Biochemical risk assessment of first trimester miscarriage by evaluating serum estradiol progesterone and beta human chronic gonadotropin levels

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ABSTRACT

Objective: The current study was carried out to predict outcome of first trimester pregnancy by evaluating serum estradiol, progesterone and beta human chorionic gonadotropin levels.

Material and Methods: This cross-sectional study was conducted at the Department of Chemical pathology and endocrinology AFIP, for a period of six months (from January 2023 to June 2023). Non-probability consecutive sampling was used for the selection of participants. All females presented with singleton pregnancy of 05-07 weeks from 21-40 years age were asked to sign informed consent and enroll in study. All patients with assisted reproductive techniques facilitated pregnancy, known thyroid, diabetes and hypertension were excluded from the study. Chemical biomarkers including Serum beta HCG, estradiol and progesterone were compared at the time of 7-9 weeks and 10-12 weeks. Statistical analysis was performed using Mann Whitney U test and relative risk analysis and p-Value ≤ 0.05 was considered significance.

Results: Median of Beta HCG at 7-9 weeks IU/L, Estradiol 7-9 weeks gestation, Beta HCG at 10-12 weeks IU/L, Estradiol at 11-12 weeks pmol/L and Progesterone at 11-12 weeks nmol/L were low in Miscarriages 6574.0 (9876.0 – 4321.0), 760.0 (913.3 – 634.0), 18356.0 (67893.0 – 15000.0), 1011.0 (1987.0 – 900.0) and 65.60 (164.0 – 32.50) respectively as compare to healthy groups and showed statistically highly significant difference as p values < 0.001. Median of Progesterone at 7-9 weeks nmol/L also low in Miscarriages group but showed non statistically significant difference as p value = 0.062.

Conclusion: It was concluded that estradiol levels can effectively predict miscarriage in the first trimester, with higher sensitivity at 7-9 weeks. Early monitoring of estradiol can aid in identifying at-risk pregnancies, enabling timely interventions to improve outcomes.

Keywords: First trimester miscarriage, Beta HCG, Estradiol, Progesterone

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INTRODUCTION

First-trimester miscarriage defined as the loss of a pregnancy before the 12th week of gestation, is a distressing event for couples and healthcare professionals alike. Unfortunate but statistically, pregnancy loss occurs in approximately 15–25% of pregnancies out of which 2.9% occurs within the first trimester of gestation. Despite living in the world, trying to explore the black-hole and set a step in meta-verse, the aforesaid loss is still the most common pregnancy complication affecting women's physical and mental health. Repeated Clinical examinations and treatments for threatened abortion also leads to economic and mental burdens on patients. In nutshell, impacts of pregnancy loss are manifold; affecting all realms of life [1]. Hossain *et al*., reported a high prevalence of miscarriages, with an estimated rate of 22.5% among women of reproductive age [2]. Understanding the underlying causes of first-trimester miscarriage is essential for appropriate management and counseling of

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affected couples. Biochemical risk assessment in the context of first-trimester miscarriage involves serum levels of estradiol, progesterone, and beta-human chorionic gonadotropin (β-hCG) that can play a crucial role in identifying potential causes and guiding interventions. These markers provide valuable information about hormonal balance, placental function, and embryonic development during early pregnancy. Factors such as maternal age, underlying medical conditions, lifestyle factors, and access to quality prenatal care may influence the incidence of miscarriages in the country [3]. Estradiol is the primary form of estrogen in the body which plays a critical role in the establishment and maintenance of pregnancy. Estradiol levels rise steadily during first trimester reflecting the activity of the developing placenta. Low estradiol levels may indicate insufficient placental function, while excessively high levels could suggest abnormal fetal development or an increased risk of gestational complications [4]. Progesterone is a hormone essential for maintaining pregnancy by promoting endometrial receptivity, inhibiting uterine contractions, and supporting early embryonic development. Low progesterone levels may result in inadequate endometrial preparation, leading to implantation failure or early pregnancy loss. Progesterone supplementation has been used as a potential intervention to support pregnancies at risk [5]. β-hCG is a hormone produced by the placenta during pregnancy. It is commonly used as a marker for pregnancy detection and monitoring. Abnormal β-hCG patterns, such as slow or fluctuating rise, can indicate an increased risk of miscarriage or potential chromosomal abnormalities in the fetus [6]. Several studies have explored the relationship between serum estradiol, progesterone, and β-hCG levels and the risk of first-trimester miscarriage. Lathi *et al*. found that lower serum estradiol and progesterone levels were significantly associated with an increased risk of miscarriage [7]. Another study by Chung *et al*. examined β-hCG levels in pregnancies with threatened miscarriage and found that higher initial β-hCG levels were associated with a reduced risk of miscarriage [8].

There is a scarcity of comprehensive and recent data specifically focused on first-trimester miscarriages in Pakistan. The aim of the study is to predict outcome of first trimester pregnancy by evaluating serum estradiol, progesterone and beta human chorionic gonadotropin levels. The study's hypothesis suggests that abnormal levels of estradiol, progesterone, and beta-human chorionic gonadotropin (β-HCG) during the first trimester can serve as early indicators of high-risk pregnancies, potentially enabling timely therapeutic interventions to improve pregnancy outcomes.

MATERIAL AND METHODS

The study was Cross Sectional conducted on 272 pregnant females at Armed Forces Institute of Pathology (AFIP) / National University of Medical Sciences (NUMS) in collaboration with Obstetrics & Gynaecology Department, Combined Military Hospital, Rawalpindi. Data was collected from January 2023 to June 2023 for the duration of 6 months after approval of Institutional Review Board (IRB).

The sample size was calculated with the help of cohort sample size calculating formula study by using the WHO calculator, with a prevalence of recurrent miscarriage being 2.9% (0.195) in the local population with a confidence interval of 95%, and 5% margin of error, sample size was come out to be 156.Sampling was done by non-probability consecutive sampling technique.

All females presented with singleton pregnancy of 05-07 weeks from 21-40 years were thoroughly informed about the study's purpose and asked to sign informed consent to enroll in study. They were assured of Confidentiality and their right to withdraw at any time. Age was categorized within 04 groups as < 25 years, 26-30 years, 31-35 years and 36-40 years. Females with pregnancy achieved by assisted reproductive technique, thyroid disease, diabetes or known hypertensive were excluded from the study.

After selection, all relevant patient's data was recorded in a profroma specially designed for this purpose. The participants were then asked to get their blood sampling for estradiol, progesterone and β-HCG levels during 5th to 7th weeks, while second sampling was done at 9th to 11th weeks of gestation again for estradiol, progesterone and β-HCG levels in. Hormone Levels were compared to assess the risk of miscarriage. Outcome of pregnancy was recorded after 13th weeks of gestation, and then the participants were divided into two groups depending on the outcome.

Data was analyzed by using Statistical Package for Social Sciences (SPSS) 22.00. Normality of data was checked by using Kolmogorov-Smirnov test. Data were not distributed normally and were represented using median (IQR). Qualitative data was represented by using percentage and frequency. Mann Whittney U-test (for non-normal quantitative data) was applied and p-value of ≤ 0.05 was considered as statistically significant".

RESULTS

Total 156 females were registered in the study during study, mean age was 35.0 (37.0 – 28.0) years. Median weight was 74.5 (83.3 – 66.0) kgs, Basal Metabolic Index for Asian population was used to determine BMI categories, results indicated maximum frequency in obesity class I (BMI of 31-34) with 106 (67.3%), followed by overweight (BMI of 25-29.9) with 24(15.4%), Obesity class II and Class III was reported in 24(15.4%), and 3 (1.9%) respectively.

Median value of gravida, parity and previous number of miscarriages were 3.0 (4.0 – 2.0), 1.0 (2.0 – 0.0) and 1.0 (2.0 – 0.0) respectively.

Patients were divided into two groups of healthy pregnancy and miscarriage; Comparison of demographics between miscarriage and healthy pregnancy groups shown in Table-I. Thyroid stimulating hormone and fasting blood glucose levels were evaluated at 10-12 weeks of gestation, indicating comparatively lower values of TSH and highest value of FBG in miscarriage groups, as 1.4 (2.9 – 1.1) and 4.3 (4.6 – 3.7) respectively. P-values were insignificant with 0.005 & 0.135 (Table-II). The Table-III compares serum hormone levels between healthy pregnancies and miscarriages at 7-9 and 10-12 weeks of gestation. Significant differences are observed in β-HCG, Estradiol, and Progesterone levels between the two groups, with lower hormone levels in miscarriages (P-Values < 0.05).

Table-03 results showed that , Median of Beta HCG at 7-9 weeks IU/L, Estradiol 7-9 weeks gestation , Beta HCG at 10-12 weeks IU/L , Estradiol at 11-12 weeks pmol/L and Progesterone at 11-12 weeks nmol/L were low in Miscarriages 6574.0 (9876.0 – 4321.0), 760.0 (913.3 – 634.0), 18356.0 (67893.0 – 15000.0), 1011.0 (1987.0 – 900.0) and 65.60 (164.0 – 32.50) respectively as compare to healthy groups and showed statistically highly significant difference as p values < 0.001. Median of Progesterone at 7-9 weeks nmol/L also low in Miscarriages group but showed non statistically significant difference as p value = 0.062.

Table-I: Comparison of demographics variables between miscarriage and healthy pregnancy groups (n=156).

Variables	Healthy Pregnancy (n=62) Median (IQR)	Miscarriages (n=94) Median (IQR)	p-Value
Age	29.0 (37.0 – 25.0)	35.0 (39.0 – 29.8)	< 0.001
BMI	34.1 (35.7 – 24.9)	31.7 (33.8 – 26.7)	0.480
Gravida	2.0 (3.0 – 1.0)	4.0 (5.0 – 3.0)	< 0.001
Parity	2.0 (1.0 – 0.0)	1.0 (2.0 – 0.0)	0.589

Table-II: Comparison thyroid stimulating hormone and fasting blood glucose levels between the groups.

Variables	Healthy Pregnancy (n=62) Median (IQR)	Miscarriages (n=94) Median (IQR)	P-Value
TSH	2.6 (3.5 – 1.2)	1.4 (2.9 – 1.1)	0.005
F. Blood Glucose	3.9 (4.4 – 3.5)	4.3 (4.6 – 3.7)	0.135

Table-III: Comparison of biochemical markers between miscarriages and healthy pregnancy groups

Variables	Healthy Pregnancy (n=62) Median (IQR)	Miscarriages (n=94) Median (IQR)	p-Value
Beta HCG at 7-9 weeks IU/L	19987.0 (20187.0 – 12897.0)	6574.0 (9876.0 – 4321.0)	< 0.001
Estradiol 7-9 weeks gestation	1076.5 (1167.0 – 971.0)	760.0 (913.3 – 634.0)	< 0.001
Progesterone at 7-9 weeks nmol/L	29.0 (53.3 – 25.0)	26.6 (39.8 – 22.0)	0.062
Beta HCG at 10-12 weeks IU/L	54384.0 (67893.0 – 23000.0)	18356.0 (67893.0 – 15000.0)	< 0.001
Estradiol at 11-12 weeks pmol/L	1997.0 (2234.0 – 1156.0)	1011.0 (1987.0 – 900.0)	< 0.001
Progesterone at 11-12 weeks nmol/L	31.70 (65.60 – 29.67)	65.60 (164.0 – 32.50)	< 0.001

DISCUSSION

Our findings confirmed prior findings that blood oestrogen, progesterone, and β-HCG levels increase by gestational phase between 7 and 12 weeks [10]. Estradiol and progesterone levels stood suggestively lesser in the miscarriage cohort. Previous research studies found that the intensities of these markers were lower, demonstrating adverse pregnancy results [11]. However, the significance of these factors in predicting miscarriage remains unknown. Our findings suggest that blood indicators within the first 9 weeks of gestation can be used to distinguish between a normal pregnancy and a first-trimester loss. Declining serum estradiol at 7-9 and 10-12 weeks, as well as progesterone levels at 7-9 weeks, were found to be predictive, but β-HCG levels had no influence [12]. β-HCG had no effect on the analytical usefulness of estradiol in combination with progesterone or estradiol at 7-9 weeks for miscarriage [13]. This is explained by the robust extrapolative effect of estradiol, which remains significant even when influenced by β-HCG [14]. At 7-9 weeks, the analytical conclusion of twin or multi-indicators was lower than at 10-12 weeks.[15] β-HCG & progesterone levels alone have little prognostic significance, but when combined with estradiol, they could boost estradiol's predictive effect at 7-9 weeks [16]. A combination of β-HCG and estradiol, in particular, might function better. As a result, decreased levels of estradiol are the greatest interpreter of miscarriage between 7 and 12 weeks. Our findings are similar to the findings of Yang Li and colleagues [17]. The aim of the study was to assess chances of miscarriage within 12 weeks, whereas Yang Li and colleagues' [17] goal was to rule out other undesirable consequences of usual pregnancy, such as biochemical ectopic pregnancy and miscarriage. In our investigation, blood progesterone increase during 7-9 weeks of conception associated to 10-12 weeks of gestation [13,18].

At 7-9 weeks, progesterone levels did not indicate miscarriage in the first trimester. However, progesterone levels at 7-9 weeks can be used to predict miscarriage, however, they are no more effective than serum estradiol levels at 7-9 weeks. Because significant progesterone production begins in the seventh gestational week, our findings suggest that progesterone might be a predictor at 7-9 weeks [19].

Similar to prior research, a high progesterone level at the time of embryo transmission projected a greater risk of continued gestation. According to the findings of Ku CW *et al*, [20] blood progesterone quantity improved with gestation till 13 weeks of typical pregnancies, but those with impulsive miscarriage exhibited a bordering rise [20]. Our findings also revealed that progesterone levels were greater at 7-9 gestational weeks than at 5-6 gestational weeks in a normal pregnancy. Similarly, around 7-9 weeks of gestation, women who miscarried had lower progesterone levels

than typical pregnant women [21]. According to the research, progesterone has an important function in promoting an early pregnancy. In our investigation, progesterone levels at 7-9 weeks that were lower than the cut-off value of 15.27ng/ml might predict miscarriage. This is consistent with the findings of the study by Lek SM *et al*. [22] They also established that the serum progesterone cut-off value (35nmol/L) has therapeutic significance and allows doctors to stratify patients into high and low-risk groups for spontaneous miscarriage [22]. Because serum HCG increases at a rate of 66% per 48 hours in normal pregnancy, a dynamic level of β-HCG may be more useful. A β-HCG rise rate of less than 66% suggests an unfavorable pregnancy outcome [23].

In comparison to those findings, β-HCG was evaluated just twice at 7-9 weeks in our investigation, which is insufficient to predict the total miscarriage fate during 12 weeks. It might be because pregnancy is an uncertain and vulnerable time. However, at 7-9 weeks, β-HCG coupled with estradiol significantly enhanced the prediction. It might be due to the HCG plateauing during this time frame. Our findings were consistent with recent research that revealed that low levels of estradiol and β-HCG, as well as low growth rates, likely signal poor pregnancy outcomes [24].

However, another study found that β-HCG and oestrogen levels were greater, not lower, during the first 6 weeks of pregnancy, indicating a new link between β-HCG, oestrogen, and threatening abortion [25].

After a woman has a vaginal hemorrhage or stomach aches, a pelvic ultrasound is frequently used to diagnose an early miscarriage. If an ultrasound at 8.5 weeks revealed embryonic survival, 95% of pregnancies would not result in miscarriage by 14 weeks. Although literature supporting ultrasound scans, such as subchorionic hemorrhage, fetal heart rate, and yolk sac diameter related to pregnancy loss has existed however the findings were argumentative [26].

As a result, prediction indicators before 8.5 weeks must be scrutinized. In our investigation, we discovered that estradiol at 7-9 weeks of gestation had a significant effect on the prediction of miscarriage in the first trimester.

The existing discoveries vary from prior studies, which found that the levels of estradiol at each gestational week from 5 to 8 weeks might calculate the threat of miscarriage. There are two explanations behind our study's 7-9 weeks and 10-12 weeks groups.

LIMITATIONS

This study has limitations due to its single-center design and small sample size, and the use of non-probability sampling techniques introduces potential bias. For more accurate results this study should be conducted on the large scale and for longer time period.

CONCLUSION

Constant assessment through ultrasound and β-HCG levels are known as the best markers to help forecast miscarriage risk and high-risk pregnancy before medical indications appear. Although the effects of estrogen and progesterone on pregnancy results are anticipated, our study is among the first to investigate the timing and results of hormone analysis for miscarriage prediction in our population. Our results discovered that estradiol levels can predict miscarriage in the first trimester, and the sensitivity of the cut-off value at 7-9 weeks of conception is greater. Additionally, our findings suggest that at 7-9 weeks of gestation, β-HCG or progesterone in combination with estradiol may offer superior predictive value. Our study contained a small number of instances, and further case and multicenter investigations are needed for validation of findings.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHORS CONTRIBUTION

Saqibah Rehman: Conception, data collection, formal analysis, investigation and resources, accountable for all aspects of the work

Muhammad Usman Munir: Interpretation of the work, accountable for all aspects of the work

Ayesha Shuja: Designing the study content, review writing, accountable for all aspects of the work

Muhammad Qaiser Alam Khan: Critical review, overall supervision, accountable for all aspects of the work

Zujaja Hina Haroon: Data collection, analysis, investigation, accountable for all aspects of the work

Muhammad Younas: Revisions, Accountable for all aspects of the work

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