The Hormonal Profile in Ectopic Pregnancies

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Abstract

We prospectively investigated the maternal serum level of beta- human chorionic gonadotropin (fl-hCG) progesterone (P), estradlol (E2), human placental lactogen (HPL), alfafetoprotein (AFP) and cancer antigen 125 (CA 125) during the first trimester of normal and abnormal pregnancies. Serum samples were obtained from 20 women with normal intro-uterine pregnancy (IUPs). Fifteen whose pregnancies were complicated with spontaneous abortion and 31 wIth surgically and pathologically confirmed ectopic pregnancies (EPs). The mean serum levels of fi-hCG, E2 and P In patients with Eps (9490.55±3071.2 mlU/ml, 1001±22.09 pg/mi, 4.18±1.19 ng/ml, respectively) were significantly lower than those measured In normal IUPs (73796.8±15554.7 mlU/ml, 500.15±98.84 pg/mI, 19.2±2.8 ng/ml respectively($p<0.001$) and significantly lower than in patients with spontaneous abortIon (22524±6213 mIU/ml, $p<0.05$, 339.8±112.16 pg/mI, $p<0.01$, 10.59±3.03 ng/ml, $p.<0.05$ respectively). No significant difference was recorded with respect to serum levels of HPL, AFP and CA 125 among the groups. We also investigated the diagnostic value of simple E2 and P in patients with EPs. We could not identify a discriminatory cutoff value because there was a considerable overlap in serum P ans E2 levels between the patients with IUPs and EPs. In conclusion, It is not possible to define a cutoff discriminatory value of P and E2 that completely separates ectopic from IUPs. but the addition of these assays to the workup of a patient with suspected EP may facilitate the earlier diagnosis of EP (JMPA 44 : 45, 1994).

Introduction

The incidence of ectopic pregnancy appears to be rising dramatically and this has been attributed to the increasing rate of pelvic inflammatory disease, current widespread use of the intrauterine devices, increasing availability of assisted reproduction and tubal microsurgery and finally to improved methods of diagnosing and reporting[1,2]. Although there has been a decrease in deaths, ectopic pregnancy is still the major cause of maternal mortality in the first trimester of pregnancy and accounts for about 10 percent of maternal deaths[2,3]. Its occurrence also has a significant detrimental effect on future fertility and less than half of the cases will conceive again[4]. Although major advances in the diagnosis of ectopic pregnancy occurred, the early diagnosis is still a challenge for the clinician. Serial quantitative measurements of theft sub unit of human chorionic gonadotropin (b-hCG) has accepted to the most beneficial nut two blood samples must be obtained atleast 2 to 3 days a part[1,5]. Accurate interpretation of sonographic findings depends on the duration of amenorrhea, the experience of the sonographer and the equipment used and it also requires correlation with the patients serum B-hCG level[1,5,6]. Therefore, several biochemical markers have been investigated for their use in the early diagnosis of ectopic pregnancy, but most of the results are contradictory. We therefore conducted a study to evaluate the levels of various hormones in ectopic pregnancy and to determine whether they might be useful in the early diagnosis.

Materials and Methods

The serum values of B-hCG E2, P, APP, HPL and CA-125 were measured in a total 66 pregnancies

with an estimated gestational age of 6 to 8 weeks based on transvaginal ultrasound and menstrual dating. Serum samples from 31 EPs were collected at the time of surgery and in all cases it was confirmed with pathological examination. The control group consisted of 20 patients with normal IUPs and 15 cases with early spontaneous abortions. Blood samples were collected from antecubital veins and immediately centrifugated and serum was stored at -40°C until analysed. B-hCG and HPL (Medgenix Diagnostic, Belgium), AFP (Immuno Diagnostic System Limited England) and CA-125 (Sorm Biomedical, Italy) were determined by immunoradiometric assay. E2 and P (IDS, England) were determined by using double antibody radioimmunoassay (RIA) according to supporters instructions. One way analysis of variance (ANOVA) followed by student's "t" test were used to determine the significance of differences between the hormone levels in normal and abnormal pregnancies.

Results

Table I. Serum levels of b-hCG, progesterone, estradiol, human placental lactogen, alpha feto protein and cancer antigen 125 in cases of ectopic pregnancy and controls.

Subjects	Intrauterine pregnancy (n=20)	Spontaneous abortion (n=15)	Ectopic pregnancy (n=31)	P (ANOVA)
βHCG (mIU/ml)	73796.8±15554.7	22524±6213	9490.55±3071.2	p<0.0001
P(ng/ml)	19.25±2.8	10.59±3.03	4.8±1.19	p<0.0001
E2(pg/ml)	500.15±98.84	339.8±112.16	100.1±22.09	p<0.0001
HPL (μgr/ml)	0.22±0.02	0.18±0.05	0.23±0.03	p>0.05
AFP (ng/ml)	3.66±0.61	4.97±0.75	5.98±1.28	p>0.05
CA-125 (U/ml)	52.89±7.79	66.41±20.81	49.11±9.44	p>0.05

Table I shows the mean, standard error and P values of each hormone in the 31 women with EPS, the 20 normal pregnant controls and the 15 patients with spontaneous abortion. The mean duration of pregnancy in the three groups were not statistically different. There were no statistically significant differences for AFP, HLP and CA-125 levels between all groups. However, the mean levels B-hCG E2 and P in patients wth EPs were significantly lower than those measured in normal and abnormal intrauterine pregnancies (P< 0. 0001). The serum P and E2 for EPs ranged from 0.3 to 36.4 ng/ml and 10 to 705 pg/mI, for normal IUPs, 7.9 to 64 ng/ml and 91 to 1586 pg/mi, for abnormal IUPs, 0.7 to 31.4 ng/ml and 21 to 1234 pg/mI, respectively. We tried to find out discriminatory zones for P levels of 5 to 20 ng/ml, and for E2 levels of 150 to 250 pg/mi, to see whether these could be of value in differentiating an Ep from normal and abnormal IUPs (Table II and III).

Table II. The cutoff serum progesterone values in ectopic and intrauterine pregnancies (IUP)

Progesterone ng/ml	Ectopic pregnancy n=31 R=0.3-36.4 ng/ml	Normal IUP n=20 R=7.9-64 ng/ml	Spontaneous abortion n=15 R=0.7-31.4 ng/ml
>20	3.2 % (1)	35 % (7)	20 % (3)
<20	96.7 % (30)	65 % (13)	80 % (12)
>15	6.4 % (2)	60 % (12)	26.6 % (4)
<15	93.5 % (29)	40 % (8)	73.3 % (11)
>10	9.6 % (3)	85 % (17)	33.3 % (5)
<10	90.32 % (28)	15 % (3)	66.6 % (10)
>5	29.03 % (9)	100 % (20)	46.6 % (7)
<5	70.96 % (22)	- (0)	57.3 % (8)

n = number of patients in each diagnostic category
R = range of values in each diagnostic category

Table III. The cutoff serum estradiol values in ectopic and intrauterine pregnancies (IUP).

Estradiol (pg/ml)	Ectopic pregnancy n=31 R=10-705 pg/ml	Normal IUP n=20 R=91-1586 pg/ml	Spontaneous abortion n=15 R=21-1234 pg/ml
>250	3.2 % (1)	55 % (11)	33.3 % (5)
<250	96.7 % (30)	45 % (9)	66.6 % (10)
>225	3.2 % (1)	65 % (13)	33.3 % (5)
<225	96.7 % (30)	35 % (7)	66.6 % (10)
>200	9.6 % (3)	75 % (15)	33.3 % (5)
<200	90.3 % (28)	25 % (5)	66.6 % (10)
>175	9.6 % (3)	90 % (18)	46.6 % (7)
<175	90.3 % (28)	10 % (2)	53.3 % (8)
>150	12.9 % (4)	90 % (18)	46.6 % (7)
<150	87.09 % (27)	10 % (2)	53.3 % (8)

n = number of patients in each diagnostic category
R = range of values in each diagnostic category

But, although the mean values from all three groups were significantly different, we could not identify a discriminatory cutoff value because there was a considerable overlap in serum P and E2 levels between patients with EPs and IUPs. It is especially difficult to differentiate an EP from an abnormal IUP because hormone levels were similarly depressed.

Discussion

Although there is a classical clinical picture of ectopic pregnancy, its early stages may mimic the symptoms of other gynaecologic conditions such as PID, ruptured corpus luteum, dysfunctional uterine bleeding and threatened or incomplete abortion[1]. The conventional diagnostic approach to the patient with suspected ectopic pregnancy involves clinical examination, serial quantitative serum b-hCG determinations and ultrasonography[1,5,6]. Most patients with ectopic pregnancies have some abnormality with sonographic examination but most of these findings are nonspecific5'7 and definitive diagnosis can be made only when the sonographer visualizes an extrauterine gestational sac that contains a fetus with heart motion[7]. In the absence of this condition the diagnosis requires either the quantitative serum B-hCG level to be above the discriminatory zone (_6500 mIU/ml) associated with ultrasonography demonstrating no evidence of an IUP or two sequential B-hCG determinations 48 hours apart with <66% increase[6,9]. However, an early normal IUP and abnormal IUP could also have similar features[5,9].

Protein and hormone synthesis by trophoblast, endometrium and gestation[1,10]. Several of these hormones including progesterone[10-19], estradiol[10-13], human placental lactogen, prolactin[20], alpha fetoprotein, schwangerschafta protein 1[21], pregnancy associated plasma protein A[22] , alpha-amylase[23] CA125[24] have been evaluated by several investigators to improve the diagnostic accuracy in ectopic pregnancy. But most of the results are contradictory and remain unproven or are of limited value in the diagnosis of ectopic pregnancy. In this study, no significant difference was recorded with respect to serum levels of HPL, AFP and CA-125 between the groups. We think that their use as a diagnostic aid for ectopic pregnancy is unnecessary. In the last decade, many reports appeared in the literature about the usefulness of serum P determinations in differentiating between EPs and normal or abnormal IUPs. The value of a random serum P in the diagnosis of EPs was first reported by Matthews et al[14]. and similar results were later reported br others[13,15,16]. A cutoff P value of 15ng/ml by Matthews[14] and Yeko[16] and 23 ng/ml by Guillaume[13] have been identified for the diagnosis of ectoRic pregnancy. But recently, Bucket al[15] and Gelder et al[9] were unable to identify a discriminatory value because there was a considerable overlap in serum P levels between patients with IUPs and EPs. Estradiol levels have also been reported to be significantly lower in patients with EPs than those with IUPs[10-13]. Guillaume et al[13] suggested that the addition of the estradiol assay, with or without progesterone to the early evaluation of patients suspected of haying an ectopic pregnancy may be helpful in diagnosis. Their data showed that the mean levels of E2 were significantly lower in the ectopic pregnancy patients than in either control group and if a cut off value of650 pg/mI is chosen, all of the ectopic pregnancy had E2 values below this level, whereas all but one of the control patients had E2 levels above 650 pg/nil. In this study, although the mean levels of P and E2 were significantly lower in patients with EPs than in either control group, we were unable to identify a discriminatory cutoff value for P and E2 that completely separates EPs from IUPs. Both P and E2 levels showed a wide variation between individuals within the same and different clinical conditions. In conclusion, our data suggest that the levels of HPL, APP and CA-125 were not significantly different in the three groups and their use in the diagnosis of ectopic pregnancy is of no value. Although P and E2 levels were significantly different between groups, a single serum assay for P and E2 alone cannot differ an EP from IUP because there was no certain discriminatory zone. Therefore, hCG remains the primary biochemical diagnostic test used in women suspected of an ectopic pregnancy. However, the addition of depressed levels of P or/and E2 to the conventional diagnostic methods may increase the likelihood of ectopic gestation.

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