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Biochemical Markers for Prediction of Pregnancy Outcome in Cases of Recurrent Pregnancy Loss

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Abstract
Objective To predict pregnancy outcome by studying the relation between serum βHCG, progesterone and CA125 and the occurrence of miscarriage in the first trimester, in cases with history of recurrent pregnancy loss.
Methods Serum βHCG, progesterone and CA125 levels in fifty pregnant women with history of recurrent pregnancy loss were compared to 50 pregnant women with no history of abortion, and to another group of women (No = 50) who failed to complete the 1st trimester of pregnancy during the study.
Results Serum B-hCG showed a sensitivity of 100%, a specificity of 50%, a PPV of 50% and a NPV of 100%. Serum progesterone showed a sensitivity of 24%, a specificity of 73%, a PPV of 55.07% and a NPV of 85.18%, while serum CA125 showed a sensitivity of 15.6%, a specificity of 58.59%, a PPV of 16.32% and a NPV of 57.42%.
Conclusion The value of CA125 in recurrent abortions is still unclear and cannot recommended on routine basis. On the other hand, β-HCG is highly sensitive as a single serum measurement for the prediction of pregnancy outcome.
Keywords Miscarriage, ectopic pregnancy, B-hCG, CA125, progesterone

Introduction

Early pregnancy loss is perhaps the most common medical problem in women of reproductive age. These conditions are a large burden to health services as well as to the physical and psychological wellbeing of women and their partners. In recent times, there have been major changes in our approach to the management of early pregnancy problems.[1] These findings used in combination with biochemical markers to give a more complete evaluation or 'profile' of the pregnancy. Serum levels of human chorionic gonadotrophin (hCG) and progesterone are the most commonly used biochemical markers, the optimum way to utilize them in the diagnosis and management of early pregnancy problems remains contentious. The move away from surgical treatment for early pregnancy problems has economic and clinical advantages. Problems occur however when medical or expectant management is unsuccessful and surgical intervention is required later, often in an 'emergency.[2,3] The lack of well-defined criteria to differentiate between pregnancies that will spontaneously resolve and those that will not is an ongoing problem for expectant management and is certainly off-putting for patients and clinicians. Expectant management often takes weeks to complete and success rates vary widely.[3] Failure of expectant management after prolonged follow-up is particularly disappointing for women and reduces overall benefits of the management strategy. A number of novel biochemical markers of the luteal-trophoblastic axis have emerged in the last decade.[3] The aim of this thesis was to investigate these novel biochemical markers in the diagnosis and management of cases of recurrent pregnancy loss.

Method

The study carried out on 150 pregnant women of comparable age (range from 17–39 years) and gestational age in Al-Kadhimiya Teaching Hospital, from January 2017 until October 2017. They divided into 3 groups. The control group comprising 50 normal pregnant women with no history of miscarriage (**Group A**), the recurrent abortions group comprising 50 pregnant females with history of two or more 1st trimester pregnancy losses (**Group B**) and the last group of 50 patients who failed to complete the 1st trimester of pregnancy (aborting for the first time) during the study (**Group C**). All groups subjected to history taking and thorough physical examination. Serial maternal serum levels of **βHCG, progesterone** and **CA125** were determined. The level of B-hCG estimated by a single sample at the time of ultrasound scan. Blood was collected by vein puncture, allowed to clot and serum separated by centrifugation at room temperature. The sera were collected and stored in deep freeze (–70°C) to be assessed quantitatively when suitable. The technique used in the present work is the diagnostic kit prepared by Eurogenetics: Belgium (Headquarters Tessendrlo-Belgium) using βHCG Elisa coated microtiterstrips. Estimation of Progesterone in serum carried out using the kit manufactured by Spectria Progesterone [I] 125-coated tube Radioimmunoassay. (Orion Diagnostica Espoo, Finland). The technique principally based on the widely used radioimmunoassay method. A sample containing an unknown amount of the substance to be assayed (unlabelled antigen) added to a standard amount of a labeled derivative of the same antigen (labeled antigen). The labeled and unlabelled antigens allowed competing for the limited number of the high affinity binding sites of the antibody. After washing away the free (unbound) antigen, the amount of labeled antigen in the sample is inversely proportion to the concentration of unlabeled antigen. The actual concentration in unknown sample obtained by means of a standard curve based on known concentration. Determination of Cancer antigen CA125 obtained by using a special kit for the detection of CA125 based on a new antibody (monoclonal) that binds to CA125 specifically.

The quantitative determination is a one-step immunoenzymatic assay (IEMA) based on the formation of a sandwich between the analytic to detect and two specific monoclonal antibodies directed to different epitopes on the CA125 molecules. Expected values for the test by the manufacturers in normal conditions are less than 37 IU/ml in serum.

Statistical Analysis

SPSS 25.0 used to perform statistical analysis of the study. The work out data formulated as counts and percentages. Chi-square and Fisher exact tests used to describe the association of these data. Level equal to 0.05 or below is the lower level of accepted statistically significant difference.

Results

One hundred & fifty cases were included in this study. Their mean age's ± SD were 26.44 ± 5.43 years (range from 17–39 years). There is no statistical difference between groups regarding the age (*P* value = 0.468). Serum β-hCG showed a sensitivity of 100%, a specificity of 50%, a positive predictive value (PPV) of 50% and a negative predictive value (NPV) of 100% (Table 1).

Evaluation parameters regarding serum β-HCG in different gestational age groups shown in Table 2.

The mean level of serum β-hCG were statistically highly significant (*P* value = 0.0001) between groups for all gestational ages (from 6–11 weeks of gestational age). (Table 3)

Serum progesterone showed a sensitivity of 24%, a specificity of 73%, a PPV of 55.07% and a NPV of 85.18%. Evaluation parameters regarding serum progesterone in different gestational age groups shown in Table 4.

The mean level of serum progesterone were statistically highly significant (*P* value = 0.001) between groups for 8–9 week of gestational age only. (Table 5)

Serum CA125 showed a sensitivity of 15.6%, a specificity of 58.59%, a PPV of 16.32% and a NPV of 57.42%. Evaluation parameters regarding serum CA125 in different gestational age groups shown in Table 6.

Concerning the serum CA125 level, there were highly statistically significant differences between the group A and group B at 6–7 weeks. (Table 7)

Discussion

There are many methodological challenges when designing and conducting research in patients with early pregnancy problems. The diagnosis of a miscarriage, ectopic pregnancy or a PUL is a distressing and potentially traumatic time for a woman.[2] At the time of diagnosis there is a large amount of clinical information to take in and decisions to make, many

Table 1. **Evaluation parameters of different markers in different gestational age groups**

Markers	Sensitivity	Specificity	PPV	NPV
Serum B-hcg	100%	50%	50%	100%
Progesterone	24%	73%	55.07%	85.18%
CA125	15.6%	58.59%	16.32%	57.42%

Table 2. **Evaluation parameters of serum β-HCG in different gestational age groups**

Serum β-HCG	Sensitivity	Specificity	PPV	NPV
6–7 weeks	100%	50%	55.55%	100%
8–9 weeks	100%	58.82%	51.72%	100%
10–11 weeks	100%	36.36%	43.24%	100%

Table 3. **Mean and standard deviations of Serum β-hCG**

β-HCG	6–7 weeks	8–9 weeks	10–11 weeks
	Mean ± SD	Mean ± SD	Mean ± SD
Group A	18185.19 ± 8200.57	12612.1 ± 4975.65	17988.07 ± 8077.46
Group B	6921.19 ± 3473.44	4650.79 ± 3890.07	7477.53 ± 2136.55
Group C	576.65 ± 422.86	2118.00 ± 760.83	2894.19 ± 1027.22
P value	0.0001*	0.0001*	0.0001*

**P* value was highly significant by using ANOVA test.

Table 4. **Evaluation parameters of serum progesterone in different gestational age groups**

Serum progesterone	Sensitivity	Specificity	PPV	NPV
6–7 weeks	55%	53.12%	39.5%	60.71%
8–9 weeks	33.33%	79.41%	58.82%	84.37%
10–11 weeks	0%	78.78%	0%	60%

Table 5. **Mean and standard deviations of serum progesterone**

Progesterone	6–7 weeks	8–9 weeks	10–11 weeks
	Mean ± SD	Mean ± SD	Mean ± SD
Group A	21.30 ± 2.443	18.94 ± 2.794	20.81 ± 5.456
Group B	19.28 ± 1.978	18.52 ± 2.161	21.18 ± 2.939
Group C	19.18 ± 3.487	14.61 ± 4.437	19.00 ± 2.130
P value	0.054	0.001*	0.194

**P* value was highly significant by using ANOVA test.

Table 6. **Evaluation parameters of serum CA125 in different gestational age groups**

Serum CA125	Sensitivity	Specificity	PPV	NPV
6–7 weeks	10%	50 %	11.11%	47.05%
8–9 weeks	0%	44.11%	0%	50%
10–11 weeks	37.5%	62.79%	50%	72.97%

Table 7. **Mean and standard deviations of serum CA125**

Serum CA125	6–7 weeks	8–9 weeks	10–11 weeks
	Mean ± SD	Mean ± SD	Mean ± SD
Group A	19.73 ± 3.32	32.81 ± 7.12	35.97 ± 2.12
Group B	49.88 ± 12.75	36.56 ± 10.96	32.95 ± 5.79
Group C	25.88 ± 6.86	18.66 ± 3.99	35.20 ± 7.10
P value	0.001*	0.156	0.287

**P* value was highly significant by using ANOVA test.

women feel unable or unwilling to consider taking part in research for these reasons. The symptoms of bleeding and pain in early pregnancy are very common and can be very worrying for women; this can lead to suitable cases being missed.[1,2] It is clinically important to predict the outcome of patients with history of recurrent abortion at an early stage of gestation.[4] The prognostic predictive value of maternal serum CA125 measurement investigated in different studies with conflicting results.[5] Ocer F, et al. found that the mean serum CA125 level of the patients with an unfavorable pregnancy outcome was significantly higher than that of the patients with a favorable outcome.[6] Sherif et al. also found that the serum CA125 might developed as a cheap, sensitive and specific predictor of outcome in cases of threatened abortion.[7] In the present study, the serum CA125 in the control group (group A) showed no significant differences between different gestational age groups. The comparative data between the 3 groups showed a significant increase between group A and group B at 6–7 weeks. Although CA-125 levels seem to be predictive of clinical pregnancy, they are not predictive of its outcome. Higher CA-125 concentrations may reflect higher endometrial receptivity but do not predict the number or viability of implanted embryos.[8] On the other hand, in the present study, serum B-hCG showed highly statistically significant differences ($P < 0.0001$) between the control mean value and that of the second and third group at all gestational ages being highest in the control group and lowest in-group C. Serum B-hCG showed a sensitivity of 100%, a specificity of 50%, a PPV of 50% and a NPV of 100% with relatively equal values in different age groups. This matches well with other investigators who found that the best predictor of ongoing pregnancy was βHCG concentration.[9]

In the present study, in the control group mean progesterone values were within the normal ranges described. Moreover, serum progesterone showed no significant difference in serum levels of women of different gestational ages in the control group. However, the level in-group C was found to be significantly lower than in the control group ($P < 0.001$) at 8–9 weeks. The effectiveness of progesterone estimation obviously would not depend only on absolute levels or even rising levels during pregnancy. At least, the effectiveness would also depend on endometrial and vascular bed receptivity to progesterone and probably also on the original basic structure of the tissue in question.[10] These data suggests that progesterone measurement is of some, but limited use in the assessment of early pregnancy complications and that a cutoff value on which we can evaluate 1st trimester pregnancies cannot be devised.[1] It should always-kept in mind that it is not possible to identify the cause of the recurrent early pregnancy loss in approximately half of the cases and this could be the limiting factor for any biochemical marker.[11]

Conclusion

The value of CA125 in recurrent abortions is still unclear and cannot recommended on routine basis. On the other hand, β-HCG is highly sensitive as a single serum measurement for the prediction of pregnancy outcome.

Conflicts of Interest

None.

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