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Original Research Article

Relationship of IL-6 and IL-8 levels with tubal ectopic pregnancy

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ABSTRACT

Background: The frequency of ectopic pregnancy (EP) has increased worldwide during the last 30 years, particularly in underdeveloped countries with low early diagnostic rates. Ectopic pregnancy is the major cause of first-trimester deaths. Interleukins are immunomodulatory cytokines that modulate inflammatory responses and help humans conceive. Aim of the study was to evaluate the predictive value of interleukin-6 and interleukin-8 in tubal ectopic pregnancy.
Methods: This case control research was undertaken in the Department of Obstetrics and Gynaecology at Al-Emamein Al-Kadhemein Medical City/Baghdad from January 1, 2022 to January 1, 2023. The study analysed 30 patients with missed cycles, positive β-HCG tests, vaginal bleeding, and ruptured tubal ectopic pregnancy diagnosed via transvaginal ultrasound (group A) and 30 patients with intrauterine missed miscarriage (group B). The control group (group C) included 30 ladies with uncomplicated intrauterine pregnancies of matched gestational age.
Results: Interleukin-6 was substantially greater in ectopic pregnancy than miscarriage and normal intrauterine pregnancy. Ectopic pregnancy and miscarriage had higher levels of interleukin-8 than normal intrauterine pregnancy, but there was no difference. Interleukin-6 levels ≥76.1 pg/ml were linked to 90% sensitivity and 85% specificity in predicting ectopic pregnancy. Interleukin-8 was neither sensitive nor specific for ectopic pregnancy.
Conclusions: Measurement of IL-6 may have a predictive value in cases of ruptured tubal ectopic pregnancy. IL-8 was a poor predictor for ectopic pregnancy.

Keywords: Ectopic, IL-6, IL-8, Levels, Pregnancy, Relationship, Tubal

INTRODUCTION

Ectopic pregnancy (EP) is a significant medical condition where a fertilized egg implants outside the uterine cavity, commonly in the fallopian tubes.[1] It poses critical challenges for maternal health, accounting for a considerable portion of first-trimester pregnancy-related deaths. Globally, the incidence is about 1-2% of all pregnancies, with a rising trend especially in developing countries where access to early diagnosis is limited.[2,3] Developed nations report a substantially lower case-fatality rate of 1-3% in hospital-based studies, a fraction compared to those in developing countries.[4-6] The majority (95%) of EPs occur in various segments of the fallopian tube. The most common sites for tubal implantation include the ampulla (70%), isthmus (12%), and fimbria (11%).[1,4] The fallopian tube is particularly vulnerable to rupture due to its lack of a submucosal layer, making EP a potentially life-threatening condition.[7,8] There are rare cases where the embryo implants in unusual sites like the cervix, ovary, or abdomen, making diagnosis and treatment more challenging.[9] Ectopic pregnancies also have a molecular dimension involving interleukins (ILs), which are cytokines with immunomodulatory functions. Studies indicate that levels of IL-6 and IL-8 are significantly elevated in the fallopian tubes near the implantation site during an ectopic pregnancy, affecting local tissue behavior and possibly contributing to the

abnormal implantation.[10,11] EPs significantly impact both short- and long-term health-related quality of life, causing symptoms like pelvic pain and vaginal bleeding and possibly leading to long-term issues like infertility.[6] Women who have had an ectopic pregnancy are at a higher risk of having another, although subsequent intrauterine pregnancies reduce this risk.[12] The aim of study to evaluate the predictive value of Interleukin-6 and Interleukin-8 in tubal ectopic pregnancy.

METHODS

Study design and setting

A case-control study was conducted at the Department of Obstetrics and Gynecology at Al-Emamein Al-Kadhemein Medical City/Baghdad between January 1, 2022, and January 1, 2023. Administrative and departmental approvals were obtained. Verbal consent was acquired from all participants, ensuring anonymity and confidentiality.

Study population

The patients were enrolled into following group: 1) Group A: 30 patients with ruptured tubal ectopic pregnancy, 2) Group B: 30 patients with intrauterine missed miscarriage, 3) Control Group (Group C): 30 females with uneventful intrauterine pregnancy.

Inclusion criteria

Patients who missed menstrual cycle, positive β-HCG test, and presentation with vaginal bleeding were included.

Exclusion criteria

Patients with active infections, including COVID-19, inflammatory or chronic diseases, and use of certain medications like anti-inflammatory drugs or steroids were excluded.

Data collection

After stabilization, a pre-designed questionnaire was administered to collect demographic, obstetrical, and medical information. Physical and transvaginal ultrasound examinations were also conducted. Blood samples were taken for IL6 and IL8 analysis.

Laboratory analysis

Blood samples were processed using Elabscience® Human IL-6 and IL-8 ELISA Kits. IL6 and IL8 levels were measured using ELISA analyzers.

Statistical analysis

Data were entered into Microsoft Excel and analyzed using IBM-SPSS. Chi-square, Fisher's exact, or one-way ANOVA tests were applied for categorical and continuous variables, respectively. Receiver operator characteristics curve analysis was utilized to determine the best cutoff points for each variable. A p-value <0.05 was considered statistically significant.

RESULTS

The study included 90 cases, 30 cases in each group. There was no statistically significant difference regarding the maternal and gestational ages. This was intentionally selected to eliminate selection bias. As well there was no statistically significant difference in gravidity, parity, or previous miscarriage rates. The body mass index also was not significantly different among the three groups as shown in Table 2.

Table 1: Distribution of demographical data.

Variables	Ectopic	Miscarriage	Normal IUP	P value*		
	Mean±SD	Mean±SD	Mean±SD	P1	P2	P3
Age	30.8±6.06	29.83±5	30.27±6.01	0.78	0.937	0.95
Gravida	6±2.56	6.13±2.67	5.7±2.48	0.979	0.89	0.793
Parity	4.43±2.49	4.63±2.53	4 ±2.41	0.949	0.773	0.583
Previous miscarriage	0.57±0.63	0.5±0.68	0.7±0.6	0.918	0.677	0.453
Gestational age	8.34±1.33	9.07±1.15	8.61±1.28	0.068	0.693	0.327
Body mass index	28.22±2.6	28.17±3.37	28.63±3.28	0.997	0.852	0.850

*P1: represent difference between ectopic and miscarriage groups; P2: represent difference between ectopic and normal groups; P3: represent difference between miscarriage and normal groups.

Regarding presence of booking antenatal care visits, educational level, and residency there was no statistical difference among the three groups, as shown in Table 2.

Regarding presentation 16.7% (5) of ectopic pregnancy cases presented with vaginal bleeding, and the majority (83.3%) presented with abdominal pain, as illustrated in 1.

Regarding vital signs during presentation, the mean systolic and diastolic blood pressure were significantly lower and pulse rate was significantly higher in cases of ectopic pregnancy than both cases of missed abortion and cases of normal intrauterine pregnancy, while cases of miscarriage were not different from normal intrauterine pregnancy, as shown in Table 3.

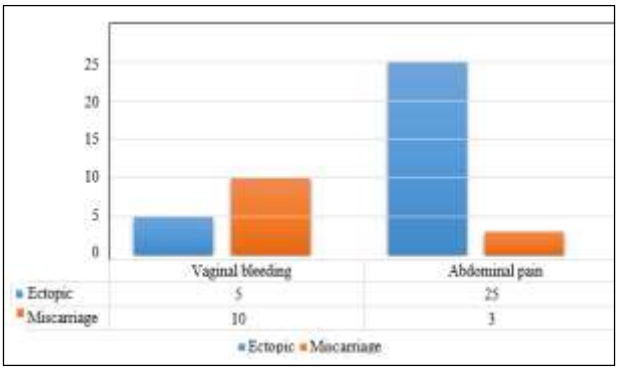

Figure 1: Presentation of cases of ectopic pregnancy and miscarriage.

Regarding complications of ectopic pregnancy, the most common complications were requirement for ICU admission. No cases of organ failure or death reported. Figure 2 shows the reported complications of cases of ectopic pregnancy.

Length of hospital stay was significantly different between the three groups; cases of ectopic pregnancy had the highest hospital stay as shown in Figure 3.

Regarding IL6 level, we found that IL6 was significantly higher in cases of ectopicpregnancy than both cases of miscarriage and cases of normal intrauterine pregnancy. Furthermore, cases of miscarriage were not different than normal intrauterine pregnancy, this mean elevate IL6 was unique to cases of ectopicpregnancy. The level of IL8 was also elevated in cases of ectopic pregnancy and miscarriage more than cases of normal intrauterine pregnancy, and there was no difference between cases of ectopic pregnancy and miscarriage regarding to IL8 level. In other words, IL8 elevation was not exclusive for cases of ectopic pregnancy as shown in Table 4.

Table 2: Educational level, antenatal care visits, and residency distribution.

Variables		Ectopic	Miscarriage	Normal IUP	P value
		No. (%)	No. (%)	No. (%)	
Booking visits	Yes	26 (86.7)	22 (73.3)	27 (90)	0.186
	No	4 (13.3)	8 (26.7)	3 (10)	
Education	Illiterate	4 (13.3)	5 (16.7)	4 (13.3)	0.979
	Primary	16 (53.3)	15 (50)	16 (53.3)	
	Secondary	8 (26.7)	7 (23.3)	6 (20)	
	Higher	2 (6.7)	3 (10)	4 (13.3)	
Residency	Urban	25 (83.3)	23 (76.7)	25 (83.3)	0.748
	Rural	5 (16.7)	7 (23.3)	5 (16.7)	

Table 3: Distribution of vital signs.

Variables	Ectopic (n=30)	Miscarriage (n=30)	Normal IUP (n=30)	P value*		
	Mean ±SD	Mean ±SD	Mean ±SD	P1	P2	P3
SBP	103.67 ±12.49	122.13 ±11.28	118.8 ±12.6	<0.0001	<0.0001	0.531
DBP	63.73 ±5.39	68.13 ±6.35	69.17 ±6.57	0.015	0.003	0.81
PR	110.83 ±12.39	90.27 ±10.01	91.13 ±10.21	<0.0001	<0.0001	0.941

*P1: represent difference between ectopic and miscarriage groups; P2: represent difference between ectopic and normal groups; P3: represent difference between miscarriage and normal groups

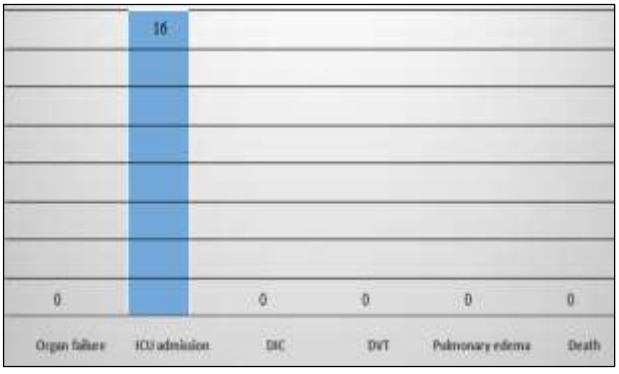

Figure 2: Reported complications in cases of ectopic pregnancy.

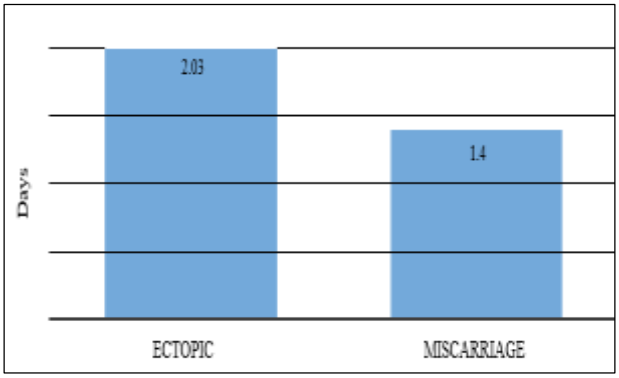

Figure 3: Distribution of hospital stay.

The level of IL 6 ≥76.1 pg/ml was found to be associated with high sensitivity (90%) and specificity (85%) in prediction of ectopic pregnancy. While IL8 was neither sensitive nor specific for cases of ectopic pregnancy as shown in Table 5.

Table 4: Distribution of ILs level.

Variables	Ectopic	Miscarriage	Normal	P value*		
	Mean ±SD	Mean ±SD	Mean ±SD	P1	P2	P3
IL 6	168.97±75.14	51.43±32.53	28.41±17.88	<0.0001	<0.0001	0.162
IL 8	190.34±135.95	170.94±89.32	115.54±58.17	0.792	0.023	0.017

*P1: represent difference between ectopic and miscarriage groups; P2: represent difference between ectopic and normal groups; P3: represent difference between miscarriage and normal groups

Table 5: Predictive ability of ILs.

Predictor	IL 6	IL 8
	Level	Level
Area under the curve	0.938	0.6
95% confidence interval	0.877-0.998	0.452-0.748
Cutoff point (pg/ml)	≥76.1	≥155.5
Sensitivity (%)	90	60
Specificity (%)	85	60
Positive predictive value (%)	75	42.9
Negative predictive value (%)	94.5	75
Accuracy (%)	86.7	60
Odd ratio	51	2.25
95% confidence interval	12.736-204.228	0.92-5.504

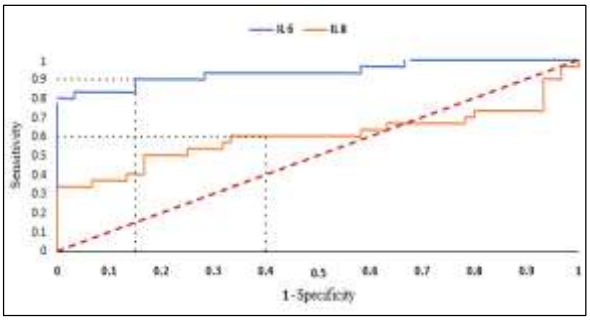

Figure 4: ROC curve analysis.

DISCUSSION

This study sought to determine the potential diagnostic value of IL6 and IL8 in ectopic pregnancy. In contrast to existing literature, demographic variables such as maternal age, gravidity, previous miscarriages, BMI, and level of education did not differ significantly among the groups studied.[13-16] This could be attributed to our effort to minimize selection bias. The majority of ectopic pregnancy cases presented with abdominal pain and were related to ruptured tubal pregnancies.[17] Physiologically, these patients had lower blood pressure but higher pulse rates, largely attributed to intraperitoneal bleeding.[18] They also had longer hospital stays and were more likely to require blood products and ICU admission. Regarding biomarkers, IL6 levels were significantly higher in ectopic pregnancies than in other groups, aligning with findings from Rajendiran et al.[11] IL6 demonstrated high accuracy in predicting ectopic pregnancy, with a sensitivity of 90% and specificity of 85% at a cutoff level of 76.1 pg/ml. This suggests that IL6 could be a powerful diagnostic tool for ectopic pregnancy.[11] In contrast, IL8 levels were not a reliable indicator for distinguishing ectopic pregnancies from other outcomes. Although they were elevated in both ectopic and miscarriage cases, their predictive ability was low.[19] The contrasting findings of IL6 and IL8 further imply that inflammation, particularly the upregulation of IL6, could be a central process in the development of ectopic pregnancies.[20] Our findings indicate that IL6 could be instrumental in early diagnosis, which is critical for appropriate treatment and reducing complications.[21] Therefore, the study supports the use of IL6 as a promising diagnostic marker for ectopic pregnancies, while further investigations are recommended to confirm the role of IL8.[11,19]

CONCLUSION

The study indicates that IL-6 is a promising diagnostic marker for ruptured tubal ectopic pregnancy, with high sensitivity and specificity levels of 90% and 85%, respectively. On the other hand, IL-8 was found to be a poor predictor, with both sensitivity and specificity only reaching 60%. Overall, IL-6 shows superior predictive qualities over IL-8 in diagnosing ectopic pregnancies, offering higher accuracy, sensitivity, and specificity.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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