Human Reproduction vol.7 no.5 pp.711–717, 1992

The value of serum levels of oestradiol, progesterone and β-human chorionic gonadotrophin in the prediction of early pregnancy loss

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Serial serum levels of oestradiol, progesterone and the β-subunit of human chorionic gonadotrophin (β-HCG) had been performed in 674 cycles in women conceiving a singleton pregnancy, either spontaneously or as a result of assisted conception. To determine the value of these estimations in the prediction of early pregnancy loss, frequency distribution curves and receiver operating characteristic curves were derived for the respective hormones measured at weeks 4–7 of gestation and expressed as multiples of the median (MoM) values in pregnancies occurring both with and without ovarian stimulation. A cut-off level of β-HCG <0.5 MoM gave a sensitivity of 68% with an odds ratio of 4.0 at 7 weeks in unstimulated cycles in the prediction of pregnancy failure. A cut-off of 0.8 MoM for progesterone gave a sensitivity of 59% and an odds ratio of 2.8. Prospective hormonal monitoring during the early weeks of gestation may be useful in the prediction of early pregnancy loss and should help to avoid the emergency presentation of some of the complications of early pregnancy, in particular ectopic pregnancy. The limitations imposed by multiple pregnancies and uncertain gestation due to menstrual data may restrict the use of this strategy to specialist fertility centres.

Key words: assisted reproduction/early pregnancy failure/ectopic pregnancy/spontaneous abortion

Introduction

Early pregnancy loss remains an important cause of reproductive failure despite considerable research initiatives aimed at determining the causes. Success in predicting those pregnancies which are destined to fail has been limited. What has emerged is that early pregnancy failure represents the end point of a heterogeneous group of conditions which present with painful vaginal bleeding after variable periods of amenorrhoea. Various groups have reported clinical criteria, measurement of the hormones and proteins of fetal, placental and ovarian origin, biophysical tests and diagnostic ultrasound examination with varying sensitivities and specificities for the prediction of early pregnancy loss (Salem *et al.*, 1984; Westergaard *et al.*, 1985; Stabile *et al.*, 1989). Most efforts have proved inconclusive due to the failure to distinguish between the various causes of pregnancy failure and uncertainty in the menstrual data used for estimating the gestational age.

In recent years, assisted conception treatments have allowed close examination of women likely to conceive and attention has focused on the conception cycle and events occurring during early pregnancy, with accurate monitoring of the timing of ovulation and conception. Earlier work has demonstrated the potential for hormonal monitoring in the prediction of pregnancy outcome (Yovich, 1986; Yovich *et al.*, 1986). In this paper, we present data gathered at a single centre where conception has occurred under close surveillance with prospective collection and measurement of the serum levels of hormones of ovarian and trophoblastic origin. Analysis of these data indicates that some of those pregnancies which are destined to fail can be identified as early as the time of the first missed period using hormonal evidence alone. Furthermore, for each individual, an explicit risk factor may be estimated on the basis of the results of the hormone analysis. Individuals may thus be identified for more intensive monitoring to forewarn of potential ectopic pregnancies, or identify those who may benefit from progestational support.

The heterogeneous nature of the conditions must be borne in mind and the level of expectation of the tests adjusted accordingly; however, our data suggest that there is a place for hormonal monitoring in specialist fertility clinics where the timing of ovulation is well documented and the risk of early pregnancy wastage is high.

Materials and methods

Subjects and clinical procedures

A prospective study was made of 674 singleton pregnancies which were conceived as a result of treatment or investigation of infertility at the PIVET Medical Centre between 1985 and 1989. Conception occurred after either spontaneous ovulation or ovarian stimulation with clomiphene citrate or human menopausal gonadotrophin (HMG) combined with 'timed' sexual intercourse, artificial insemination or a variety of in-vitro fertilization-related procedures (Yovich and Grudzinskas, 1990). Pregnancy was diagnosed when serum levels of β-human chorionic gonadotrophin (β-HCG) were >25 IU/l on or after day 16 of the luteal phase, with a significant rise occurring over the ensuing week. Although women conceiving after assisted conception procedures usually received luteal phase support of 1000 IU HCG i.m. (Profasi; Serono) on days 4, 7, 10 and 13 after the HCG trigger, the effect of this on day 16 serum β-HCG levels was known to be negligible (Yovich, 1990). Trans-

abdominal pelvic ultrasound using a 3.5 MHz sector scanner was performed at 7 weeks of gestation or earlier if clinically indicated.

Definitions

Pregnancies with falling serum β-HCG levels and no detectable gestation sac on ultrasound examination by 28 days after ovulation were considered to be subclinical or 'biochemical' pregnancies (Yovich and Grudzinskas, 1987). Curettage was not performed in such cases and these women were not included in the present analysis as pregnant subjects. Pregnancies in which a gestation sac was demonstrated but without evidence of a viable intrauterine fetus were regarded as 'blighted ovum' or anembryonic pregnancies. Pregnancies which miscarried after the detection of embryonic heart activity were diagnosed as spontaneous abortions. Ectopic pregnancies were diagnosed when the serum β-HCG titre was elevated but no intrauterine pregnancy could be identified by ultrasound at 7 weeks gestation or earlier when the clinical condition dictated. The diagnosis was confirmed at laparoscopy.

Blood samples

Blood samples were taken between 0700 h and 0930 h each week until either the 12th week of gestation or definitive treatment was instigated, whichever was the sooner. The serum was separated by centrifugation within 4 h of collection and the levels of oestradiol, progesterone and β-HCG were analysed in daily assays as described below.

Assays

Measurements of the serum levels of oestradiol, progesterone and β-HCG were performed initially using commercially available radioimmunoassay kits. Oestradiol was assayed using a coated tube competitive assay (Diagnostic Products Corporation, Los Angeles, USA), progesterone and β-HCG were assayed using a liquid phase competitive immunoassay (Amersham Amerlex-M, Amersham International plc, UK). Since April 1989, an enhanced luminescence immunoassay system (Amerlite, Amersham International plc, UK) with improved performance characteristics has been used. In order to assess the correlation between the two assays, 162 samples were measured using both systems. For the purposes of this paper, the more recent oestradiol and progesterone results were transformed to the reference ranges of the radioimmunoassays using the appropriate correlation coefficients. The levels of β-HCG were not found to be significantly different and were left unchanged.

Statistical analysis

To allow for the appreciable variation in hormone levels in the early part of the first trimester of pregnancy, hormone concentrations were expressed as multiples of the median (MoM) values for ongoing pregnancies at the same gestational age. Low serum levels of β-HCG, progesterone or oestradiol were proposed as positive tests for early pregnancy loss. Various cut-off levels could be chosen. Whereas a higher cut-off level increased the detection rate or sensitivity it also increased the false positive rate. The accepted practice was followed whereby 'sensitivity' was defined as the proportion of failing pregnancies correctly identified by a positive result, and the 'false positive rate' was defined as the proportion of normal pregnancies incorrectly identified by a positive result. The relationship between sensitivity and false positive rate could be expressed graphically as a receiver operating characteristic curve (Metz, 1978; Richardson *et al.*, 1985).

The ratio of sensitivity/false positive rate gave a measure of the likelihood of losing the pregnancy. This was expressed as an odds ratio and was preferred to the predictive value since comparisons between values were more easily understood. For instance an odds ratio of 4 corresponded to a predictive value of 80% whilst an odds ratio of 9, clearly more than twice as likely, corresponded to a predictive value of 90%.

Results

The results are presented for weeks 4–7 from the last menstrual period. After week 7, the numbers of patients in the groups diagnosed as early pregnancy loss diminished as the diagnosis had usually been confirmed. The number of observations made at each week of gestation is shown in Table I.

The serum levels of the ovarian steroids, oestradiol and progesterone, were considerably elevated following ovarian stimulation compared with unstimulated cycles. The results obtained for these two groups were therefore considered separately. No significant difference was observed between the serum levels of β-HCG in cycles with and without ovulation induction.

Figures 1, 2 and 3 show the frequency distribution curves for serum oestradiol, progesterone and β-HCG levels, respectively, for ongoing pregnancies and early pregnancy losses following spontaneous ovulation at each week of gestation. The hormone levels were expressed as MoM values of the normal ongoing population at each week of gestation. In each case, the discrimination between viable and non-viable pregnancies increased with gestational age. Similar curves were produced for pregnancies conceived after ovulation induction but are omitted from this report.

Table I. Classification of pregnancies including those diagnosed as early pregnancy loss, showing the number of observations made at gestational weeks 4–7 for each category

	Ongoing	Sp. abort	Bl. ovum	Ectopic
Unstimulated conception cycles				
Week 4	66	12	17	14
Week 5	149	18	38	24
Week 6	185	25	45	19
Week 7	198	18	47	14
Total	260	36	56	32
Stimulated conception cycles				
Week 4	122	26	69	36
Week 5	125	29	79	40
Week 6	127	29	79	34
Week 7	125	29	65	23
Total	130	32	87	42

Sp. abort = spontaneous abortion, Bl. ovum = blighted ovum

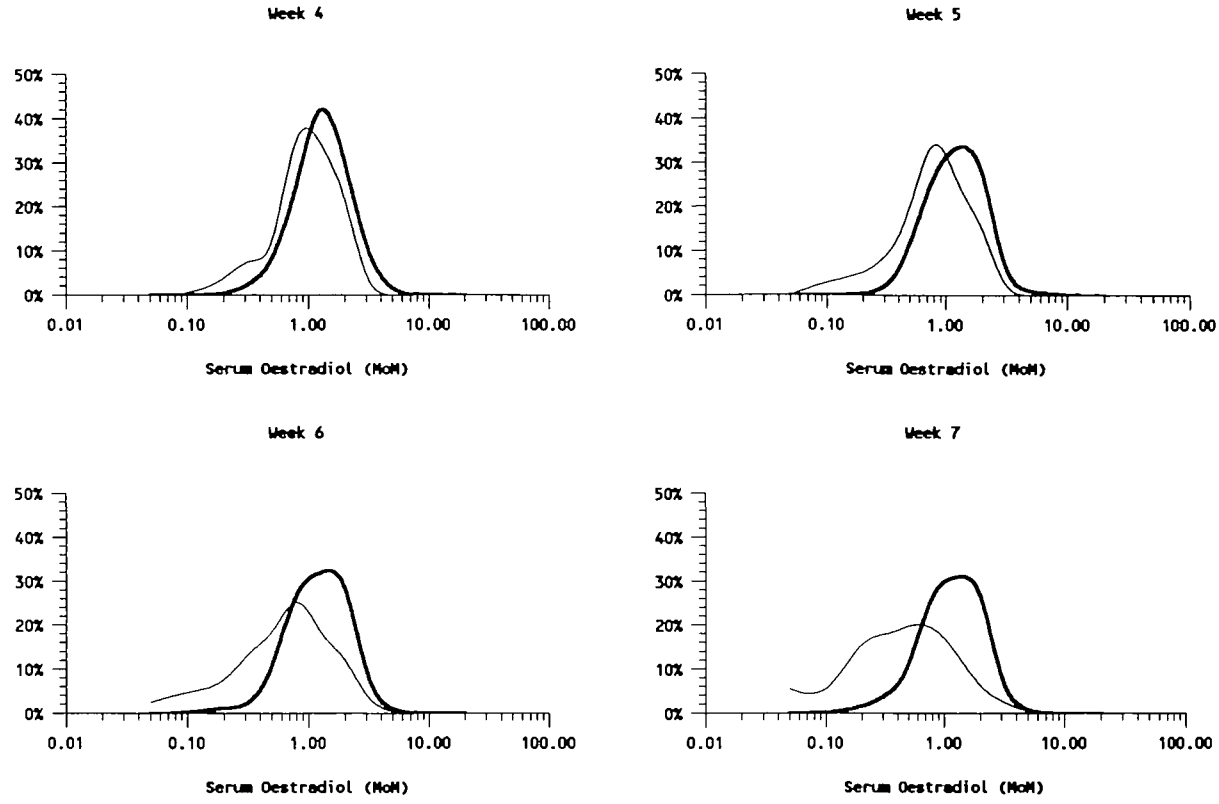

Fig. 1. Frequency distribution curves for serum oestradiol levels for ongoing (bold line) and failing pregnancies (faint line) at weeks 4–7 of gestation following spontaneous ovulation. Hormone levels were expressed as multiples of the median (MoM) values of the normal ongoing population at each week of gestation.

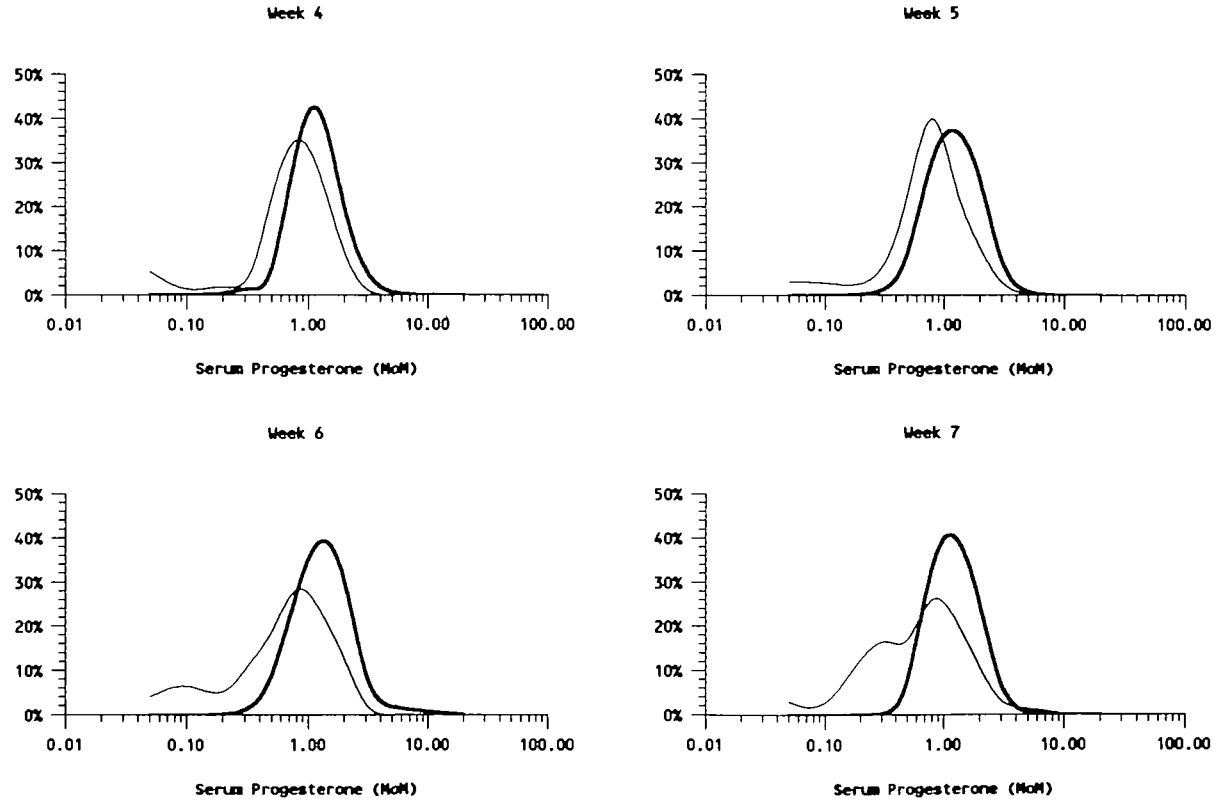

Fig. 2. Frequency distribution curves for serum progesterone levels for ongoing (bold line) and failing pregnancies (faint line) at weeks 4–7 of gestation following spontaneous ovulation. Hormone levels were expressed as described for Figure 1.

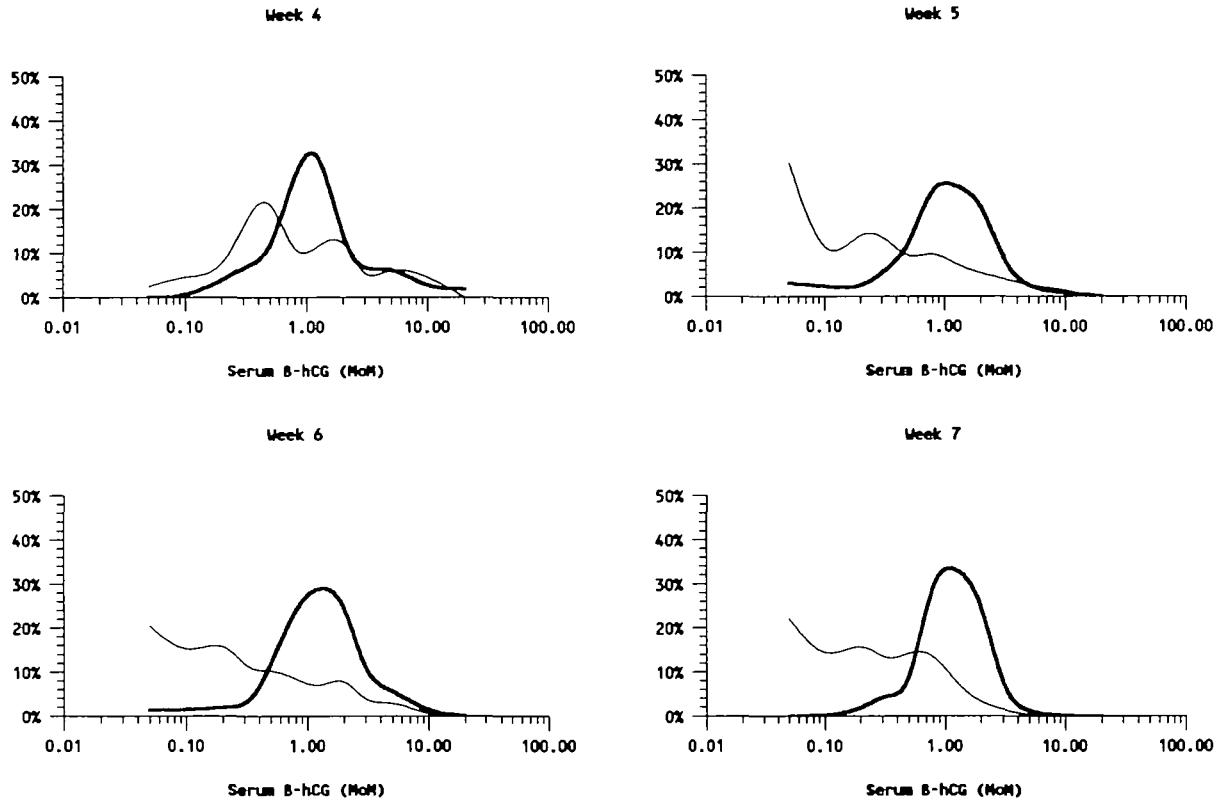

Fig. 3. Frequency distribution curves for serum β-HCG levels for ongoing (bold line) and failing pregnancies (faint line) at weeks 4–7 of gestation following spontaneous ovulation. Hormone levels were expressed as described for Figure 1.

The receiver operating characteristic curves for oestradiol, progesterone and β-HCG following spontaneous ovulation are shown in Figures 4–6. The curves further demonstrate that discrimination between failing and ongoing pregnancies improves as gestational age increases.

Table II shows the likelihood of an early pregnancy loss determined by serum levels of β-HCG, progesterone and oestradiol below various arbitrary limits in unstimulated cycles. The likelihood was expressed both as an odds ratio and predictive value. Where a value of 0 appeared in the denominator, i.e. no false positives were detected, an odds ratio of >99 was assigned. For example, if a cut-off value of 0.5 MoM was chosen for progesterone, the odds ratio increased from 7 (predictive value 88%; sensitivity 29%) at week 4 to 37 (predictive value 97%; sensitivity 41%) at week 7 of gestation in unstimulated pregnancies. If a cut-off level of 0.8 MoM was chosen, the odds ratio was reduced to 3.3 (predictive value 77%; sensitivity 64%). At this cut-off level, the values varied little with gestational age. The values in stimulated cycles are shown in Table III.

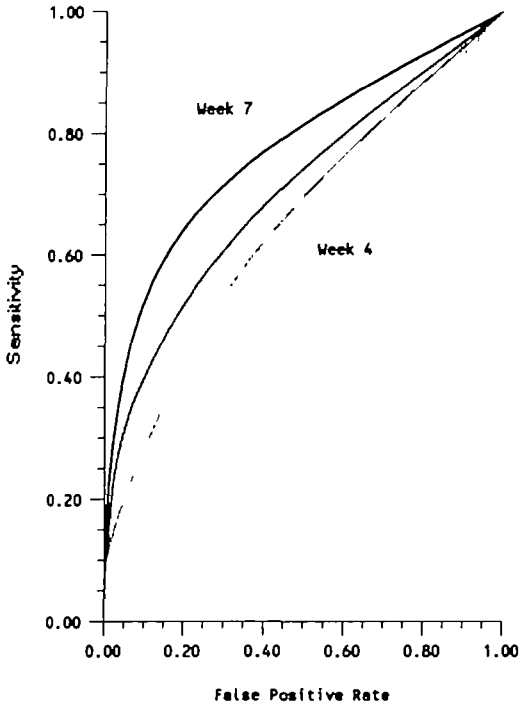

Fig. 4. Receiver operating characteristic curves for serum oestradiol levels for weeks 4–7 of gestation. (Boldness of the lines increases with gestational age.)

Discussion

This study analyses hormonal and ultrasound data collected prospectively during pregnancies achieved in a subfertile population attending a specialist infertility clinic. The study was undertaken to determine whether a subgroup of pregnancies destined to fail could be identified from endocrine measurements made prior to definitive examination by transabdominal pelvic ultrasound in the seventh week. Unfortunately, a transvaginal ultrasound scanner was not available at the time of the study. Subsequent reports would suggest that transvaginal

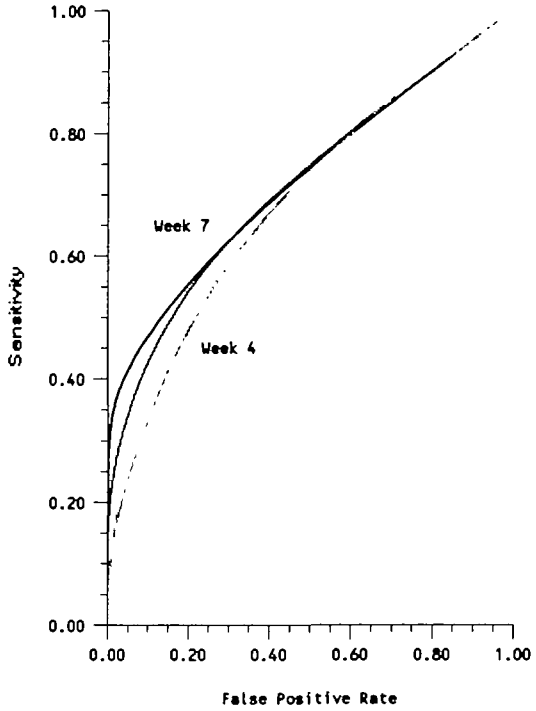

Fig. 5. Receiver operating characteristic curves for serum progesterone levels for weeks 4–7 of gestation.

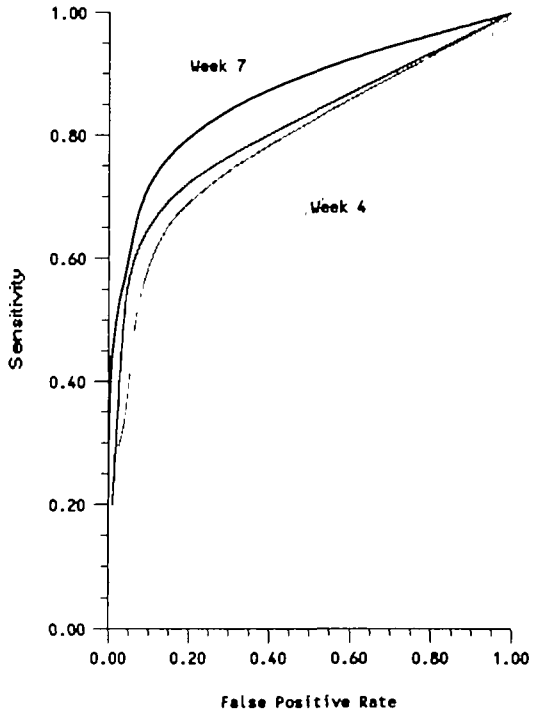

Fig. 6. Receiver operating characteristic curves for serum β-human chorionic gonadotrophin (β-HCG) levels for weeks 4–7 of gestation.

ultrasonography may improve the diagnostic accuracy of this investigation.

The method of data presentation adopted follows that recently reported in early pregnancy screening for the detection of fetal abnormality (Wald *et al.*, 1988). This approach not only affords

Table II. The likelihood of early pregnancy loss in unstimulated pregnancies determined by serum levels of β-human chorionic gonadotrophin (HCG), progesterone and oestradiol below various arbitrary limits, expressed as odds ratio and predictive value (in parentheses)

MoMs	Week 4	Week 5	Week 6	Week 7
β-HCG				
0.05	>99 (100%)	9.5 (90%)	20 (95%)	>99 (100%)
0.1	>99 (100%)	4 (80%)	7.3 (88%)	>99 (100%)
0.2	20 (95%)	3.2 (76%)	6.7 (87%)	16 (94%)
0.33	1.6 (62%)	3.4 (77%)	6 (86%)	6.3 (86%)
0.5	1.8 (64%)	2.7 (73%)	4.4 (81%)	4 (80%)
0.8	1.7 (63%)	2.2 (69%)	2.8 (74%)	3.3 (77%)
Progesterone				
0.05	>99 (100%)	>99 (100%)	>99 (100%)	>99 (100%)
0.1	>99 (100%)	>99 (100%)	>99 (100%)	>99 (100%)
0.2	>99 (100%)	>99 (100%)	>99 (100%)	>99 (100%)
0.33	>99 (100%)	>99 (100%)	>99 (100%)	>99 (100%)
0.5	7 (88%)	11.5 (92%)	10.3 (91%)	37 (97%)
0.8	3.3 (77%)	2.7 (73%)	3.1 (76%)	2.8 (74%)
Oestradiol				
0.05	>99 (100%)	>99 (100%)	>99 (100%)	>99 (100%)
0.1	>99 (100%)	>99 (100%)	>99 (100%)	>99 (100%)
0.2	>99 (100%)	>99 (100%)	7 (88%)	11 (92%)
0.33	3.5 (78%)	20 (95%)	3.5 (78%)	10 (91%)
0.5	1.8 (64%)	5.2 (84%)	2 (67%)	4.4 (81%)
0.8	2.1 (68%)	2.3 (70%)	2.1 (68%)	2.9 (74%)

MoM = multiples of the median value of the normal ongoing population at each week of gestation.

Table III. The likelihood of early pregnancy loss in stimulated cycles determined by serum levels of β-human chorionic gonadotrophin (HCG), progesterone and oestradiol below various arbitrary limits, expressed as odds ratio and predictive value (in parentheses)

MoMs	Week 4	Week 5	Week 6	Week 7
β-HCG				
0.05	>99 (100%)	>99 (100%)	>99 (100%)	>99 (100%)
0.1	>99 (100%)	10 (91%)	40 (98%)	>99 (100%)
0.2	3.9 (80%)	9 (90%)	16.3 (94%)	20.3 (95%)
0.33	1.5 (60%)	3.9 (80%)	10 (91%)	8.8 (90%)
0.5	1.3 (57%)	2.8 (74%)	5.7 (85%)	5.3 (84%)
0.8	1 (50%)	2 (67%)	2.1 (68%)	2.4 (71%)
Progesterone				
0.05	>99 (100%)	>99 (100%)	>99 (100%)	>99 (100%)
0.1	>99 (100%)	>99 (100%)	>99 (100%)	>99 (100%)
0.2	7.5 (88%)	24 (96%)	>99 (100%)	>99 (100%)
0.33	3.8 (79%)	6.3 (86%)	6.3 (86%)	19.5 (95%)
0.5	3.1 (76%)	3.2 (76%)	4 (80%)	5.4 (84%)
0.8	1.7 (63%)	1.8 (64%)	2.2 (69%)	2 4 (71%)
Oestradiol				
0.05	>99 (100%)	>99 (100%)	>99 (100%)	>99 (100%)
0.1	>99 (100%)	>99 (100%)	>99 (100%)	>99 (100%)
0.2	3.5 (78%)	7 (88%)	16 (94%)	30 (97%)
0.33	3.3 (77%)	6 (86%)	5.3 (84%)	14.7 (94%)
0.5	1.8 (64%)	2.5 (71%)	3.8 (79%)	4.8 (83%)
0.8	1.5 (60%)	1.7 (63%)	2 (67%)	2 (67%)

MoM = multiples of the median value of the normal ongoing population at each week of gestation.

application by other laboratories but also allows a unique risk of failure to be ascribed for any given patient on the basis of the serum hormone level from the ratio of the heights of the two curves at that hormone level. For instance a patient with a progesterone level of 0.5 MoM at week 4 gestation has an odds ratio of 4.3 for pregnancy loss (predictive value 81%).

The results indicate that monitoring serum hormone levels can be of value during early pregnancy prior to the stage at which ultrasound examination has been shown to be helpful (Stabile *et al.*, 1987). Considering the three hormones measured in this study, β-HCG levels were of greater predictive value than progesterone levels, which were more useful than oestradiol levels.

A proportion of failing pregnancies can be identified at an early stage, even at the time of the first missed menstrual period. Early identification might offer the potential for therapeutic intervention depending upon the reason for failure. Therapeutic agents which may be contemplated include progesterone, medroxyprogesterone acetate and HCG (Yovich *et al.*, 1988; Yovich and Grudzinskas, 1990). At least 50% of pregnancy losses are known to be due to chromosomal disorders of the embryo (Boué *et al.*, 1975, 1985; Lower *et al.*, 1991); however, there could be a subgroup where inadequate function of the corpus luteum is the underlying cause. It is possible that these women may respond favourably to treatment with progestational agents, although this hypothesis has not been tested. Previous trials of progestational agents have not excluded chromosomally abnormal pregnancies and this may explain why there was a failure to demonstrate significant advantages. Moreover, earlier identification of early pregnancy failure may decrease the likelihood of emergency presentation. In this context, it should be noted that almost 25% of the pregnancy losses were ectopic pregnancies. Nevertheless, the mainstay of this diagnosis should still be by ultrasound scan and quantitative β-HCG.

Caution must be exercised in extrapolation from a selected study of this nature to the wider clinical situation, since multiple pregnancies have been excluded and the gestational age was always accurately known. The presence of multiple gestation sacs will usually be identified at an early ultrasound scan. These pregnancies warrant closer examination because of the potential complications; in particular, the influence on serum hormone levels and the effect of the vanishing sac on pregnancy outcome need to be fully investigated. Inaccurate dating of pregnancies conceived spontaneously may adversely affect the reliability and usefulness of hormone estimations; however, this caveat does not apply in the case of pregnancies conceived after assisted conception where complications, particularly ectopic pregnancy, are more common and any decrease in the rate of early pregnancy loss would be welcomed. It is also important to bear in mind the considerable emotional and financial investment in such pregnancies when considering the cost–benefit analysis.

The data presented here support previous reports from this centre (Yovich *et al.*, 1986). Other reports have independently confirmed that depressed levels of oestradiol, progesterone and β-HCG were of prognostic significance in pregnancies conceived following IVF–embryo transfer (ET) (Yamashita *et al.*, 1989). The evidence elsewhere has been conflicting; Whittaker *et al.* (1989) observed similar rates of production of ovarian steroids in 72 normal pregnancies and 33 failing pregnancies up to 6 weeks of gestation and found that HCG was not a sensitive predictor of subsequent pregnancy failure. Westergaard *et al.* (1985) and Salem *et al.* (1984) provided evidence from pregnancies not associated with IVF–ET with which our findings agree. Recent reports indicate that the rate of change of serum levels of β-HCG may be useful in identifying pregnancies which are likely to fail (Lenton, 1990). Hahlin *et al.* (1990) found that a single progesterone estimation of <30 nmol/l discriminated 88% of ectopic pregnancies and 83% of spontaneous abortions in their series. This series included women presenting rather late in pregnancy and in whom there was clinical suspicion of ectopic pregnancy, i.e. with pain and vaginal bleeding or anamnestic risk factor. They were unable to distinguish between ectopic pregnancy and spontaneous abortion using this test alone.

Receiver operating characteristic curves demonstrate graphically the relationship between sensitivity and the false positive rate. The high false positive rate at earlier gestational age does not detract from the value of such monitoring, since the consequences of a false positive result are not serious. At worst, this may lead to unnecessary exposure to hormonal support treatment and closer surveillance. In our experience, progestational therapy does not cause the retention of abnormal fetuses (Yovich *et al.*, 1988).

In conclusion the data presented demonstrate that monitoring of serum hormones may be of substantial benefit to a number of pregnancies where the risk of early failure is high and the use of early obstetric endocrine support may be contemplated.

Acknowledgements

The authors are grateful to their colleagues at PIVET Medical Centre for assistance with this manuscript, particularly Paul Shenton and Fiona O'Shea who conducted the hormone assays and also to Professor J.G.Grudzinskas for helpful comments.

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Received on July 26, 1991; accepted on January 17, 1992