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Pregnancy of unknown location- can serum creatinine phophokinase point towards tubal ectopic gestation?: A pilot study

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Abstract
Background: Pregnancy of unknown location (PUL) is defined as the situation when the urine or serum pregnancy test is positive but there are no signs of intrauterine or extra-uterine pregnancy on ultra-sonography and serum beta HCG is in the window period. Among all possible outcomes of pregnancy of unknown location, ectopic pregnancy is the most feared outcome. A delay in diagnosis might increase the maternal mortality and morbidity.
Methods: A prospective observational study conducted at Sri Ramachandra Institute of Higher Education and Research, Chennai, between February 2018 and April 2019. Women who had beta HCG in the discriminatory zone with an inconclusive transvaginal ultrasound were included in the study. Serum Creatinine phosphokinase levels were measured along with beta HCG.
Results: Among the 12women with PUL, 11 of them were eventually diagnosed with ectopic gestation and one of them remained to be a pregnancy of unknown location. All the patients diagnosed with ectopic gestation had their initial serum CPK levels above the cut off value of 51IU/lit.
Conclusion: Serum CPK levels in PUL can be used as a marker for early diagnosis of ectopic gestation when beta HCG and ultrasound are inconclusive. Larger studies are required to ascertain the significance.

Keywords: Pregnancy of unknown location, creatine phosphokinase, tubal ectopic gestation, pilot study, serum beta hCG

Introduction
Pregnancy of unknown location (PUL) is defined as the situation when the urine or serum pregnancy test is positive but there are no signs of intrauterine or extra-uterine pregnancy on ultra-sonography. The general incidence of PUL is 8–31% among women undergoing early pregnancy scans, although a lower incidence of 8–10% has been observed in specialized scanning units [1]. The final outcome in a woman initially classified as a PUL could be- Intrauterine pregnancy (IUP – this can either be viable (VIUP) or non-viable (NVIUP)); Failed PUL (FPUL), Ectopic pregnancy (EP), Persistent PUL (PPUL).
Follow up with sonographic evaluation in addition to interval serum human chorionic gonadotropin (hCG) measurements is essential for determination of the location of pregnancy. However, it is not always possible to determine the location of the pregnancy in cases of PUL.
Among all possible outcomes of pregnancy of unknown location, ectopic pregnancy is the most feared outcome. Incidence of ectopic gestation among PUL is about 58% [2]. Late diagnosis might increase the maternal mortality and morbidity, will reduce the success of medical treatment and might require a surgical intervention more frequently, which may further negatively affect fertility of the women.

Methods
It was a prospective observational study done at Sri Ramachandra Institute of Higher Education and Research, Chennai over a period of 14months, between February 2018 and April 2019. Women who had UPT positive and beta HCG below the discriminatory zone with an inconclusive transvaginal ultrasound (designated as pregnancy of unknown location) were included in the study.
Women who are known hypothyroid, who received multiple intra-muscular injections, who had muscle, heart or liver disease or had recent surgery in less than 3weeks were excluded from the study.

Serum CPK values were obtained along with the initial beta HCG. They were followed up with serum beta HCG and transvaginal ultrasound.

A complete history and physical examination along with pelvic ultrasound was done and documented. About 2ml of blood sample was collected by venipuncture before administering any intramuscular injections. Sample was allowed to clot. Serum was separated from the cells promptly to minimize hemolysis and contamination caused by adenylate kinase from the red blood cells. Serum CPK was measured in the biochemistry laboratory using spectrophotometric analysis on Beckman Coulter AU 5800 automated analyzer.

Results

When we studied the efficacy of serum CPK as a marker for tubal ectopic gestation, we came across 12 women who presented with positive pregnancy test and ultrasound did not detect any intra-uterine or extra-uterine gestational sac. Their serum beta HCG were less than 1500mIU/lit. They were followed up with beta HCG and repeat ultrasound. These women required beta HCG to be repeated thrice, on an average. Among the 12 women, 11 of them were eventually diagnosed with ectopic gestation and one of them remained to be a pregnancy of unknown location.

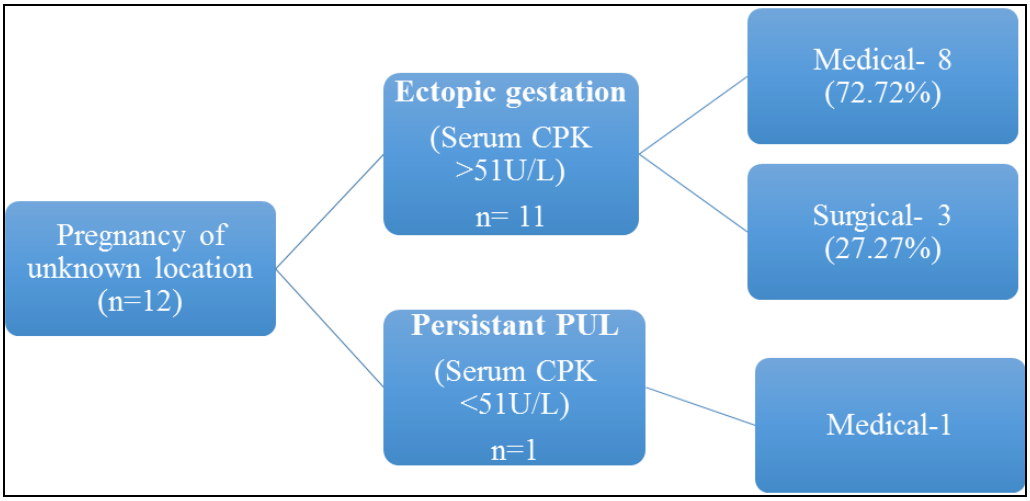

Fig 1: Outcomes in pregnancy of unknown location

In all these patients of pregnancy of unknown location, Beta HCG was repeated every 48hours and scan, after one week. 11 out of 12 patients (91.67%) had CPK levels above the cut off value of 51IU/lit.

Table 1: Pregnancy of unknown location

Parity	Gestational age (by LMP)	Serum CPK (U/lit)	Serum beta HCG (mIU/lit)	Final diagnosis
G1	7W 2D	123	1063	Unruptured ectopic pregnancy
G4 P2L2A1	5W 4D	86	1000	Unruptured ectopic pregnancy
G1	7W 4D	66	345	Unruptured ectopic pregnancy
G2P1L1	6W 4D	53	1012	Unruptured ectopic pregnancy
G2 A1	6W 3D	59	1527	Unruptured ectopic pregnancy
G2P1L1	6W 2D	68	161	Unruptured ectopic pregnancy
G3P2L2	5W	51	549	Unruptured ectopic pregnancy
G2 A1	6W 4D	59	1446	Unruptured ectopic pregnancy
G1	7W 6D	52	553	Unruptured ectopic pregnancy
G3A2	6W 6D	52	867	Unruptured ectopic pregnancy
G1	5W 2D	85	224	Unruptured ectopic pregnancy
G1	6W 6D	38	872	Pregnancy of Unknown location

These patients had repeat beta HCG values which showed an increase of less than 66% and scan repeated confirmed the diagnosis of ectopic gestation in all of them, except for one who remained as persistent PUL.

Discussion

Ectopic gestation is still the leading cause of maternal mortality and morbidity in the first trimester. Even with the advent of ultrasound and serum beta HCG for diagnosis of early intra-uterine or extra-uterine pregnancy, we still see women coming in a state of shock due to delay in diagnosis. An earlier diagnosis of tubal ectopic pregnancy also buys us time to institute successful medical management which helps in preserving the fallopian tubes. Due to paucity of markers for diagnosing ectopic gestations, various enzymes and hormones are studied widely. One among them is serum creatinine phosphokinase (CPK).

Serum Creatinine phosphokinase as a marker for ectopic gestation was studied with varying results by various authors. It was Lavie *et al.* [3], who first proposed that serum creatinine phosphokinase could be used as a diagnostic tool for detection of ectopic pregnancy, owing to the fact that fallopian tube lacks a sub-mucous layer. Plewa *et al.* [4], in 1998 found a significant increase in creatinine phosphokinase levels among ectopic pregnancies compared to abortive and normal pregnancies, but concluded that a significant overlap in CPK values makes the use of this serum marker unreliable for detecting ectopic pregnancy. Following this Birkhahn *et al.* [5] in 2000, Wazir *et al.* [6], in 2009 and Ganta *et al.* [7], in 2017 studied that creatinine kinase values to be significantly increased in ectopic gestations

compared to normal intrauterine pregnancies.
Serum CPK levels in women with pregnancy of unknown location, has not been studied till date. In our study, a single value of serum CPK was able to diagnose tubal ectopic gestation in all the patients. Thus it could be used as an early marker in diagnosing ectopic gestation earlier, therby reducing the maternal morbidity and mortality.

Conclusion
This can be regarded as a pilot study, for further research in serum creatine phosphokinase levels in pregnancy of unknown location. However, follow-up of these patients with ultrasound is mandatory to initiate treatment.

Strength of the study
Serum Creatinine phosphokinase is a single measurement as opposed to multiple measurements required of serum beta HCG, thus reducing the cost of healthcare.

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