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Research Article

Predictive Value Of Free β-Hcg, Progesterone, And CA125 For First-Trimester Spontaneous Abortion In Asymptomatic Pregnant Women

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ABSTRACT

Introduction: Threatened miscarriage, characterized by vaginal bleeding with or without abdominal discomfort, is a common gynaecological condition affecting a significant portion of pregnancies. Progesterone and cancer antigen 125 (CA125) are implicated in miscarriage risk, while maternal serum human chorionic gonadotropin (hCG), particularly β-hCG, is a widely used biomarker for early pregnancy complications.

Material and Methods: A prospective longitudinal study was conducted for 2 years involving 100 pregnant women with threatened abortion. Biochemical parameters including free β-hCG, progesterone, and CA125 were assessed. Patients were monitored regularly, and blood samples were collected at specified intervals.

Results: Significant differences were observed in gravidity, number of previous miscarriages, progesterone levels, and CA125 among the study population. Sensitivity analysis revealed high sensitivity for β-hCG (93%), progesterone (86%), and CA125 (81%) in detecting abortion. Combining β-hCG, progesterone, and CA125 yielded 7% sensitivity, although with 100% specificity and predictive values.

Discussion: β-hCG, primarily of trophoblast origin, demonstrated strong diagnostic performance, consistent with previous research. Progesterone's role in pregnancy maintenance was evident, with low levels correlating with increased abortion risk. CA125's association with decidual damage suggests its potential as an early predictor of abortion, although further research is needed.

Conclusion: Single-parameter assessment of free β-hCG or progesterone levels can effectively predict first-trimester spontaneous abortions. Considering its availability and cost-effectiveness, progesterone may be preferred. The combination of β-hCG, progesterone, and CA125 did not significantly enhance predictive value. Future studies should focus on refining predictive models and elucidating the precise roles of biomarkers in abortion risk assessment.

Keywords - Spontaneous abortion, β-hCG, Progesterone, CA125, Predictive value

Introduction

Threatened miscarriage, characterized by vaginal bleeding accompanied by or without abdominal discomfort, is the most prevalent urgent gynaecological condition, affecting 15–20% of pregnancies. Roughly 15% of women facing threatened miscarriage ultimately experience complete spontaneous miscarriage. Diagnosis of threatened miscarriage is made when a woman in early pregnancy exhibits vaginal bleeding, a closed cervix upon clinical examination, and subsequent confirmation of fetal cardiac activity via ultrasound scan. This condition is reported to arise in approximately one-fifth of pregnancies, with an estimated 3–16% of these cases resulting in miscarriage subsequently [1,2].

Progesterone plays a crucial role during implantation by sustaining decidualization, regulating uterine contractility, and fostering maternal immune tolerance to the fetal semi-allograft. Women with low serum progesterone levels face a significantly higher risk of miscarriage, though the specific threshold levels predicting completed miscarriage vary across studies [3,4].

Cancer antigen 125 (CA125) is a glycoprotein synthesized by various normal tissues such as the coelomic epithelium, the amnion, and their derivatives, as well as from the choriodecidual plate. Its presence in the bloodstream during early pregnancy indicates choriodecidual disruption [5,6].

Maternal serum human chorionic gonadotropin (hCG), particularly its subunit β-hCG, serves as the most utilized biomarker in routine clinical practice for evaluating women suspected of early pregnancy complications. The β-hCG level correlates directly with the quantity of active villous trophoblast, doubling approximately every 1.4–1.6 days from its initial detection until day 35 of pregnancy, and then increasing every 2.0–2.7 days until day 42 of pregnancy [7,8].

Material and method

A prospective longitudinal study was conducted for 2 years at SGT Hospital, SGT University Gurgaon, involving the Departments of Biochemistry and Obstetrics and Gynaecology. The study aimed to analyze biochemical parameters in 100 pregnant women with threatened abortion.

Inclusion criteria included pregnant women aged 18 to 35 visiting the outpatient department at SGT Medical College and Hospital between the 5th and 13th week of gestation, diagnosed with threatened abortion based on vaginal bleeding with or without pain and a positive ultrasound showing embryo cardiac activity. Willingness to participate was required.

Exclusion criteria involved unwilling participants, multiple gestation, blighted ovum, missed, inevitable, or incomplete abortion, ectopic pregnancy, gestational trophoblastic disease, recurrent pregnancy loss (two or more clinical pregnancy losses before 20 weeks), and age below 18 or above 35 years.

The methodology included assessing anthropometric indices and measuring biochemical parameters. One hundred eligible pregnant women were enrolled and monitored every four weeks in the outpatient department for clinical and ultrasound examinations.

Blood samples were collected twice during the study: first between the 5th and 13th weeks of gestation and second at delivery, complete abortion, or stillbirth.

The study aimed to evaluate the predictive value of serum levels of free β-hCG, progesterone, and CA125 alone and in combination for first-trimester abortion, as well as to investigate potential risks associated with early pregnancy bleeding in viable intrauterine pregnancies.

Results

Table 1 illustrates the overall features of cases upon admission, along with the average levels of b-hCG, progesterone, and CA125 for every category. In this study involving 100 patients, several criteria were evaluated, and their respective means ± standard deviations (S.D.) were reported along with associated P-values. The criteria included Age, Gravidity, Gestation of presentation (in weeks), Number of previous miscarriages, Free β HCG, Progesterone, and CA125.

The mean age of the participants was 25.58 years with a standard deviation of 4.15, and the associated P-value was greater than 0.05, indicating that there was no statistically significant difference in age among the study population.

On the other hand, Gravidity, Number of previous miscarriages, Progesterone, and CA125 showed statistically significant differences with P-values less than 0.05. Gravidity had a mean of 2.79 ± 1.37, suggesting variations in the number of pregnancies among the participants. The mean number of previous miscarriages was 1.09 ± 0.95, indicating a range of previous pregnancy loss experiences.

Progesterone levels were reported with a mean of 9.18 ± 0.99, and CA125 had a mean of 55.17 ± 6.16. Both criteria showed statistically significant differences, implying potential associations with the condition under investigation.

These findings suggest that certain factors, such as gravidity, previous miscarriages, progesterone levels, and CA125, may play a role in the studied condition, warranting further investigation and consideration in the overall assessment and management of the patients involved in the study.

Table - 1

Criteria	Mean ± S.D.	P Value
Age	25.58 ± 4.15	>0.05
Gravidity	2.79 ± 1.37	<0.05
Gestation of presentation (in weeks)	7.26 ± 1.40	>0.05
Number of previous miscarriages	1.09 ± 0.95	<0.05
Free b HCG	14.42 ± 3.52	>0.05
Progesterone	9.18 ± 0.99	<0.05
CA125	55.17 ± 6.16	<0.05

Table – 2 The comparison of b-hCG values upon its estimation values.

β -HCG	Continuous Pregnancy	Abortion	p-value
20 ng/ml	54	4	<0.05
<20/ng/ml	4	38	
Total	58	42	

The above table shows that 54 pregnancies continued and 4 pregnancies resulted in the Abortion of the fetus when there was an increase in β HCG levels by 20 ng/ml. However, only 4 pregnancies continued and 42 pregnancies resulted in abortion when β HCG levels were not raised or raised < 20 ng/ml from their levels at the first visit.

Table – 3 The comparison of progesterone values upon its estimation values.

Serum Progesterone	Continuous Pregnancy	IUD	p-value
15 ng/ml	50	8	<0.05
<15 ng/ml	8	34	
Total	58	42	

The above table shows that 50 pregnancies continued and 8 pregnancies resulted in Intra intra-uterine death of the fetus when there was an increase in Serum Progesterone levels by 15 ng/ml. However, only 8 pregnancies continued and 42 pregnancies resulted in intra-uterine death when Serum Progesterone levels were not raised or raised < 15 ng/ml from their levels at the first visit.

Table – 4 The comparison of CA125 values upon its estimation values.

CA-125	Continuous Pregnancy	IUD	p-value
65 U/ml	44	10	<0.05
>65 U/ml	14	32	
Total	58	42	

The above table shows that 44 pregnancies continued and 10 pregnancies resulted in Intra Uterine Death of the fetus when there was an increase in CA-125 levels by 65 U/ml. However, only 10 pregnancies continued and 42 pregnancies resulted in intra-uterine death when CA-125 levels were not raised or raised <65 U/ml from their levels at the first visit.

Table – 5 - The sensitivity of detecting abortion when solely considering individual parameters such as free b-hCG (<20 ng/ml), progesterone (<15 ng/ml), and CA125 (>65 U/ml) levels.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
β-HCG	93	90	93	90
Serum progesterone	86	81	86	81
CA-125	81	76	81	70

The table presents key diagnostic performance metrics for three biomarkers—β-HCG, Serum Progesterone, and CA-125—evaluated in the context of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

β-HCG demonstrated high sensitivity (93%), indicating its ability to correctly identify individuals with the condition. The specificity of 90% suggests a low rate of false positives. The PPV of 93% indicates that when β-HCG is positive, there is a 93% probability that the individual truly has the condition, emphasizing its reliability in confirming positive cases. The NPV of 90% implies a 90% likelihood that a negative β-HCG result accurately rules out the condition.

Serum Progesterone exhibited a slightly lower sensitivity (86%) but still performed well in identifying true positives. Specificity at 81% suggests a moderate rate of false positives. The PPV of 86% indicates a high probability of true positives when Serum Progesterone is positive, while the NPV of 81% underscores its ability to reliably exclude the condition with a negative result.

CA-125 displayed sensitivity, specificity, PPV, and NPV values of 81%, 76%, 81%, and 70%, respectively. These metrics collectively indicate CA-125's effectiveness in both identifying positive cases and ruling out the condition in negative instances, although with slightly lower precision compared to β-HCG and Serum Progesterone.
In summary, the table provides a comprehensive overview of the diagnostic accuracy of β-HCG, Serum Progesterone, and CA-125, offering valuable insights into their performance characteristics in detecting and excluding the studied condition.

Table – 6 The sensitivity in identifying abortion when all three parameters, including free b-hCG (<20 ng/ml), progesterone (>15 ng/ml), and CA125 (>65 U/ml), are considered collectively.

	Sensitivity	**Specificity**	**PPV**	**NPV**
B-HCG + Progesterone +CA 125	7	100	100	83

The presented table combines the diagnostic parameters for a combination of biomarkers, specifically β-HCG and Progesterone, along with CA-125. The sensitivity of 7% indicates a low ability of this combination to correctly identify true positive cases. However, the specificity of 100% suggests a complete absence of false positives. The positive predictive value (PPV) and negative predictive value (NPV) are both 100%, underscoring the reliability of this biomarker combination in confirming positive cases and excluding those without the condition. While the combination demonstrates high specificity and predictive values, the low sensitivity implies potential limitations in identifying individuals with the studied condition.

Discussion

Total hCG is a glycoprotein hormone consisting of two subunits, designated as alpha (α) and beta (β). Synthesis of hCG primarily occurs in syncytiotrophoblasts. Its production is primarily controlled by the quantity of the beta subunit, with GnRH, activin, and inhibin released from cytotrophoblasts contributing to this regulation. When assessing the prognosis of threatened abortion, hCG is commonly utilized alone or in conjunction with progesterone, estradiol, testosterone, CA125, HPL, and ultrasonography. [9-12].
Literature consensus favors beta-hCG (b-hCG) over total hCG for reflecting immature trophoblast metabolic state more accurately with higher specificity. Hence, b-hCG replaced total hCG in this study. Numerous studies by De Leon et al., Al Sebai et al., Yaron et al., Ong et al., and Dugoff et al. have associated lower b-hCG levels with abortion. Our study's results, in line with prior research, demonstrated significantly reduced b-hCG in abortion cases, likely due to trophoblast origin. This correlation is expected given the role of b-hCG in reflecting trophoblast function, particularly evident in inevitable, complete, and incomplete abortion scenarios. [13-19].
Al-Sebai compared healthy pregnancies with those facing threatened abortion or tubal pregnancy, setting maternal serum b-hCG at 20 ng/ml. They reported b-hCG's sensitivity at 88%, a positive predictive value at 83%, stressing its diagnostic significance. Osmanagaoglu et al. found 91% sensitivity, 82% specificity, and 46% positive predictive value at the same b-hCG level for abortions. In our study, with b-hCG at 20 ng/ml, we found 93% sensitivity, 90% specificity, and 93% positive predictive value for abortions, aligning with Al-Sebai's findings. Our data suggests a single b-hCG study is beneficial for early abortion detection in asymptomatic pregnant women. The onset and maintenance of pregnancy are primarily regulated by endocrine factors, with the corpus luteum and placenta-released progesterone playing crucial roles. Progesterone levels in the blood slightly decrease between the 7th and 10th weeks, during which synthesis involves both the corpus luteum and placenta. Subsequently, the placenta becomes the exclusive producer, leading to increased progesterone levels until the end of pregnancy. The released progesterone supports the decidua, ensuring nutrition for conception and the pregnancy's continuity.

Inadequate progesterone levels increase the risk of pregnancy loss, leading to spontaneous abortion. Hahlin et al. witnessed spontaneous abortion in 83% of rats with progesterone at 59.4 ng/ml. McCord et al. noted a 22% spontaneous abortion rate in healthy pregnancies with serum progesterone below 15 ng/ml, compared to 62% in those with similar levels. Similarly, Osmanagaoglu et al. found 60% spontaneous abortion cases with progesterone below 15 ng/ml. Our study observed 42% spontaneous abortion cases with progesterone below 15 ng/ml, aligning with previous findings regarding the association between low progesterone levels and spontaneous abortion. [20-21].
Daily et al. reported 75% sensitivity and 78% specificity, using 15 ng/ml as a threshold to differentiate between normal and abnormal pregnancies. Al Sebai et al. demonstrated 88% sensitivity and 88% specificity, using a 13 ng/ml threshold to distinguish abnormal (abortion or ectopic pregnancies) from viable pregnancies within the first 18 weeks. Osmanagaoglu et al. found 91% sensitivity and 89% specificity in abortion detection, with a 15 ng/ml threshold. Our study showed 86% sensitivity and 81% specificity at the 15 ng/ml threshold for abortion detection, aligning with Al Sebai et al. and Daily et al.'s findings. We propose both b-hCG and progesterone as valuable standalone markers for abnormality detection. However, considering potential enhancements in sensitivity and specificity, we chose to assess both parameters jointly. [22-24].

Jouppila et al. identified abortion in 93% of 188 pregnant women by combining low hCG and low progesterone levels. Bora et al. found 83% sensitivity and 96% specificity when assessing b-hCG and progesterone together for threatened abortion prognosis, suggesting early spontaneous abortion detection. However, our study indicates no added benefit in sensitivity by using both b-hCG and progesterone compared to either alone. Despite b-hCG's higher independent ratio in multiple regression analysis and its common use in trophoblast prognosis, ectopic pregnancy, and threatened abortion, considering its cost and availability, we recommend using progesterone alone for detecting abortions in asymptomatic pregnancies. Single-parameter analysis in multiple regression may be more appropriate. [25-26].

Although CA125's significance is well-established in gynaecological oncology, its role in pregnancy remains uncertain. It's noted to rise in serum during the first week after menstruation, peaking within the initial 3 weeks, and then stabilizing. CA125, a glycoprotein, is studied for its prognostic value in early spontaneous abortion detection and threatened abortion prognosis. Two theories explain its elevation in maternal serum during the first trimester. The tubal reflux theory by Quirk et al. suggests CA125, originating from decidua, enters the maternal circulation through tubal reflux and increases after absorption by peritoneal lymphatics. As pregnancy progresses, tubal fusion leads to functional obstruction, decreasing CA125 levels. The second theory attributes CA125 passage to maternal circulation to decidual cell damage during chorionic villus invasion and placental preparation. These theories provide insights into the dynamics of CA125 in pregnancy but warrant further investigation for comprehensive understanding.[27-28].

The elevation of CA125 in maternal circulation during in-utero death is linked to decidua damage. While some studies suggest a correlation between high CA125 levels and spontaneous abortion, others find no significant difference. Hornstein et al. and Brumsted et al. observed lower mean CA125 levels in pregnancies with spontaneous abortion, though insignificantly. In contrast, our study detected 81% sensitivity and 76% specificity for abortion detection using a threshold of 465 U/ml. [29-32].

Several studies suggest CA125's prognostic value by comparing threatened abortion cases resulting in abortion with those that didn't. They found higher CA125 levels in threatened abortion cases compared to healthy pregnancies, linking maternal serum CA125 increase to decidua and fetal membrane damage. [33-35].

Our study aimed to determine whether abortion could be identified upon initial admission in asymptomatic pregnant women with confirmed fetal heart activity. While we propose CA125 originates from the decidua, some authors argue its fetal origin. Genetic analysis post-abortion revealed 45XO in one case and Trisomy 13 and 21 in the others. They suggested CA125 elevation in asymptomatic pregnancies may indicate abortion risk. This suggests CA125's potential as an early predictor of abortion risk, especially in asymptomatic pregnancies. However, further research is needed to elucidate its origin and role in pregnancy, considering its implications for prenatal care and risk assessment.

Two limitations of this study include the relatively small sample size of 100 pregnant women, which may limit the generalizability of findings, as larger cohorts are typically needed for more robust conclusions. Additionally, the study's single-center design could introduce biases and limit the diversity of patient characteristics and outcomes, potentially affecting the study's external validity. While efforts were made to ensure thorough data collection and analysis within the specified parameters, the findings may not fully capture the complexities and variations present in a broader population. Future research could benefit from larger sample sizes and multi-center collaborations to overcome these limitations, allowing for more comprehensive evaluations of the predictive value of biomarkers for first-trimester spontaneous abortions across diverse populations and settings.

Conclusion

In summary, both free b-hCG and progesterone, when considered independently, exhibited statistically significant predictive capability for abortion. Therefore, either free b-hCG or progesterone levels alone can be effectively utilized by clinicians for predicting first-trimester spontaneous abortions. Preferential recommendation may lean towards progesterone due to its widespread availability and lower cost compared to free b-hCG.

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