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A Prospective Randomized Trial Comparing the Use of Vaginal Utrogestan and Intramuscular Progesterone for Luteal Phase Support following Intracytoplasmic Sperm Injection

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ABSTRACT

Introduction: Progesterone for luteal phase support in in-vitro fertilization cycles has traditionally been given as daily intramuscular (IM) injections. Vaginal suppositories have been proposed as a more convenient alternative. It is also possible that with intracytoplasmic sperm injection (ICSI), where the oocyte is denuded deprived of paracrine P activity at an early stage, the vaginal route may be even more efficacious.

Materials and Methods: A prospective single-centre randomized trial was conducted to compare the efficacy and tolerability of vaginal Utrogestan with intramuscular progesterone (IM P) specifically in ICSI cycles. Primary endpoints were serum progesterone levels on Day 8 following embryo transfer and clinical pregnancy. Secondary endpoints included drug side effects.

Results: A total of 27 patients were recruited in the Utrogestan arm and compared to 26 patients in the IM P arm. There were no significant differences in demographics and other characteristics between the two groups. Post embryo transfer serum progesterone levels in Utrogestan and IM P group were 218 nmol/L and 158 nmol/L respectively. Clinical pregnancy rates were 11 (40.7%) and 11 (42.3%) respectively. Most patients also tolerated vaginal Utrogestan well.

Conclusion: The results of this small prospective randomized study suggest that vaginal progesterone may be equally as effective for luteal support compared to IM P. It is also well tolerated and beneficial not only for patients but also medical and nursing staff in terms of cost and convenience.

Keywords : Luteal phase support, Utrogestan, intramuscular progesterone

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INTRODUCTION

Following ovulation, the luteal phase of a natural cycle is characterized by the formation of a corpus luteum, which secretes steroid hormones including progesterone. Normal luteal function is essential for maintaining pregnancy as evidenced by studies, which have shown that removal of the corpus luteum during early pregnancy results in complete abortion [1].

A luteal phase deficiency in IVF cycles may result from the use of GnRH agonists for pituitary down-regulation, leading to prolonged LH suppression. It may also result from poor progesterone production after granulose cell removal during follicular aspiration. Luteal phase support has been shown to have a positive effect on outcome [2,3]. Progesterone has become the agent of choice for luteal supplementation, because hCG is associated with a higher risk of ovarian hyperstimulation syndrome (OHSS) [4,5]. However, the ideal route of progesterone administration remains controversial.

Progesterone supplementation can be given intramuscularly (IM P), orally or intravaginally. IM P supplementation requires daily prolonged injections of progesterone in oil which can result in inflammatory reactions, sterile abscesses and patient discomfort. An effective alternative to IM P is clearly desirable. Oral micronized progesterone is easy to administer but is subject to the first-pass liver effect, resulting in rapid metabolization by the liver and significant side effects [6,7]. Vaginal suppositories containing micronized progesterone have instead been recommended as an alternative to IM P. Cicinelli et al. [8] found that serum progesterone levels were higher after IM administration than after vaginal gel administration but endometrial levels were significantly higher after vaginal gel possibly as a result of a uterine first-pass effect. Interestingly, a retrospective study [9] comparing the effectiveness of vaginal progesterone with IM P found that the two routes of luteal supplementation might result in different outcomes depending on whether ICSI was involved or not. Manno et al. postulate that the effect of progesterone on the oocyte, zygote and embryo might be different in ICSI and classic IVF cycles. In ICSI, before microinjection, the oocyte is completely denuded or separated by a mechanical-enzymatic treatment (hyaluronidase) from the cumulus-corona cells that actively produce progesterone. Therefore in ICSI, the oocyte/zygote is deprived of any paracrine action of progesterone from a very early stage. This may have detrimental effects its early developmental competence.

We conducted a prospective randomized study to compare the efficacy and tolerability of vaginal Utrogestan with IM P specifically in ICSI cycles. Vaginal Utrogestan is affordable and easy to administer. If shown to be more effective than IM P in providing better pregnancy outcome, it would not only be advantageous in terms of improving fertility, it would also help avoid the side effects of IM P, and would also benefit the patient and medical/ nursing staff in terms of cost and convenience. This study would therefore, help to clarify the efficacy and tolerability of vaginal Utrogestan in comparison with IM P specifically in ICSI cycles. To our knowledge, this is the first randomized prospective study on luteal phase support which specifically assesses the outcome of ICSI cycles.

MATERIALS & METHODS

A prospective randomized trial involving patients undergoing IVF/ICSI was performed. Patients who fulfilled the inclusion criteria and consented to participation were randomized to either receiving vaginal Utrogestan or IM P for luteal phase support.

Inclusion criteria included patients under 40 years, undergoing fresh ICSI cycles as well as undergoing their first three ICSI cycles. Exclusion criteria included blastocyst transfers, donor sperm, thaw cycles, peanut allergy as well as contra-indications to the study drug. Contra-indications included severe disturbances of liver function (including porphyria), undiagnosed vaginal bleeding, mammary or genital tract carcinoma, thrombophlebitis, thromboembolic disorders and cerebral haemorrhage. Consent was obtained by doctor when obtaining consent for IVF/ICSI. Randomization was then performed when patients were ready to undergo oocyte pick-up and embryo transfer.

All patients received the long protocol for down regulation with leuprolide acetate (Lupron: TPA Pharmaceuticals, USA) beginning on Day 21 of the previous cycle for 10 to 14 days. Once pituitary suppression was achieved as evidenced by ultrasound showing all follicles <10 mm, endometrial thickness <8 mm and estradiol levels <183 pmol/ml, ovarian stimulation with recombinant follicle stimulating hormone (rFSH, Puregon: Organon, France) was initiated. A standard ovulating dose of human chorionic gonadotrophin (hCG, Profasi: Italy) was given when ultrasound showed three follicles of 17-18 mm in diameter. Oocytes were retrieved 36-38 hours after hCG administration and fertilized via ICSI with sperm collected from fresh semen samples obtained on the day of oocyte retrieval. ICSI is performed for all cases of male factor infertility. ICSI is also performed in around 2/3rds of the recovered oocytes in our centre in cases of non-male factor infertility. Oocytes were assessed for fertilization at 18-24 hours post ICSI. Embryo quality was assessed at 44 hours post ICSI for day two, or 68 hours post ICSI for day three transfers. Embryos were transferred on day two or three (if day two fell on a Sunday) after oocyte retrieval, using Wallace 1816N soft catheter (SIMS, U.K.).

Luteal support in our centre is usually provided with either hCG or IM P depending on the estimated risk of ovarian hyperstimulation syndrome. When < or = 15 eggs or embryos were obtained or if the patient was > 40 years old, hCG is given. However, if patients are at risk of ovarian hyperstimulation with > 15 eggs or embryos obtained, or if the patient had ovarian hyperstimulation syndrome previously, IM P is given up till Day 17. In this study, patients eligible for IM P were randomized to either IM P or vaginal Utrogestan. Progesterone in oil is given traditionally at a dose of 50 mg a day intramuscularly initiated on the day of embryo transfer for 17 days. Utrogestan is a natural micronized progesterone given at a dose of 200 mg intravaginally three times a day under the same conditions. Therefore, 2 capsules of Utrogestan (amounting to 200 mg) were administered intravaginally three times a day.

Patients were asked to return on Day 8 post embryo transfer for measurement of luteal phase serum progesterone level and trans-abdominal ultrasound of endometrial thickness. Biochemical pregnancy was established on Day 17 with serum level of βhCG. Clinical pregnancy was determined by identifying the presence of a gestational sac at 6 weeks gestation on trans-vaginal ultrasound evaluation. Both intra- and extra-uterine pregnancies were included in the analysis. Biochemical pregnancies were excluded from the analysis. Clinical pregnancy rate was defined as the fraction of embryo-transfers resulting in a gestational sac. Implantation rate was defined as the fraction of transferred embryos resulting in a gestational sac. When a positive titre of serum βhCG is measured, all women are to continue with oral progesterone supplementation until week 12 of pregnancy.

A questionnaire was also given at the end of the luteal phase support to assess the use of the method assigned. For data safety monitoring, patients were given the IVF centre telephone number to call if there were any queries regarding drug application and side effects. Patients were then given a 'data collection' form at the end of the luteal phase progesterone support to provide detailed information regarding any side effects experienced. All serious adverse events that were unexpected and related to the study drug would have been reported to the Health Sciences Authority, Singapore (HSA).

Subjects could withdraw voluntarily from participation in the study at any time. Subjects could also withdraw voluntarily from receiving the study intervention for any reason. If voluntary withdrawal occurred, the subject would be asked to complete the questionnaire regarding the use of the medication and would be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the subject's condition becomes stable. The trial protocol was approved by the ethics committee of the hospital's Institution Review Board.

Statistical analysis was performed using SPSS version 11.0 (SPSS Inc, Chicago, Illinois). Student's T test and Independent Sample T test were used to investigate correlation between variables, with $p<0.05$ considered as significant. Primary endpoints were efficacy of luteal phase support in terms of serum progesterone level, ultrasound characteristics e.g endometrial thickness, and pregnancy rates. Secondary endpoints were drug side effects, admission for severe ovarian hyperstimulation syndrome and drug satisfaction.

RESULTS

Over a nine month period between April 2009 to January 2010, 52 patients who fulfilled the inclusion criteria and had embryo transfers following ICSI were recruited into the trial. A total of 27 patients were randomized to the Utrogestan arm and compared to 26 patients randomized to the IM P arm.

The demographic data for the women are shown in Table 1. As can be seen from the table, there were no significant differences in the patient characteristics between the two arms. Interestingly, the serum progesterone on Day 8 post embryo transfer tended to be higher following vaginal Utrogestan compared with IM P. However, this did not reach statistical significance. There was also no correlation between higher serum progesterone levels and endometrial thickness on ultrasound scan.

In terms of outcome, there were also no significant differences in ongoing pregnancy rate, miscarriage and ectopic pregnancy rates as shown in Table 2. The implantation rate calculated was 29.09% for the Utrogestan arm and 28.84% for the IM P arm.

Compliance was good with most patients tolerating Utrogestan well and none withdrawing from the study because of adverse events or intolerant side effects as seen in Table 3 and Figure 1.

DISCUSSION

Progesterone has become the agent of choice for luteal supplementation, because hCG is associated with a higher risk of OHSS [10]. However, questions remain regarding the optimal route of administration. A consensus meeting in 2001 [11] concluded that the pregnancy rates with both IM and vaginal preparations were comparable. However, it has been criticized that this conclusion was based on results of non-randomized trials. A meta-analysis of randomized trials including 5 comparing IM P with vaginal progesterone carried out between 1995-2001 [12] concluded that

the IM route conferred higher clinical pregnancy and delivery rates than the vaginal route. However, a more recent meta-analysis of randomized trials including 10 comparing IM P with vaginal progesterone, performed between 1984-2003 [13] concluded that the optimal route of progesterone administration remains to be established.

Interestingly, a retrospective study comparing the effectiveness of vaginal with IM P found that the two routes of luteal supplementation might result in different outcomes depending on whether ICSI was involved or not [9]. It was found that significantly higher rates of implantation and clinical pregnancies were observed in the vaginal supplemented ICSI subgroup than in the IM one (13.3 vs. 8.8% and 28.7 vs. 18.6% respectively). In contrast, the rates in the classic IVF cycles were not statistically different. The authors postulate that the effect of progesterone on the oocyte, zygote and embryo might be different in ICSI and classic IVF cycles. In ICSI, before microinjection, the oocyte is completely denuded or separated by a mechanical-enzymatic treatment (hyaluronidase) from the cumulus-corona cells that actively produce progesterone. Therefore in ICSI, the oocyte/zygote is deprived of any paracrine action of progesterone from a very early stage. This may have detrimental effects on its early developmental competence. In contrast, in classic IVF, the oocytes are surrounded by cumulus corona cells until the fertilization check 18 hours after insemination. Studies on the oocyte culture medium have shown progesterone levels of about 50 ng/ml in classic IVF but undetectable levels in ICSI. The authors suggest that the best route of progesterone administration might differ according to the type of treatment performed. They point out that in the meta-analysis by Pritts et al. [11], the conclusion that IM P conferred the most benefit was drawn from 5 studies of which all but one examined classic IVF cycles. Only the study by Anserini et al. [14] examined a mixed series of classic and ICSI treatments and they were analysed together. Indeed, most previous studies did not differentiate the type of treatment, and where ICSI was performed for 'severe male factor', the cycles were usually included in the overall analysis.We therefore conducted a prospective randomized study to compare the efficacy and tolerability of vaginal Utrogestan with IM P specifically in ICSI cycles. To our knowledge, this is the first randomized prospective study on luteal phase support which specifically assesses the outcome of ICSI cycles.

In terms of efficacy, we were unable to show an increased efficacy with the vaginal route. Both routes were found to have comparable pregnancy rates. Interestingly, the serum progesterone levels were found to be higher following vaginal Utrogestan but this did not reach statistical significance. This result is unexpected but may be explained by the small numbers in the study. Further statistical analysis found no correlation between serum progesterone levels and endometrial thickness with pregnancy rates.

The major limitation of this study is of course the small sample size. A pre-study power analysis found that assuming a 35% clinical pregnancy rate based on our own center's current statistics with use of IM P, 328 subjects would be required in each arm to detect a difference of 10% between the two groups (with a power of 80%). However, due to strong staff preference as well as patient demand for the vaginal route, the trial was stopped early. The vaginal route clearly affords greater convenience for the staff and less cost for the patients. In terms of tolerability, most patients found the vaginal route acceptable. There were no withdrawals due to adverse side effects in the vaginal arm.

In conclusion, the results of this small prospective randomized study suggest that vaginal progesterone may be equally effective for luteal support compared to IM P. It is also well tolerated and beneficial not only for patients but also medical and nursing staff in terms of cost and convenience.

Acknowledgement

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Table 1. Demographic data, infertility and ART- specific characteristics of patients

	Utrogestan	IM Progesterone
No. of Patients	27	26
Mean Age ± SD	32.67 ± 3.8	31.96 ± 4.03
Diagnosis (n,%)	n=27	n=26
Male Factor	18(66.67%)	16(61.54%)
Tubal Factor	4(14.81%)	1(3.85%)
Ovulatory Disorder/PCOS	2(7.41%)	7(26.92%)
Idiopathic Infertility	3(11.11%)	2(7.69%)
Mean No. of Oocyte Retrieved ± SD	22.07 ± 7.29	20.8 ± 6.2
Mean No. of Embryo Transfer ± SD	2.03 ± 0.19	2 ± 0
Mean Embryo Score ± SD	4 ± 0.31	4.07 ± 0.4

Table 2. Summary of outcome

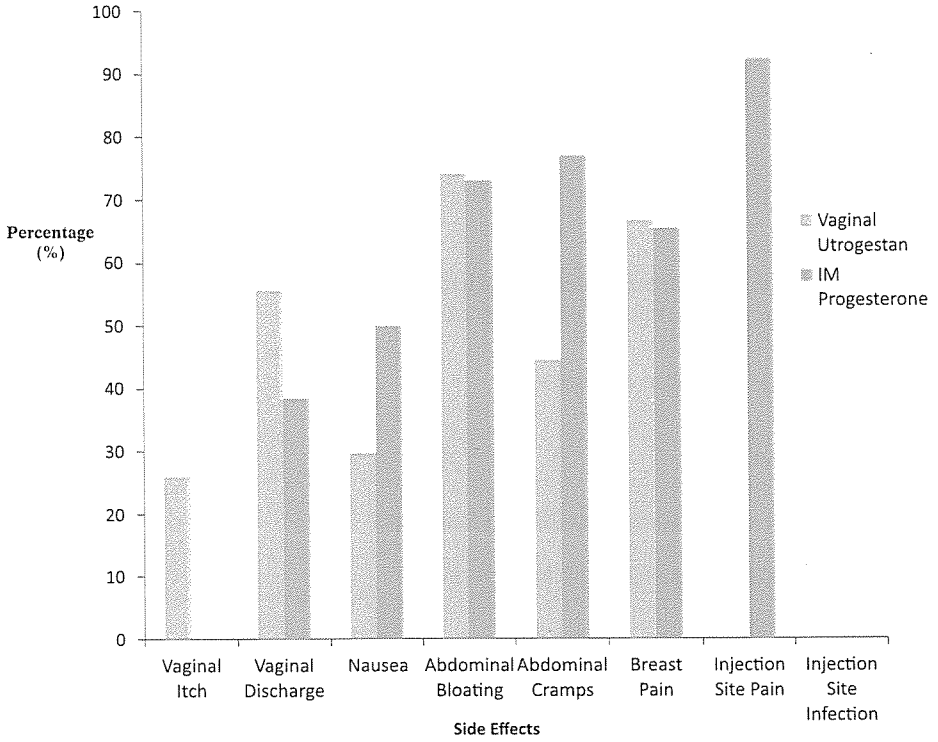
	Utrogestan	IM Progesterone
Mean Endometrial Thickness ± SD	10 ± 1.44	11.38 ± 2.15
Mean Post ET P4 level	217.97	158.01
Pregnancy (n,%)	12(44.44%)	13(50.00%)
Ongoing Pregnancy (n,%)	11(40.74%)	11(42.31%)
OHSS (n,%)	0(0.00%)	1(3.85%)
Miscarriage (n,%)	1(3.70%)	1(3.85%)
Ectopic Pregnancy (n,%)	0(0.00%)	1(3.85%)

Table 3. Adverse side effects from questionnaire

	Utrogestan (n=27)					
Event	Not affected	Minimal	Mild	Moderate	Severe	Intolerable
Vaginal Itch	20	4	2	1	0	0
Vaginal Discharge	12	7	4	3	1	0
Nausea	19	4	4	0	0	0
Abdominal Bloating	7	3	6	5	6	0
Abdominal Cramps	15	4	4	4	0	0
Breast Pain	9	6	3	6	3	0

	IM Progesterone (n=26)					
Event	Not affected	Minimal	Mild	Moderate	Severe	Intolerable
Vaginal Itch	26	0	0	0	0	0
Vaginal Discharge	16	9	1	0	0	0
Nausea	13	11	2	0	0	0
Abdominal Bloating	7	6	3	9	0	1
Abdominal Cramps	6	9	6	3	2	0
Breast Pain	7	5	7	3	2	0
Injection Site Pain	2	5	5	8	6	0
Injection Site Infection	0	0	0	0	0	0

Fig 1. Percentage of patients experiencing side-effects



REFERENCES

1. *Csapo AI, Pulkkinen MO, Kaihola HL. The relationship between the timing of luteectomy and the incidence of complete abortions. Am J Obstet Gynecol. 1974 Apr 1;118(7):985-9.*

2. *Soliman S, Daya S, Collins J, Hughes EG. The role of luteal phase support in infertility treatment: a meta-analysis of randomized trials. Fertil Steril. 1994 Jun;61(6):1068-76.*

3. *Shamma FN, Penzias AS, Thatcher S, DeCherney AH, Lavy G. Corpus luteum function in successful in vitro fertilization cycles. Fertil Steril. 1992 May;57(5):1107-9.*

4. *McClure N, Leya J, Radwanska E, Rawlins R, Haning RV Jr. Luteal phase support and severe ovarian hyperstimulation syndrome. Hum Reprod. 1992 Jul;7(6):758-64.*

5. *MacDougall MJ, Tan SL, Jacobs HS. In-vitro fertilization and the ovarian hyperstimulation syndrome. Hum Reprod. 1992 May;7(5):597-600.*

6. *Licciardi FL, Kwiatkowski A, Noyes NL, Berkeley AS, Krey LL, Grifo JA. Oral versus intramuscular progesterone for in vitro fertilization: a prospective randomized study. Fertil Steril. 1999 Apr;71(4):614-8.*

7. *Arafat ES, Hargrove JT, Maxson WS, Desiderio DM, Wentz AC, Andersen RN. Sedative and hypnotic effects of oral administration of micronized progesterone may be mediated through its metabolites. Am J Obstet Gynecol. 1988 Nov;159(5):1203-9.*

8. *Cicinelli E, de Ziegler D, Bulletti C, Matteo MG, Schonauer LM, Galantino P. Direct transport of progesterone from vagina to uterus. Obstet Gynecol. 2000 Mar;95(3):403-6.*

9. *Manno M, Marchesan E, Cicutto D, Zadro D, Favretti C, Tomei F. Greater implantation and pregnancy rates with vaginal progesterone in intracytoplasmic sperm injection but not in in-vitro fertilization cycles: a retrospective study. Fertil Steril. 2005 May;83(5):1391-6.*

10. *Daya S, Gunby JL. Luteal phase support in assisted reproduction cycles. Cochrane Database Syst Rev. 2008 Jul 16;(3):CD004830.*

11. *Penzias AS. Luteal phase support. Fertil Steril. 2002 Feb;77(2):318-23.*

12. *Pritts EA, Atwood AK. Luteal phase support in infertility treatment: a meta-analysis of the randomized trials. Hum Reprod. 2002 Sep;17(9):2287-99.*

13. *Daya S, Gunby J. Luteal phase support in assisted reproduction cycles. Cochrane Database Syst Rev. 2004(3):CD004830.*

14. *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 Aug;53(4): 297-301.*