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Association of Serial Beta Human Chorionic Gonadotropin and Serum Progesterone Levels with Outcome in Pregnancy of Unknown Location

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ABSTRACT

Objective: To explore the association of serial Beta hCG and serum progesterone levels with outcome in women with pregnancy of unknown location managed at a teaching hospital.

Study Design: Prospective observational study

Place And Duration Of Study: Department of Gynecology and obstetrics Pak Emirates Military Hospital Rawalpindi, Pakistan from Jun 2022 to Jul 2023

Methodology: All the women who were diagnosed as having pregnancy of unknown location by consultant obstetrician based on ultrasound findings were recruited in the study. Serum progesterone and Beta hCG levels were carried out at baseline and then beta HCG levels were repeated at 48 hours. Study participants were followed up for 10 weeks to look for immediate intrauterine outcome of pregnancy. All statistical analysis was performed by using the Statistics Package for Social Sciences.

Results: Out of 101 women with pregnancy of unknown location, 44(43.6%) were primiparous while 57(56.4%) were multiparous. Mean age of women recruited in this study was 27.82 ±4.28 years. At the end of 10 weeks of gestation on transvaginal scan, 38(37.6%) had intrauterine pregnancy, 14(13.8%) had ectopic pregnancy, 35(34.6%) had failed/failing pregnancy while 14(13.8%) had persistent pregnancy of unknown location. Statistical analysis showed that progesterone levels of >10ng/ml and beta hCG ratio >60% had statistically significant relationship with intrauterine and ectopic pregnancy (*p*-value<0.001).

Conclusion: Serum Progesterone levels of more than 10 ng/ml and ratio of beta hCG levels at 48 hours and at baseline >60% had statistically significant association with outcome of pregnancy as intrauterine or ectopic at ultrasound done at 10th week of gestation.

Keywords: Beta hCG; Pregnancy of unknown location; Progesterone; Outcome

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INTRODUCTION

Women of fertile age group and those who are sexually active usually suspect pregnancy once they miss menstrual periods or get a positive urine for pregnancy test.[1] It is confirmed by the obstetrician on transvaginal ultrasound on first ante-natal visit in most of the cases.[2] Sometimes obstetrician despite history of missed menstrual period and positive urine for pregnancy test does not find an intrauterine gestational sac.[3] There are set protocols for women with pregnancy of unknown location but they have been constantly evolving based on new scientific evidence.

Outcome of pregnancy for unknown location may vary from being spontaneous conversion to intrauterine pregnancy to failed pregnancy.[4] Ectopic pregnancies may also be an outcome in such patients.[5] Very few persist with status of unknown location up to 10th week of gestation. Other than ultrasound there is no gold standard investigation which could be performed in these patients to ascertain the outcome. Multiple biochemical markers have been researched if they could be used to predict the outcome and pick up high risk cases from the time diagnosis of pregnancy of unknown location is made.[6]

Multiple hormones are studied to predict outcome of pregnancy both in apparently normal and high risk pregnancies. Systematic review published by Huang et al highlighted the role of serum progesterone and beta hCG levels in predicting outcome of pregnancies and complications associated with pregnancy. They concluded that altered levels of these hormones at the start of pregnancy predict poor outcome and complication during the pregnancy. Therefore, women with derangement of these hormones should be dealt as high risk cases.[7]Puget et

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al. published a prospective study on women presenting with pregnancy of unknown viability. They studied role of serial hCG levels and progesterone levels in predicting outcome of pregnancy in these women and revealed that serial beta hCG levels alone and in combination with TVS were useful in predicting outcome in these patients.[8] Another study published in 2022 highlighted the role of serum progesterone, estradiol and beta hCG in predicting miscarriage with in nine weeks of gestation.[9]

In a developing country like Pakistan with compromised antenatal care, there is a need for simple and efficient markers to pick up high-risk cases and ensure proper engagement of team with these cases. Follow up on antenatal visits remain poor as well in our part of the world especially rural region. A recent local study summarized the findings related to outcome of pregnancy of unknown location at Lady Wellington Hospital Lahore. It was revealed that failing pregnancy and ectopic pregnancy were the most common outcomes. Limited local data has been available regarding role of different biochemical in predicting outcome of pregnancy in these women. This study was planned with the rationale to explore the association of serial Beta hCG and serum progesterone levels with outcome in women with pregnancy of unknown location managed at PEMH Rawalpindi.

METHODOLOGY

This Prospective observational study was conducted in Gynecology and obstetrics department Pak Emirates Military Hospital Rawalpindi, Pakistan from June 2022 to July 2023.WHO Sample Size Calculator was used for sample size calculation with population prevalence proportion of pregnancy of unknown location as 5%.[11] Nonprobability consecutive sampling technique used to gather the sample for this study.

Inclusion Criteria: All the women who had missed menstrual period and/or had positive urine for pregnancy test but did not have gestational sac visible on TVS were recruited.

Exclusion Criteria: Women with diagnosed ectopic pregnancy or those with history of any benign or malignant tumors of gynecological or abdominal regions were excluded. Those women who lost to follow up after first antenatal checkup were not included in the study. Those who refused to undergo biochemical testing were also not included in the study.

Ethical approval was obtained from Internal Review Board of Pak Emirates Military Hospital (IREB Letter no: A/28/EC/3681/2021). Study was explained and informed consent was taken from all the women who were included in the study. Pregnancy of unknown location was assessed by consultant obstetrician based on TVS done around 6th week of gestation.[12] After the diagnosis was made, all the women underwent baseline laboratory investigations including serum progesterone levels and beta hCG levels. Beta hCG levels were repeated after 48 hours as well and all the values were recorded on a separate sheet. Cut off level used for serum progesterone levels was 10ng/ml.[13] while for ratio of beta hCG at base line and 48 hours was 60%.[14] All the women were followed up to 10th week of gestation and TVS was repeated every week. Outcome was ascertained at the end of 10 weeks on the basis of TVS findings and categorized as intrauterine pregnancy, failed or failing pregnancy, ectopic pregnancy or persistent pregnancy of unknown location.

All statistical analysis was performed by using the Statistics Package for Social Sciences version 24.0 (SPSS-24.0). Mean and standard deviation for the age of study participants was calculated. Frequency and percentages for patients with ectopic pregnancy, intrauterine pregnancy, failed pregnancy and persistent pregnancy of unknown location were calculated. Chi-square test was applied to look for association between the serum progesterone levels and ratio of beta HCG levels at 48 hours and baseline and outcome of pregnancy. The *p*-values of less than or equal to 0.05 were considered as significant.

RESULTS

Out of 101 women with pregnancy of unknown location, 44(43.6%) were primiparous while 57(56.4%) were multiparous. Mean age of women recruited in this study was 27.82±4.28 years. Table-I showed general clinical and demographic profile of women included in this study. At the end of 10 weeks of gestation on transvaginal scan, 38(37.6%) had intrauterine pregnancy, 14(13.8%) had ectopic pregnancy, 35(34.6%) had failed/failing pregnancy while 14(13.8%) had persistent pregnancy of unknown location.

Table-II showed the results of statistical analysis. It was revealed that serum progesterone levels of >10ng/ml and beta hCG ratio >60% had statistically significant relationship with intrauterine and ectopic pregnancy (*p*-value<0.001).

Table-I: Demographic and Outcome Characteristics of Women diagnosed with Pregnancy of Unknown Location (n=101)

Parameter(s)	Values
Age (years) Mean + SD	27.82 ±4.28 years
Parity Primiparous Multiparous	44(43.6%) 57(56.4%)
Baseline progesterone levels >10ng/ml <10ng/ml	53(52.4%) 48(47.6%)
Body mass index Normal Overweight Obese	64(63.4%) 22(21.8%) 15(14.9%)
Outcome at 10 weeks Intrauterine pregnancy Ectopic pregnancy Failed pregnancy Persistent pregnancy of unknown location	38(37.6%) 14(13.8%) 35(34.6%) 14(13.8%)

surveillance of high risk pregnancies. Multiple hormonal levels and indices are in use for clinical and research purpose regarding assessment of outcome of pregnancies of unknown location.[13-14]

Ayesha Ajmi published a study from Lahore and tried to look for association of serum progesterone levels and serial beta hCG levels with outcome in pregnancy of unknown location. She came up with the conclusion that association existed between >60% rise in 48-hour repeat HCG and progesterone >30 ng/dl with viable intrauterine pregnancy and ectopic pregnancy.[15] We used cut-off of 10 ng/dl for serum progesterone levels and had obtained similar results in our data set.

Bignardi et al. in 2010 studied women with pregnancy of unknown location and predicted outcome of pregnancy in them by using human chorionic gonadotropin ratio and progesterone. They found out that human chorionic gonadotropin ratio was better in predicting outcome as compared to

Table-II: Association of Hormonal Levels with Outcome in Women diagnosed with Pregnancy of Unknown Location (n=101)

Hormone(s)	Intrauterine pregnancy 38 (37.6%0	Ectopic pregnancy 14 (13.8%0	Failed pregnancy 35 (34.6%)	Persistent pregnancy of unknown location 14 (13.8%)	*p*-value
Serum progesterone levels >10ng/dl ≤10ng/dl	33(86.8%) 05(13.2%)	09(64.3%) 05(35.7%)	07(20.0%) 28(80.0%)	04(28.6%) 10(71.4%)	<0.001
Ratio of beta HCG at 48 hours and at baseline >60% ≤60%	27(55.3%) 11(44.7%)	10(71.4%) 04(28.6%)	07(20.0%) 28(80%)	03(21.4%) 11(78.6%)	<0.001

DISCUSSION

This study was conducted to explore the association of serial Beta HCG and serum progesterone levels with outcome in women with pregnancy of unknown location managed, it was found that Serum Progesterone levels of more than 10 ng/ml and ratio of beta HCG levels at 48 hours and at baseline >60% had statistically significant association with outcome of pregnancy as intrauterine or ectopic at ultrasound done at 10th week of gestation.

Pregnancy of unknown location pose a challenge to obstetrics team as it needs careful monitoring and thorough engagement with the patient till the time outcome is confirmed. Ultrasound alone is a tool available for obstetricians to ascertain the outcome of pregnancy of unknown location. Biochemical markers sometimes can predict the outcome or give a clue of high risk cases[5]. Combining biochemical markers with radiological investigations may be more beneficial for single reading of serum progesterone.[16] We did not compare the two biochemical markers but our results showed that both could be used to predict the outcome in women having pregnancy of unknown location.

A study was published from Karachi Pakistan in 2022 regarding establishing a protocol for women with pregnancy of unknown location on basis of serum progesterone and beta hCG level. It was concluded that serum progesterone and beta hCG ratio have good sensitivity and specificity for prediction of outcome of pregnancy of unknown location.[17] We did not study predictive values but in our study participants, serum Progesterone levels of more than 10 ng/ml and ratio of beta HCG levels at 48 hours and at baseline >60% had statistically significant association with outcome of pregnancy as intrauterine or ectopic at ultrasound done at 10th week of gestation.

Ghaedi et al. published a systematic review and meta-analysis regarding role of single reading of serum progesterone levels for predicting viability of pregnancy. They revealed that levels less than 6.3ng/ml were mostly seen in women with non-viable pregnancy, and more than 20ng/ml were seen in women with viable pregnancy. We used cut off of 10ng/ml and found that levels more than this cut-off are associated with ectopic or intrauterine pregnancy.

LIMITATION OF STUDY

We only included women who could follow-up from initial ultrasound till 10th week of gestation. Exclusion of non-follow-up patients may have created bias in our data set. Moreover, management of patients and other demographic factors may have impacted the outcome therefore association of levels of hormones could not be ascertained with outcome of pregnancy with this study design. Long term follow up may also change the outcome status.

CONCLUSION

Serum Progesterone levels of more than 10 ng/ml and ratio of beta HCG levels at 48 hours and at baseline >60% had statistically significant association with outcome of pregnancy as intrauterine or ectopic at ultrasound done at 10th week of gestation.

Conflict of Interest: None.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MM & SH: Data acquisition, data analysis, critical review, approval of the final version to be published.

MT & QUAA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SP & S: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Kennedy CE, Yeh PT, Gholbzouri K, Narasimhan M. Self-testing for pregnancy: a systematic review and meta-analysis. BMJ Open 2022; 12(2): e054120. https://doi.org/10.1136/bmjopen-2021-054120
2. Murugan VA, Murphy BO, Dupuis C, Goldstein A, Kim YH. Role of ultrasound in the evaluation of first-trimester pregnancies in the acute setting. Ultrasonography 2020; 39(2): 178-189. https://doi.org/10.14366/usg.19043
3. Pereira PP, Cabar FR, Gomez ÚT, Francisco RPV. Pregnancy of unknown location. Clinics 2019; 74: e1111. https://doi.org/10.6061/clinics/2019/e1111
4. Dawodu O, Wu J, Gallop R, Barnhart KT. Perinatal Outcomes of Pregnancies of Unknown Location With Human Chorionic Gonadotropin Concentration Above the Discriminatory Zone. Obstet Gynecol 2022; 140(5): 793-795. https://doi.org/10.1097/aog.0000000000004939
5. Mullany K, Minneci M, Monjazeb R, C Coiado O. Overview of ectopic pregnancy diagnosis, management, and innovation. Womens Health 2023; 19(2): 17455057231160349. https://doi.org/10.1177/17455057231160349
6. Deng W, Sun R, Du J, Wu X, Ma L, Wang M, et al. Prediction of miscarriage in first trimester by serum estradiol, progesterone and β-human chorionic gonadotropin within 9 weeks of gestation. BMC Pregnancy Childbirth 2022; 22(1): 112. https://doi.org/10.1186/s12884-021-04158-w
7. Huang J, Liu Y, Yang H, Xu Y, Lv W. The Effect of Serum β-Human Chorionic Gonadotropin on Pregnancy Complications and Adverse Pregnancy Outcomes: A Systematic Review and Meta-Analysis. Comput Math Methods Med 2022; 2022(1): 8315519. https://doi.org/10.1155/2022/8315519
8. Puget C, Joueidi Y, Bauville E, Laviolle B, Bendavid C, Lavoué V et al. Serial hCG and progesterone levels to predict early pregnancy outcomes in pregnancies of uncertain viability: A prospective study. Eur J Obstet Gynecol Reprod Biol 2018; 220: 100-105. https://doi.org/10.1016/j.ejogrb.2017.11.020
9. Deng W, Sun R, Du J, Wu X, Ma L, Wang M et al. Prediction of miscarriage in first trimester by serum estradiol, progesterone and β-human chorionic gonadotropin within 9 weeks of gestation. BMC Pregnancy Childbirth 2022; 22(1): 112. https://doi.org/10.1186/s12884-021-04158-w
10. Wajid R, Ahsan A, Riaz R, Abbas M, Noor M. Frequency of outcomes of patients with pregnancy of unknown location at a tertiary care hospital. Pak J Med Health Sci 2022; 16(8): 186-188. https://doi.org/10.53350/pjmhs22168186
11. Boyraz G, Bozdağ G. Pregnancy of unknown location. J Turk Ger Gynecol Assoc 2013; 14(2): 104-108. https://doi.org/10.5152/jtgga.2013.74317
12. Milman T, Walker M, Thomas J. Pregnancy of unknown location. CMAJ 2020; 192(39): E1132. https://doi.org/10.1503/cmaj.200142
13. Ku CW, Allen JC Jr, Lek SM, Chia ML, Tan NS, Tan TC. Serum progesterone distribution in normal pregnancies compared to pregnancies complicated by threatened miscarriage from 5 to 13 weeks gestation: a prospective cohort study. BMC Pregnancy Childbirth 2018; 18(1): 360. https://doi.org/10.1186/s12884-018-2002-z
14. Fistouris J, Bergh C, Strandell A. Classification of pregnancies of unknown location according to four different hCG-based protocols. Hum Reprod 2016; 31(10): 2203-2211. https://doi.org/10.1093/humrep/dew202
15. Ajmi A. Association of Serial Beta HCG And Progesterone Level With Outcome In Pregnancy of Unknown Location. J Bahria Univ Med Dent Coll 2018; 8(1); 21-25.
16. Bignardi T, Condous G, Kirk E, Calster BV, Huffel SV, Timmerman D et al. Viability of intrauterine pregnancy in women with pregnancy of unknown location: prediction using human chorionic gonadotropin ratio vs. progesterone. Ultrasound Obstet Gynecol 2010; 35(6): 656-661. https://doi.org/10.1002/uog.7669
17. Izhar R, Husain S, Tahir MA, Ala SH, Imtiaz R, Husain S, et al. Triaging Women with Pregnancy of Unknown Location: Evaluation of Protocols Based on Single Serum Progesterone, Serum hCG Ratios, and Model M4. J Reprod Infertil 2022; 23(2): 107-113. https://doi.org/10.18502/jri.v23i2.8995
18. Ghaedi B, Cheng W, Ameri S, Abdulkarim K, Costain N, Zia A et al. Performance of single serum progesterone in the evaluation of symptomatic first-trimester pregnant patients: a systematic review and meta-analysis. CJEM 2022; 24(6): 611-621. https://doi.org/10.1007/s43678-022-00332-x