in a future meta-analysis on this issue.

**Statistical tests**

Analysis was performed according to the intention-to-treat (ITT) associated with a secondary per protocol analysis (PP) conducted on outcomes. Continuous variables were compared with the t-test for independent samples or the Mann-Whitney test, depending on the normality of their distribution. Proportions were compared with the Fisher’s exact test or the chi-square test where appropriate. Statistical significance was set at \( P < 0.05 \).

**Results**

Initially, 468 women undergoing IUI with clomiphene citrate were randomized, either to receive micronized progesterone as luteal support or not. Four patients (progesterone group: \( n = 2 \), no progesterone group: \( n = 2 \)) did not start an IUI cycle after the initial consultation for personal reasons. Twelve patients (progesterone group: \( n = 7 \), no progesterone group: \( n = 5 \)) did not start stimulation because of abnormal steroid levels 1 day before the start of the stimulation, while 52 patients (progesterone group: \( n = 38 \), no progesterone group: \( n = 14 \)) that started ovulation induction were further excluded owing to no response (absence of follicle). Finally, 400 patients were analysed further (progesterone group: \( n = 196 \), no progesterone group: \( n = 204 \)).

Demographic, baseline characteristics and stimulation data of the study participants are shown in Table I. No differences between groups were observed for the compared parameters, except for the number of follicles (mean ± SD) ≥17 mm on the day of hCG administration in the progesterone versus no progesterone group, respectively (1.2 ± 0.3 versus 1.3 ± 0.4, \( P = 0.02 \)), however, this was most likely just a chance result arising from the randomization.

<table>
<thead>
<tr>
<th>Table I</th>
<th>Characteristics of patients and stimulation data for normo-ovulatory women who received luteal phase progesterone, or no progesterone, following stimulation with clomiphene citrate for intrauterine insemination in a RCT.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Progesterone group (n = 196)</strong></td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.1 (3.6)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.6 (2.8)</td>
</tr>
<tr>
<td>Cause of infertility (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>46 (23.5)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>70 (35.7)</td>
</tr>
<tr>
<td>Lesbian</td>
<td>56 (28.6)</td>
</tr>
<tr>
<td>Single mother</td>
<td>24 (12.2)</td>
</tr>
<tr>
<td>Type of sperm (%)</td>
<td></td>
</tr>
<tr>
<td>Partner</td>
<td>99 (50.5)</td>
</tr>
<tr>
<td>Donor</td>
<td>97 (49.5)</td>
</tr>
<tr>
<td>Basal FSH (IU/l)</td>
<td>7.2 (2.1)</td>
</tr>
<tr>
<td>Basal E₂ (pg/ml)</td>
<td>41.9 (16.8)</td>
</tr>
<tr>
<td>Basal progesterone (ng/ml)</td>
<td>0.6 (0.3)</td>
</tr>
<tr>
<td>Basal LH (mIU/ml)</td>
<td>5.5 (2)</td>
</tr>
<tr>
<td>Length of follicular phase (days)</td>
<td>11.6 (1.6)</td>
</tr>
<tr>
<td>FSH on hCG day (IU/l)</td>
<td>5.4 (3.1)</td>
</tr>
<tr>
<td>E₂ on hCG day (pg/ml)</td>
<td>513 (248)</td>
</tr>
<tr>
<td>Progesterone on hCG day (ng/ml)</td>
<td>0.7 (0.3)</td>
</tr>
<tr>
<td>LH on hCG day (mIU/ml)</td>
<td>10.6 (9.9)</td>
</tr>
<tr>
<td>Endometrial thickness on hCG day (mm)</td>
<td>6.8 (2.1)</td>
</tr>
<tr>
<td>Number of follicles ≥17 mm on the day of hCG</td>
<td>1.2 (0.3)</td>
</tr>
<tr>
<td>Number of follicles between 16 and 14 mm on the day of hCG</td>
<td>0.3 (0.5)</td>
</tr>
</tbody>
</table>

Values are mean (SD) or cases (percentage). No significant differences between the two groups except* for the number of follicles ≥17 mm on day of hCG \( P = 0.02 \). E₂, estradiol.

Pregnancy outcome is shown in Table II. No significant differences were observed between progesterone and no progesterone groups in terms of ongoing pregnancy \( 8.7 \text{ versus } 9.3\% \text{ difference: } -0.6\% \); 95% confidence interval (CI), \( -6.4 \text{ to } +5.2 \) and early pregnancy loss rate \( 1.5 \text{ versus } 2\% \text{ difference: } -0.5\%; 95\% \text{ CI, } -3.6 \text{ to } +2.7 \) on the basis of the PP analysis. A total ongoing twin pregnancy rate of 1.5% was observed in the present study. Similar clinical outcomes were found using the ITT analysis. The trend towards a higher pregnancy rate in the no progesterone group could be easily explained by the fact that women in this group had more follicles ≥17 mm on the day of hCG administration.
Discussion

In this study, it was shown that in normo-ovulatory patients stimulated with clomiphene citrate for IUI, luteal phase support with vaginal progesterone is not associated with a higher ongoing pregnancy rate compared with patients without luteal phase support (8.7 versus 9.3%). While IUI is one of the most frequently applied techniques to increase the probability of conception in couples with subfertility, questions about the quality of the luteal phase and the necessity of luteal support remain unanswered. Despite the fact that it has been well documented that stimulated IVF/ICSI cycles have a deficient luteal phase, we still ignore if the luteal phase is also impaired (Cohlen, 2009) when only two or three corpora lutea are present (as in superovulated IUI cycles). Luteal phase support is regularly used in infertility practice in order to improve clinical outcomes, and intravaginal progesterone is the most commonly used therapeutic agent. To the best of the authors’ knowledge, this is the first prospective randomized trial evaluating the impact of intravaginal progesterone given as luteal phase support on pregnancy rates in ovarian simulation and IUI cycles with clomiphene citrate in normo-ovulatory patients.

Clomiphene citrate is able to stimulate ovulation by competing with estrogen for binding to hypothalamic estrogen receptors. Blockade of estrogen receptors leads to an increase in GnRH. Additionally, clomiphene citrate increases the pituitary sensitivity to GnRH in a similar fashion to E2. As a result, FSH and LH secretion are increased during clomiphene citrate administration (Dickey et al., 1965). It has been postulated that high LH levels are responsible for a low fertilization rate in IVF (Stranger and Yovich, 1985; Howles et al., 1986) and increased rates of miscarriage (Shoham et al., 1990). On the other hand, LH is responsible for maintenance of the corpus luteum during the luteal phase (Casper and Yen, 1979).

Clomiphene citrate may also have a direct effect on the ovary, making the granulosa cell more sensitive to pituitary gonadotrophin. Serum progesterone and E2 concentrations are increased during the luteal phase of the cycle in a direct dose–response relationship with clomiphene citrate (Hammond and Talbert, 1982; Fukuma et al., 1983). Dickey (1984) showed that serum progesterone levels during the mid-luteal phase averaged 2700 ng/dl in spontaneous cycles and 3200 ng/dl in clomiphene citrate cycles of pregnancies which went to term: the increased progesterone concentration continues until the 11th post-ovulation week before returning to the values found in a spontaneous pregnancy (Dickey and Hower, 1995).

The fact that clomiphene citrate occupies hypothalamic estrogen receptors for a longer period than estrogens (Dickey and Holtkamp, 1996) might account for the greater luteal LH concentration in the clomiphene citrate cycles (Tavaniotou et al., 2002). Maruncic and Casper (1987) evaluated whether administration of the estrogen receptor blocker clomiphene citrate during the luteal phase would have any impact on LH secretion, and demonstrated that an increase of LH pulse frequency was present after the administration of clomiphene citrate in the luteal phase. The authors speculated that these findings could be explained by a decrease in opioid peptide activity caused by clomiphene citrate.

Moreover, the increase in LH pulse frequency subsequent the clomiphene citrate administration results in a significant increase of serum E2 and progesterone levels, with a lengthening of the luteal phase. These findings point to a complex interplay among ovarian steroids, gonadotrophins and opioid peptides in the human luteal phase and possibly the onset of luteolysis. On the basis of this knowledge, it would be worth examining the possibility of rescuing the luteal phase of agonist-triggered antagonist cycles with the administration of clomiphene citrate during the luteal phase.

As pulsatile LH secretion in the luteal phase is primarily responsible for maintenance of the corpus luteum, this could explain why the necessity of luteal phase supplementation was not demonstrated in our study.

An interesting finding of our study is that the use of clomiphene citrate for stimulation of normo-ovulatory women does not fulfill the purpose of administration. A lower than expected pregnancy rate in both of the groups was the reason why the study was terminated prematurely (De Brucker et al., 2009). Our results suggest that stimulation with clomiphene citrate in IUI cycles may have adverse effects
in normo-ovulatory women trying to achieve pregnancy. A direct adverse effect of clomiphene citrate administered during the follicular phase on the endometrium has been presumed, and interference with estrogen receptor-mediated endometrial estrogen receptor and progesterone receptor induction has been implicated as the mechanism responsible for a negative impact on the endometrium. Previous studies have shown that the anti-estrogenic effect of clomiphene citrate is linked to its long half-life (Geier et al., 1987) and manifested as a thinner endometrium (Gonen and Casper, 1990; Rogers et al., 1991). Failure of conception and preclinical abortions are related to endometrial thickness prior to ovulation in clomiphene citrate cycles (Dickey and Holtkamp, 1996).

It is crucial that the selection of clomiphene citrate for stimulation is based on the cause of infertility, for which there is evidence of a beneficial effect. Even for the use of clomiphene citrate for unexplained infertility there is no evidence of clinical benefit but at least it has no adverse effect, as in the case of our study where clomiphene citrate was used also for other indications (Bhattacharya et al., 2008; Hughes et al., 2010). Another Cochrane review (Cantineau et al., 2007) indicates that gonadotrophins are the most effective treatment when IUI is combined with ovulation induction.

In conclusion, our results have shown that luteal phase supplementation with progesterone does not appear to raise the probability of conception in normo-ovulatory women who are <37 years old and stimulated with clomiphene citrate for IUI. Although the current study is the first RCT to test the need for luteal support in IUI stimulated with clomiphene citrate for IUI. The current Cochrane review (Cantineau et al., 2007) indicates that gonadotrophins are the most effective treatment when IUI is combined with ovulation induction.


Stranger JD, Yovich JL. Reduced in vitro fertilization of human oocytes from patients with raised basal luteinizing hormone levels during the follicular phase. *Br J Obstet Gynaecol* 1985;92:385–393.

