

Pitfalls in the Use of a Single Rapid Progesterone Assay to Diagnose Early Ectopic Pregnancy

*Jerome H. Check, M.D., Jeffrey S. Chase, M.D.,
Kosrow Nowroozi, M.D., Richard Epstein, M.D.
and Beth Vetter, M.L.T.*

Abstract

Yeko et al have suggested that a single serum progesterone level determination (15 ng/ml) may be used to make an earlier diagnosis of an ectopic pregnancy in high-risk patients than the more established diagnostic approaches.¹ In order to test this hypothesis, early serum progesterone and 17-hydroxyprogesterone (17-OHP) levels in patients who had an ectopic pregnancy (n = 31) were examined retrospectively and compared to findings in a control group of patients who had normal intrauterine pregnancies (n = 78). Since a tubal factor had been responsible for their previous infertility, all patients were considered to be at risk for ectopic pregnancy. The results of this study indicated a substantial overlap in the range of progesterone and 17-hydroxyprogesterone levels in patients with normal intrauterine pregnancies and ectopic pregnancies, regardless of whether they received progesterone supplementation or ovulation-inducing drugs (OVID). In

our series of patients, a serum progesterone level of 15 ng/ml would have identified only 8 of 16 untreated patients, and 7 of 15 patients who took OVID, who later developed ectopic pregnancies. The use of exogenous progesterone also made it less likely that a patient who was subsequently diagnosed with ectopic pregnancy would have a serum progesterone level < 15 ng/ml. The 15 ng/ml cutoff value failed to identify some of the untreated patients who developed ectopic pregnancies and, due to the effect of progesterone supplementation and OVID therapy on this measurement, we suggest that a low serum progesterone level be used only as an adjunct to the more established procedures of serial HCG measurements and pelvic sonography for monitoring asymptomatic patients at risk for ectopic pregnancy.

Introduction

In a recently published study, Yeko et al suggested that a single serum progesterone level determination could be used to diagnose an early ectopic pregnancy.¹ According to the authors, a serum progesterone level < 15 ng/ml, when measured in women considered to be at risk for ectopic pregnancy, was 100%

From the Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Cooper Hospital/University Medical Center, Robert Wood Johnson Medical School, The University of Medicine and Dentistry, Camden, New Jersey. Reprint requests should be addressed to: Jerome H. Check, M.D., 7447 Old York Road, Melrose Park, PA 19126.

predictive ($n = 28$) of either an ectopic or a non-viable intrauterine pregnancy. From these results, they speculated that if a dilatation and curettage (D&C) were performed on the basis of a single progesterone concentration < 15 ng/ml, with laparoscopy reserved for cases where chorionic villi were absent, there would be little risk of aborting a potentially viable fetus. Moreover, they suggested that this approach, when compared to the use of serial human chorionic gonadotropin (HCG) measurements and pelvic sonography, would lead to an earlier diagnosis of ectopic pregnancy.

We suggest that there are several limitations to the use of a single serum progesterone level measurement as the sole criterion for diagnosing ectopic pregnancy in at-risk women. These include the use of ovulation-inducing drugs (OVID) or supplemental progesterone by at-risk patients. This subgroup of patients was not evaluated in the earlier study.¹

The present study was designed to assess the utility of a single serum progesterone level measurement in a population of previously infertile women. In these patients, the influence of OVID and progesterone therapy on the serum progesterone values was assessed, and the findings compared to those in high-risk women who had normal intrauterine pregnancies. Finally, measurements of 17-hydroxyprogesterone (17-OHP) were evaluated to determine if low levels were predictive of ectopic pregnancy in high-risk patients, especially those taking progesterone supplements.

Methods

Serum progesterone and 17-hydroxyprogesterone levels from two groups of previously infertile women, i.e., those who developed surgically confirmed ectopic pregnancies ($n = 31$) and those who had normal intrauterine pregnancies ($n = 78$), were examined retrospectively. Data from these

patients were obtained between 1984 and 1988. The group of patients with ectopic pregnancies was divided into patients who had been taking OVID ($n = 15$) and those who had not ($n = 16$); a further subdivision of these two groups was made on the basis of whether or not the women were taking progesterone supplements at the time the progesterone determinations were made. The group of women who had normal intrauterine pregnancies, all of whom were maintained on progesterone supplements, were also divided into those who had taken ($n = 40$) or not taken ($n = 38$) OVID.

Progesterone levels were measured using a solid phase radioimmunoassay (Diagnostic Products, Los Angeles, CA) and 17-hydroxyprogesterone levels were measured using a double antibody radioimmunoassay (Pantex, Santa Monica, CA).

For the purposes of this analysis, the first progesterone measurement, obtained during the second through sixth week post-ovulation, was tabulated. Differences in progesterone levels between and among the various groups were evaluated by analysis of variance. Between-group differences in 17-hydroxyprogesterone levels, which were obtained during the first six weeks post-conception, were analyzed using Fisher's least significant difference test. In all cases, statistically significant differences were denoted by p -values less than 0.05. Data are expressed as mean values \pm standard deviation.

Results

The mean serum progesterone level in patients with ectopic pregnancies who had taken OVID (22.2 ± 17.2) was significantly lower ($p < 0.05$) than the mean level in patients with normal intrauterine pregnancies who had taken OVID (59.9 ± 34.3) (Figure 1). Among the patients with ectopic pregnancies who had taken OVID, the mean serum progesterone level was higher in those taking

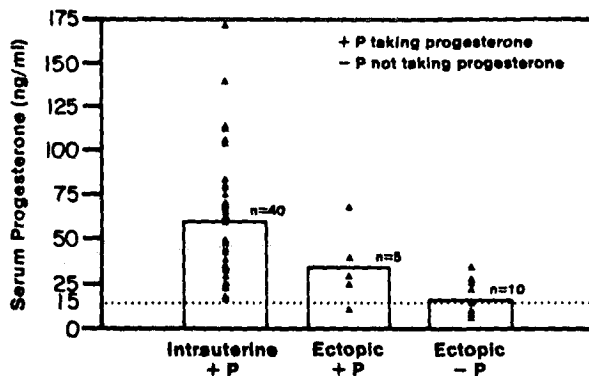


Figure 1. Early first trimester serum progesterone (P) levels in women who conceived following the use of ovulation inducing drugs (OVID). Serum P levels in patients with ectopic pregnancies who either took P supplementation (Ectopic + P) or who did not take P supplementation (Ectopic - P) were compared to serum P levels taken at comparable times from women with intrauterine pregnancies who were supplemented with P. The height of the histogram indicates the mean progesterone level.

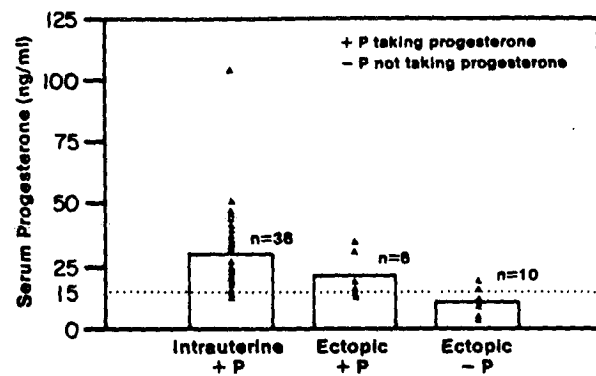


Figure 2. Early first trimester serum progesterone (P) levels in women who conceived without the use of OVID. Serum P levels in patients with ectopic pregnancies who either took P supplementation (Ectopic + P) or who did not take P supplementation (Ectopic - P) were compared to serum P levels taken at comparable times from women with intrauterine pregnancies who were supplemented with P. The height of the histogram indicates the mean progesterone level.

progesterone supplements (34.8 ± 21.3) than in those not receiving exogenous progesterone (15.9 ± 11.2); however, the difference between these values was not statistically significant.

The mean serum progesterone level among patients following natural ovarian cycles was also significantly lower ($p < 0.05$) in patients with ectopic pregnancies (14.9 ± 8.5) than in the corresponding control group (30.1 ± 15.8) (Figure 2). In the subgroup of patients with ectopic pregnancies and natural ovarian cycles, progesterone supplementation resulted in higher serum progesterone levels (21.5 ± 9.2) than those observed in patients who did not receive exogenous progesterone (11.0 ± 5.2). As in the case of patients with ectopic pregnancies who received OVID, the difference associated with progesterone supplementation did not reach statistical significance.

There was a considerable overlap in the serum progesterone levels of patients with ectopic and intrauterine pregnancies who had been taking OVID and those who were following natural ovarian cycles (Figures 1, 2). Among the patients who took OVID, a lower

serum progesterone limit of 15 ng/ml would have correctly identified all 40 patients who subsequently had normal intrauterine pregnancies, but only 7 of 15 patients who had ectopic pregnancies. In those patients who did not take OVID, 35 of 38 normal intrauterine pregnancies, and only 9 of 16 ectopic pregnancies, would have been correctly identified. Moreover, a progesterone level < 15 ng/ml was observed in only 8 of 16 patients with ectopic pregnancies who did not receive either OVID or progesterone supplementation.

As shown in Figures 3A and 3B, 17-hydroxyprogesterone levels were lower in patients with ectopic pregnancies than in those who had normal intrauterine pregnancies. These differences were statistically significant for serum levels obtained during the third week post-ovulation in patients taking OVID, and for the third through fifth week post-ovulation in patients not taking OVID. However, it should be noted that there was a considerable overlap in the range of individual 17-hydroxyprogesterone values observed in those patients with ectopic and intrauterine pregnancies who had taken OVID

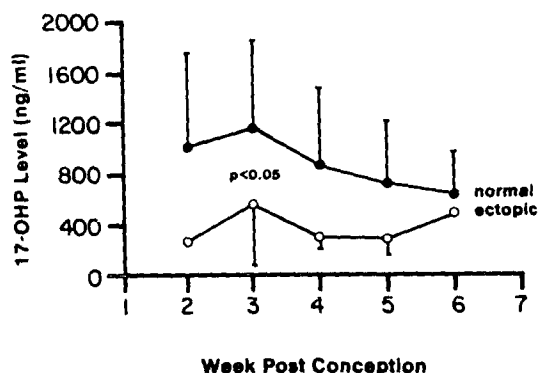


Figure 3A. Mean 17-hydroxyprogesterone levels in women with ectopic and normal pregnancies who conceived following the use of OVID. Serum samples were dated according to the time interval from conception. Error bars indicate one standard deviation from the mean.

and in those who had not taken OVID (Figures 4A and 4B).

Discussion

The results of this retrospective survey support the findings of previous reports that serum progesterone levels are lower in patients who develop ectopic pregnancies than in those who have normal intrauterine pregnancies.^{2,3} Similarly, data from the present study demonstrate that 17-hydroxyprogesterone levels among patients with ectopic pregnancies are also lower than those of normal control patients. However, the results of this investigation do not support the use of a 15 ng/ml progesterone cutoff value, first suggested by Matthews et al and later by Yeko et al, to distinguish between patients with ectopic and normal intrauterine pregnancies.^{1,4} While the 15 ng/ml progesterone cutoff value would have identified all 58 asymptomatic patients in the Yeko study who were subsequently diagnosed with ectopic pregnancies, this approach would have failed to identify two of seven asymptomatic patients of known high-risk potential who subsequently developed ectopic pregnancies. It should be noted that none of these seven patients received either progesterone supplementation or OVID.

Another important limitation in the use of

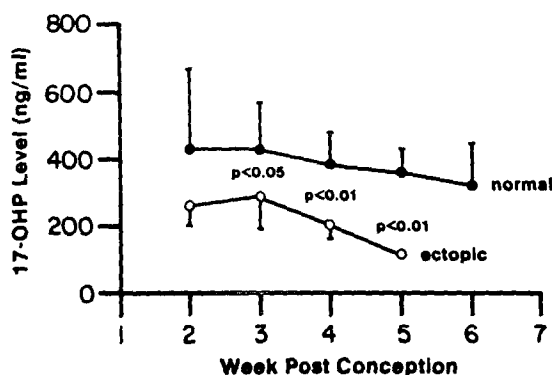


Figure 3B. Mean 17-OHP levels in women with ectopic and normal pregnancies who conceived without the use of OVID. Serum samples were dated as in Figure 3A and error bars indicate one standard deviation.

low serum progesterone levels in identifying patients with ectopic pregnancy is the use of OVID. In the present study, some patients with ectopic pregnancies who had been treated with OVID had serum progesterone levels >50 ng/ml. Although the elevated serum progesterone levels in these patients may have been related, in part, to progesterone supplementation, the data suggest that this alone could not have accounted for these high levels. For example, one patient who had an ectopic pregnancy and had been receiving OVID, but no exogenous progesterone, had a serum progesterone level above 25 ng/ml.

As expected, progesterone supplementation also reduces the utility of a serum progesterone level <15 ng/ml as a predictive factor for ectopic pregnancy. In our study, the use of exogenous progesterone resulted in a mean serum progesterone level above the 15 ng/ml cutoff, even in those patients who had an ectopic pregnancy and who did not receive OVID.

The possibility exists that the same serum sample measured by Yeko at 15 ng/ml might be as high as 20 ng/ml in our laboratory. If this were so, then none of the 10 patients with ectopic pregnancies who had not taken OVID or progesterone would have been missed as having an ectopic pregnancy. How-

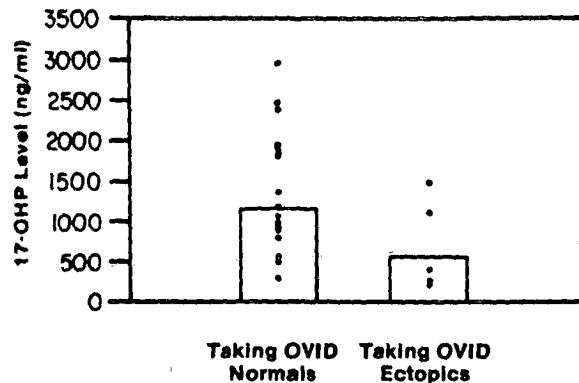


Figure 4A. 17-OHP levels at the third week post-conception in women with normal intrauterine pregnancies and ectopic pregnancies who conceived following the use of OVID. The height of the histogram indicates the mean 17-OHP level.

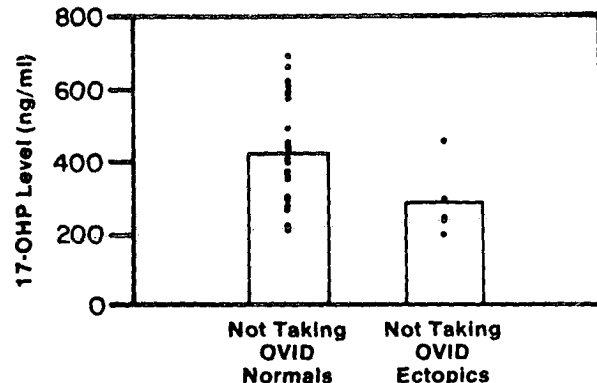


Figure 4B. 17-OHP levels at the third week post-conception in women with normal intrauterine pregnancies and ectopic pregnancies who conceived without the use of OVID. The height of the histogram indicates the mean 17-OHP level.

ever, we previously demonstrated that 70% of intrauterine pregnancies in patients with serum progesterone levels < 15 ng/ml may be saved by aggressive progesterone therapy.⁵ Therefore, by raising the limits, sensitivity would be improved, but specificity would be reduced, thus making a D&C even more likely to cause the death of a viable fetus by making a decision based merely on a serum progesterone level. Even a progesterone level of 20 ng/ml would still have missed ectopic pregnancies in women taking OVID or in 2 of 16 women not taking OVID, whether on progesterone or not.

The results of this study suggest that the 17-hydroxyprogesterone level may be helpful in identifying ectopic pregnancies in women not taking OVID, even if they are receiving progesterone supplementation, with significant differences found between three to five weeks post-conception. The 17-hydroxyprogesterone assay only showed a significant dif-

ference ($p < 0.05$) at the three-week post-conception levels. The doses of progesterone used for supplementation in pregnancies (100 mg-400 mg daily) have been previously demonstrated to raise mean serum progesterone levels an additional 4.3-9.4 ng/ml (unpublished data).

Conclusion

Because of the limitations revealed by this study, our findings suggest that neither a single serum progesterone determination, nor a single serum 17-hydroxyprogesterone measurement, should be considered diagnostic for ectopic pregnancy. Instead, if one is aware of the limitations of these measurements, they may be of clinical value as an adjunct to the more standard procedures, i.e., serial HCG levels and serial pelvic sonograms, for evaluating the location of a pregnancy.

References

1. Yeko TR, Gorrill MJ, Hughes LH, Rodi DA, Buster JE, Sauer MV et al: Timely diagnosis of early ectopic pregnancy using a single blood progesterone measurement. *Fertil Steril* 48:1048-1050, 1987.
2. Milwidsky A, Segal S, Menashe M, Adoni A, Palti Z et al: Corpus luteum function in ectopic pregnancy. *Int J Fertil* 29:244-246, 1984.
3. Radwanska E, Frankenberg J, Allen EI et al: Plasma progesterone levels in normal and abnormal early human pregnancy. *Fertil Steril* 30:398-402, 1978.
4. Matthews CP, Coulson PB, Wild RA et al: Serum progesterone levels as an aid in the diagnosis of ectopic pregnancy. *Obstet Gynecol* 68:390-394, 1986.
5. Check JH, Winkel CA, Check ML: Abortion rate in progesterone treated women presenting initially with low first trimester serum progesterone levels. *Am J Gyn Health* 4(2):63-64, 1990.