Original Article

The Effect of Luteal Phase Support on Pregnancy Rates of the Stimulated Intrauterine Insemination Cycles in Couples with Unexplained Infertility

Mahbod Ebrahimi, M.D.*, Firoozeh Akbari Asbagh, M.D., Soodabeh Darvish, M.D.

Obstetrics and Gynecology Department, Mirza Koochak Khan Hospital, Faculty of Medicine, Tehran University, Tehran, , Iran

Abstract

Background: To assess the efficacy of luteal phase support (LPS) with vaginal progesterone (P) on pregnancy rates of the stimulated intrauterine insemination (IUI) cycles in couples with unexplained infertility (UEI).

Materials and Methods: This was a single-center, prospective, randomized, blinded control trial undertaken at a tertiary care university fertility center between October 2007 and December 2008. A total of 200 couples with UEI underwent 511 consecutive stimulated IUI cycles.

Clomiphene citrate (Cc) and human menopausal gonadotropin (hMG) were used for ovulation induction. After IUI, patients were randomized into two groups. The study group (n=98) received intra-vaginal P (Cyclogest) for LPS. The patients randomized into the control group (n=102) received no drug for LPS. The main outcome was the comparison of clinical pregnancy rate (PR) and live birth rate (BR) per cycle and patient between the control and study groups.

Results: There were no differences in demographic characteristics between the groups. PR per patient and cycle were similar in the study group (30.6% and 11.5%, respectively) and in the control group [25.5% and 10.03%, respectively] ($p>0.05$). There were no statistically significant increases in BR per patient and cycle between the study group (19.4% and 7.5%, respectively) and the control group [14.7% and 5.7%, respectively] ($p> 0.05$).

Conclusion: Administration of vaginal P (Cyclogest) for LPS does not improve the reproductive outcome of stimulated IUI cycles (Registeration Number: IRCT1389 01283737N1).

Keywords: Clomiphene Citrate, Human Menopausal Gonadotropin, Progesterone, Infertility

Introduction

Infertility in 15% of couples is due to unexplained causes (1-3). Impairment of endometrial receptivity for embryonic implantation has often been seen in women with unexplained infertility (UEI) (4). Progesterone (P) produced by the corpus luteum in response to stimulation by luteinizing hormone (LH) and human chorionic gonadotropin (hCG) during the luteal phase is essential for secretory transformation of the endometrium that permits implantation (5). P not only supports endometrial development but also potentially sustains the survival of the embryo by shifting the immune system toward production of non-inflammatory T-helper (Th) 2 cytokines (6).

Luteal phase dysfunction (LPD) is associated with inadequate P production and consequent implantation failure. P supplementation is the most commonly used treatment when LPD can reasonably be assumed (7). Controlled ovarian hyper-stimulation (COH) combined with intrauterine insemination (IUI) or *in vitro* fertilization (IVF) are commonly used treatment protocols for couples with UEI (8, 9). LPD and lack of P may also occur as part of assisted reproductive techniques, including aspiration of granulosa cells (10) or the use of gonadotropin releasing hormone (GnRh) agonist or antagonist (11, 12); therefore LPS with P is a common practice in IVF cycles (13). The existence of LPD in stimulated IUI cycles is controversial (14-16). In COH cycles, multifollicular development and supraphysiologic steroid serum concentration may adversely affect LH secretion via a long-loop mechanism. Disturbed LH secretion may induce LPD with premature luteolysis, reduced luteal phase LH concentration, low P level and a shortened luteal phase (17, 18).

Some recent studies have shown that LPS with P

Received: 15 Dec 2009, Accepted: 25 Apr 2010
*** Corresponding Address: P.O.Box: 1597586511, Obstetrics and Gynecology Department, Mirza Koochak Khan Hospital, Faculty of Medicine, Tehran University, Tehran, Iran**
Email: maeb214@yahoo.com

Royan Institute
International Journal of Fertility and Sterility
Vol 4, No 2, Jul-Sep 2010, Pages: 51-56

significantly affects the success of ovarian stimulation and IUI cycles in patients with UEI (14, 15). Ozornek et al. reported no benefit of luteal support in patients who underwent stimulated IUI cycles (16). Therefore the previous studies have produced conflicting results and the amount of data from well-controlled clinical trials is limited. Thus further studies are required to characterize the impact of treatment with P for LPS in stimulated IUI cycles.
The main aim of this study was to evaluate the effect of vaginal P (Cyclogest, 400 mg progesterone, vaginal pessaries, Cox Pharmaceuticals, Barn Staple, UK) on pregnancy and live birth rates of stimulated IUI cycles in couples with UEI.

Materials and Methods

Study design

This was a single-center, prospective, randomized, linded control trial designed to determine the impact of luteal support with a vaginal administered P (Cyclogest) in improving reproductive outcome in women undergoing ovarian stimulation and IUI. The local Institutional Ethics Committee approval was obtained. Patients were counseled individually about the study and protocols by a nurse coordinator. Patients who elected to participate gave their written informed consent before participation.

Subjects

Women diagnosed with UEI who underwent IUI treatments at Mirza Koochak Khan Hospital (Tehran, Iran) between October 2007 and December 2008 were included in this study. The diagnosis of UEI was made by normal semen analysis based on World Health Organization criteria (19), normal early follicular phase ultrasound (no cyst, no endometrioma, and no fibroma), normal FSH (follicular stimulating hormone) and LH (luteinizing hormone) (<10 IU/L), midluteal phase serum P levels >20 nmol/L, patent tubes and normal uterine cavity as confirmed by hysterosalpingography. Patients were excluded from the study if female partners were over the age of 36, had a diminished ovarian reserve (basal FSH level >10 IU/ L), one ovary, polycystic ovaries on ultrasound examination, previous ovarian surgery, endometriosis or any type of endocrine diseases.
Patients who fulfilled the inclusion criteria (200 cases) were randomized by systemic randomization in which cases were sequentially allocated to two treatment groups. This systemic randomization was done by the nurse coordinator on the IUI day in the absence of the clinicians.

Ovarian stimulation protocol

All cycles were gently stimulated after baseline transvaginal ultrasonography (FUKUDA ESAOTE-AU 350, MHZ transducer) with 50 mg oral tablets of clomiphen citrate (Cc, Iran Hormone, Tehran, Iran) twice daily for 5 days starting on day 3 of the menstrual cycles and a starting dose of 75 IU human menopausal gonadotropin (hMG, Menogan, Ferring, Germany) on days 7-9 of the cycles. All patients were re-evaluated by ultrasound on day 10 for quality of the ovarian response, which was repeated every 2-3 days. The dosage of hMG was adjusted according to the ovarian response. Stimulation continued until one to three follicles reached a mean diameter of 18 mm, then 5000 IU hCG (Profasi, Serono, Geneva, Switzerland) was administered and the single IUI was performed 36 hours later. The experimental group received Cyclogest vaginal pessaries (Cox Pharmaceutical, Barnstaple, UK) 400 mg daily for luteal support beginning 2 days after IUI. If the patient conceived, luteal support was continued through the tenth week of pregnancy. In the control group, no drug for LPS was used. Serum hCG was obtained 2 weeks after hCG administration and intrauterine pregnancy was confirmed by detection of a gestational sac using transvaginal ultrasound 4 weeks after insemination. A clinical pregnancy was defined as the presence of a gestational sac on ultrasound or by histological examination of products of conception in patients who aborted. Live birth was defined as having a baby who was living at one week after birth. In the absence of pregnancy, this protocol was consecutively repeated.

Statistical analysis

Data were statistically analyzed using the SPSS computer package (SPSS version 16, SPSS Inc., Chicago, IL) with the student's t-test and Chi-square test. Results were expressed as mean and standard error of mean. $p<0.05$ was considered statistically significant. Sample size calculation, before the study, showed that each arm should contain at least 52 patients to have a 90% power at 95% confidence interval (CI) when a 20% difference in pregnancy rate was expected between the groups.

Results

The study was comprised of a total of 200 women (511 cycles). The mean number of cycles per woman was 2.5 in both groups. There was no statistically significant difference between the two groups with regards to age, duration of infertility, basal day 3 FSH, Esradiol (E_2) levels and basal sperm parameters (Table 1).

Table 1: Demographic data of patients undergoing treatment with (study group) or without (control group) luteal phase progesterone support

Variable	Study group	Control group	P-value
No. of couples	98	102	NS
No. of cycles	252	259	NS
Age	27.9 ± 3.3	28.4 ± 4.1	NS
Duration of infertility	4.82 ± 2.6	4.84 ± 2.6	NS
Primary infertility (%)	71.4	69.6	NS
Basal FSH level	6.1 ± 2.7	6.7 ± 2	NS
Basal E_2 level	33.3 ± 14.9	37.4 ± 12.9	NS
Basal sperm count ($\times 10^6$/mL)	55.3 ± 22.6	66.5 ± 23.5	NS
Basal sperm motility (%)	64.9 ± 12.3	66.4 ± 10.6	NS

Towenty-six patients had only one cycle; 42 patients had two cycles, and 132 patients had 3 cycles. During the study period 21 patients (10.5%) dropped out during the second cycle for various reasons. Of these 21 patients, 11 were in the study group and 10 were in the control group, thus the difference was not significant. Cycle characteristics of the two groups are shown in (Table 2).

There were no differences noted between the two groups with regard to cycle characteristics.

Of 511 cycles, a total of 64 pregnancies occurred; 34 pregnancies ended with delivery, one patient in the study group and two patients in the control group continue pregnancy in 2nd or 3rd trimesters. The other pregnancies ended with biochemical pregnancy (8 patients) abortion (16 patients), and Ectopic pregnancy (3 patients).

There was no significant difference in clinical abortion rates per cycle between both groups (3.5% in the study group and 2.7% in the control group).

There were 7 twin pregnancies (3 sets in the study group and 4 sets in the control group) which was not significant. No higher order pregnancy or ovarian hyperstimulation syndrome occurred in either group. Thirty clinical pregnancies were observed in the study group and 26 in the control group. The PR per patient and per cycle in the study group were 30.6% and 11.5%, respectively and the control group rates were 25.5% and 10.03 %, respectively. BR per patient and per cycle in the study group were 19.4% and 7.5%, respectively and in the control group rates were 14.7% and 5.7%, respectively. There were no statistically significant differences in clinical PR and BR per patient or per cycle between both groups ($p>0.05$).

Table 2: Clinical characteristics of patients undergoing treatment with (study group) or without (control group) luteal phase progesterone support

Variable	Study group	Control group	P-value
Total hMG dose (IU)	285 ± 103.4	292.6 ± 98	NS
No. of follicles 9-16 mm	1.5 ± 0.7	1.5 ± 0.6	NS
No. of dominant follicles (>16 mm)	2.02 ± 0.75	2.2 ± 0.8	NS
Endometrial thickness on the day of hMG	10.5 ± 1.8	10.6 ± 2.3	NS
Total progressive motile sperm number after sperm preparation($\times 10^6$/mL)	28.67 ± 9.71	32.95 ± 4.63	NS
Total pregnancy rate per cycle (%)	35/252 (13.5)	29/259 (11.2)	NS
Clinical pregnancy rate per cycle (%)	30/252 (11.5)	26/259 (10.03)	NS
Live birth rate per cycle (%)	19/252 (7.5)	15/259 (5.7)	NS
Clinical pregnancy rate per patient (%)	30/98 (30.6)	26/102 (25.5)	NS
Live birth rate per patient (%)	19/98 (19.4)	15/102 (14.7)	NS
Multiple pregnancy rate (%)	3/35 (8.5)	4/29 (10.3)	NS

Discussion

The results of the present study suggest that supplementation of the luteal phase with P does not improve clinical pregnancy and live birth rates of the stimulated IUI cycles in couples with UEI.

Normal corpus luteum function requires optimal follicular development in the follicular phase, FSH stimulation and adequate LH surge during ovulation, and luteinization of granulosal cells and continuous tonic LH pulses during the luteal phase. Corpus luteum secretes P that causes secretory transformation of the endometrium so that implantation can occur (18). In assisted reproduction, both the use of GnRH analogues to prevent the premature LH surge and aspiration of granulosal cells during the oocyte retrieval may impair the ability of the corpus luteum to produce sufficient P (13, 20), and create iatrogenic LPD, impairment of endometrial receptivity, decreased implantation and pregnancy rates (21).

In an attempt to compensate for this abnormality, practitioners have employed luteal supplementation (13, 20). Although P supplementation during the luteal phase in IVF cycles is a logical step to help improve the chance of success (20, 22), there is little consensus among practitioners regarding the use of luteal phase P supplementation in stimulated IUI cycles, especially in patients with UEI (14-16).

If the objective of the ovarian stimulation in IUI cycles is to stimulate the development of multiple follicles, the treatment overrides the physiological feedback mechanisms which normally ensure that only one or two large follicles reach ovulation. As a result, multiples follicles and corpora lutea secrete large amounts of E_2 and P. The luteal phase of these cycles is characterized by a temporary high level of one or both hormones which, together with inhibin A, suppress the levels of LH and FSH to very low levels (12). It has suggested that the low level of LH may result in a lack of luteotrophic support manifested by low P levels and/or a short luteal phase (23). This is in agreement with previous work by Erdem et al. who found LPS with vaginal P positively affects the success of stimulated IUI cycles in patients with UEI (15), but other studies reported no benefit of LPS with either P, GnRH agonist or hCG in patients who underwent ovulation induction (16, 24, 25).

To the best of our knowledge, this study is the first prospective and randomized clinical trial study showing the use of luteal phase P (Cyclogest) supplementation in patients with UEI that underwent ovarian stimulation and IUI with Cc and hMG. Various hormonal treatment protocols have been used for ovarian stimulation. Cc and low dose hMG alone or in combination are one of the best protocols during IUI cycles (26, 27). It has been our observation that patients much prefer Cc and/or hMG because of lower treatment cost and less complications. Therefore, patients in both groups received Cc and hMG for ovulation induction. The PR and BR were not statistically higher in patients with LPS (Table 2). The results observed in this study differ from other reports (14, 15) because the data extrapolated from stimulated cycles with FSH may not be applicable to stimulated cycles with Cc and hMG. Tavaniotou has suggested that defective LH secretion in the luteal phase is one of the mechanisms of LPD in gonadotropin stimulated cycles (28). Tavanitou discovered that luteal LH serum concentrations were significantly higher in patients administered Cc (29). In a preliminary study, other investigators have shown that controlled ovarian stimulation with hMG in the follicular phase was an effective treatment for luteal phase defects associated with recurrent pregnancy loss (30). These observations would help to explain the benefits of Cc and hMG on the luteal phase and the similar PR in the study group and control group (30.6%, and 25.5%, respectively).

In IVF cycles, the use of GnRH analogs and gonadotropins cause multifollicular development, alteration of the hormonal environment higher steroid serum concentration and LPD (9). In our study, the mean numbers of follicles of diameters 9-16 mm and dominant follicles were 1.5 and 2, respectively. Some studies have noted that in IUI cycles with mildly stimulated ovaries and less pronounced follicular development (such as our study), and lower levels of E 2, there is no biological evidence that treatment with P in the luteal phase is necessary or improves pregnancy rates (31).

Experience from induction ovulation with gonadotropins in hypophysectomized women had demonstrated that it was necessary to provide continued support in the form of hCG at least until the mid-late luteal phase (32). But women undergoing ovarian stimulation during IUI cycles are not totally hypogonadotrophic, so they need no support in luteal phase. Moreover the half life of hCG is relatively long if at least 5000 IU (dosage of hCG in our study) are used for ovulation induction, a biologically significant amount persists for at least 10 days by which time the embryo is secreting hCG (27).

Aspiration of follicles in IVF removes a significant mass of granulosal cells. This mechanical injury to the follicles may contribute to corpus luteum insufficiency (33). There is no mechanical

follicular damage in IUI cycles. Although it has been suggested that in stimulated IVF cycles with multifollicular growth, the advanced endometrium in the early luteal phase interferes with endometrial receptivity (34). Until now, no data has been available in the literature regarding endometrial receptivity and the effect of exogenous P administration on endometrial development in stimulated IUI cycles.

We evaluated the role of luteal phase vaginal P in the stimulated IUI model and failed to find any benefit regarding outcome. Whether this result is due to lack of LPD in mildly stimulated cycles (such as the present study, Table 2) or due to the direct positive effect of Cc and/or hMG or hCG on luteal phase or endometrial receptivity is not clear.

However, with ovulation induction followed by IUI, the incidence of multiple pregnancies increases, ranging from 7.5%-29% per couple (35, 36). In the present study, we had acceptable multiple pregnancy rates (8.5% in the study group and 10.3% in the control group). All were twin pregnancies. None of the patients developed ovarian hyperstimulation syndrome. Thus we offered our stimulation regiment (Cc and low dose hMG; Table 2).

In the present study, clinical abortion rates were similar between the two groups, although luteal supplementation was continued through the 10th week of pregnancy if the patient conceived. From this observation, it can be suggested that luteal phase support was unnecessary for prevention of abortion in patients with UEI.

The results of our study question the positive conclusion of reports by Atmaca et al. and Erdem et al. regarding the benefit of P supplementation in the luteal phase (14, 15). Perhaps the failure to observe a consistent effect of P on luteal phase function in the different studies may be explained, in part, by either small study sizes, inadequate statistical power to detect a significant difference or the use of different drugs for ovarian stimulation, as well as different types and dosages of progestogens for LPS. Thus further studies should be conducted to determine follicular and luteal phase changes in stimulated IUI cycles, including the E_2 and P profiles, follicular development and histological changes of the endometrium, and the effects of various drugs on these parameters.

Conclusion

Undoubtedly there is a need for prospective, controlled studies to confirm the real clinical benefit of luteal phase P administration (if any) before it is introduced into daily clinical practice. Based on the current study, the theoretic and clinical benefits of this approach have not been proven. The premature incorporation of unproved practices that have not been conclusively tested can lead to unexpected and undesirable side-effects (37).

Acknowledgements

The authors thank the clinical and para-clinical staff of Mirza Koochak Khan Hospital for their assistances in the preparation of this manuscript. There is no conflict of interest in this article.

References

1. Collins JA, Crosigani PG. Unexplained infertility; a review of diagnosis / prognosis / treatment efficacy and management. Int J Gnaecol Obstet. 1992; 39: 267-275.
2. Templeton AA, Penney GC. The incidence / characteristics / and prognosis of patients whose infertility is unexplained. Fertil Steril. 1982; 37: 175-182.
3. Guzick DS, Grefenstette I, Baffone K, Berga SL, Krasnow JS, Stovall DW, et al. Infertility evaluation in infertile women: A model for assessing the efficacy of infertility testing. Hum Reprod. 1994; 9: 2306-2310.
4. Donaghay M, Lessey BA. Uterine receptivity: alteration associated with benign gynaecological disease. Semin Reprod Med. 2007; 25: 461-475.
5. Blacker CM, Ginsburg KA, Leach RE, Randolph J, Moghissi KS. Unexplained infertility: evaluation of luteal phase; result of the national center for infertility research at Michigan. Fertil Steril. 1997; 67: 437-442.
6. Druckmann R, Druckmann MA. Progestrone and immunology of pregnancy. J Sterid Biochem Mol Biol. 2005; 97: 389-396.
7. Balasch J, Vanrrel JA, Marquez M, Burzaco L, Conzalez-Merio J. Dehydogesteone versus vaginal Progestrone in the treatment of the endometrial luteal phase insufficiency. Fertil Steril. 1982; 37: 751-754.
8. Keck C, Gerber-Schafer C, Breckwoldt M. Intrauterine insemination as first line treatment of unexplained male factor infertility. Eur J Obstet Gynecol. 1998; 79: 193-197.
9. Devroey P, Fauser Bc, Diedrich K, Alviggi C, Baart E,Barrat C, et al. Approaches to improve the diagnosis and management of infertility. Hum Reprod update. 2009; 15; 4: 391-408.
10. Garcia J, Jones GS, Acosta AA, Wright GL Jr. Corpus luteum functions after follicle aspiration for oocyte retrieval. Fertil Steril. 1981; 36; 565-572.
11. Olivennes F. The use of gonadotropin-releasing hormone antagonist in ovarian stimulation. Clin Obstet Gynecol. 2006; 49: 12-22.
12. Diluigi AJ, Nulsen JC. Effect of gonadotropin-releasing hormone agonist and antagonist on luteal function. Curr Opin Obstet Gynecol. 2007; 19: 258-265.
13. Pritts EA, Atwood AK. Luteal phase support in infertility treatment: a meta-analysis of the randomized trial. Hum Reprod. 2002; 17; 2287-2299.
14. Atmaca S, Erdem A, Guier I. The impact of luteal phase support on pregnancy rates in intrauterine insemination cycles, a prospective randomized study. Fertil Steril. 2007; 88 Suppl; s163.
15. Erdem A, Erdem M. Impact of luteal phase support

on pregnancy rates in intrauterine insemination cycles: a prospective randomized study. Fertil Steril. 2009; 91: 2508-2513.
16. Ozornek MH, Ozay A, Ergin E. Any need of luteal phase support in IUI cycles. Fertil Steril. 2008; 90 Suppl: s415.
17. Fauser BC, Devroey P. Reproductive biology and IVF: ovarian stimulation and luteal phase consequences. Trend Endocrinol Metab. 2003; 14: 236-242.
18. Tavaniotou A, Albano C, Smitz J, Devroey P. Impact of ovarian stimulation on corpus luteum function and embryonic implantation. J Reprod Immunol. 2002; 55: 123-130.
19. World Health Organization, Laboratory manual of the examination of human semen and sperm-mucus interaction. Cambridge: Cambridge University press; 1992.
20. Daya S. Luteal support: progestogens for pregnancy protection. Maturitas. 2009; 65 Suppl 1: s29-34.
21. Macklon NS, Fauser BC. Impact of ovarian hyperstimulation on the luteal phase. J Reprod Fertil. 2000; 55 Suppl1: 101-108.
22. Hudayter ZR, Muasher SJ. Luteal supplimentaion in in vitro fertilization: more questions than answers. Fertil Steril. 2008; 89; 749-757.
23. Abu-Heija AT, Fleming R, Yates RW, Coutts JR. Pregnancy outcome following exposure to gonadotropin- releasing hormone analogue during early pregnancy: comparisons in patients with normal or elevated luteinizing hormone . Hum Reprod 1995; 10: 3317-3319.
24. Bellvery J, Labarta E, Bosch E, Melo MA, Vidal C, Remohi J, et al. GnRH agonist administration at the time of implantation does not improve pregnancy outcome in intrauterine insemination cycles: randomized controlled trial. Fertil Steril. 2009; (In press).
25. Zayed FF, El-Jallad MF, Al-Chalabi HA. Luteal phase support in ovarian induction cycles using human chorionic gonadotropin or progestogens. Saudi Med J. 2003; 24: 1: 34-36.
26. March CM, Tredway DR, Mishell DR Jr. Effect of clomiphen citrate upon the amount and duration of human menopausal gonadotropin therapy. Am J Obstet Gynecol. 1976; 125: 699-704.
27. Crosignani PG. Intrauterine insemination. The ESHRE Capri Workshop Group. Hum Reprod Update. 2009; 15(3): 265-277.
28. Tavaniotou A, Albano C, Smitz J, Devroey P. Comparison of LH concentration in the early and mid-luteal phase in IVF cycles afer h MG alone or in association with GnRH antagonist cetrorelix. Hum Reprod. 2001; 16: 663-667.
29. Tavaniotou A, Albano C, Smitz J, Devroey P. Effect of clomiphen citrate on follicular and luteal phase luteinizing hormone concentration in invitro fertilization cycles stimulated with gonadotropin and goadotropin- releasing hormone antagonist. Fertil Steril. 2002; 77: 733-737.
30. Li TC, Ding SH, Anstie B, Tuckerman E, Wood K, Laird S. Use of human menopausal gonadotropin in the treatment of endometrial defects associated with recurrent miscarriage: preliminary report. Fertil Steril. 2001; 75: 434-437.
31. Ragni G, Vegetti W, Baroni E, Colombo M, Arnoldi M, Lombroso G, et al. Comparison of luteal phase in gonadotropin stimulated cycles with or without a gonadotropin-releasing hormone antagonist. Hum Reprod. 2001; 16: 2258-2262.
32. Lunenfeld B. Historical perspectives in gonadotropin therapy. Hum Reprod Update. 2004; 10: 453-467.
33. Kreitman O, Nixon WE, Hodgen GD. Induced corpus luteum dysfunction after aspiration of the preovulatory follicle in monkeys. Fertil Steril. 1981; 35: 671-675.
34. Garcia JE, Acosta AA, Hsiu JG, Jones HW Jr. Advanced endometrial maturation after ovulation induction with human gonadotropin / human gonadotropin for invitro fertilization. Fertil Steril. 1984; 41: 31-35.
35. GoldfarbJM, Peskin B, Austin C, Lisbona H. Evaluation of predictive factors for multiple pregnancies during gonadotropin / IUI treatment. J Assist Reprod Genet. 1997; 14: 88-91.
36. Valbuena D, Simon C, Romero JL, Remohi J, Pellicer A. Factors responsible for multiple pregnancies after ovarian stimulation and intrauterine insemination with gonadotropin. J Assist Reprod Genet. 1996; 13: 663-668.
37. Boukaert Y, Robert F, Englert Y, De Baker D, De Vuyst P, Delbaere A. Acute eosinophilic pneumonia associated with intramascular administration of progesterone as luteal phase support after IVF: Case report. Hum Reprod. 2004; 19: 4: 1806-1810.