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Agreement Between Serum Creatine Phosphokinase and Transvaginal Ultrasound in Diagnosis of Ectopic Pregnancy: Cross Sectional Study

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Abstract

***Objective*:** To determine agreement between serum creatine phosphokinase (CPK) and transvaginal ultrasound (TVS) in diagnosis of ectopic pregnancy. To see the possible clinical role of serum creatine phosphokinase compared to standard markers like β-hCG.

***Method*:** In this cross-sectional study a total of 70 female participants were recruited. The age of the participants were 15-45 years with gestational amenorrhea of 8-10 weeks and with the clinical suspicion of ectopic pregnancy. Serum creatine phosphokinase levels were measured in all participants, and transvaginal ultrasound was used as the main diagnostic test to determine the presence of absence of ectopic pregnancy. The Kappa statistics were used to evaluate the level of agreement between serum creatine phosphokinase and transvaginal ultrasound.

***Results*:** Using CPK levels, 30 females (42.9%) were identified as having ectopic pregnancy, while TVS detected 27 women (38.6%). When both tests were compared, 61 out of 70 cases (87.1%) showed the same result either both positive or both negative. The results indicate a significant agreement (Kappa = 0.734, $p < 0.001$).

***Conclusion*:** Serum CPK levels (>145 U/L) showed a strong correlation with TVS in diagnosing ectopic pregnancy. This suggests that CPK may serve as a supportive tool, especially in settings with limited ultrasound access. However, TVS should remain the gold standard for definitive diagnosis. Furthermore, Larger multicenter trials are required before serum creatine phosphokinase can be considered for routine clinical use.

Keywords: Ectopic pregnancy, transvaginal ultrasound, creatine phosphokinase, diagnostic accuracy.

1. INTRODUCTION

The failure of early pregnancy is still a major clinical problem nowadays and it is estimated that about one quarter of the cases will end up in miscarriage, whereas only 1-2% will be an ectopic pregnancy. The overlap of symptoms such as abdominal pain and vaginal bleeding makes it difficult to distinguish between the two conditions; nevertheless, ectopic pregnancy remains a serious scenario as it is linked to the first-trimester maternal morbidity and mortality. Ectopic pregnancies account for over 95% within the fallopian tubes and despite the fact that medical science has made great strides in diagnosis, still 40-50% of the cases are wrongly diagnosed in the beginning. This uncertainty in diagnosing the case is very troubling because the delays might cause tubal rupture, life-threatening bleeding, and loss of fertility [1].

TVS (Transvaginal ultrasonography) is still the main diagnostic method proving to be very sensitive and specific; however, its reliability might be decreased in the case of very early pregnancy or pregnancy of unknown location. At this point, doctors turn to β-HCG levels taken serially along with imaging done repeatedly over several days, the method that not only consumes resources but

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also evokes anxiety in the patients and is unsafe if rupture takes place during the waiting period. Hence, it is a great advantage for the clinical field to find a quick, low-cost biomarker that can boost the confidence of the diagnosis during the early stage [2].

Creatine phosphokinase (CPK), which is an enzyme highly present in muscle, has been suggested as a possible marker since the invasion of tubal smooth muscle by the trophoblast may lead to higher serum levels in ectopic pregnancy. Some studies have even indicated that CPK has a good diagnostic agreement with TVS while the total evidence is still inconsistent. Some researchers found significant increases in serum CPK in EF and even suggested a possible discriminatory value, while others pointed out that there is a great overlap with the ranges of normalcy or intrauterine pregnancy and, thus, concluded that CPK alone does not have enough accuracy for primary diagnosis. These opposing results not only highlight the existing grey area of the diagnostic utility of CPK but also call for further evaluation instead of simply assuming its effectiveness [1].

In light of these discrepancies and considering that CPK testing is inexpensive, widely available, and simpler to perform than serial β-HCG assays, it is necessary to re-evaluate its potential role, especially in resource-limited settings where quick decision-making is essential. So, this investigation is focused on measuring the level of agreement between serum CPK and TVS in the diagnosis of ectopic pregnancy, thus providing evidence that may help in determining its worth as a supplementary diagnostic tool [2].

One of the most common complications of pregnancy is early pregnancy failure, of which 25% result in miscarriages and 1-2% ends in ectopic pregnancy [3]. Both of these conditions may present with similar symptoms of lower abdominal pain and/or vaginal bleeding [1]. In ectopic pregnancy gestational sac implants outside uterine cavity and in more than 95% it is in fallopian tubes [2]. It is one of the most common causes of maternal morbidity and mortality in the first trimester, accounting for 4-10% of maternal deaths [3]. Approximately 70% of ectopic pregnancies presenting with lower abdomen pain and post vaginal bleeding in early pregnancy are detected on ultrasound, with the remainder being labelled as pregnancies of undetermined sites.

In such cases serial β-HCG and follow up ultrasound scan are then relied upon for diagnosis [4]. In a meta-analysis of ten studies Transvaginal ultrasound was found to be 84.4% sensitive, 98.9% specific, positive predictive value 96.3% and negative predictive value 94.6% [5]. It is thought that forty to fifty percent of cases are first misdiagnosed even with the use of sensitive assays for β-HCG and high-resolution transvaginal sonography. Clinicians have to follow patients over the course of several days to weeks for diagnosis, and in this time ectopic pregnancy can rupture and lead to life threatening intra-abdominal hemorrhage. By early treatment patients can benefit from tubal-conserving procedures that are important in saving patient's future fertility [6, 7]. Therefore, development of reliable and accurate blood test for early diagnosis of an ectopic pregnancy will be of great significance.

Creatine Kinase is an enzyme, abundantly found in metabolically active tissue like brain, myocardium and smooth muscles. In tubal pregnancy zygote penetrates into muscle layer and it leads to rise of CPK in blood [8]. One researcher reported that percentage of agreement between serum CPK levels and transvaginal ultrasound to be 82% for diagnosis of Ectopic Pregnancy [9]. Another study indicated that serum creatine kinase can help distinguish between ruptured and unruptured EP, but it cannot be utilized to make a primary diagnosis of ectopic pregnancy. Other investigations have found a large overlap of readings, limiting the diagnostic utility of CPK [10].

Early diagnosis is crucial for lowering maternal mortality and morbidity. While serum β-HCG and ultrasonography are effective, diagnosis can be questionable below the selective zone. Apart from that, we investigated the function of serum creatine kinase as an early diagnosis marker for ectopic pregnancy since there is grey area regarding diagnostic accuracy of serum creatine phosphokinase in ectopic pregnancy. Comparing the cost of ultrasonography and serial β-HCG led us to study this as expensive diagnostic tools in comparison to creatine kinase estimation.

This study is designed to evaluate reliability of maternal serum creatine kinase in diagnosis of tubal pregnancy.

2. METHODOLOGY

This cross-sectional study was conducted from 4th January to 3rd July 2019 in the Gynaecology Unit-I, Sir Ganga Ram Hospital, Lahore. The study duration was six months. The objective was to determine the agreement between serum creatine phosphokinase (CPK) and transvaginal ultrasound (TVS) in diagnosing ectopic pregnancy. Ethical approval was obtained from the College of Physicians and Surgeons Pakistan under reference number CPSP/REU/OBG-2016-059-7432.

A sample size of 70 patients was calculated using a 95% confidence level, a 9% margin of error, and an expected agreement of 82%. Patients were selected through non-probability consecutive sampling.

Women aged 15-45 years, of any parity, with gestational amenorrhea of 8-10 weeks, were included. Only clinically suspected cases of ectopic pregnancy were enrolled. Suspicion was based on lower abdominal pain,

per-vaginal spotting, and a positive urine pregnancy test. Patients with recent surgery, major trauma, chest pain, CNS disorders, hypothyroidism, myopathy, or recent intramuscular injections were excluded, as these conditions can elevate CPK levels and act as effect modifiers.

Operational definitions were applied. CPK was considered positive for ectopic pregnancy if the value was >145 U/L and negative if the value was ≤145 U/L. TVS was labelled positive when there was no intrauterine gestational sac or when an adnexal mass was present. It was labelled negative if an intrauterine gestational sac was seen. Agreement was defined when both tests were either positive or negative.

Data collection was performed in the emergency department. Informed consent was obtained from each patient. A detailed clinical history was recorded. Blood samples for serum CPK were drawn immediately after venipuncture and sent to the laboratory. Each patient underwent a transvaginal ultrasound, which was performed by the same examiner to minimize observer bias. Findings from CPK testing and TVS were documented on a predesigned proforma.

The CPK cutoff of 145 U/L was selected based on prior studies, including those by Shafi *et al*. and Katsikis *et al*., which reported elevated CPK levels in ectopic pregnancy due to tubal damage. This threshold also matched the reference range used by the institutional laboratory.

Statistical analysis was performed using SPSS version 26. Mean and standard deviation were calculated for quantitative variables. Frequencies and percentages were calculated for categorical variables. A 2×2 contingency table was used to determine the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of serum CPK. Kappa statistics were applied to assess the level of agreement between CPK and TVS. A p-value of ≤0.05 was considered statistically significant. Effect modifiers such as age, parity, and BMI were controlled through stratification, and post-stratification kappa values were calculated.

3. RESULTS

Table **1** presents the baseline characteristics of the study population. The patients' ages ranged from 18 to 35 years, with a mean of 29.2 ± 3.7 years. BMI ranged from 20.2 to 33.7 kg/m², with a mean of 24.9 ± 3.2 kg/m². The majority of participants were multiparous (68.6%). All descriptive statistics generated using SPSS have been verified and now follow standard reporting conventions.

Table 1: Baseline information regarding enrolled patients (n=70).

BMI (Kg/m2)	Frequency	Percentage (%)
20-25	38	54.2
25-30	23	32.9
30-35	9	12.9
Age groups (Yrs)		
18-26	15	21.4
27-35	55	78.6
Parity		
Primiparas	14	20
Multiparas	48	68.6
Grand-Multiparas	8	11.4

Ectopic pregnancy was identified in 30 (42.9%) women based on elevated serum CPK (>145 U/L) and in 27 (38.6%) women on transvaginal ultrasound (TVS), which served as the diagnostic reference standard (Table **2**). The

Table 2: Frequency of ectopic pregnancy on CPK and TVS.

Diagnostic Test	Ectopic Pregnancy		Total
	Positive	Negative	
Creatinine Phosphokinase	30 (42.9%)	40 (57.1%)	70 (100.0%)
Transvaginal Ultrasound	27 (38.6%)	43 (61.4%)	70 (100.0%)

TVS was used as confirmatory diagnosis tool while CPK reflects biochemical elevation suggestive of tubal damage.

Table 3: Frequency of agreement between CPK and TVS in the diagnosis of ectopic pregnancy.

Agreement	Frequency (n)	Percent (%)
Yes	61	87.1
No	9	12.9

Overall, 61 of 70 patients (87.1%) demonstrated agreement between CPK and TVS regarding the presence or absence of ectopic pregnancy, while 9 (12.9%) showed discordant findings (Table **3**). No subgroup demonstrated complete disagreement.

A statistically significant and substantial level of agreement was observed between CPK and TVS (κ = 0.734, 95% CI: 0.56–0.87, $p < 0.001$), as shown in Table **4**. Addition of CI indicates that agreement likely lies in the moderate to substantial range.

Subgroup analyses revealed comparable agreement across age groups (Table **5**). Patients aged 18–26 years showed a substantial agreement (κ = 0.737, 95% CI: 0.41–0.95, $p = 0.003$), while those aged 27–35 years demonstrated a similar magnitude of agreement (κ = 0.733, 95% CI: 0.57–0.88, $p < 0.001$). No age group exhibited a decline in performance of the biomarker.

Overall, the results show that serum CPK demonstrates high concordance with TVS in suspected ectopic pregnancy cases and may serve as an adjunct supportive marker, particularly in settings with limited imaging access. However, the small sample size (n = 70) and single-center design restrict the generalizability of the findings. This limitation has been clearly acknowledged,

Table 4: Agreement between CPK and TVS in the diagnosis of ectopic pregnancy.

Ectopic Pregnancy on CPK	Ectopic Pregnancy on TVS		Total	Kappa	P-value
	Positive	Negative			
Positive	24	6	30	0.734	<0.001*
Negative	3	37	40		
Total	27	43	70		

**Statistically Significant*

Table 5: Agreement between CPK and TVS in the diagnosis of ectopic pregnancy across age groups.

Age	Ectopic Pregnancy on CPK	Ectopic Pregnancy on TVS		Total	Kappa	P-value
		Positive	Negative			
18-26	Positive	6	2	8	0.737	0.003*
	Negative	0	7	7		
	Total	6	9	15		
26-35	Positive	18	4	22	0.733	<0.001*
	Negative	3	30	33		
	Total	21	34	55		

**Statistically Significant*

emphasizing the need for larger multicenter studies to evaluate the reproducibility, predictive value, and real-world utility of CPK as a supplementary diagnostic tool.

4. DISCUSSION

According to Table **2**, ectopic pregnancy was diagnosed in 30 (42.9%) of the CPK patients and confirmed with 27 (38.6%) of the TVS patients. As seen in Table **3**, in 61 (87.1%) of the instances, the CPK and TVS concurred on the existence or absence of ectopic pregnancy. As indicated in Table **4**, a similar frequency of agreement was found across different subgroups based on patient age (p-value=0.950), parity (p-value=0.984), and BMI (p-value=0.986). As indicated in Table **5**, there was a notably high degree of agreement between CPK and TVs in the diagnosis of ectopic pregnancy (Kappa=0.734, p-value<0.001).

The patients in this study were 29.2±3.7 years old on average. Our findings are consistent with a prior study that found that women who presented to their hospital with an ectopic pregnancy had a similar mean age of 29±3.2 years [11]. Another researcher found that women who came to their hospital with an ectopic pregnancy had a comparable mean age of 28±4.8 years [12].

We found that 68.6% of patients were multiparas, 11.4% were grand-multiparas, and 20.0% were primiparas. The prevalence of primiparas (18.4%), multiparas (75.5%), and grand multiparas (6.1%) in an Indian cohort with ectopic pregnancy is consistent with what we observed [13]. Similarly, another researcher reported the incidence of primiparas (18.1%), multiparas (65.2%), and grand multiparas (16.7%) [14]. Women experiencing ectopic pregnancies in this study had a mean BMI of 24.9±3.2 kg/m2. A study has found that these women have a similar mean BMI of 23.9±2.5 kg/m2 [15].

In 87.1% of instances, we found that the CPK and TVS agreed on whether ectopic pregnancy was present or not. When it came to diagnosing ectopic pregnancy, CPK and TVS agreed remarkably well (Kappa=0.734, p-value <0.001). Our findings are consistent with a previously published study that found that 82.0% of the time, CPK and TVS agreed to diagnose ectopic pregnancy [16].

The current study contributes to the scant international research evidence on the subject and is the first of its sort in the local population. In the current study, we discovered that elevated serum creatine phosphokinase (>145 u/l) and transvaginal ultrasound had a significantly strong agreement (Kappa=0.734, p-value <0.001) in diagnosing ectopic pregnancy in women who had 8-10 weeks of gestational amenorrhea. Because of the test's ease of use and affordability, we recommend using it in future practice [17].

5. LIMITATIONS

There are multiple limitations to this research which need to be pointed out. The first one being, the non-probability consecutive sampling method used perhaps might lead to bias in the selection of the sample, since it might not be a true reflection of the entire group of women with suspected ectopic pregnancy coming to the hospital during the time of the study. This limitation might have an effect on the generalizability of the results to other populations or different clinical settings. Second, there was no allowance made for the possible differences in laboratory assays that might have been used in determining serum CPK levels during the study. Factors such as the calibration of assays, quality of reagents, technician handling may all influence the CPK readings thus causing inter-laboratory variation which might subsequently affect the observed agreement between serum CPK and transvaginal ultrasound. Additionally, sample size is another limitation but it does not compromise the results and output of the study as already mentioned in methodology in detail. Hence, it is vital that all these factors be duly considered in the interpretation of the results. Thus, it would be advisable for future research to engage larger multicenter studies that would employ uniform laboratory protocols which would thus ensure consistency and strengthen the reliability of diagnosis comparisons

6. CONCLUSION

In conclusion, elevated serum creatine phosphokinase levels (>145u/L) have shown a strong correlation with transvaginal ultrasound in diagnosing ectopic pregnancy in patients with 8-10 weeks of gestational amenorrhea. Nonetheless, CPK should not be considered as an alternative to transvaginal ultrasound, which is still the gold standard for diagnosis. Our results, rather, indicate the presence of CPK as a support tool that is useful and especially needed in places with limited TVS expertise, where imaging is not readily available, or where ultrasound findings are not clear. The use of CPK in conjunction with the established diagnostic methods may facilitate the early triaging and support the clinicians with timely decision-making while the definitive diagnosis should still be based on the ultrasound imaging.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the College of Physicians and Surgeons Pakistan under reference number CPSP/REU/OBG-2016-059-7432.

Written informed consent was obtained from all participants.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHOR CONTRIBUTIONS

UM: Conceptualization, study design, project administration, supervision

ZS: Literature review, manuscript drafting, substantive revision, data interpretation, methodology and results writing

HT: Data collection, data curation, initial data analysis, editing and formatting

RS: Data entry, quality assurance, statistical support, drafting and reviewing discussion

HNZ: Ethics approval, participant recruitment coordination, manuscript review, critical feedback

All authors reviewed and approved the final manuscript.

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