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Prognostic Value of Biochemical Markers- Ca 125, Serum Beta HCG And Serum Progesterone in Cases of Recurrent Pregnancy Loss In The First Trimester of Pregnancy

Dr. Ela Jha[1], Dr Arun Kumar Jha ; Dr. Annie Samuel[2]
[1]*Associate Professor of Department of Obstetrics & Gynaecology*
2.Associate Professor, Department of Pathology
[3]*Post Graduate Resident of Department of Obstetrics & Gynaecology*
Mahatma Gandhi Medical College & Hospital,
Jamshedpur, Jharkhand, India 831020
Corresponding Author: Dr. Ela Jha

Abstract: Introduction*: Recurrent pregnancy loss is defined as the sequence of two or more spontaneous abortions as documented by either sonography or on histopathology, before 20 weeks (American Society Of Reproductive Medicine guidelines 2013). It affects nearly 1% of women in reproductive age group & the risk of recurrence increases with each successive abortion. It becomes nearly 30% after three consecutive losses. Various biochemical markers have been identified as predictors of miscarriage in the first trimester of pregnancy.*

Cancer Antigen- 125 (CA 125) is a high molecular weight glycoprotein, expressed by foetal chorionic membrane, amniotic fluid & maternal decidua. Therefore, in cases of disruption of decidua or foetal membranes, its levels in maternal serum would rise. Similarly, beta HCG is a glycoprotein synthesized by syncytiotrophoblasts, which sustains the corpus luteum & hence early pregnancy. Progesterone, is a C-21 steroid hormone, required in maintenance of pregnancy & its main source is the corpus luteum, until the 10th week of gestation. After a transition period from the 7th -10th week, this function is taken over by the placenta. Hence, these markers at different gestational ages in the first trimester can be used as prognostic tools for predicting the risk of abortion in cases of habitual aborters & threatened pregnancies.

Aim*: To evaluate the prognostic efficacy of serum beta HCG, CA-125 & serum progesterone as biochemical predictors of pregnancy loss at different gestational ages in the first trimester of pregnancy*

Methodology*: A prospective study was conducted on 125 women in the age group of 20-35 years, with history of recurrent pregnancy loss, in the Department of Obstetrics & Gynaecology, MGM MCH. The cases were divided into three groups. Group A is the control group consisting of 45 normal pregnant women with no history of miscarriage. Group B consisted of 40 subjects with history of two or more 1st trimester pregnancy loss. Group C comprised of 40 subjects who failed to complete the pregnancy till the first trimester, aborting for the first time during the study.*

These three groups were subdivided into three subgroups on the basis of weeks of gestation. Group I with 6-7 weeks, group II with 8-9 weeks & group III with 10-11 weeks of gestation. The subdivision was done in order to increase the comparability of the results.

The study was carried out for a period of one year from June 2017. The cases in which the pregnancy continued were followed upto 22 weeks of gestation. The levels of the three biomarkers were evaluated & correlated with the pregnancy outcomes. The groups & subgroups were comparable in demographic features. The results were statistically analysed.

Results*: Serum beta HCG showed a sensitivity of 100%, a specificity of 55.9%, a PPV of 52.7%, a NPV of 100%.*

Serum progesterone showed a sensitivity of 37.42%, a specificity of 82.34%, a PPV of 54.91%, a NPV of 80.53%

Serum CA 125 showed a sensitivity of 88.97%, a specificity of 74.89%, a PPV of 68.93%, a NPV of 82.58%

The combined sensitivity & specificity of the three serum biomarkers is 98.9% & 83.4%, with area under ROC curve estimated to be 0.982.

Conclusion*:Serum beta HCG & CA 125, as independent variables, have shown statistically significant sensitivities in predicting pregnancy outcome in cases of recurrent pregnancy loss & threatened abortion. However, combined estimation of all the three serum biomarkers further improves the chances of identifying high risk pregnancies & their management can be planned accordingly.*

Keywords*: Beta HCG, CA-125, Progesterone, Recurrent pregnancy loss*

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I. Introduction

Recurrent pregnancy loss is a problem encountered in nearly 1% of women in the reproductive age group. It has multifactorial etiology, with the risk of abortion increasing in successive pregnancies. Therefore, prediction of occurrence of a miscarriage in a high risk case, or identification of unfavourable factors in a threatened gestation becomes all the more necessary. There can be no single serum biomarker or radiological investigation that can accurately predict the risk of recurrence of abortion. However, with a combination of serum biomarker evaluation & ultrasonography, it can be possible to a certain extent to foresee the outcome of a pregnancy that whether it would abort or continue till the age of viability. Even if a threatened pregnancy advances, there is an increased risk of preterm birth & low birth weight baby. The risk of antepartum haemorrhage due to placental abruption or placenta praevia also increases by 2.5 fold. 80% of abortions occur before the 12^{th} week & the rest between 12^{th} -20^{th} week. The most common cause of spontaneous abortion is chromosomal abnormality (50%), out of these autosomal trisomy being the most common (50%), 22% due to polyploidy. Other important factors include immunological, autoimmune, metabolic, anatomic causes & infections.

CA 125 is a cell surface glycoprotein antigen with a high molecular weight. It is a mucin like antigen found in 80% cases of ovarian carcinomas of epithelial origin. It is also secreted by normal tissues of the body such as amnion, mesenteric organs, respiratory & coelomic epithelium, & epithelium of the female genital tract. Hence a baseline level of CA- 125 is found in serum. Its level rise in pregnancy due to due to invasion of decidua by chorionic villi, peak levels are seen in the 1^{st} trimester &immediately after birth, i.e whenever there is decidual disintegration due to blastocyst implantation or placental separation, baseline values reach by 3^{rd} trimester. Its normal range is 1-35 IU/ml. CA 125 level rises in cases of carcinomas of various organs, hepatic & renal pathologies, pelvic inflammatory disease, uterine fibroids, endometriosis, pancreatitis, systemic lupus erythematosus, pericarditis. In cases of threatened abortion or habitual aborters, rising trends of CA 125 has been observed as compared to cases of normal pregnancy. There is a positive correlation between serum CA 125 levels & subchorionic hematoma's. It has also been observed that its levels are lower in cases of ectopic pregnancies as compared to intrauterine gestations, however its role in differentiating both the two entities has not yet been established

Serum beta HCG is also a high molecular weight glycoprotein with two subunits- alpha & beta. It is synthesized from the syncytiotrophoblasts. Its doubling time in maternal serum is 1.4-2.0 days. Its maximum levels are reached between 60-70 days of pregnancy, thereafter the levels remain constant with a slight rise at 32 weeks. It disappears from the circulation 2 weeks following delivery. Its main function is to maintain the corpus luteum for the sustenance of pregnancy. The serial measurements of beta HCG is used in cases of ectopic pregnancies & cases of abortion.

Progesterone is a C-21 steroid hormone derived from cholesterol. It is secreted from the corpus luteum, under the influence of HCG. It is one of the major factors in sustaining a pregnancy. It makes the uterine endometrium secretory for implantation of the blastocyst. It also modulates maternal immune responses to prevent graft rejection of the embryo, also it decreases uterine contractions making the uterine environment suitable for the developing embryo.

Hence, based on the combined evaluation of these biomarkers, prognosis of pregnancy outcome can be done in cases of recurrent pregnancy loss & threatened abortions.

II. Aims And Objectives

The aim of this study is to evaluate the effectiveness of serum beta HCG, serum progesterone & CA 125 in predicting the pregnancy outcome, in cases of recurrent pregnancy loss, at different gestational ages, in the first trimester. Hence further course of management can be outlined on the basis of risk assessment done by these biomarkers in threatened cases of pregnancy, & pregnancies likely to abort.

III. Materials And Methods

A cohort of 125 women, with history of occurrence of two or more abortions, in the age group of 20-35 years, were evaluated & followed up in the Out Patient Department of Obstetrics &Gynaecology, MGM MCH, Jamshedpur, East Singhbhum, Jharkhand.

A prospective study was carried out over a period of one year from June 2017. The cases were divided into three groups. Group A is the control group consisting of 45 normal pregnant women with no history of miscarriage. Group B consisted of 40 subjects with history of two or more 1^{st} trimester pregnancy loss. Group C

comprised of 40 subjects who failed to complete the pregnancy till the first trimester, aborting for the first time during the study.

These three groups were subdivided into three subgroups on the basis of weeks of gestation. Group I with 6-7 weeks, group II with 8-9 weeks & group III with 10-11 weeks of gestation. The subdivision was done in order to increase the comparability of the results. The cases in which the pregnancy continued were followed upto 22 weeks of gestation. The levels of the three biomarkers were evaluated & correlated with the pregnancy outcomes. The groups & subgroups were comparable in demographic features. The results were statistically analysed.

Criteria of Diagnosis:
CA 125- Normal range 31.7-50.7 IU/ml (In 1st trimester)
Serum progesterone- Normal range 11.2-90.0ng/ml (In 1st trimester)
Serum beta HCG- Normal range
6-7 weeks- 1,080-56,500 mIU/ml
8-9 weeks- 7,650- 2,29,000 mIU/ml
10-11 weeks- 25,500- 2,88,000 mIU/ml

Inclusion criteria:
1. Any gravidity & parity
2. Gestational age between 6-12 weeks
3. Maternal age between 20-35 years
4. Singleton pregnancy

Exclusion criteria:
1. Multiple pregnancies
2. Gestational age <6 weeks &>12 weeks
3. Cases of inevitable abortion i.e in cases of open cervical os& missed abortion
4. Anembryonic pregnancy, pregnancies with blighted ovum, molar pregnancy, ectopic pregnancy, history of ovulation induction.
5. Pregnant women on treatment with oral or injectable progesterone
6. Maternal conditions that increase CA 125 such as uterine fibroid, endometriosis, PID, carcinoma of the ovary, colon, lung, endometrium & pancreas, SLE, hepatic, renal, lung & pancreatic pathologies
7. History of smoking

STUDY DESIGN: Prospective study

METHODOLOGY: 125 cases, who fulfilled the inclusion criteria, after giving written informed consent, were selected for the study. Detailed history taking & complete general & obstetric examination was done. The gestational age & viability of foetus was determined by ultrasonography & LMP dating. All other pathologies were excluded. Condition of cervical os was assessed by pelvic examination.

Sample collection: 3ml of venous blood sample was collected by venepuncture, after taking sterile aseptic precautions. The sample was allowed to clot & serum separated by centrifugation at room temperature. The collected sera was stored at a temperature of -70 degree Celsius.
Serum beta HCG estimation was done using ELISA coated microtitre strips. Serum progesterone estimation was done by radio immunoassay method. CA 125 estimation was done using radio immunoassay method using IEMA WELL KIT (immunoenzymatic assay).

Statistical analysis: Data is expressed in terms of mean & standard deviation. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under ROC (Receiver Operating Characteristic) curve were calculated. A probability value (P- value) less than 0.001 was considered to be significant. ANOVA & t-test were used as the tests of significance. All calculations were done using statistical software.

IV. Results And Distribution

Table I: Mean age, parity & gestational age (in weeks) in groups A, B, C & subgroups I, II, III

MEAN AGE	GROUP A	GROUP B	GROUP C
	23.92	22.89	24.67

PARITY	GROUP A	GROUP B	GROUP C
P0	14 (31.1%)	38 (95%)	35 (87.5%)
P1	7 (15.5%)	2 (5%)	5 (12.5%)
P2	20 (44.4%)	-	-
P3	4 (0.09%)	-	-

GEST. AGE (IN WEEKS)	GROUP A	GROUP B	GROUP C
I (6-7 wks)	18 (40%)	10 (25%)	15 (37.5%)
II (8-9 wks)	12 (26.6%)	22 (55%)	16 (40%)
III (10-11 wks)	15 (33.3%)	8 (20%)	9 (22.5%)

Table II: Mean serum beta HCG levels in groups A, B, C & sub groups I, II, III

S.beta HCG mIU/ml	GROUP A	GROUP B	GROUP C
I (6-7 wks)	17892±10899	6487±4021	492± 760
II (8-9 wks)	13287± 6122	5189±3876	2032±1328
III (10-11 wks)	17880± 7639	7401±9978	2794±3115

Table III: Mean serum progesterone levels in groups A, B, C & subgroups I, II, III

S.Progesterone (ng/ml)	GROUP A	GROUP B	GROUP C
I (6-7 wks)	21.67±2.64	10.12±6.35	11.23±4.92
II (8-9 wks)	22.59±8.21	9.78±5.73	10.69±3.78
III (10- 11 wks)	19.86±7.62	12.66±5.41	9.89±8.25

Table IV: Mean CA-125 levels in groups A, B, C & subgroups I, II, III

S. CA-125 (IU/ml)	GROUP A	GROUP B	GROUP C
I (6-7 wks)	25.49±12.02	72.34±47.92	68.92±45.37
II (8-9 wks)	22.67±16.31	69.83±52.75	70.16±50.82
III (10-11 wks)	23.52±10.98	75.69±48.24	62.38±47.46

Table V: Serum beta HCG- Area under ROC curve, sensitivity, specificity, PPV, NPV & P-value

	SENSITIVITY	SPECIFICITY	PPV	NPV	AREA UNDER ROC CURVE	P-VALUE
6-7 wks	100%	52.2%	55.4%	100%	0.817	<0.001
8-9 wks	100%	56.7%	53.2%	100%	0.892	<0.001
10-11 wks	100%	48.5%	39.8%	100%	0.913	<0.001

Cut off level of serum beta HCG:
6-7 weeks- 5,500 mIU/ml
8-9 weeks- 8,750 mIU/ml
10-11 weeks- 25,900 mIU/ml

Table VI: Serum Progesterone- Area under ROC curve, sensitivity, specificity, PPV, NPV & P-value

	SENSITIVITY	SPECIFICITY	PPV	NPV	AREA UNDER ROC CURVE	P-VALUE
6-7 wks	56.72%	53.16%	37.28%	61.28%	0.901	<0.001
8-9 wks	28.61%	89.25%	56.47%	79.41%	0.897	<0.001
10-11 wks	0%	80.92%	0%	82.33%	0.926	<0.001

Cut off level of serum progesterone: 21.20ng/ml

Table VII: CA 125- Area under ROC curve, sensitivity, specificity, PPV, NPV & P-value

	SENSITIVITY	SPECIFICITY	PPV	NPV	AREA UNDER ROC CURVE	P-VALUE
6-7 wks	88.16%	79.58%	72.21%	87.43%	0.963	<0.001
8-9 wks	89.25%	82.69%	68.10%	85.08%	0.889	<0.001
10-11 wks	78.99%	76.42%	69.82%	67.74%	0.935	<0.001

Cut off level of serum CA 125: 57.68 IU/ml

Table VIII: Area under ROC curve, sensitivity & specificity of combined tests of all serum biomarkers

SENSITIVITY	SPECIFICITY	AREA UNDER ROC CURVE
98.9%	83.4%	0.982

Table IX: Statistical parameters of different serum biomarkers

MARKERS	SENSITIVITY	SPECIFICITY	PPV	NPV
S. BETA HCG	100%	55.9%	52.7%	100%
S. PROGESTERONE	37.42%	82.34%	54.91%	80.53%
S. CA 125	88.97%	74.89%	68.93%	82.58%

Table X: Pregnancy outcome in group A & group B (number of cases completed pregnancy in the first trimester)

GESTATIONAL AGE (IN WEEKS)	GROUP A	GROUP B
I (6-7 weeks)	16 (88.8%)	4 (40%)
II (8-9 weeks)	10 (83.3%)	12 (54.5%)
III (10-11 weeks)	15 (100%)	3 (37.5%)

V. Discussion And Observation

The mean maternal age for group A is 23.92, for group B 22.89 & for group C 24.67, which is statistically not significant at P- value <0.001. Age, parity & gestational age showed no statistical difference between the three groups. **(Table 1)**

Serum beta HCG

The mean values of serum beta HCG in group A, subgroup I is 17892 with a standard deviation (SD) of 10899, in sub group II 13287 (SD- 6122), in sub group III 17880 (SD- 7639). In group B, subgroup I mean beta HCG is 6487 (SD- 4021), sub group II 5189 (SD- 3876),sub group III 7401 (SD- 9978). In group C, serum beta HCG in subgroup I is 492 (SD- 760), sub group II 2032 (SD- 1328),sub group III 2794 (SD- 3115). Low levels of beta HCG are seen in sera of patients who are recurrent aborters & those who failed to complete pregnancy in the 1st trimester**.(Table II)**

Serum progesterone

The mean values of serum progesterone in group A, subgroup I is 21.67 (SD- 2.64), sub group II 22.59 (SD- 8.21), sub group III 19.86 (SD- 7.62). In group B, subgroup I it is 10.12 (SD- 6.35),sub group II 9.78 (SD- 5.73),sub group III 12.66 (SD- 5.41). In group C, subgroup I 11.23 (SD- 4.92), sub group II 10.69 (SD- 3.78), sub group III 9.89 (SD- 8.25). Serum progesterone levels tend to be low in group B & group C, hence supporting the fact that optimum progesterone levels are necessary for sustaining pregnancy, & that low levels in the first trimester is an indicator of poor prognosis & unfavourable outcome. **(Table III)**

Serum CA-125

CA 125 has a mean value of 25.49 (SD- 12.02) in group A, subgroup I. In sub group II 22.67 (SD- 16.31), subgroup III 23.52 (SD- 10.98). In group B, subgroup I it is 72.34 (SD- 47.92), subgroup II 69.83 (SD- 52.75), subgroup III 75.69 (SD- 48.24). In group C, subgroup I 68.92 (SD- 45.37), subgroup II 70.16 (SD- 50.82), subgroup III 62.38 (SD- 47.46).

From the above mentioned values it can be inferred that CA 125 levels rise in cases of pregnancies which are likely to get aborted. This shows a positive correlation between increased levels of CA 125 & abortion, most probably due to decidual separation & sub chorionic hematoma formation as seen in cases of threatened pregnancies. **(Table IV)**

Serum beta HCG has shown a sensitivity of 100%, with a specificity of 52.2% (6-7wks), 56.7%(8-9 wks), 48.5% (10-11 wks). Its PPV is 55.4%, 53.2% & 39.8% in different gestational age groups, with NPV of 100% at the given cut off level. The area under ROC curve is estimated to be 0.817, 0.892 & 0.913 respectively, at p value <0.001, which is highly statistically significant. Hence, it is a very sensitive marker in predicting the pregnancy outcome.**(Table V)**

Serum progesterone has a sensitivity of 56.72% (6-7 wks), 28.61% (8-9 wks), 0% (10-11wks). It has a specificity of 53.16%, 89.25% & 80.92% respectively. Its PPV is 37.28%, 56.47%, & 0% & NPV of 61.28%, 79.41%, 82.33% in the different gestational age groups respectively, at the given cut off level. The area under ROC is estimated to be 0.901, 0.897 & 0926, at p value <0.001. Hence serum progesterone has a relatively low sensitivity & specificity as a serum marker of prognostic value in recurrent cases of pregnancy loss. **(Table VI)**

The sensitivity of serum CA 125 is 88.16% (6-7 wks), 89.25% (8-9 wks), 78.99 % (10-11 wks). Its specificity is 79.58%, 82.69% & 76.42%, accordingly in different sub groups. Its PPV is 72.21%, 68.10% & 69.82% with NPV of 87.43%, 85.08% & 67.74% at the given cut off level. The area under ROC is 0.963, 0.889 & 0.935 at p-value <0.001. Hence serum CA 125 has shown to be a sensitive marker in the first trimester of pregnancy & can be reliably utilised in combination with serum beta HCG & serum progesterone in cases of threatened gestations & recurrent abortions. **(Table VII)**

The combined sensitivity & specificity of all the serum biomarkers is 98.9% & 83.4% respectively, with area under ROC 0.982. **(Table VIII)**

The overall statistical parameters of all the biomarkers has been estimated. **(Table IX)**

The number of cases who completed the pregnancy in the first trimester is as follows. In group A, subgroup I 88.8%, subgroup II 83.3% & subgroup III 100%. In group B, subgroup I 40%, subgroup II 54.5%, subgroup III 37.5% cases continued their pregnancy successfully till the first trimester. These cases were further followed up till 22 weeks of gestation.**(Table X)**

Various biomarkers are used in combination, along with imaging studies such as ultrasonography in determining the prognosis of threatened abortion.

The study of Mehmet et al. shows the relationship between low beta HCG levels & abortion.

Darwish et al. in a prospective study concluded that serum progesterone is not a significant marker in the 6-7th week of gestation, in a study of pregnant women from 6-11th week of gestation. Sensitivity- 43%, specificity- 50%, PPV- 38%, NPV- 56%.

Hanita et al. conducted a study in 95 pregnant women, with 13 weeks or less period of amenorrhoea. Progesterone was found to be significantly lower in cases of threatened abortion (23.3$\pm$ 12.0) as compared to normal viable pregnancy (89.7$\pm$ 33.2), p value<0.001, cut off value 32.7ng/ml. The cut off is kept high due to prior treatment with progesterone in the study.

Duan et al. in their study of 245 women (175 threatened abortion, 70 control) concluded that sserum beta HCG & progesterone in combination can predict the outcome of threatened abortion.

Fiegler et al. showed in their study that a single serum CA 125 estimation is significant in cases of imminent abortion.

Sotiriadis et al. conducted a study in 239 pregnant women in 1st trimester & concluded that higher levels of CA 125 are found in cases of patients with vaginal bleeding (40.5 IU/ml $\pm$ 55.0) as compared to those without bleeding (28.9 IU/ml $\pm$ 28.8).

Ayaty et al. studied the relationship between CA125 levels & abruptio placentae & concluded that average levels of CA 125 are higher in cases of abruptio placentae than in women with other sources of vaginal bleeding & those without bleeding.

Belon et al. in their study positively correlated CA 125 levels with the tropho decidual hematoma volume. Hence concluded that the extension of decidual destruction & trophoblast separation from decidual cells was the major source of maternal CA 125 elevation.

Scarpellini et al. showed that serial measurements of CA 125 appear to be a highly sensitive prognostic marker in viable pregnancies at risk of abortion.

VI. Conclusion

From the present study it can be concluded that measurement of beta HCG, serum progesterone & CA 125 in combination is highly sensitive in identifying the high risk pregnancies & their outcome. Even a single measurement of CA125 is highly valuable in cases with symptoms of threatened miscarriage. If this screening is done in the initial stages, the pregnancy outcome would potentially be improved by increasing ante natal monitoring & timely management.

VII. Recommendations

The benefits of a screening test are maximised when targeted in a population at greatest baseline risk of a disease. Hence women in the high risk group for abortion & those who are suffering from recurrent pregnancy loss are ideal candidates for use of these screening tests, so as to further corroborate the findings in a larger sample population. Serum CA 125 alone & in combination with other serum biomarkers has shown to be a valuable prognostic marker with a high sensitivity & it has a promising scope in diagnosis & management of cases of recurrent pregnancy loss & threatened abortions.

Conflicts of interest:

The authors declare no conflicts of interest.

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