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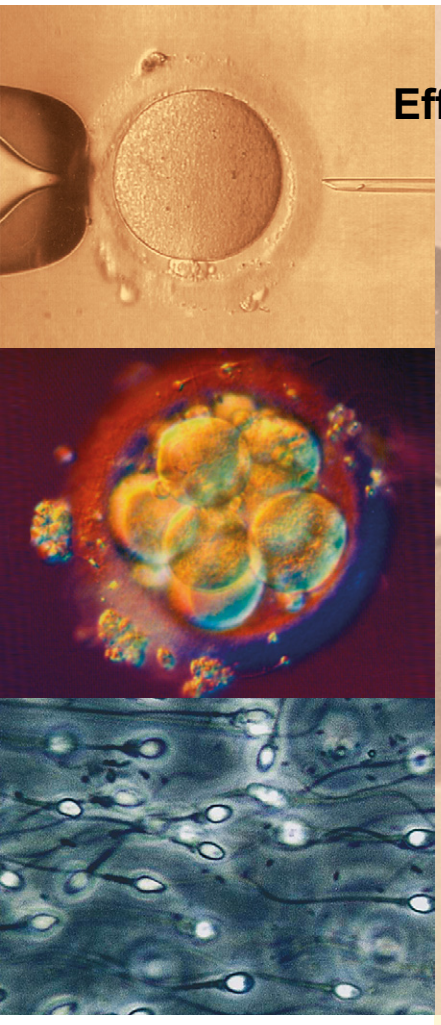

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Effects of Luteal Phase Support Comparing Early (Day 1) and Late (Day 4) Initiation with Pregnancy Rates*

M. Feichtinger, J. Hajek, P. Kemeter, W. Feichtinger

Even though luteal phase support is a standard method in fertility treatment the ideal time to start supplementation is still unknown. Therefore we evaluated different (early and late) initiation points of luteal phase support in a prospective randomized trial. 1111 Women undergoing an IVF/ICSI treatment in a private IVF clinic have been randomized after egg retrieval into two groups of luteal support. Group one initiated luteal phase support on day one after egg retrieval, group two initiated luteal phase support on day 4 after retrieval. Patients received either a classical long (agonist) or antagonist ovarian stimulation protocol. Main outcome measure was the on going pregnancy rate. As a secondary outcome measure we evaluated the early or late begin in the long versus antagonist protocol. There have been no significant differences between the two study groups concerning pregnancy rates (early: 29.3%/late: 31.2%; p = 0.55). Furthermore there where no differences in pregnancy rates within patients receiving a GNRH agonist protocol (early: 30.0%/late: 32.9%; p = 0.48) as well as within patients applying a GNRH antagonist protocol (early: 26.9%/late: 32.1%; p = 0.38). Starting luteal phase support on day one compared to day 4 makes no difference concerning pregnancy rates no matter which kind of stimulation protocol is being used.

Key words: luteal phase support, progesterone, in vitro fertilization, gonadotropin-releasing hormone agonists and antagonists, pregnancy rates, estrogen

Effektiver Beginn der Lutealunterstützung – Analyse der Schwangerschaftsraten bei frühem (Tag 1) und spätem (Tag 4) Behandlungsbeginn. Obwohl die Lutealphasen-Unterstützung zu den Standardmethoden in der Reproduktionsmedizin zählt, ist der ideale Beginnzeitpunkt der Therapie noch unbekannt. Daher untersuchten wir 2 unterschiedliche Startpunkte (früh und spät) der Lutealphasen-Unterstützung in einer prospektiv randomisierten Studie. 1111 Frauen die sich einer IVF/ICSI-Behandlung in einer privaten IVF-Klinik unterzogen haben, wurden nach der Punktion in 2 Gruppen aufgeteilt. Gruppe 1 begann die Lutealphasen-Unterstützung am Tag 1 nach Punktion, Gruppe 2 begann die Behandlung am Tag 4 nach Punktion. Die Patienten wurden entweder mit einem klassischen Long- (Agonisten-) oder Antagonisten-Protokoll behandelt. Wir analysierten die Schwangerschaftsraten und verglichen den frühen und späten Beginn der Behandlung im Long- und Antagonisten-Protokoll. Es konnten keine Unterschiede in den Schwangerschaftsraten (Tag 1: 29,3 %/Tag 4: 31,2 %; p = 0,55) festgestellt werden. Außerdem fanden sich keine Unterschiede in den Schwangerschaftsraten im Long (Tag 1: 30,0 %/Tag 4: 32,9 %; p = 0,48) sowie im Antagonisten-Protokoll (Tag 1: 26,9 %/Tag 4: 32,1 %; p = 0,38). **J Reproduktionsmed Endokrinol 2011; 8 (4): 288–90.**

Schlüsselwörter: Lutealphasen-Unterstützung, Progesteron, In-vitro-Fertilisation, Schwangerschaftsrate, Östrogen

Background

Luteal phase supplementation is a standard method in fertility treatment, however there are still a lot of questions concerning application mode, duration of the treatment, combination with additional estrogens and the right time to start supplementation. Normally progesterone or derivatives are applied IM, IV or intravaginally starting on day one after egg retrieval and maintained for 8–10 weeks in case the patient is pregnant.

Concerning the initiation of the treatment the current standards are based more on habit than on evidence. A recent literature review [1] showed the necessity of further investigation in this poorly studied field. There have been a couple of randomized trials but still there is no good evidence about the right starting point. Adams et al. [2] recognized a lower pregnancy rate when increasing the P4 dose at an early stage (day 2 or 3) in patients receiving egg donation but not during a later stage (day 4 or 5) and Sohn et al. [3] reported a significantly lower implantation rate when luteal phase support was started on the day before oocyte retrieval compared with the day of retrieval. Another study reported no difference in pregnancy rates when luteal phase support was started on the day of oocyte retrieval compared to the day of embryo transfer (ET) (day 2) [4]. Mochtar et al. reported no differences between pregnancy rates comparing the day of egg retrieval and the day of ET (day 3) [5].

Design

All patients have been treated between November 2007 and August 2009 in a private clinic specialized in reproductive medicine in Vienna, Austria. 1111 Patients have been treated with standard stimulation protocols within an IVF/ICSI treatment in a prospectively randomized study (Fig. 1). Our trial has been designed according to the recommendations of the CONSORT-Statement [6] and assessors were blinded to group assignment. Randomization was achieved by using a computer generated random number table and was carried out by the embryologist (third party randomization). Two groups of patients have been investigated: one group starting luteal phase support the first day after oocyte retrieval (n = 526) whereas the other group started luteal phase supplementation with the same medication on day 4 after retrieval (n = 527). The treatment consisted of a combination of micronized progesterone (3 × 200 mg), (Utrogestan, Meda Pharma, Austria) and 2 mg of estradiol valerate (Progynova, Schering,

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Germany) and 20 mg of dydrogesterone (Duphaston, Solvay, Austria) orally. Since estrogen levels tend to drop just like progesterone levels when pituitary suppression is admitted we decided to treat patients with a combination containing estrogens and progesterones. The benefit of applying estrogen during luteal phase is still uncertain and literature in this specific field shows an extreme heterogeneity [7, 8] but a recent study showed the benefits of applying estrogen during luteal phase support [9]. IRB-approval was not necessary since treatment with the combination mentioned above is standard registered medication for the indication of luteal phase support and no off-label use. Until 2009 there was no IRB approval necessary in Austria if the study was carried out with a registered medication without any offlable use.

All patients consented concordantly to participate in the randomized study and signed a respective informed consent form.

Analysis

Main outcome measure was the on going pregnancy rate. As a secondary outcome measure we chose early or late start of luteal support in the long versus antagonist protocol. The sample size calculation was based on the results of a comparable study published by Mochtar et al. [5], showing an insignificant difference of 1,8% between the biochemical pregnancy rates of the early and the late luteal support (30.5 vs 32.3%). When a 2% difference is considered, a minimum of 274 cases is necessary to prove the null hypothesis at a beta-error of $p < 0.05$ and a power of 95%. For data evaluation a standard statistic program was used (Spss). Chi-square tests and Students T-Tests where used to compare the two groups.

Results

There have been no differences in the patients collective (Tab. 1). The 2 groups did not differ in terms of endometrium thickness and did not show any differences concerning the number of collected (early: 8.7/late: 8.9; $p = 0.72$) and mature oocytes (early: 6.4/late: 6.5; $p = 0.60$). In both groups the same amount of oocytes got fertilized (early: 76.0%/late:75.8%; $p = 0.90$). The day of ET was equal (early: 3.4/late: 3.5; $p = 0.46$) and in both groups 1.9 preembryos have been transferred ($p = 0.45$) (Tab. 2).

The patients had on average 2 IVF/ICSI-attempts prior to participating in the study.

The group starting with luteal support on day 1 did not show any significant differences concerning pregnancy rates compared with the group that started luteal support on day 4 (early: 29.3%/late: 31.2%; $p = 0.55$). Furthermore there were no differences in pregnancy rates within patients receiving GNRH agonist proto-

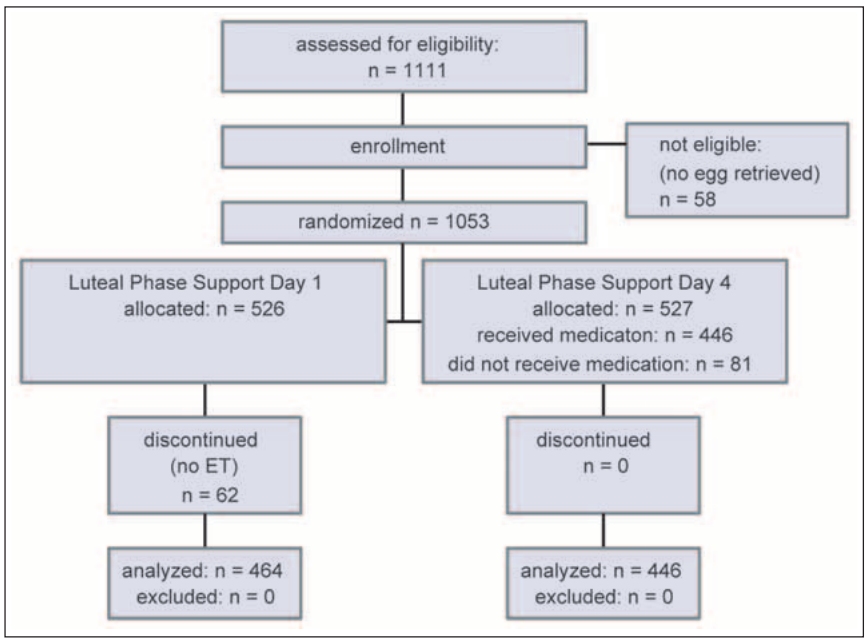

Figure 1. Flow Diagram of the Patient Assessment.

Table 1. Patient Collective

Age	Day 1 (n = 464)	Day 4 (n = 446)	Significance
up to 34, n (%)	193 (50)	193 (50)	n. s.
35–37, n (%)	88 (47.1)	99 (52.9)	n. s.
38–40, n (%)	110 (55.8)	87 (44.2)	n. s.
41+, n (%)	73 (52.1)	67 (47.9)	n. s.
BMI	23.09	23.26	n. s.
Previous Attempts	2.00	2.02	n. s.

n. s. = not significant

Table 2. IVF-Data Including Pregnancy Rates

Age	Day 1 (n = 464)	Day 4 (n = 446)	P-value
Endometrium	11.49	11.46	n. s.
Oocytes retrieved	8.74	8.88	n. s.
Mature Eggs	6.40	6.55	n. s.
Fertilization rate (%)	76.02	75.82	n. s.
ET-Day	3.44	3.50	n. s.
Abortions n (%)	40 (29.2)	41 (29.7)	n. s.
Pregnancies n (%)	136 (29.3)	138 (31.2)	n. s.
Pregnancies Agonist-Protocols (n = 501) n (%)	73 (30)	85 (329)	n. s.
Pregnancies Antagonist-Protocols (n = 239) n (%)	35 (26.9)	35 (32.1)	n. s.

n. s. = not significant

cols (early: 30.0%/late: 32.9%, p = 0.48) as well as within patients receiving GNRH antagonist protocols (early: 26.9%/late: 32.1%; p = 0.38) (Tab. 2).

Discussion

Our results show that there is no difference between early and late start of luteal phase support. There is the question whether luteal phase support is necessary in general to establish implantation or to maintain pregnancy. One meta analysis [10] and 2 other, more recent studies [11 12] showed the need of luteal phase support. The question is if luteal phase support has an effect on the implantation window. Escribá et al. [13] could not find any differences in pregnancy rates comparing day 1 before oocyte retrieval, the day of retrieval and the day after oocyte retrieval in an egg donation program. Williams et al. [14] reported a significant lower pregnancy rate if luteal phase support was initiated on day 6 compared to day 3 after egg retrieval. These studies and a recent meta analysis pointed out that achieving high levels of progesterone too early in the luteal phase might have a detrimental effect on the pregnancy rates [15, 16]. Performing late luteal phase support could result in a better synchronization between the embryo and the endometrium when blastocyst transfer is carried out. Already in the late eighties the group of Chang et al [17] reported that they could not find a significant difference in pregnancy rates if luteal support was conducted 4 days after surgery compared to the day of surgery using gamete intrafrallopian transfer (GIFT). Late onset luteal support implies less expensive treatment for the patient. In February 2010 the costs for the daily dose of the medication in Austria were the following: Utrogestan € 2.22, Duphaston € 1.2, Progynova € 0.17 which means a saving of € 13.6 per patient and concerning the whole study group (n = 527) a saving of € 7167.2 if luteal phase support was initiated on day 4.

A possible weakness of the study could be that we did not evaluate the different application routes of luteal phase support. However several studies did not show a significant difference concerning pregnancy rates comparing the different application routes [18, 19]. We did not register any information on side effects, thus we are unable to provide information if shorter luteal phase support would be beneficial in this term. These side effects are well established: fatigue, headaches and urinary frequency [20].

In case of fertilization failure, luteal phase support on day 4 is superior because the patient does not have to start the medication when no ET (∅ day 3,4) is carried out. We may therefore recommend onset of luteal phase support on day 4 rather than on day 1 after egg retrieval.

Acknowledgements

The authors want to thank Prof. Dr. Anselm Eder for his contribution to the statistical analysis

Conflict of Interest

The authors declare no conflict of interest.

Relevancy to Practice

Later luteal phase support results in:
- Shorter treatment for the Patient
- Less costs
- Possibly less side effects
- Possibly better luteal synchronization in blastocyst transfers

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