Route of progesterone administration for luteal phase support may affect outcome of controlled ovarian hyperstimulation for IVF with ICSI using GnRH antagonist

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Abstract

Purpose This study evaluated the impact of route of progesterone administration as luteal phase support on the outcome of assisted conception cycles.

Methods Intramuscular progesterone in oil (IMP) at 100 mg daily was administered to 903 women following oocyte retrieval whereas vaginal progesterone gel (VMP) at 90 mg was administered twice daily to 1,110 women. Retrospective analysis was performed according to the type of GnRH analogue used. Implantation (IR), clinical pregnancy (CPR) and biochemical pregnancy rates (BPR) were main outcomes.

Results In GnRH agonist cycles, neither IR, CPR or BPR differed according to the route of progesterone. However, in GnRH antagonist cycles, IR and CPR were significantly lower in VMP group compared to IMP group. BPR also was significantly higher in VMP group compared to IMP group.

Conclusion Our results suggest that route of progesterone administration for luteal phase support can be an important prognostic factor according to the type of GnRH analogue used for controlled ovarian hyperstimulation.

Keywords Progesterone · Vaginal · Intramuscular · IVF

Luteal phase support following ovarian stimulation and oocyte retrieval has been used traditionally since the beginning of assisted reproductive technologies (ART). The rationale of using luteal phase support is to recover deficient progesterone secretion resulting from either collection of granulosa-theca cell during oocyte retrieval procedure or luteolytic effect of GnRH agonists. Relatively newly introduced GnRH antagonists are also associated with reduced in vivo progesterone activity and therefore LPS has been advocated for controlled ovarian hyperstimulation (COH) cycles in which GnRH antagonists were utilized [1, 2]. It is also of note that GnRH antagonist used cycles for controlled ovarian hyperstimulation is increasing in clinical practice [3].

LPS can consist of the administration of progesterone or human chorionic gonadotropin (hCG). Administration of hCG for LPS, however, has been associated with reduced pregnancy rates and increased incidence of ovarian hyperstimulation syndrome (OHSS) [4]. Thus, progesterone is used most frequently for LPS. The durations of progesterone effect following oocyte retrieval, depending on the different routes of administration, remain unclear. For example, oral administration of progesterone has been associated with inconsistent serum levels and reduced implantation rates, and hepatic metabolites of progesterone have unwanted sedative effects [5]. Therefore current clinical practice consists of intramuscular injection of progesterone in oil (IMP) or vaginal administration of micronised progesterone (VMP). Although several clinical randomized studies have compared the effects of administration routes of progesterone on ART outcomes, a Cochrane review concluded that the optimal route of progesterone administration has not yet been established [6].

The route of progesterone administration is chosen by each individual physician and patient, based on their

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Table 1 Agonist cycles

	Parenteral progesteron (<i>n</i> =256)	Vaginal progesterone (<i>n</i> =295)	
Mean age	32.2±4.8	32.3±5.0	0.4
Peak E ₂ (pg/ml)	2690.7±1235.3	2555.3±1189.4	0.1
Gonadotropins consumed (units)	3952.5±1537.5	3901.5±1487.5	0.8
HMG/Total gonadotropin ratio (%)	11.9	11.1	0.5
Total oocytes retrieved	17.1±9.1	16.8±8.0	0.6
Fertilization rates	2515/3481 (72.2)	2716/3724 (72.9)	0.3
Surgically retrieved spermatozoa cycles	30 (11.7)	37 (12.5)	0.8
Blastocyst stage ET ratio (%)	26.5	25.2	0.7
Mean ET	2.6±0.8	2.7±0.7	0.2
Implantation rate (%)	32.4	32.5	0.9
(+)βhCG	145 (56.6)	172 (58.3)	0.7
Clinical pregnancy/ET	134 (52.3)	156 (52.8)	0.9
Biochemical pregnancy	9 (6.2)	13 (7.5)	0.8
Ectopic pregnancy	2 (1.3)	3 (1.7)	0.8

preferences and the availability of progesterone preparations on the local pharmaceutical market. Although our center used to use IMP for LPS following oocyte retrieval, legal litigation starting in April 2007 has made IMP unavailable, and all of our patients have utilized VMP since that time. We have therefore retrospectively compared our data for the rates of implantation, pregnancy and biochemical pregnancy according to the route of LPS.

We compared cycles of COH for ICSI between August 2006 and March 2007 in which IMP was used and cycles between April and December 2007 in which VMP was used. These two groups were further subdivided into two groups, each according to the type of GnRH analogue used. Throughout both time periods, embryology laboratory conditions and clinical practice have remained constant, including the brands of gonadotropins and GnRH analogues utilized.

Briefly, Lucrin (Abbott, Aubonne Switzerland) was used for the long protocol or the microdose protocol for GnRH

agonist cycles, and Ganirelix (Orgalutran, Organon, Netherlands) was used in a multidose protocol for antagonist cycles. The gonadotropins r-FSH (Puregon, Organon) and HMG (Menogon, Ferring, Sweden) were administered and titrated according to the ovarian response of the individual patient. HCG (5,000–10,000 IU) was administered for ovulation triggering. ICSI was used universally as the assisted conception method. Embryo transfers (ET) were performed under ultrasound guidance 2–5 days after oocyte retrievals. Luteal phase support consisted of 100 mg daily IMP (G. Streuli and Co., Switzerland) or 90 mg VMP daily twice (Crinone 8%, Serono, Switzerland). Serum bHCG concentrations were measured in all patients 12 days after ET. The type of commercial kits utilized to measure serum concentrations of E₂ and βhCG remained constant throughout the study period. Pregnancy was defined as a serum βhCG concentration >5 mMIU/ml on at least two occasions. Clinical pregnancy was defined as the demonstration of an intrauterine gestational sac with yolk sac by trans-

Table 2 Antagonist cycles

	Parenteral progesteron (<i>n</i> =647)	Vaginal progesterone (<i>n</i> =815)	
Mean Age	33.2±5.3	33.6±5.6	0.1
Peak E ₂ (pg/ml)	2253.3±1100.5	2174.0±1293.1	0.2
Gonadotropins consumed (units)	3982.5±1507.5	3860.5±1636.3	0.1
HMG/Total gonadotropin ratio (%)	23.0	23.6	0.8
Total oocytes retrieved	15.2±9.2	14.5±9.5	0.1
Fertilization rates	73.7	73.6	0.9
Surgically retrieved spermatozoa cycles	79 (12.2)	106 (13.0)	0.9
Blastocyst stage ET ratio (%)	16.8	17.1	0.8
Mean ET	2.5±0.7	2.6±0.8	0.2
Implantation rate	26.6	23.3	0.02 OR: 1.1, 95%CI: 1.0–1.3
(+)βhCG	344 (53.1)	402 (49.3)	0.1
Clinical pregnancy	319 (49.3)	356 (43.6)	0.03 OR: 1.2, 95%CI: 1.0–1.5
Biochemical pregnancy	17 (4.9)	38 (9.4)	0.02 OR: 0.4, 95%CI: 0.2–0.9
Ectopic pregnancy	8 (2.3)	8 (1.9)	0.9

vaginal ultrasonography (TVUS) 3 weeks after ET. On going pregnancy rate was calculated as gestations continuing beyond 20 weeks per ET cycle. Biochemical pregnancy was defined as a temporary rise in serum bHCG, along with the absence of signs of intra- and extra-uterine pregnancy by TVUS. Biochemical pregnancy rate was calculated as the ratio of biochemical pregnancies to (+) β hCG cases. Mann Whitney *U* tests, unpaired *t* tests and χ^2 tests were employed in statistical calculations.

Table 1 shows the clinical outcomes of agonist cycles and Table 2 shows the clinical outcomes of antagonist cycles. During the two time periods, mean patient age, mean peak E_2 concentrations, mean number of oocytes retrieved, mean LH content of the gonadotropin preparations, and the mean number of surgically retrieved spermatozoa cycles did not differ, in both agonist and antagonist cycles. Fertilization rates also did not differ between the two LPS protocols during these time periods. The timing of embryo transfer policy has not been changed during the assessed periods as seen ratios of blastocyst transfers were not different to cleavage stage embryo transfers in both groups. The mean number of embryos transferred per patient was also not different between groups. For patients receiving GnRH agonist, there were no differences in implantation rates and clinical and biochemical pregnancy rates between IMP and VMP. In patients receiving GnRH antagonists, however, the implantation and clinical pregnancy rates were significantly lower among patients using VMP while the biochemical pregnancy rate was significantly lower among patients receiving IMP. Ongoing pregnancy rates among women receiving GnRH agonist did not differ in IMP and VMP groups (48% vs 48.4% respectively, $p=0.9$, OR=0.1, 95%CI=0.7–1.3). Although IMP group had higher ongoing pregnancy rate among women receiving GnRH antagonist compared to VMP group, this difference was not statistically significant (41.1% vs 36.5% respectively, $p=0.08$, OR=0.8, 95%CI=0.6–1).

Compared with oral progesterone, vaginal progesterone provides much greater bioavailability and less relative variability [7]. In addition, VMP has also been shown to have more pronounced effects on endometrium than IMP [8, 9]. Similarly higher serum progesterone concentrations have been observed following IMP and higher progesterone concentrations on endometrium following VMP, resulting in an increased ratio of endometrial to serum progesterone concentration with VMP [8]. Moreover, biochemical pregnancy rates are higher following VMP than following IMP [10–12]. In contrast, other studies found no differences in outcome between IMP and VMP [13–16]. A meta-analysis found that clinical pregnancy rates were higher in patients using IMP than in those using VMP [17]. In addition, the use of VMP has been associated with significantly higher rates of modest vaginal bleeding before

obtaining the results of pregnancy tests [16]. Recently Dal-Prato et al prospectively evaluated the effect of two different LPS approaches in a randomized study and concluded that no difference was detected in terms of implantation, clinical pregnancy and biochemical pregnancy rates between IMP and VMP groups [18]. On the other hand, all of the aforementioned studies, however, evaluated COH cycles in which down regulation was achieved by GnRH agonists. Thus, our study is unique in comparing clinical outcomes between IMP and VMP according to the GnRH analogue used in COH cycles. The underlying mechanism responsible for this difference in GnRH antagonist cycles is not clear but may be related to the indirect effect of GnRH antagonists on endometrium, as previously shown [19].

The clinical outcome differences between IMP and VMP can be attributed to possible different infertility etiologies existing in patients groups such as relative increased fraction of women with diminished ovarian reserve or male factor infertility in any assessed group could lead to increased pregnancy loss. However it was shown that neither the type of infertility etiology nor ovarian response during COH among women undergoing ICSI affected early pregnancy loss rates [20, 21].

The results generated from our study still should be interpreted cautiously, since there are several limitations in the study due to design. The patients who were enrolled in the study and received either intramuscular progesterone in oil or vaginal progesterone gell were treated in different periods and this was the result of the unavailability of intramuscular progesterone preparations on the local market rather than a result of a scientific schedule. Moreover, this study was not designed to compare the effects of IMP and VMP on live birth rates (LBR), the gold standard of success in ART. Therefore, it is unclear whether the increase in subclinical pregnancy losses observed in the VMP group would have any impact on LBR. Thus ongoing pregnancy rates did not differ statistically, although a clear trend of increased ongoing pregnancy rate was observed in IMP patients compared to VMP patients. Well powered prospective randomized trials comparing IMP and VMP relative to the GnRH antagonist used in COH cycles are warranted.

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