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Salivary and serum progesterone concentrations during two luteal support regimens used in in vitro fertilization treatment

Luteal support effect in IVF has been evaluated by measurement of serum progesterone (1) and the effect of progesterone on the endometrium (2). Intramuscular hCG treatment produces higher serum progesterone concentrations than does vaginally administered micronized progesterone, which produces higher and longer-sustained plasma progesterone levels than the same oral dose. Salivary progesterone measurement can be used for longitudinal monitoring of luteal function (3), and it displays both free and total serum progesterone levels during normal menstrual cycle and in pregnancy. During a normal menstrual cycle, salivary progesterone levels are 0.223–0.382 nmol/L (4).

We monitored serum and salivary progesterone levels in the luteal phase of IVF cycles using two luteal support regimens to explore the correlation between salivary progesterone concentrations and outcome of IVF.

The study was approved by the institutional review board of the hospital. Eighty-nine successive patients in a university hospital IVF unit were enrolled. Patients with polycystic ovary disease, a previous case of ovarian hyperstimulation syndrome, and a large number of oocytes (>20) were excluded. After pituitary down-regulation with buserelin acetate, stimulation was begun with hMG (Humegon; Organon, the Netherlands), 150–225 IU/d. Human chorionic gonadotropin, 5000 IU (Pregnyl; Organon) was administered when the largest follicle was ≥ 18 mm in diameter. Oocyte retrieval was performed 36 hours later. After the last day of follicular ultrasonography, the patients were randomly assigned to one of two luteal support groups: intramuscular hCG (n = 45), in which hCG (Pregnyl; Organon), 1500 IU, was administered on days 3, 6, and 9 after oocyte retrieval; or intravaginal micronized natural progesterone (n = 44) (Lugesteron; Leiras), two 100-mg capsules three times daily (total dose, 600 mg/d) from the day of oocyte retrieval for 2 weeks and continuing for 4 weeks if the pregnancy test was positive.

The first saliva sample was obtained on the day of the oocyte retrieval, and the second was obtained on the day of embryo transfer. The next three samples were obtained every fourth day thereafter, and the last sample was obtained 14 days after oocyte retrieval. Saliva samples (2 mL) were collected without stimulation at home in the morning between 7:00 and 10:00 A.M. Samples were stored at −70°C until analysis by radioimmunoassay with a sensitivity of 40 pmol/L (intraassay and interassay coefficients of variation, 2.8% and 4.4%) (19). Two serum samples were drawn on the day of oocyte retrieval and 14 days thereafter, and serum progesterone was analyzed by using a competitive recombinant immunoassay (intraassay and interassay coefficients of variation, 4.6% and 6.0%, respectively). Because the variables were not normally distributed, medians and nonparametric methods (Mann–Whitney *U* test) were used.

Study groups did not differ in demographic characteristics, except that the hCG group had a higher number of oocytes than the progesterone group (10 [range, 2–24] vs. 7 [range, 2–14]) (P=.001). The pregnancy rates per embryo transfer and implantation rates were similar in the hCG and progesterone groups: 29.5% and 17.4% versus 31.1% and 18.4%, respectively. On the day of oocyte retrieval, serum and saliva progesterone concentrations were similar in the two groups, but 14 days after oocyte retrieval, the hCG group had significantly higher serum progesterone levels than the progesterone group (48.6 nmol/L vs. 20.4 nmol/L) (P<.005). Salivary progesterone levels were 10–30 times higher in the progesterone group than the hCG group (P<.005) throughout the study.

In both groups, patients who became pregnant had higher serum progesterone concentrations 14 days after the oocyte retrieval (median values, 560 nmol/L in the hCG group and 77.1 nmol/L in the progesterone group) than did those who did not become pregnant (104 nmol/L in the hCG group and 46.4 nmol/L in the progesterone group) (P<.005). However, within groups, there was no statistically significant difference in salivary progesterone concentrations between patients who became pregnant (median values, 3.14 nmol/L in the hCG group and 26.5 nmol/L in the progesterone group) and those who did not (1.42 nmol/L in the hCG group, and 22.7 nmol/L in the progesterone group) (Table 1).

In our study, serum progesterone levels were significantly lower in patients who received vaginal progesterone than in those who received hCG. This may have resulted from a higher number of functioning

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TABLE 1

Serum and salivary progesterone levels in hCG and vaginal progesterone recipients.

	Serum progesterone level on day 0	Salivary/g progesterone level (nmol/L)					Serum progesterone level (nmol/L) on day 14
		Day 0	Day 2	Day 6	Day 10	Day 14	
hCG recipients	16.7 (4.4–48.3)	0.17 (0.04–7.0)	1.11 (0.2–4.71)	1.37 (0.1–6.26)	1.23 (0.25–13.4)	1.54 (0.03–21.0)	204 (2.0–1010.0)
Vaginal progesterone recipients	20.9 (3.1–65.5)	0.19 (0.03–2.3)	17.3 (1.33–200)	36.1 (1.60–230)	29.1 (0.70–200)	25 (0.19–200)	48.6 (4.7–609.0)
P value[a]	0.06	0.412	<0.005	<0.005	<0.005	<0.005	<0.005

Note: Values are the median (range).

[a] Two-tailed.

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hCG-supported corpora lutea in hCG recipients. In contrast, continuous administration of vaginal progesterone, which produces steady serum progesterone concentrations, may suppress LH secretion of the pituitary and negatively affect the function of the corpus luteum (5). Good corpus luteum function, as evidenced by pregnancy rates in hCG recipients, explains the higher salivary and serum progesterone concentrations in pregnant patients.

A new and interesting finding of our study was that vaginal progesterone recipients had significantly higher salivary progesterone concentrations (Table 1). Even when the serum levels are lower, vaginally administered progesterone yields a high progesterone concentration in the endometrium compared with other delivery routes (6). A direct pathway for vaginally administered progesterone to the uterus has been proposed; this may occur by direct diffusion through tissues, direct passage through cervical lumen, transport via venous or lymphatic circulatory system, or countercurrent vascular exchange with diffusion between uterovaginal veins or lymphatic vessels and arteries (7).

Our finding of high salivary progesterone concentrations during vaginal progesterone administration suggests that vaginally administered progesterone might have extraordinary pharmacokinetics compared with other administration routes. For example, the proportion of the protein carrier free progesterone and its concentration in other tissues, such as fat and breast, is not known.

Our results suggest that the serum and salivary progesterone measurements do not provide valuable information on which to base clinical decisions in IVF treatment, but they raise questions about the pharmacokinetics of vaginally administered progesterone.

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References

1. Smitz J, Devroey P, Faguer B, Bourgain C, Camus M, Van Steirteghem AC. A prospective randomized comparison of intramuscular or intravaginal natural progesterone as a luteal phase and early pregnancy supplement. Hum Reprod 1992;7:168–75.
2. Pasquale SA, Bachmann GA, Foldesy RG, Blackwell RE, Levine JP. Peripheral progesterone (P) levels and endometrial response to various dosages of vaginally administered P in estrogen-primed women. Fertil Steril 1997;68:810–5.
3. Lipson SF, Ellison PT. Reference values for luteal progesterone measured by salivary radioimmunoassay. Fertil Steril 1994;61:448–54.
4. Vuorento T, Lahti A, Hovatta O, Huhtaniemi I. Daily measurements of salivary progesterone reveal a high rate of anovulation in healthy students. Scand J Clin Lab Invest 1989;49:395–401.
5. Mores N, Krasmanovic LZ, Catt KJ. Activation of LH receptors expressed in GnRH neurons stimulates cyclic AMP production and inhibits pulsatile neuropeptide release. Endocrinology 1996;137:5731–4.
6. Miles RA, Paulson RJ, Lobo RA, Press MF, Dahmoush L, Sauer MV. Pharmacokinetics and endometrial tissue levels of progesterone after administration by intramuscular and vaginal routes: a comparative study. Fertil Steril 1994;62:485–90.
7. Cicinelli E, de Ziegler D. New hypothesis. Transvaginal progesterone: evidence for a new functional "portal system" flowing from the vagina to the uterus. Hum Reprod Update 1999;5:365–72.