Comparison of Oral Micronized Progesterone and Dydrogesterone as a Luteal Support in Intrauterine Insemination Cycle

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자궁강내인공수정시 황체기 보강으로서 경구 미분화 프로게스테론과 디드로게스테론의 비교

장은정[1] · 지병철[1,2*] · 김상돈[1] · 이정렬[1] · 서창석[1,2]

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목 적: 과배란유도 후 자궁강내 인공수정 시술시 황체기 보강으로서 경구 미분화 프로게스테론 투여법과 경구 디드로게스테론 투여법의 임상적 효용성을 비교하고자 하였다.

연구방법: 2007년 1월부터 2009년 8월까지 시행된 과배란유도 후 자궁강내 인공수정 시술 183주기를 후향적으로 분석하였다. 과배란유도는 성선자극호르몬 단독 또는 클로미펜과 성선자극호르몬의 병합요법을 사용하였다. 136주기에서는 황체기 보강으로서 경구 미분화 프로게스테론을 하루 300 mg으로 투여하였고 47주기에서는 디드로게스테론을 일일 20 mg으로 투여하였다.

결 과: 여성의 연령, 불임 인자, 성숙난포수 (≥16 mm), 총운동성정자수, triggering 날의 자궁내막 두께는 두 군간 유의한 차이가 없었다. 자궁내 태낭이 확인되는 임상적 임신율은 미분화 프로게스테론 투여군에서 21.3%, 디드로게스테론 투여군에서 19.1%로 차이가 없었다 (p=0.92). 유산율은 미분화 프로게스테론 투여군에서 다소 높은 경향을 보였으나 통계학적인 차이는 없었다 (34.5% vs. 11.1%, p=0.36).

결 론: 황체기 보강으로서 경구 디드로게스테론 투여법은 경구 미분화 프로게스테론 투여에 비하여 비슷한 임신율과 유산율을 보였다. 그러나 상대적으로 디드로게스테론 투여군의 수가 적어 좀더 많은 환자를 대상으로 한 전향적 연구가 필요하다. **[Korean. J. Reprod. Med. 2010; 37(2): 153-158.]**

중심단어: 황체기 보강, 미분화 프로게스테론, 디드로게스테론, 자궁강내인공수정

Although luteal phase support is not a major requirement in intrauterine insemination (IUI) cycles,[1] it became established as a routine clinical practice in stimulated IUI cycles. This is associated with the findings that ovarian stimulation usually results in a defective luteal phase.[2~4] Moreover, a recent randomized controlled trial (RCT) reported a significantly higher pregnancy rate in luteal support group compared with non-supplementation group in gonadotropin-stimulated IUI cycles.[5]

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Various formulations of progesterone (P) are currently available, including oral, vaginal, and (intramuscular) forms. Despite its convenience, oral forms have not been preferred for luteal support because its bioavailability is diminished by the liver first pass.[6] In *in vitro* fertilization (IVF) cycles, one RCT reported that oral micronized P has similar pregnancy, delivery, and miscarriage rate compared with vaginal gel.[7] However, subsequent two RCTs denoted significantly lower implantation rate in oral micronized P compared with vaginal micronized P[8] or IM P,[9] although pregnancy rates were similar between two comparative groups.

In contrast to micronized P, dydrogesterone has a relatively higher oral bioavailability; it is another natural preparation of P as a retroprogesterone with lower side effect.[10] Oral dydrogesterone has been used worldwide for treatment of recurrent abortion.[11~13] Currently two RCTs are available demonstrating the efficacy of oral dydrogesterone as a luteal support in IVF. In the most recent trial, use of oral dydrogesterone resulted in a significantly higher pregnancy rate than vaginal micronized P.[14] Previous one RCT reported similar clinical outcomes compared to vaginal micronized P.[15]

Currently, the efficacies of oral micronized P as well as dydrogesterone have not been demonstrated in IUI cycles. In the present study, we compared the clinical outcomes retrospectively when oral micronized P and dydrogesterone used as a luteal support in IUI cycles.

MATERIALS AND METHODS

Since 2004, oral micronized P was used as a routine luteal supplementation for IUI cycles in our center.[16] However, oral dydrogesterone was predominantly used since 2008 according to the physician's preference. The data were collected from 183 IUI cycles (134 couples) performed between January 2007 and August 2009 at the Seoul National University Bundang Hospital.

All couples were eligible for superovulation and IUI with duration of infertility that lasted one year or more. The mean age of female was 32.3±3.3 years old; the mean duration of infertility was 44.0±27.4 months. Tubal patency was confirmed by hysterosalpingography in all subjects. Semen parameters were interpreted by the World Health Organization (1999) criteria. The infertility factors of the subjects were identified as unexplained (n=93), ovulatory (n=23), endometriosis (n=19, stage III for all), uterine (n=18), tubal (n=16, unilateral tubal occlusion for all), and male (n=14).

Superovulation was performed by using urinary (hMG, Pergonal®, Serono, Geneva, Switzerland) or recombinant gonadotropins (rFSH, Gonal-F®, Serono or Menopur®, Ferring, Malmo, Sweden) with or without co-treatment of clomiphene citrate (Clomiphene®, Youngpoong Pharma, Incheon, Korea) in a dose of 100 mg/day given on day 3~7 of menstrual cycle. When mature leading follicle(s) reached 19 mm in diameter and the urinary LH test was negative, recombinant hCG (Ovidrel®, Serono) in a dose of 250 μg was given; IUI was then performed 36~40 hours later. When the urinary LH test was positive, IUI was performed the next morning.

The luteal phase was supported by oral micronized P 300 mg/day (Utrogestan®, Laboratories Besins International, Paris, France) (n=136 cycles) or dydrogesterone 20 mg/day (Duphaston®, Solvay Pharmaceuticals, Weesp, Netherlands) (n=47 cycles) from day of insemination. If clinical pregnancy was established, the medication continued up to 8 gestational weeks. Clinical pregnancy was defined when an intrauterine gestational sac(s) was visible by ultrasonography.

Data were analyzed with SPSS ver. 10.0.1 (SPSS Inc., Chicago, IL, USA). The chi-square test was used to compare proportions, and the Student's t-test to compare means. A p-value of <0.05 was considered statistically significant.

RESULTS

Female age, duration of infertility, previous IUI trials, the profiles of infertility factors, days of hCG administration, mature follicle and serum estradiol level on hCG day were comparable between the micronized P and the dydrogesterone group (Table 1). Total doses of gonadotropin were significantly higher in the dydrogesterone group; this was mainly attributed by the predominant use of gonadotropin-only protocol in the dydrogesterone group. No cancelled cycles occurred due to excessive stimulation. No significant difference was found in endometrial thickness measured on triggering day between the two groups.

Clinical pregnancy rates per cycle were comparable in the two groups (21.3% vs. 19.1%, p=0.92). However, the clinical miscarriage rate tended to be 3-fold higher in the micronized P group although statistically not significant (34.5% vs. 11.1%, p=0.36). Multifetal gestations occurred in five cycles (four twins and one triplet). One triplet and two cases of ectopic pregnancy occurred in the micronized P group.

DISCUSSION

In IVF cycles, oral micronized P supplementation was reported to be similar pregnancy, delivery, and miscarriage rate compared with vaginal gel in a RCT including 283 women,[7] but a significantly lower implantation rate was noted in subsequent two RCTs when compared with vaginal micronized P[8] or IM P.[9] Thereafter oral micronized P supplementation is the least common method in IVF cycles. However, subsequent two RCTs included relatively low number of study subjects (64 and 43, respectively) thus suffering from low statistical power. Moreover, clinical pregnancy rates were similar between two comparison groups in both RCTs; one study included high responder only. Nonetheless, in general, oral micronized P was considered to be unsuitable option for luteal phase support during assisted reproduction cycles.[17]

The efficacy of oral micronized P supplementation is unknown in IUI cycles; the lack of evidence may be mainly attributed by the predominant use of vaginal micronized P in most IUI cycles. In the present study, oral micronized P supplementation yielded an acceptable clinical pregnancy rate, but relatively high miscarriage rate was unacceptable.

In contrast to oral micronized P, use of oral dydrogesterone in IVF cycles has been reported to have much better[14] or similar[15] clinical outcomes when compared to vaginal micronized P in two large-scaled RCTs. One retrospective study also reported a similar pregnancy, implantation and miscarriage rate when compared with IM P.[18] In fact, since publication of two recent RCTs, we have changed routine luteal support for IUI cycles from oral micronized P to dydrogesterone. Although the present study was a retrospective one, we observed that oral dydrogesterone has a similar pregnancy rate. Although statistically not significant, oral dydrogesterone had slightly lower miscarriage rate than oral micronized P. Since relatively small number of patients was included in the oral dydrogesterone group, further large-scaled randomized study would be required to confirm our findings.

The natural preparations of P include progesterone, dydrogesterone, and medrogestone. Dydrogesterone has similar pharmacological effects to endogenous progesterone and has selective progestational activity without clinically relevant androgenic, estrogenic or mineralocorticoid activity.[10] Taking dydrogesterone during pregnancy does not appear to cause congenital birth defects when used in a range of indications including infertility due to luteal insufficiency and threatened or habitual abortion.[13]

Table 1. Clinical outcomes of 183 IUI cycles using oral progesterone as a luteal support

	Micronized progesterone (n=136)	Dydrogesterone (n=47)	*p*-value
Age of female (yr)	32.2±3.1	32.8±3.6	NS
Duration of infertility (mon)	43.6±27.7	45.1±26.7	NS
Previous IUI trials	0.51±0.79	0.49±0.71	NS
Infertility factors			
Unexplained	74 (54.4)	19 (40.4)	NS
Ovulatory	16 (11.8)	7 (14.9)	
Tubal	14 (10.3)	2 (4.3)	
Uterine	12 (8.8)	6 (12.8)	
Endometriosis	12 (8.8)	7 (14.9)	
Male	8 (5.9)	6 (12.8)	
Ovarian stimulation regimen			
Clomiphene + gonadotropin	123 (90.4)	22 (46.8)	<0.001
Gonadotropin only	13 (9.6)	25 (53.2)	
Total gonadotropin dose (IU)	478.1±405.0	938.3±705.8	<0.001
Days of triggering	11.8±2.8	11.4±3.1	NS
At triggering day			
No. of follicle (≥16 mm)	2.5±1.4	2.4±1.5	NS
No. of follicle (≥12 mm)	2.9±1.5	3.9±1.7	<0.001
Serum estradiol level (pg/mL)	781±609	1,375±1,227	NS
Endometrial thickness (mm)	8.3±2.5	8.7±2.6	NS
Total motile sperm count ($\times 10^6$)	127.4±164.7	169.7±212.1	NS
Ectopic pregnancy	2	0	NS
Clinical pregnancy	29 (21.3% per cycle)	9 (19.1% per cycle)	NS
Clinical abortion	10 (34.5)	1 (11.1)	NS
Livebirth/ongoing	19 (65.5)	8 (88.9)	NS
Multiple pregnancy	3	2	NS

Values are presented as mean ± SD or number (%).
IUI, intrauterine insemination; NS, not significant.

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Oral administration of micronized P is generally associated with systematic side effects due to unphysiological metabolites, e.g. drowsiness, flushing, nausea, fluid retention, sedative and hypnotic effect.[19]

In a previous study, drowsiness occurred in 44% of patients taking oral micronized P; this was significantly more frequent than vaginal gel.[7] However, the tolerability appears to be better with oral dydrogesterone; vaginal application of micronized P resulted in vaginal discharge and irritation in 10.5% of patients and significantly more patients given dydrogesterone were satisfied than vaginal micronized P group in a previous report.[15] IM P can also produce side effects such as local inflammatory reactions, sterile abscesses, and discomfort.[3]

From our observation, supplementation of oral dydrogesterone as a luteal support has similar clinical outcomes compared with oral micronized progesterone. Since our study was a retrospective one, side effects or tolerability could not be assessed. Relatively small number of patients was enrolled in the dydrogesterone arm. Moreover, the regimen of ovarian stimulation was different between the two groups. Hence further well-controlled studies will be needed to clarify the superiority oral dydrogesterone and to determine ideal dose in stimulated IUI cycles.

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= **Abstract** =

Objective: To compare the clinical outcomes between oral micronized progesterone and dydrogesterone as a luteal phase support in stimulated intrauterine insemination (IUI) cycles.

Methods: A retrospective analysis was performed in 183 IUI cycles during January 2007 to August 2009. Superovulation was achieved by using gonadotropins combined with or without clomiphene citrate. The luteal phase was supported by oral micronized progesterone 300 mg/day (n=136 cycles) or dydrogesterone 20 mg/day (n=47 cycles) from day of insemination.

Results: There were no significant differences in clinical characteristics such as age of female, infertility factors, number of mature follicles (≥16 mm), total motile sperm counts, and endometrial thickness on triggering day between the two groups. The clinical pregnancy rates per cycle were similar between the two groups (21.3% in the micronized progesterone group vs. 19.1% in the dydrogesterone group, p=0.92). The clinical miscarriage rate tended to be 3-fold higher in the micronized progesterone group (34.5% vs. 11.1%, p=0.36).

Conclusion: Supplementation of oral dydrogesterone as a luteal support has similar clinical outcomes compared with oral micronized progesterone. Large-scaled randomized study would be required to confirm our findings.

Key Words: Luteal support, Micronized progesterone, Dydrogesterone, Intrauterine insemination