

Low Ovarian Stimulation Using Tamoxifen/FSH Compared to Conventional IVF: A Cohort Comparative Study in Conventional IVF Treatments

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Abstract

Background: Over the last decade, the laboratory procedures in artificial reproduction have improved, thus fewer eggs are necessary. Therefore mild stimulations have been introduced to reduce the risk for the patient and patient drop-outs in treatment. The present study was designed to evaluate the efficacy of low stimulation with Tamoxifen and FSH in a routine IVF clinic.

Material and methods: A total of 2,709 regular short antagonist IVF cycles were compared to 170 Tamoxifen low stimulation IVF cycles. All patients were recruited in the same time period and allocated to the different treatments on their own request.

Results: No differences in age and number of previous cycles were found in between the groups. The clinical pregnancy rate was found to be significantly lower in the Tamoxifen treated group (20% vs. 26%), however we did not find any significant pregnancy rate following transfer (31% Tamoxifen group vs. 28% in conventional IVF). We found lower numbers of visits, lower costs for medication, less side effects and better acceptance for treatment in the Tamoxifen group.

Conclusion: Although we found a lower pregnancy rate per started cycle, the pregnancy rate per transfer was equal and better accepted by the patients.

Keywords: Tamoxifen; Ovarian stimulation; Clomiphene; IVF

Background

Low stimulation has been associated with lower pregnancy rate or efficacy in ART without proper documentation. With the new and better laboratory technologies [1] the number of eggs retrieved for achieving a pregnancy can be reduced, thus the need for ovarian stimulation can be questioned. Old types of medicine such as Tamoxifen and Clomiphene have been introduced in the market again [2] for several reasons, such as safety [3], less stress for the patient and convenience [4]. The wide spread use of single embryo transfer makes it unnecessary to harvest more than a few eggs in an IVF cycle [4]. It has been demonstrated that the health of off-springs from mild stimulation is comparable to conventional IVF [5]. The potential negative effect of Clomiphene on the endometrium might be overcome by transferring the embryos in later cycles using vitrification of the embryos [6].

Another very important aspect of low stimulation is the finding that low stimulation is associated with less drop-outs from the IVF treatment. This again increases the success rate for IVF due to a higher cumulative pregnancy rate during time for the individual couple in treatment [7].

In this paper we report the results from 2,709 regular IVF cycles and 170 Tamoxifen cycles in a cohort study. The new finding but old knowledge in this paper is that Tamoxifen blocks the spontaneous LH surge sufficiently when administered during the whole length of stimulation, avoiding the need for any antagonist treatment and making everything much easier for the patient.

Material and Methods

In a cohort study including all patients admitted to IVF for unexplained infertility, aged between 18 and 38, male factor or tubal factor was included. The study was conducted between January 2007 and November 2012. The patients decided on their own to go for regular IVF using a short antagonist protocol or low stimulation using

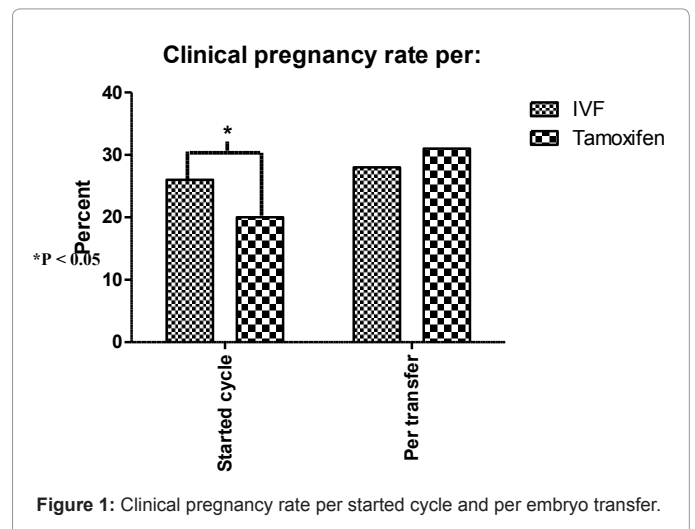


Figure 1: Clinical pregnancy rate per started cycle and per embryo transfer.

Tamoxifen 40 mg daily from day 3 to hCG day and every 3rd day 150 IU Gonal-f.

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Type	No. started	No. oocyte retrieval	No. transfer	No. clinical pregnancies	Mean no. oocytes retrieved	Mean no. embryos transferred	Implantation rate
IVF	2,709	2,225	2,519	702	7	1.7	29.3
Tamoxifen	170	147	109	34	3.6	1	25

Table 1: The number of started cycles in regular IVF and Tamoxifen low stimulation, their outcome in relation to oocyte retrieval, clinical pregnancies, mean number of oocyte retrieved and implantation rates in these 2 groups.

1,693 individual women requested short protocol and 125 requested low stimulation and all who requested this were allowed to do so. All the patients had a regular menstrual cycle.

The stimulation protocols

Low stimulation protocol: Low stimulation using Tamoxifen 20 to 40 mg daily was administered orally from day 3 in the cycle until the day before inducing final oocyte maturation. Human menopausal gonadotropin (hMG) or recombinant FSH was added in the form of injections (50 to 150 IU/every other day) in order to obtain 1 to 4 mature follicles. Ultrasound monitoring was usually initiated on day 8 and continued every other day until ovulation induction using Ovitrelle injection.

Conventional stimulation protocol: The conventional short antagonist treatment included 150 IU FSH daily from day 3 in the cycle until the follicles had reached 17 mm in diameter, and at this point an Ovitrelle injection was given to induce final maturation. From the 6th day of FSH stimulation 0.25 mg Orgalutran was administered daily to avoid premature ovulation. Monitoring ultrasound scans were initiated at day 3 in the cycle and hereafter on day 9 and on the day of ovulation induction.

Statistical methods

For statistical evaluation of data the Graphpad software©2013 (GraphPad Software, Inc) was used.

The two groups were found to follow a normal Gaussian distribution and a non-paired T-test was used to compare the means for the two groups. A *P*-value less than 0.05 was considered to be significant.

Results

A total of 2,709 cycles were carried out using the short protocol and 170 cycles were initiated using the low stimulation protocol. Results as reported in table 1 and figure 1.

The pregnancy rate per transfer was equal between the protocols, however a proportion of low stimulation cycles were cancelled prior to oocyte retrieval because of few follicles.

The mean number of FSH units used in conventional IVF was 1,350 IU and 450 IU for low stimulation. The mean number of visits during the conventional stimulation was 3 prior to oocyte collection versus 1 visit for the low stimulation protocol. Thus a significant lower number of FSH ampoules were used and a significant lower number of visits were found in the low stimulation group compared to the conventional stimulated.

The costs for medication and the time spent in the clinic were found to be significantly lower in the low stimulation group as well as patients' distress during treatment.

No significant differences in age, number of previous cycles or primary indication for ART were found in between the groups. Thus a mean age of the Tamoxifen treatment group was found to be 32.5 years and for the conventional IVF group 33, 7 years of age.

The clinical pregnancy rate per started cycle was found to be significantly lower (*P*=0.03) in the low stimulation (20% vs. 26%) group, mainly due to the cancellation rate before oocyte retrieval. Hereafter

the results were found to be equal. Specifically the implantations rate was found to be the same (29.3% vs. 25%)

Conclusion

Low stimulation using Tamoxifen 40 mg daily from day 3 to hCG injection, when follicles have reached 17 mm in diameter and supplementation with Gonal-f 150 IU every 2nd day until hCG, without any other agonist or antagonist, is an efficient treatment regime and fully comparable to conventional IVF for women aged 18 to 38. These data are among the first to present the benefits of Tamoxifen in IVF stimulation. The stimulation of the endometrium by Tamoxifen [8] compared to Clomiphene might explain the high implantation rate found in this study. This preliminary study supports previous findings by Kato et al. [4,5], reporting the same high pregnancy rate in fresh cycles using low stimulation. Adding the frozen thaw data will undoubtedly increase the success rates.

Therefore we are convinced that the low stimulation will be the preferred treatment by patients in the future, due to excellent pregnancy rates following oocyte collection, less stress, fewer drop-outs [7] and a reduced economic burden.

In Scandinavia, selected single embryo transfer has been employed for more than 10 years now [9] showing the benefits of singletons following IVF, concerning both the health of the baby, safety for the mother and low costs for the society as neonatal services are reduced. Our results should be seen in this perspective, as we now are not only making single embryo transfer easier, but also lower the costs for the treatment for IVF itself. Another important issue is the peak Estradiol level in a conventional IVF treatment, which seems to have a serious impact on the following pregnancy including small for gestational age and preeclampsia [10]. This will be avoided using low stimulation.

Conflicts of Interest

None of the authors have reported any conflicts of interest. This study was not supported by any external funding.

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