

The Impact of High Progesterone Levels in the Follicular Phase of in Vitro Fertilization (IVF) Cycles: A Comparative Study

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Estrogen (E₂) and plasma progesterone (P₄) levels are valuable parameters for follicular development in in vitro fertilization (IVF) cycles. Furthermore, the progesterone concentration prior to, during, and following human chorionic gonadotropin (hCG) administration is an important marker for the detection of early luteinization and premature ovulation. The pattern of hormonal profile in relation to the number of oocytes retrieved, fertilized, and cleaved and the fate of the pregnancies achieved were compared in three groups of patients treated by the same protocol. Group I included 22 women who conceived with high progesterone levels on day hCG+1 (P₄, >2.5 ng/ml). Group II included 43 women who conceived with low P₄ values (P₄, <2.5 ng/ml), while group III included 46 patients in whom no pregnancies occurred. A significant decrease in fertilization, cleavage, and pregnancy rates was observed in patients with high progesterone levels on day hCG+1, compared to those with normal levels. Nevertheless, it is suggested that cycles with high P₄ levels in the preovulatory phase should not be canceled, as a fair chance for pregnancy still exists.

KEY WORDS: progesterone levels; in vitro fertilization (IVF); follicular phase; early luteinization; premature ovulation.

INTRODUCTION

Most protocols for the induction of ovulation in in vitro fertilization (IVF) cycles measure estradiol

(E₂) and plasma progesterone (P₄) levels as parameters for follicular development. Progesterone concentrations prior to, during, and following the administration of human chorionic gonadotropin (hCG) are a valuable marker for the detection of early luteinization and premature ovulation cycles. Indeed, according to accepted criteria most fertility centers cancel treatment cycles when P₄ levels surpass 1.5 ng/ml on hCG day or reach 2.5 ng/ml on day hCG+1. Cancellation is especially indicated when coincident E₂ values have dropped 30% or more between hCG day and day hCG+1; it is relative when a further increase in or only flattening of the curve has occurred in plasma estrogen levels (1).

The purpose of the present study was to evaluate the pattern of the hormonal profile as well as the outcome of pregnancies achieved in our unit, as related to the number of oocytes aspirated, following fertilization and cleavage. Furthermore, we also examined the fate of pregnancies in a group of 22 women (Group I) who became pregnant while plasma progesterone levels on day hCG+1 were 2.5 ng/ml.

MATERIALS AND METHODS

This study consisted of 305 women with mechanical infertility who underwent in vitro fertilization in our unit between October 1985 and December 1987. No patients with other etiologies for infertility were included in the group.

All patients were treated by the same laboratory and clinical team during this period. Of these, 249

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women underwent embryo transfer. The protocol used for induction of ovulation was based on high-dose Pergonal (Serono Laboratories, Inc., Randolph, MA) treatment, starting on day 3 of the menstrual cycle as described elsewhere (2). Conditions required for the administration of hCG were two follicles of diameter of at least 15 mm, as monitored on ultrasound scan of the ovaries, E_2 levels higher than 400 pg/ml, and P_4 concentrations not greater than 1.5 ng/ml on hCG day. This day was designated day 0, and on day hCG + 1 plasma concentrations of E_2 and P_4 were determined; if there was no decrease in E_2 larger than 30%, and no signs of ovulation were obvious on ultrasound evaluation (disappearance of follicular structure, the presence of fluid in the pouch of Douglas), the cycle was continued without consideration of plasma P_4 concentrations.

Patients were divided into three groups for comparison:

- Group I, 22 women who conceived with high progesterone levels on day hCG + 1 (P_4 , >2.5 ng/ml);
- Group II, 43 women who conceived with low P_4 values on day hCG + 1 (P_4 , <2.5 ng/ml); and
- Group III, 46 patients randomly chosen of 184 in whom embryo transfers were performed but no pregnancies were achieved.

Fertilization, cleavage, and pregnancy rates in all patients having undergone embryo transfer were compared. E_2 and P_4 levels were examined around hCG day in all three groups.

fer (ET)-treated patients and fertilization, cleavage, and pregnancy rates. The mean concentration of P_4 on day hCG + 1 in Group I was 4.1 ± 1.5 ng/ml, with the range of 2.6–6.7 ng/ml. The mean in Group II was 2.1 ± 0.3 ng/ml, with a range of 1.3–2.4 ng/ml, while in Group III the mean P_4 concentration was 2.3 ± 0.1 , with a range of 1.1–2.4 ng/ml (Fig. 1).

The mean levels of E_2 on hCG day were 1362 ± 162 , 1136 ± 87 , and 964 ± 69 pg/ml, respectively, in Groups I, II, and III.

On day hCG + 1 E_2 concentrations were 1692 ± 217 , 1303 ± 106 , and 1247 ± 96 pg/ml, respectively, in the three groups (Fig. 2).

The average number of oocytes aspirated was 11.6 ± 4.2 in Group I, 7.6 ± 2.1 in Group II, and 6.7 ± 1.9 in Group III. There was a statistically significant difference in the number of oocytes aspirated between Group I, and Groups II and III ($P < 0.001$). Fertilization rates were 54.6, 78.9, and 79.6% in Groups I, II, and III, respectively.

There were no statistically significant differences in the average number of embryos transferred in Groups I and II. In 22 pregnancies achieved in Group I there were 16 singletons, 5 pairs of twins and 1 quadruplet. Five pregnancies terminated in first-trimester abortion, i.e., 22.7%.

In Group II, of 43 pregnancies there were 32 singletons, 10 pairs of twins, and 1 triplet. There were 9 first-trimester abortions, i.e., 20.9%. The pregnancy rate per embryo transfer was 8.8% in Group I, while Group II established 17.2% pregnancies, with a mean of 26% per embryo transfer. The difference was statistically significant ($P < 0.001$). There were no pregnancies in patients in Group III.

RESULTS

Table I indicates the relationship between progesterone levels in three groups of IVF-embryo trans-

DISCUSSION

While the present study does not allow us to point out precisely which factor is responsible for re-

Table I. The Relationship Between Progesterone Levels on Day hCG + 1 and Fertilization, Cleavage, and Pregnancy Rates in All Groups

Group	P_4 level on day hCG + 1 (ng/ml, M \pm SD)	No. of patients	No. of embryos per ET (M \pm SD)	Fertilization rate		Cleavage rate		Pregnancy rate	
				N/N	%	N/N	%	No. of pregnancies per ET	%
I	4.1 ± 1.5	22	2.3 ± 0.9	140/256	54.6	117/256	45.7	22/249	8.8
II	2.1 ± 0.3	43	2.6 ± 0.6	261/331	78.9	211/331	66.7	43/249	17.2
III	2.3 ± 0.1	46	2.4 ± 0.7	246/309	79.6	196/309	63.4	—	—
Total								65/249	26.1
P	<0.001	—	—	—	<0.001	—	<0.001	—	<0.001

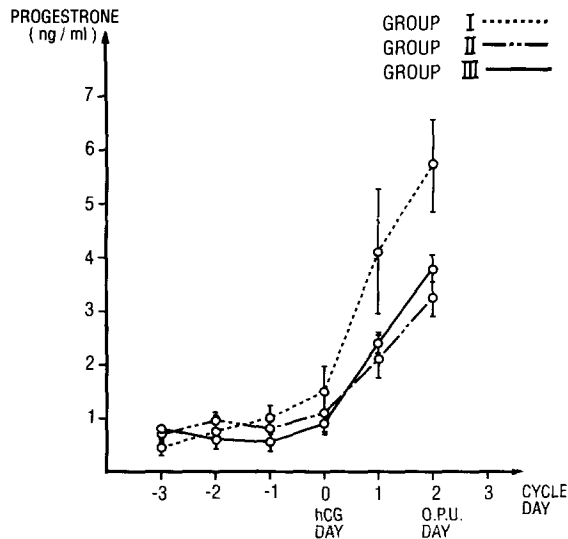


Fig. 1. Comparison of progesterone levels to hMG/hCG stimulation in all groups (mean \pm SD).

duced fertilization and implantation rates after embryo transfer in Group I, several mechanisms seem to play a role. Mainly, it may be speculated that high P_4 levels on day hCG + 1 are an expression of high luteinizing hormone (LH) levels. Since the latter is considered to stimulate steroidogenic activity of the thecal tissue of the growing follicle (13), sustained exposure to elevated LH levels increases both P_4 and androgen levels (12) and could potentially result in an altered hormonal environment within the antrum. This hypothesis may be relevant since in the experimental isolated mouse follicle,

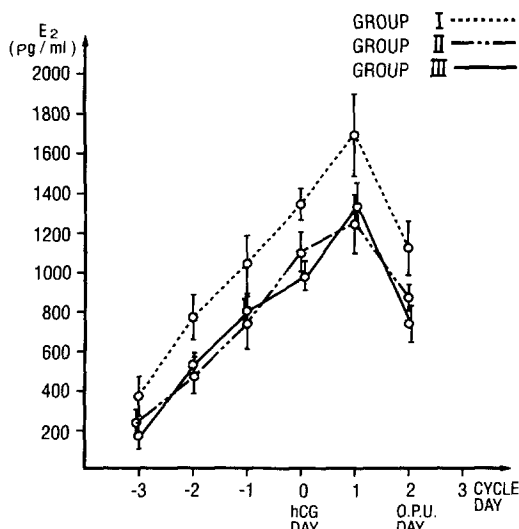


Fig. 2. Comparison of E_2 patterns to hMG/hCG stimulation in all groups (mean \pm SD).

high progesterone levels induced oocyte atresia and increased the number of meiotically inactive oocytes (14,15). Moreover, reduced fertilization rates of ovine oocytes and abnormal embryo development in vitro have been shown in the presence of elevated progesterone levels (16). We suggest that in spite of high progesterone levels, the average number of oocytes aspirated in Group I was high, i.e., 50% higher than in Group II; a small proportion of oocytes was, nevertheless, fertilized. Although under these conditions embryos may have been of a lesser quality, a certain number of good embryos resulted in implantation and a low 8.8% pregnancy rate per transfer. Also, endometrial receptivity may be adversely affected due to relatively excessive E_2 and P_4 concentrations on day hCG + 1. This hypothesis is supported by recent studies demonstrating considerable ultrastructural abnormalities of the endometrium in high- E_2 and - P_4 cycles (17). Furthermore, the histologic appearance of and progesterone receptor concentration in the endometrium have been shown to be related to the E_2 concentration (11). In fact, a delicate equilibrium may possibly exist between E_2 and P_4 levels on day hCG + 1 and progesterone receptors in the endometrium. Thus, high P_4 concentrations on this critical day oppose E_2 induction of progesterone receptors and the preparation of the endometrial milieu for embryonic receptivity and implantation. We feel that this process is individual and varies with various patients. Consequently, the endometrium which is histologically not disrupted by high P_4 levels may still allow embryonic implantation with, as a result, low rates of pregnancy.

Finally, a further possible mechanism to explain the reduced fertilization and pregnancy rates in Group I is the hypothesis that higher LH levels in this phase result in hyperstimulation of thecal cells by means of the androgen pathway production (12).

Our results indicate that despite reduced implantation rates after transfer of embryos, a certain population of oocytes recovered from these follicles was capable of implanting, thus a relatively low rate of (8.8%) pregnancies per embryo transfer was nonetheless achieved.

In conclusion, the fertilization, cleavage, and pregnancy rates of the potentially fertilizable eggs are significantly lower ($P < 0.001$) in the "high-progesterone" patients than in the "normal-progesterone" group. We suggest that cancellation of IVF-ET cycles due to high P_4 concentrations on day hCG + 1 is not always necessary. We proceeded

to oocyte recovery and to IVF-ET in the latter cases and were able to retrieve oocytes and fertilize them, although the pregnancy rates were lower than in normal progesterone cases. While high P_4 concentrations may occur coincident with high LH levels and early luteinization, this is not always the case. When a large cohort of follicles has developed in the ovary, P_4 concentrations may be expected to rise.

It is true that the pregnancy rates in high-progesterone cases are rather low, yet pregnancies do occur. Since in the ambulatory setup of our IVF-ET program, aspiration of follicles by vaginal ultrasound, with paracervical anesthesia, is a minimally invasive procedure, it is still worthwhile.

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