A Retrospective Study on the Effect of the Use of Vaginal Utrogestan® for Luteal Phase Support on Pregnancy Rate Among Patients Who Underwent Controlled Ovarian Hyperstimulation and Intrauterine Insemination (COH-IUI) Cycles

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Objective: To determine the effect of vaginal micronized Progesterone (Utrogestan)® for luteal phase support on pregnancy rate after ovarian stimulation and intrauterine insemination, and compare it with control
Design: A retrospective study.
Patients: One hundred fifty one (151) cases of controlled ovarian hyperstimulation using Clomiphene citrate 100 mg OD among couples who underwent Intrauterine insemination cycle
Intervention: Treatment group received vaginal micronized Progesterone (Utrogestan 200mg OD) on the day of IUI until 2 weeks after. The non-treatment group received no form of luteal phase support.
Main Outcome Measure: Clinical pregnancy rate.
Result(s): The demographic data were almost homogenous between the treatment and control groups. There was a higher pregnancy rate among couples who underwent COH-IUI cycles and received Utrogestan (8.4%), as compared to not receiving any luteal phase support (3.6%), but the difference between the two groups failed to reach statistical significance (P=0.339). No independent variable was significantly associated with pregnancy on multivariate analysis.
Conclusion: There was a higher pregnancy rate with luteal phase support using vaginal progesterone in the form of Utrogestan 200mg tab OD, as compared with no use of any luteal phase support after COH-IUI cycles. However, increase in the sample size is needed to prove this difference to be statistically significant.

Key words: Luteal phase support, progesterone, Utrogestan®, pregnancy rate, controlled ovarian hyperstimulation (COH), intrauterine insemination (IUI)

Introduction

The production of progesterone, which is the major function of the corpus luteum, is very crucial during implantation and in maintenance of early pregnancy, weeks before the placenta becomes developed. The progesterone is derived from the corpus luteum before 7 weeks of gestation, and is almost entirely derived from the trophoblast beyond 9 weeks age of gestation. During the interval, known as the luteal-placental shift, progesterone production comes from both sources, and to a varying extent.[1] The important role that progesterone plays in human reproduction makes exogenous supplementation a common element of treatment regimens in infertility, particularly those related to assisted reproductive technology (ART).[2] Progesterone levels during early pregnancy range widely, particularly in conceptions after treatment with ovulation induction agents. However, there are no reliable methods that diagnose progesterone deficiency in the luteal phase. Even single or serial serum progesterone measurements will not be an effective tool to give accurate gauge of luteal function. Histologic endometrial dating, which has been the gold standard to assess the quality of luteal function had also been recently

proven invalid.[2] This makes exogenous progesterone supplementation prudent in clinical circumstances where its deficiency may be presumed.

The role of luteal phase support with exogenous progesterone supplementation in IVFs where cycles are stimulated with either GnRH agonists or antagonists have been widely studied and justified. Randomized controlled trials showed significantly higher pregnancy rates among those given luteal phase support compared to those who were not.

Progesterone can be administered orally, vaginally or by intramuscular injections. The oral route has been the least common method of luteal phase support, as well as the least effective in terms of implantation and pregnancy rates, as compared with vaginal or intramuscular routes, based on randomized controlled trials performed.[2] In a study by Miles, et al. comparing vaginally administered and intramuscular progesterone oil supplementation, the former yielded lower serum concentration, but a 30-fold greater endometrial tissue concentration, as opposed to the latter.[3] However, investigations which aim to compare the efficacy of the different forms of vaginally administered progesterone, whether in gel or vaginal tablets or suppositories, have been limited. The effects of treatment with vaginal suppositories or tablets in doses ranging between 200 and 600 mg/day appear comparable to those achieved by administration of a gel containing 90mg of progesterone.[2]

In a retrospective cohort study by Mitwally, et al. in 2010, vaginal micronized progesterone (Endometrin®, 100mg, 2-3 times a day) was compared with intramuscular progesterone (in oil, 100mg per day) for luteal support in women undergoing IVF-ET after a long GnRH agonist protocol. The results showed that luteal phase support with vaginal progesterone was associated with treatment outcomes that were no different from those with intramuscular progesterone luteal phase support. Women who used vaginal P4 for luteal support had ongoing pregnancy rates (odds ratio [OR], 1.0675; 95% confidence interval [CI], 0.7587-1.5020) and rates of total pregnancy loss (OR, 1.0775; 95% CI, 0.7383-1.5727) that were not statistically different from those who used IM-P4.[4] In a prospective study by Silverberg, et al, which included 474 patients, luteal phase support after IVF cycle with vaginal Crinone® 8% gel (patients = 172) was compared with intramuscular progesterone, 25-50mg/ day (patients = 302). Patients who received vaginal P had higher pregnancy (70.9% vs 64.2%) and delivery (51.7% vs 45.4%) rates than did patients who received IMP. Patients <35 who received vaginal P had significantly higher delivery rates (65.7% vs 51.1%) than did patients who received IMP. However, there were no differences, regardless of age, in the rates of biochemical pregnancy, miscarriage, or ectopics.[5]

The vaginal route is associated with many advantages as compared to intramuscular injections. Progesterone administered vaginally gives a higher uterine progesterone concentrations and lower systemic absorption, thus reducing the local adverse and systemic side effects observed in intramuscular injections, as shown in the study by Miles, et al.[3] Another study by Nahoul, et al. evaluated plasma progesterone after oral or vaginal administration of progesterone in 6 premenopausal women. Micronized progesterone, 100mg, was administered vaginally and orally in the luteal phase of the menstrual cycle. In the second cycle, the same doses were administered, but by different routes. This resulted to circulating progesterone levels that were higher after vaginal administration than after oral administration.[6] Moreover, the vaginal route circumvents the absorption and high first-pass hepatic metabolism after an oral ingestion and facilitates a direct first uterine pass effect, giving a high uterine progesterone concentration.[3,7]

In a study by Tavaniotou, et al. luteal phase LH levels were found to be reduced in hMG only cycles, which indicates that defective LH secretion might induce a luteal phase defect in stimulated cycles.[8] Similarly, in a retrospective analysis by Messinis, et al. luteal administration of hCG induced a significant increase in duration of the luteal phase in anovulatory women.[9]

In a prospective randomized controlled trial by Erdem, et al.[10] it was shown that in patients with unexplained infertility who were given ovarian stimulation and IUI with recombinant gonadotropins, luteal phase support with vaginal P (Crinone® 8% gel) was associated with significantly higher clinical pregnancy and live birth rates (39.4% and 35.8%, respectively) compared with patients without luteal phase support (23.8% and 18.1%, respectively). Similarly, this study suggested that luteal support was unnecessary after a pregnancy had been achieved, after arriving at a similar clinical abortion rate between the study and control groups. A prospective RCT by Nyboe, et al. evaluated whether prolongation of luteal support during early pregnancy had influence on IVF outcome and found that there was no difference in pregnancy and miscarriage rates among those where progesterone supplementation was prolonged after achieving a pregnancy or among those where it was not prolonged.[11]

Utrogestan® is an exact chemical duplication (structurally similar or bioidentical) of progesterone produced by the ovary. It is not one of the progestins which are synthetic analogues of progesterone. It is synthesized from a natural precursor (diogenin) extracted

from wild yams (Diascorea sp). Its optimal bioavailability is obtained by micronization and oil suspension.[12]

The efficacy and tolerability of vaginal progesterone capsules (Utrogest®), 200mg three times a day were compared with vaginal progesterone gel (Crinone®), 8% two times a day in luteal phase and early pregnancy support during assisted reproductive techniques (ART) in a prospective RCT study by Kleinstein, et al. Results showed no relevant differences in implantation, ongoing pregnancy, and abortion rates between the two groups. Ongoing pregnancy rates were 25.2% in the Utrogest 200 group and 22.2% in the Crinone 8% group; implantation rate (14.7% vs. 11.9%, respectively) and abortion rate (18.2% vs. 19.1% respectively) were also not statistically different. The two recommended regimens of progesterone supplementation in ART proved to be equivalent and safe.[13]

Several studies have compared the use of the different forms of luteal phase support after assisted reproductive techniques - IVF. However, data on the use of vaginal progesterone for luteal phase support after controlled ovarian hyperstimulation and intrauterine insemination (COH-IUI) are limited. The use of vaginal progesterone in the form of Utrogestan vaginal tablet has not been studied. This paper aimed to study its role on clinical pregnancy rate after COH-IUI by comparing it to a control group.

Research Design

A retrospective study

Sample size estimation

A. For expected pregnancy rate

Expected pregnancy rate is about 15%. Confidence level is 95%, power of test is 80%, and a margin of error of 5%, for a total sample size of N=7.84 x 0.15 x 0.85/ 0.0025 = 399 subjects.

For a margin of error of 10%, sample size needed is 100 subjects.

B. For comparison of outcomes

Based on the figures of Erdem, et al. expected pregnancy rates were 39.4% for vaginal progesterone group and 23.8% for the no treatment group. With additional assumptions of 95% confidence level and 80% power, estimated sample size is N=151 per group, or a total of 302 cases.

Study Population and Study Protocol

The subjects included couples identified as having infertility for at least a year; with women having regular menstrual cycles, bilateral tubal patency as documented on or Hysterosalpingosonography (HSSG). All male partners had semen analyses based on WHO 2010 criteria. Patients who underwent surgery for Pelvic Endometriosis were included. Likewise, patients diagnosed with Polycystic ovary syndrome (PCOS) were not excluded.

The subjects were divided into two treatment groups. The study group was given Micronized progesterone (Utrogestan®) 200mg/tab, 1 tab OD intravaginally, on the day of the intrauterine insemination up to two weeks until a pregnancy test was obtained. In the control group, no luteal phase support was given.

Methods

All patients were given ovarian stimulation with Clomiphene citrate 50mg/tab, 1 tab BID, taken on day 2-6 of menstrual cycle. If necessary, exogenous gonadotropins (Recombinant FSH (Puregon®), 50-75 IU, given subcutaneously on day 8-10 were added. Monitoring of follicular maturation by ultrasound was started on day 11. Final oocyte maturation with hCG (Pregnyl®), 5000IU, was given when at least one dominant follicle size reached 1.8mm in diameter. Semen was collected in either of the two (2) reproductive medicine centers and standard semen washing was done, following the WHO 2010 criteria.

Intrauterine insemination was done in either of the 2 centers, about 24hours after hCG administration using an IUI catheter (Wallace ET soft catheter). The patient was maintained on supine position for 30 minutes after the procedure.

The study group was given Utrogestan® 200mg/tab, 1 tab OD intravaginally, starting on the day of IUI until pregnancy testing. The luteal phase support was continued until the 12th week if the woman conceived. The control group did not receive any form of luteal phase support.

Pregnancy testing was done 14 days after the IUI using pregnancy test kit. Clinical pregnancy was confirmed by identification of intrauterine gestational sac using transvaginal ultrasound done 2 weeks after a positive pregnancy test.

The primary outcome measure was a clinical pregnancy. Comparison of clinical pregnancy between the study and control groups was analyzed statistically. Spontaneous abortion rates in both groups were also determined. Demographic data of patients in each group were also compared.

PCOS, post CHL for PEM, others) showed value nearest to significance with P=0.1959. Non-significance may be due to the small sample size. ROC analysis shows that the variables taken together account only for 64% of the AUC.

Conclusion and Recommendations

This study suggests that there was higher pregnancy rate with luteal phase support using vaginal progesterone in the form of Utrogestan 200 mg tablet OD, as compared with no use of luteal phase support after COH-IUI. However, increase in the sample size is needed to prove this difference to be statistically significant. A study on the role of vaginal progesterone use after a pregnancy test turned positive until 12 weeks AOG is also recommended. Other variables like surgery after pelvic endometriosis, and history of PCOS may also be studied in relation to increase in pregnancy rates. Whether a routine luteal phase support using vaginal progesterone after COH-IUI is necessary or it just adds to the expense, remains uncertain, unless various local studies are carried out and investigated.

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