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Serum progesterone at the time of human chorionic gonadotrophin does not predict pregnancy in in-vitro fertilization and embryo transfer

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Controversy exists as to whether the serum concentration of progesterone on the day of human chorionic gonadotrophin (HCG) administration following ovarian stimulation for in-vitro fertilization (IVF) and embryo transfer can be used to predict the likelihood of success. This retrospective study was undertaken to answer this question by analysing a large population of IVF and embryo transfer cycles (n = 756). In addition to the concentration of progesterone on the day of HCG administration, all variables known to impact on IVF and embryo transfer success (such as patient age), indication for IVF and embryo transfer, number of oocytes retrieved and the number of embryos generated and transferred were examined. There was a significant increase in the number of oocytes retrieved with increasing progesterone concentration at the time of HCG administration. However, there was no correlation of progesterone concentration at HCG administration with pregnancy and implantation rates. It is concluded that previous reports associating a slight elevation of progesterone in gonadotrophin-releasing hormone agonist ovarian stimulation cycles for IVF and embryo transfer may be misleading because of a small sample size or the presence of confounding variables that affect IVF and embryo transfer success.

Key words: HCG/IVF and embryo transfer success/ovarian stimulation/progesterone

Introduction

The role of serum progesterone concentrations at the time of human chorionic gonadotrophin (HCG) administration during stimulated cycles for in-vitro fertilization (IVF) and embryo transfer in predicting pregnancy rates remains controversial. Before the use of gonadotrophin-releasing hormone agonist (GnRHa) for pituitary desensitization, an untimely elevation of luteinizing hormone (LH) resulted in an early increase in serum progesterone concentration and decreased fertilization and pregnancy rates (Trounson and Calabrese, 1984; Feldberg *et al.*, 1989; Munabi *et al.*, 1990; Kagawa *et al.*, 1992; Mio *et al.*, 1992). Since the introduction of GnRHa into IVF and embryo transfer stimulation cycles has become routine, the frequency of the premature LH rise has decreased (Van Uem *et al.*, 1986; Howels *et al.*, 1987). Despite the decrease in the frequency of the premature LH rise, progesterone concentration may still increase towards the end of the follicular phase in a stimulated cycle. Modest progesterone concentration elevations (>0.9 ng/ml) in the late follicular phase that are not accompanied by an LH surge are thought by a number of investigators (Abbasi *et al.*, 1990; Schoolcraft *et al.*, 1991; Silverberg *et al.*, 1991; Check *et al.*, 1992; Fanchin *et al.*, 1993) to have an adverse effect on pregnancy rate in assisted reproductive technologies.

The practical consequences of a subtle rise in progesterone concentration before HCG administration remain unclear. Serum concentrations of progesterone at the time of HCG administration have been both reported (Schoolcraft *et al.*, 1991; Silverberg *et al.*, 1991; Abbasi *et al.*, 1990; Check *et al.*, 1992; Fanchin *et al.*, 1993) and refuted (Edelstein *et al.*, 1990; Garcia *et al.*, 1991; Loughlin *et al.*, 1991; Dodson *et al.*, 1993; Givens *et al.*, 1994) as predictors of pregnancy in cycles utilizing GnRHa suppression. Explanations for the controversial results include sample size errors and the intervention of confounders contributing to pregnancy. The majority of the previous studies have had relatively small sample sizes. Therefore, type II errors could have occurred in those studies reporting no association. Confounding variables most likely to contribute to the success or failure of IVF and embryo transfer cycles are the woman's age, indication for assisted reproductive technology and the number of embryos transferred (Staessen *et al.*, 1992; American Fertility Society, Society for Assisted Reproductive Technology, 1994). In the previous studies reporting an association between elevated progesterone concentration and decreased pregnancy rates, these factors were not considered when interpreting the data. To provide a solution to the existing controversy, our study compares values of previously reported serum progesterone concentration at the time of HCG administration with maternal age, indication for assisted reproduction treatment, number of oocytes retrieved, fertilization rate, number of embryos transferred and implantation rate, as well as pregnancy rate, in a large population (n = 756).

Materials and methods

A total of 756 cycles of IVF in 756 women at the Genetics and IVF Institute, Fairfax, VA, USA between 1 January 1989 and 31 December 1991 were studied. The age of the women and the indications for IVF and embryo transfer were recorded. If a couple had a combination of aetiological factors as a cause of their infertility (anovulation,

tubal, etc.), they were included in a group designated 'mixed'; the mixed group was subdivided into two groups based on the presence or absence of an associated male factor (World Health Organization criteria). All women received the GnRHa leuprolide acetate (Lupron; TAP Pharmaceuticals, North Chicago, IL, USA), 1.0 mg/day s.c., beginning on days 24–25 of the menstrual cycle preceding the IVF treatment cycle (4–5 days before next menses). Leuprolide acetate was given daily until the day of HCG (Profasi; Serono Laboratories Inc., Randolph, MA, USA) administration. The amount of GnRHa was reduced to 0.5 mg/day at the beginning of gonadotrophin treatment. The induction of ovulation was started after down-regulation (oestradiol concentration <35 pg/ml, progesterone concentration <1.0 ng/ml) as early as 7 days after the commencement of leuprolide acetate administration. All women received 225 IU i.m. of human menopausal gonadotrophin (HMG; Pergonal; Serono Laboratories Inc.) for 3 days. Thereafter, the dose of gonadotrophins was adjusted based on the follicular growth, determined by daily transvaginal ultrasound scans (Acuson 128Xp/10, Acuson Computed Sonography and General Electric RT 3600; CA, USA) and serial serum concentrations of oestradiol, progesterone and LH. A total of 10 000 IU HCG i.m. were given when there was an appropriate rise in serum oestradiol concentration for the number of follicles (150–200 pg/mature follicle) in each particular patient, and at least one or more follicles >16 mm in mean diameter. Transvaginal follicular aspiration was performed 34–36 h later. Gamete processing, cell culture technique and transfer procedures have been described previously (Wortham *et al.*, 1983). Embryo transfer was performed 2 days later. Excess (more than three or four) zygotes or embryos at the pronuclear stage were cryopreserved. Serum β-HCG was determined 11 days after embryo transfer. Progesterone supplementation (25 mg/day i.m.) was begun on the day after follicular aspiration and was continued until the pregnancy status was determined. The number of oocytes recovered, the fertilization and cleavage rates, as well as the number of embryos transferred, were recorded. A clinical pregnancy was defined as the presence of at least one intrauterine gestational sac 3 weeks after transfer.

Hormone assays

Blood was drawn between 07:30 and 09:00 h from the antecubital vein of each woman for the determination of oestradiol and progesterone concentrations. Serum oestradiol concentrations were determined by radioimmunoassay (Coat-A-Count; Diagnostic Products, Los Angeles, CA, USA). The intra- and interassay coefficients of variation were 5 and 6% respectively. Serum progesterone concentrations were determined by radioimmunoassay (Coat-A-Count; Diagnostic Products). The intra- and interassay coefficients of variation were 5 and 8% respectively. Serum β-HCG concentrations were determined by immunoradiometric assays (Serono Maia Clone, Rome, Italy). The coefficient of variation for a β-HCG concentration of 25 mIU/ml was 5%.

Statistics

A one-way analysis of variance with the Bonferroni correction and an unpaired *t*-test were performed on continuous variables. Values are expressed as means ± SD. For discontinuous variables, χ^2 and Fisher's exact tests were performed. In all analyses, $P < 0.05$ was considered statistically significant.

Results

Table I shows the infertility indications and mean age for the 756 cycles studied, as well as the numbers of retrievals and embryo transfers carried out in the aetiological groups. The women in the mixed + male group were significantly younger than the women in the tubal group.

Results by aetiological group

No statistical difference was observed in the number of days and the dosage of gonadotrophin medication between the aetiological groups at the time of HCG injection (data not shown).

Serum concentrations of progesterone on the day of HCG administration, the number of eggs retrieved, the number of zygotes formed, the number of embryos cleaved, the number of embryos transferred and the number of sacs (reflecting implantation rate) in the different aetiological groups are presented in Table II. The mixed + male group had a lower serum progesterone concentration at HCG administration than both the tubal and the male groups ($P < 0.05$). The tubal group had a significantly higher number of fertilized oocytes and cleaved embryos than both the male-only ($P < 0.05$ and $P < 0.01$ respectively) and the mixed + male groups ($P < 0.001$ and $P < 0.001$ respectively). No statistical difference among the aetiological groups was observed in the total number of eggs retrieved.

There was no difference in the mean number of embryos transferred or the pregnancy rate per transfer and implantation rates among the aetiological groups.

Cycle outcome

Table III lists the results based on progesterone concentration ranges (<0.5, 0.5–1.0 and >1.0 ng/ml) on the day of HCG administration. Statistical differences ($P < 0.001$) were observed between the three ranges of progesterone concentration in the number of eggs retrieved. There was a positive correlation between egg number and progesterone concentration ($r^2 = 0.11$, $P < 0.001$). A decrease in the number of fertilized oocytes and the number of cleaved embryos was seen in the group with a progesterone concentration <0.5 ng/ml when compared with the other two ranges $P < 0.01$ for fertilized oocytes and $P < 0.05$ for cleaved embryos). A significant decrease was observed in the number of embryos transferred between the group with a progesterone concentration <0.5 ng/ml and the group with a progesterone concentration between 0.5 and 1.0 ng/ml ($P < 0.001$), but not with the group with a progesterone concentration >1.0 ng/ml. No statistical difference was seen in pregnancy rate per transfer or implantation rate among the progesterone concentration range groups.

Variables associated with pregnancy

Table IV compares completed cycles that resulted in pregnancy with those that did not. There was no statistical difference in progesterone concentration at the time of HCG administration. There were statistical differences between the two groups in age ($P < 0.02$), number of eggs retrieved ($P < 0.005$), fertilization rate ($P < 0.0001$), cleavage rate ($P < 0.0001$) and mean number of embryos transferred ($P < 0.02$). The pregnant group was younger and had a greater number of eggs retrieved and embryos transferred.

In Table V, cycles are grouped by age range. Statistical

Table I. Maternal mean age, indications for in-vitro fertilization and embryo transfer, and numbers of retrievals and embryo transfers

Parameters	Diagnosis of infertility						
	Tubal	Male	Endometriosis	Mixed[a] + male	Mixed[a] – male	Unexplained	Total
No. of patients (%)	274 (36)	75 (10)	26 (3)	187 (25)	99 (13)	95 (13)	756 (100)
Age (years)[b]	35.4 ± 3.4[c]	34.4 ± 4.2	34.1 ± 3.2	34.1 ± 4.1[c]	35.1 ± 3.9	34.7 ± 3.9	35.1 ± 3.8
No. of retrievals	264	70	25	178	93	91	721
No. of embryo transfers	236	49	23	120	75	75	578

[a]Combination of factors causing infertility.
[b]Mean ± SD.
[c]Significantly different, $P < 0.01$.

Table II. Serum progesterone concentration at the time of human chorionic gonadotrophin (HCG) administration and cycle parameters in different aetiological groups

Parameters	Diagnosis of infertility					
	Tubal	Male	Endometriosis	Mixed + male	Mixed – male	Unexplained
Progesterone concentration at HCG (ng/ml)[a]	0.67 ± 0.31	0.72 ± 0.29	0.61 ± 0.23	0.58 ± 0.26	0.60 ± 0.34	0.64 ± 0.27
No. of eggs[a]	9.7 ± 6.7	9.1 ± 5.2	9.3 ± 4.3	8.9 ± 5.6	7.8 ± 5.9	9.5 ± 6.9
No. of eggs fertilized[a]	4.7 ± 4.5[b,c]	3.0 ± 3.1[b]	5.3 ± 3.6	2.9 ± 3.2[c]	3.8 ± 3.6	4.3 ± 3.5
Fertilization rate (%)	48	33	57	31	49	45
No. of fertilized eggs cleaved[a]	4.5 ± 4.4[d,e]	2.6 ± 2.8[d]	5.0 ± 3.6	2.7 ± 3.1[e]	3.6 ± 3.6	3.9 ± 3.1
Cleavage rate of fertilized eggs (%)	96	87	94	93	95	90
No. of embryos transferred[a]	2.8 ± 1.1	2.6 ± 1.1	3.0 ± 1.4	2.6 ± 1.3[c]	2.6 ± 1.1	2.8 ± 1.0
No. of embryo transfers	236	49	23	120	75	75
No. of pregnant women	45	8	4	15	13	15
Pregnancy rate per no. of transfers (%)	19	16	17	13	17	20
No. of embryonic sacs	59	8	6	20	14	17
Implantation rate (%)[f]	9	6	9	6	7	9

[a]Mean ± SD.
Mixed + male group had a significantly ($P<0.05$) lower progesterone concentration at the time of HCG administration than the male and tubal groups.
Values with the same superscripts were significantly different: [b]$P < 0.05$; [c]$P < 0.001$; [d]$P < 0.01$; [e]$P < 0.001$.
[f]No. of sacs/no. of embryos transferred.

Table III. Maternal age and cycle parameters by ranges of progesterone concentration (ng/ml) at the time of human chorionic gonadotrophin (HCG) administration

Parameters	Progesterone concentration at the time of HCG administration (ng/ml)[a]		
	<0.5 (0.25 ± 0.07)	0.5–1.0 (0.72 ± 0.15)	>1.0 (1.60 ± 0.14)
No. of cycles	196	444	81
Age (years)[a]	37.0 ± 3.8	35.0 ± 4.2	35.8 ± 4.7
No. of eggs[a]	6.8 ± 5.4[b]	11.2 ± 6.2[b]	12.6 ± 6.7
No. of eggs fertilized[a]	3.3 ± 3.1[c,d]	4.8 ± 4.2[d]	5.1 ± 3.9[c]
Fertilization rate (%)	49	43	40
No. of fertilized eggs cleaved[a]	3.3 ± 3.5[e]	4.3 ± 4.0[e]	4.7 ± 3.8[e]
Cleavage rate of fertilized eggs (%)	100	90	92
No. of embryos transferred[a]	2.5 ± 1.4[c]	3.0 ± 1.2[c]	2.9 ± 0.9
No. of embryo transfers	157	356	65
No. of pregnant women	23	74	13
Pregnancy rate per no. of transfers (%)	15	21	20
No. of embryonic sacs	27	92	15
Implantation rate (%)[f]	7	9	8

[a]Mean ± SD.
[b]$P = 0.001$. The number of eggs increases significantly between progesterone concentration ranges.
Values with the same superscripts within rows were significantly different: [c]$P < 0.01$; [d]$P < 0.001$; [e]$P < 0.05$.
[f]No. of sacs/no. of embryos transferred.

Table IV. Comparison of parameters in patients becoming pregnant with those not pregnant after completed in-vitro fertilization and embryo transfer cycles (values are means ± SD)

Parameters	Not pregnant (n = 468)	Pregnant (n = 110)	P value
Age (years)	36.0 ± 4.4	34.9 ± 4.0	<0.02
Progesterone concentration at HCG (ng/ml)	0.64 ± 0.31	0.66 ± 0.26	NS
No. of eggs	8.9 ± 6.1	10.8 ± 7.0	<0.005
No. of eggs fertilized	3.7 ± 3.9	5.3 ± 3.6	<0.0001
Fertilization rate (%)	42	49	<0.0001
No. of fertilized eggs cleaved	3.4 ± 3.7	5.1 ± 3.6	<0.0001
Cleavage rate of fertilized eggs (%)	92	96	<0.0001
No. of embryos transferred	2.6 ± 1.2	2.9 ± 1.2	<0.02

NS = not significant. HCG = human chorionic gonadotrophin.

Table V. Cycles analysed by age ranges

Parameters	Age range (years)[a]			
	<30 (27.6 ± 1.7)	30–34 (32.2 ± 1.4)	35–39 (36.9 ± 1.4)	≥40 (41.1 ± 1.3)
No. of cycles	54	225	305	172
Progesterone concentration at HCG (ng/ml)	0.66 ± 0.21	0.69 ± 0.28	0.62 ± 0.27	0.66 ± 0.37
No. of eggs[a]	9.8 ± 8.0	11.3 ± 6.2	8.9 ± 5.9	6.5 ± 4.1
No. of eggs fertilized[a]	3.6 ± 4.6	4.5 ± 4.1	4.6 ± 3.6	3.3 ± 2.9
Fertilization rate (%)	37	40	52	51
No. of fertilized eggs cleaved[a]	3.4 ± 4.5	4.3 ± 4.0	4.3 ± 3.4	3.3 ± 2.8
Cleavage rate of fertilized eggs (%)	94	96	93	100
No. of embryos transferred[a]	2.8 ± 0.9	3.0 ± 1.2	2.7 ± 1.1	2.3 ± 1.1
No. of embryo transfers	39	173	237	129
No. of pregnant women	11	40	46	13
Pregnancy rate per no. of transfers (%)	28	23	19	10
No. of embryonic sacs	17	50	54	13
Implantation rate (%)[b]	19	8	9	4

HCG = human chorionic gonadotrophin.
[a]Mean ± SD.
[b]No. of sacs/no. of embryos transferred.

differences were observed between the women aged <35 (<30 and 30–34 groups) and >35 years (35–39 and ≥40 groups) in the mean number of eggs retrieved ($P < 0.01$). Women aged ≥40 years had a significantly lower mean number of embryos transferred compared with women aged 30–39 years ($P < 0.01$), as well as a lower mean implantation rate compared with all other age groups ($P < 0.005$).

Discussion

An analysis of the data from 756 cycles of IVF and embryo transfer shows no differences in pregnancy rate within various ranges of progesterone concentration on the day of HCG administration. This result is in disagreement with previous reports (Abbasi *et al.*, 1990; Schoolcraft *et al.*, 1991; Silverberg *et al.*, 1991; Check *et al.*, 1992, Fanchin *et al.*, 1993). This discrepancy can be explained by differences in the sample size of the populations studied or in patient selection introducing confounders for pregnancy rates. The sample size in our study was 756 cycles, making the power of the study 95%. Thus the probability of a type II error is remote. The confounding variables that affect pregnancy rates after IVF and embryo transfer were therefore studied.

Factors shown previously to affect pregnancy rates after IVF and embryo transfer include maternal age, indication for assisted reproductive technology and number of embryos transferred. While our results showed no association between serum progesterone concentration at the time of HCG administration and pregnancy rate, they did show a relationship between maternal age, indication for assisted reproductive technology and pregnancy rate. Women aged <40 years had higher implantation rates than those aged ≥40 years ($P < 0.005$). Cycles with male factor indications had significantly fewer pregnancies compared with cycles without male factor indications ($P < 0.01$). The decrease in pregnancy rate after IVF and embryo transfer for older women and male factor indications prior to the availability of intracytoplasmic sperm injection have been documented previously (American Fertility Society, Society for Assisted Reproductive Technology, 1994). Because of the availability of embryo cryopreservation, the average number of embryos transferred in our study was three. Therefore, no difference in serum progesterone concentration at the time of HCG administration and the number of embryos transferred was evident.

Thus, pregnancy rates after IVF and embryo transfer are associated with maternal age and indication for assisted reproductive technology (and number of embryos transferred), not with serum progesterone concentration at the time of HCG administration. Why then do other studies report an association between progesterone concentration at the time of HCG

administration and pregnancy rate? In Schoolcraft *et al.*'s (1991) study, that showed a significant increase in pregnancy rate among women with a progesterone concentration <0.5 ng/ml at HCG administration compared with a concentration >0.5 ng/ml, a significant difference in maternal age between these two groups was also reported. Therefore, the difference in pregnancy rate in the two groups compared could be explained by differences in either maternal age or progesterone concentration at the time of HCG administration. This study did not describe indications for assisted reproductive technology but included only cycles that had at least three embryos transferred (Schoolcraft *et al.*, 1991). Silverberg *et al.*'s (1991) study also showed a decrease in pregnancy rate among women with a higher progesterone concentration at the time of HCG administration compared with those with a lower concentration. However, maternal ages for each progesterone concentration group were not reported. Only 4% of cycles were for male factor indication, and the number of embryos transferred in the high progesterone concentration group was the same as that for the low progesterone concentration group (Silverberg *et al.*, 1991). It is possible that the results of that study could also be explained on the basis of maternal age if the data were available.

Fanchin *et al.*'s (1993) study also reported a decreased pregnancy rate in women with a progesterone concentration >0.9 ng/ml at the time of HCG administration compared with those with concentrations ≤0.9 ng/ml. No differences in maternal age between progesterone concentrations ≤0.9 and >0.9 ng/ml were demonstrated. Male factor indications were excluded. The average number of embryos transferred in the progesterone concentration ≤0.9 and >0.9 ng/ml groups was not reported. The implantation and pregnancy rates reported for each group suggest that the number of embryos transferred in the progesterone concentration ≤0.9 ng/ml group was greater and could account for the increased pregnancy rate reported in this group. Implantation rates were similar in the progesterone concentration ≤0.9 (14%) and >0.9 ng/ml (11%) groups. Even so, the pregnancy rates were different in the progesterone concentration ≤0.9 (28%) and >0.9 ng/ml (16%) groups. To have a similar rate of implantation per embryo transferred and different pregnancy rates in the same cycle would require different numbers of embryos to have been transferred within each group.

While we have shown no association between serum progesterone concentration at the time of HCG administration and pregnancy rate when the number of embryos transferred was limited to three, we have shown a positive correlation between serum progesterone concentration and the number of oocytes retrieved (Table III). The more oocytes retrieved, the higher the serum concentration of progesterone ($P = 0.001$). Increases in the number of oocytes retrieved and fertilization rates were also significantly correlated with increased progesterone concentrations ($P = 0.001$) in Silverberg *et al.*'s (1991) study. Others have shown a positive correlation between serum progesterone concentration and pregnancy rate. Legro *et al.* (1993) reported a significant increase in clinical pregnancy rates in women with serum progesterone concentrations >1.2 ng/ml on the day of HCG administration (53 versus 25%, $P = 0.01$). Gonen *et al.* (1993) showed an increase in progesterone concentration on the day after but not the day of HCG administration in conception compared with non-conception cycles. Harada *et al.* (1991) have shown that pregnancy occurs only in those cycles in which elevated serum progesterone concentrations were observed during or within 12 h of HCG administration. Howles *et al.* (1987) reported a highly encouraging pregnancy rate when progesterone was administered 4 h prior to HCG injection. Elevated progesterone concentrations earlier in the follicular phase have been suggested to impair follicular recruitment (Sims *et al.*, 1994). However, no differences in pregnancy rate were observed when cycles with serum progesterone concentrations >1.0 ng/ml during cycle days 2–6 were compared with cycles with no demonstrable progesterone concentration rise (Sims *et al.*, 1994). From these studies it can be concluded that the development of receptive endometrium depends upon exposure to progesterone. More information is needed to determine the timing, dosage and exact mechanism of the effects of the mid-cycle progesterone rise on IVF cycle outcome. However, it can be postulated that the state of endometrial maturation around the time of embryo transfer is important. Further studies should be undertaken to evaluate the impact of pre-ovulatory changes in progesterone concentration on endometrial maturation and treatment outcome.

Whatever the mechanism of progesterone on endometrial maturation, we have shown no association between serum progesterone concentration at the time of HCG administration and pregnancy rates. We confirm previous reports of a correlation between pregnancy rates and maternal age, indication for assisted reproductive technology and number of embryos transferred. The controversy in the literature concerning the role of serum progesterone concentration at the time of HCG administration with respect to the pregnancy rate can be explained by the above confounding variables. Therefore, progesterone concentration at the time of HCG administration alone does not predict pregnancy.

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