Comparison of Intramuscular and Intravaginal Progesterone for Luteal Phase Support in IVF Cycles: a randomized clinical trial

Katayon Berjis, M.D.; Abotaleb Sarem, M.D.; Mansoureh Moaya, MSc.;
Nahid Mohamad Alaiha M.D.

Obstetrics and Gynecology Department, Azad University of Medical Sciences, Tehran, Iran

Received September 2007; Revised and accepted July 2008

Abstract

Objective: This research was designed to compare the effectiveness of intramuscular progesterone and vaginal progesterone to support luteal phase in IVF cycles.

Materials and Methods: In this randomized clinical trial 182 infertile patients between 20-40 years old were selected for rapid ZIFT cycles. In order to support luteal phase Cyclogest suppository (400 mg BID) was used for 77 cases and the rest used intramuscular progesterone (100 mg daily). Pregnancy and abortion rates were compared between two groups.

Results: Chemical pregnancy rate (positive ß-HCG) was %27.3 in Cyclogest group and %30.6 in intramuscular progestrone group (P = 0.7). Clinical pregnancy (gestational sac visible by transvaginal ultrasound) was observed in %22.1 of cases in Cyclogest group and %27.1 of cases in intramuscular progestrone group (P = 0.4). Ongoing pregnancy rate (fetal heart action visible by transvaginal ultrasound) was %15.6 in Cyclogest group and %18.8 in intramuscular progesterone group (P = 0.6).

Conclusion: Chemical pregnancy, clinical pregnancy and ongoing pregnancy rates were similar in vaginal and intramuscular progestrone groups.

Key words: Rapid ZIFT, Chemical pregnancy, Clinical pregnancy, Progesterone

Introduction

After ovulation induction with clomiphene citrate and gonadotropins, progesterone level would be higher in comparison to natural cycle, so there is no need to additional progesterone for luteal phase support. When GnRH agonists are used for pituitary down regulation, LH secretion is inhibited and its effect will be continued in the luteal phase (1).

Abnormally low level of luteal phase LH may be insufficient to promote endometrial maturation to support an early pregnancy. Endogenous LH secretion can be suppressed for as long as ten days after GnRH agonist treatment (2, 3). In order to compensate the low level of progesterone, injection, gel and suppository forms of this steroid are used.

Numerous studies have shown that supplementary HCG increases the risk of OHSS (ovarian hyper stimulation syndrome), thereafter progesterone seems to be the wiser selection (4, 5). Intramuscular injection is painful and has side effects like abscess formation. On the other hand progesterone suppository may cause lower serum levels which may result in incomplete abortion; however numerous clinical trials in this field had paradoxical results (6-8).

Correspondence:
Katayon Berjis, 32 Irandost Avenue, Aboozar Blvd., Piroozi street, Tehran, Iran.
Tel: +98-218890002 Fax: +98-2188915959
E-mail: beauty_moaya@yahoo.com

Table 1: The comparison of variables between two groups

Support	Cyclogest (n = 77)	Progestron (n = 85)	P
Age (year)	32.3 ± 4.9	31.3 ± 4.7	0.42
Duration of infertility (year)	7.4 ± 5.3	6.9 ± 4.8	0.18
N. of follicles	6.7 ± 3.6	7.1 ± 4.2	0.16
N. of embryos	3.3 ± 1.0	3.2 ± 1.0	0.60
Age (year)	32.3 ± 4.9	31.3 ± 4.7	0.42

So through this study it is decided to compare the efficacy of intramuscular progesterone and progesterone suppository after the successful rapid ZIFT.

Materials and methods

In this randomized clinical study 284 patients were evaluated. The patients were infertile women between 20 to 40 years of age who come to Sarem Hospital from June 2004 until November 2005. After getting approval from the ethical committee of the hospital, the study was conducted following informed written consents of all participants.

After initial routine investigation all patients received daily GnRH agonist (superfact, Aventis Pharma, Germany) from 21th day of the previous menstrual cycle, and then 225-300 IU/day hMG (Menogon, Ferring Pharmaceuticals, Germany) from the second day of menstruation. From sixth day of the cycle, transvaginal sonography was done every other day to assess the folliclar growth. When there was an at least 2-3 follicles with diameter of 18 mm, 10000 unit intra muscular HCG (Pregnyl, Organon, Iran) was injected. After 36 hours, ovum pick up was done (with excluding OHSS patients), so 182 women continued the study. Patients were randomly divided in two groups using random number table. Finally 85 cases in the intramuscular group and 77 cases in the suppository group were evaluated.

One day after ovum pickup in the first group intramuscular progesterone 100mg (Aburaihan pharmaceutical Co., Iran) daily and in the second group cyclogest suppository (Actavis Group, Iceland) 400 mg twice a day were prescribed. Serum pregnancy test was performed on 15 days after per-forming ZIFT and pregnancy sac was investigated three weeks after positive ß-HCG by trans-vaginal ultrasound. Treatment was continued until 10th week of gestation.

SPSS 13.0 (SPSS Inc.chicago IL.) was used to analyze the results. Chi-square and t-test were applied for the comparison. P value less than 0.05 was considered statistically significant.

Results

As shown in table 1, two groups were matched regarding the mean age of patients and mean duration of infertility. There was no statistical difference between two groups due to infertility causes (Male and female factor). No statistical difference between two groups was seen regarding the type of infertility as well. There was no relation between the type of infertility and pregnancy rate. The rates of chemical, clinical and ongoing pregnancies are shown in table 2 with no statistical difference.

Discussion

This study showed that chemical pregnancy and clinical pregnancy rates were more in intramuscular progesterone group but regarding the number of cases there was no statistical difference between two groups. In a prospective study, which has been conducted on 206 IVF cases in Texas University in 1999 intramuscular progesterone (50mg daily) and Crinone gel 8% were compared. Vaginal bleeding (11-12 days after ovum pick up) was more frequent in Crinone gel group; however serum progesterone of intramuscular group was higher. In addition positive ß-HCG and pregnancy rate were similar in two groups (9). In present study positive ß-HCG and clinical pregnancy rates in two groups were similar. Another randomized study which has been done in Pizza University in 1995 comparing intramuscular and vaginal progesterone showed that progesterone level by using

Table 2: Comparison of pregnancy rates between two groups

	Cyclogest (n = 77)	Progestrone (n = 85)
Chemical pregnancy	21 (27.3%)	26 (30.6%)
Clinical pregnancy	17 (22.1%)	23 (27.1%)
Ongoing pregnancy	12 (15.6%)	16 (18.8%)

vaginal gel was more stable and comfortable (10). In another open label comparative assessment that has been done in Harvard University in 2001 on 201 women who used Crinione gel or intramuscular progesterone in IVF cycles, pregnancy and live birth rates were higher in the second group (11). In present study the frequency of pregnancy and alive fetus was reported to be more in intramuscular progesterone group with no statistical differences. In some studies which have been conducted from 2003-2006 cyclogest suppository was compared to Crinone gel. There was no difference in hormonal levels after embryo transfer, pregnancy rate and implantation rate between two groups, but gel was more comfortable (12-14). In a study which was done in Finland on 39 women with tubal factor infertility, endometrial histology assessment proved that vaginal progesterone is quite effective for supporting luteal phase in the IVF cycle (15). On the other hand some researches have compared vaginal gel and intramuscular progesterone to support luteal phase in IVF cycles in which vaginal gel was introduced as an alternative to support luteal phase (16-17). Another research was done at Messina infertility research center in Italy, on 156 women who received 50 mg/day intramuscular progesterone or 90 mg/day vaginal progesterone gel. Still birth and pregnancy rate in intramuscular progesterone were reported to be more (18). In another comparison which was done with intramuscular and vaginal progesterone in IVF cycle, endometrial morphology and its vascularity have been investigated. Intramuscular progesterone (100mg /day) or vaginal progesterone (200 mg/twice a day) showed similar effects on the endometrium (19). In our study the rates of chemical and clinical pregnancy in intramuscular progesterone group were more but with regard to the number of cases there was no statistical difference between two groups.

Acknowledgement

The authors wish to express sincere gratitude and appreciation to the Sarem Hospital which provided the budget for performing this study.

There exists no conflict of interest to declare.

References

1. Speroff L, Fritz MA. Clinical Gynecologic Endocrinology and Infertility, 2005, 7th ed. Wilkins: Philadelphia: Lippincott and Williams.
2. Pritts EA, Atwood AK. Luteal phase support in infertility treatment: a meta-analysis of the randomized trials. Hum Reprod 2002; 17: 2287-99.
3. Beckers NG, Macklon NS, Eijkemans MJ, Ludwig M, Felberbaum RE, Diedrich K, et al. Nonsupplemented luteal phase characteristics after the administration of recombinant human chorionic gonadotropin, recombinant luteinizing hormone, or gonadotropin-releasing hormone (GnRH) agonist to induce final oocyte maturation in in vitro fertilization patients after ovarian stimulation with recombinant follicle-stimulating hormone and GnRH antagonist cotreatment. J Clin Endocrinol Metab 2003; 88: 4186-92.
4. Buvat J, Marcolin G, Guittard C, Herbaut JC, Louvet AL, Dehaene JL. Luteal support after luteinizing hormone-releasing hormone agonist for in vitro fertilization: superiority of human chorionic gonadotropin over oral progesterone. Fertil Steril 1990; 53: 490-4.
5. Mochtar MH, Hogerzeil HV, Mol BW. Progesterone alone versus progesterone combined with HCG as luteal support in GnRHa/HMG induced IVF cycles: a randomized clinical trial. Hum Reprod 1996; 11: 1602-5.
6. Tavaniotou A, Smitz J, Bourgain C, Devroey P. Comparison between different routes of progesterone administration as luteal phase support in infertility treatments. Hum Reprod Update 2000; 6: 139-48.
7. Bourgain C, Smitz J, Camus M, Erard P, Devroey P, Van Steirteghem AC, et al. Human endometrial maturation is markedly improved after luteal supplementation of gonadotrophin-releasing hormone analogue/human menopausal gonadotrophin stimulated cycles. Hum Reprod 1994; 9: 32-40.
8. Ludwig M, Diedrich K. Evaluation of an optimal luteal phase support protocol in IVF. Acta Obstet Gynecol Scand 2001; 80: 452-66.
9. Chantilis SJ, Zeitoun KM, Patel SI, Johns DA, Madziar VA, McIntire DD. Use of Crinone vaginal progesterone gel for luteal support in in vitro fertilization cycles. Fertil Steril 1999; 72: 823-9.
10. Artini PG, Volpe A, Angioni S, Galassi MC, Battaglia C, Genazzani AR. A comparative, randomized study of three different progesterone support of the luteal phase following IVF/ET program. J Endocrinol Invest 1995; 18: 51-6.
11. Propst AM, Hill JA, Ginsburg ES, Hurwitz S, Politch J, Yanushpolsky EH. A randomized study comparing Crinone 8% and intramuscular progesterone supplementation in in vitro fertilization-embryo transfer cycles. Fertil Steril 2001; 76: 1144-9.
12. Ng EH, Chan CC, Tang OS, Ho PC. A randomized comparison of side effects and patient convenience between Cyclogest suppositories and Endometrin tablets used for luteal phase support in IVF treatment. Eur J Obstet Gynecol Reprod Biol 2007;131:182-8.
13. Tay PY, Lenton EA. The impact of luteal supplement on pregnancy outcome following stimulated IVF

cycles. Med J Malaysia 2005; 60: 151-7.
14. Ng EH, Miao B, Cheung W, Ho PC. A randomised comparison of side effects and patient inconvenience of two vaginal progesterone formulations used for luteal support in in vitro fertilisation cycles. Eur J Obstet Gynecol Reprod Biol 2003; 111: 50-4.
15. Kresanov I, Nikkanen V, Klemi P. Disturbances of the endometrium in the luteal phase of cycles stimulated for in vitro fertilization and of normal cycles treated with vaginal progesterone. Ann Chir Gynaecol Suppl 1994; 208: 33-9.
16. Anserini P, Costa M, Remorgida V, Sarli R, Guglielminetti E, Ragni N. Luteal phase support in assisted reproductive cycles using either vaginal (Crinone 8) or intramuscular (Prontogest) progesterone: results of a prospective randomized study. Minerva Ginecol 2001; 53: 297-301.
17. Marianowski P, Radwanska E. [Intramuscular vs vaginal progesterone for luteal support in cycles of in vitro fertilization]. Ginekol Pol 2000; 71: 1064-70.
18. Abate A, Perino M, Abate FG, Brigandi A, Costabile L, Manti F. Intramuscular versus vaginal administration of progesterone for luteal phase support after in vitro fertilization and embryo transfer. A comparative randomized study. Clin Exp Obstet Gynecol 1999; 26: 203-6.
19. Ragni G, Piloni S, Rossi P, Carinelli S, De Lauretis L, Vegetti W, et al. Endometrial morphology and ultrasound vascular findings. A randomized trial after intramuscular and vaginal progesterone supplementation in IVF. Gynecol Obstet Invest 1999; 47: 151-6.