

Evaluation Of Serum Vascular Endothelial Growth Factor In Ectopic Pregnancy

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Abstract:

- **Background:** Ectopic pregnancy is a common life threatening complication of early pregnancy refers to a gestation in which the fertilized ovum implants on any tissue other than the endometrial membrane lining the uterine cavity. Vascular endothelial growth factor (VEGF) is an angiogenic factor and plays a key role in the establishment of a viable pregnancy, participating in the processes of implantation and placentation, and appears to be significantly increased in early pregnancy complications.
- **Aim of study:** To determine serum level of vascular endothelial growth factor (VEGF) and evaluate their capacity to serve as a marker for diagnosis of ectopic pregnancy.
- **Methods:** A case-control study that was conducted in the Department of Obstetrics and Gynecology at Azadi Teaching Hospital/Kirkuk-Iraq, during the period of nine months from the 1st of February 2021 until 30th of October 2021. The statistical analysis included 90 women with early pregnancy at 6 weeks of gestation who attended obstetrical emergency unit and outpatient clinic. They were divided into three groups included 30 cases in each group. Group one diagnosed as ectopic pregnancy, group two diagnosed as arrested intrauterine pregnancy and group three as normal intrauterine pregnancy. They are diagnosed based on combination of their last menstrual period, transvaginal ultrasound, serum beta human chorionic gonadotropin (BhCG) results, and histopathologically proved for ectopic pregnancy. After verbal consent Serum vascular endothelial growth factor (VEGF) was measured by a kit uses enzyme linked immune sorbent assay (ELISA) for all study participants.
- **Result:** There were no statistically significant difference between the study groups in age, body mass index and parity. There was significant higher mean of vascular endothelial growth among ectopic pregnancy in comparison to arrested intrauterine pregnancy and normal intrauterine pregnancy. When cut-off concentrations ≥ 200 pg/ml for vascular endothelial growth factor VEGF were used and correlated it with beta human chorionic gonadotropin BhCG showed that it could distinguish intrauterine pregnancy IUP from Ectopic pregnancy with %98 sensitivity and 96.3% specificity.
- **Conclusion:** Vascular endothelial growth factor VEGF is a potential marker for Ectopic pregnancy, its concentrations in ectopic pregnancy are higher than in those with normal and arrested IUP.

Keywords: Arrested pregnancy, Ectopic pregnancy, Intrauterine pregnancy, Vascular endothelial growth factor

INTRODUCTION

Ectopic pregnancy is a potentially life-threatening condition occurring in 1-2 % of all pregnancies. The most common ectopic implantation site is the fallopian tube, though 10 % of ectopic pregnancies implant in the cervix, ovary, myometrium, interstitial portion of the fallopian tube, abdominal cavity or within a cesarean section scar^[1].Albucasis was the first doctor to describe ectopic pregnancy, Abul-Qasim Khalaf Ibn al-Abbas al-Zahrawi was born in 936 in Zahra in the Cordoba region. He became one of the most famous surgeons in the Muslim world, Many call him the father of modern surgery. From its indirect reference by Abulcasis (936-1013) and until the 19th century the ectopic pregnancy was known as a universally fatal accident^[2].

Vascular endothelial growth factor (VEGF) is an angiogenic factor, has essential role in the establishment of a viable pregnancy, participating in the processes of implantation and placentation which they are the early and crucial processes for the establishment of a viable pregnancy ,both being accompanied by angiogenesis, for which VEGF is mainly accountable and plays a key role^[3].

The rate of ectopic pregnancy (EP) is 11 per 1000 pregnancies, with a maternal mortality of 0.2 per 1000 estimated EPs^[4].Incidence rate of ectopic pregnancy at the maternity wards in Baghdad City hospitals was (2.217) per 1000 of population for the year of 2019^[5]. About two-thirds of these deaths are associated with substandard care . Ectopic pregnancies often occur

because an egg's movement is slowed or obstructed after fertilization, usually because a fallopian tube is scarred, misshapen or possibly infected or inflamed. Disruption of normal tubal anatomy secondary to inflammation induces tubal dysfunction which can result in retention of an oocyte or embryo. There are several local factors, such as toxic, infectious, immunologic, and hormonal, that can induce inflammation. There is up regulation of pro-inflammatory cytokines following tubal damage; this subsequently promotes embryo implantation, invasion, and angiogenesis within the fallopian tube^[5]. Pelvic inflammatory disease results in the production of interleukin 1 by tubal epithelial cells this happens to be a vital indicator for embryo implantation within the endometrium. Interleukin 1 also has a role in downstream neutrophil recruitment which would further contribute to fallopian tubal damage. Cilia beat frequency is negatively affected by smoking and infection. Hormonal variations throughout the menstrual cycle additionally have demonstrated effects on cilia beat frequency. Women with tubal ligation or other post-surgical alterations to their fallopian tubes are at risk for ectopic pregnancies as the native function of the fallopian tube would be altered^[4].

About 50% of women diagnosed with an EP have identifiable risk factors. Recognition of these risk factors can assist not only in the early diagnosis of EP, but also in reducing the risk of massive intra-abdominal hemorrhage and its morbidity and mortality^[4]. These risk factors are divided into "**High**," "**Moderate**," and "**Low**" risk depending on the strength of the association with ectopic pregnancies^[6]. In experienced hands, over 70% of EPs are seen on ultrasound on the first scan and well over 90% before surgery.

VEGF is a key regulator of physiological and pathological angiogenesis^[7]. It is part of the system that restores the oxygen supply to tissues when blood circulation is inadequate such as in hypoxic conditions. As the implantation environment in the oviduct is different from the well-vascularized endometrium, secretion and production of VEGF may be affected in EP. Implantation of the Conceptus within the oviduct might trigger increased VEGF production as a form of accommodation to the unfavorable environment^[8]

MATERIALS AND METHODS

This is a case control study that was conducted in the Department of Obstetrics and Gynecology at Azadi Teaching Hospital in Kirkuk/ Iraq From the 1st of February 2021 until 30th of October 2021. The study protocol was approved by scientific council of Obstetrics and Gynecology / Iraqi Board for Medical specializations.

The study included 90 pregnant women in early pregnancy at 6 weeks of gestational age. They were informed about the nature of study and verbal consent was obtained from them. They were divided in to three groups: Group 1: Thirty women diagnosed with ectopic pregnancy. Group 2: Thirty women diagnosed with arrested IUP. An arrested IUP was defined as an intrauterine sac without fetal tissue or fetal cardiac activity^[9]. Group 3: Thirty women with normal IUP pregnancy.

In three study groups patients gestational age matched. Patients were selected from outpatient clinic and those who were admitted to the ward and emergency obstetric unit.

Beta HCG level higher than 1500 IU/ML or serial measurement of BhCG titer. Empty cervical canal and uterine cavity but a gestational sac seen in either adnexa or tube by Transvaginal ultrasound scan served as the diagnostic criteria for ectopic pregnancy and they proved histopathologically. Selection of normal pregnancies was done in women with positive pregnancy test , last menstrual period, beta HCG titer and diagnosis confirmed by an ultrasound scan as normal intrauterine pregnancy with viable fetus. Selection of arrested Intrauterine pregnancy IUP was done in women with positive pregnancy test, last menstrual period, BhCG titer and Transvaginal ultrasound examination for assessment of embryological viability and documentation the stage of development of gestational sac and embryo.

Ultrasound examination were targeted for 6 weeks gestation at which point normally developing pregnancies have a detectable fetal pole and heart rate on ultrasound.

Exclusion criteria:Gestational age less or more than 6 weeks, Multiple pregnancy, Diabetes mellitus, Hypertensive disorder of pregnancy, Bronchial asthma, Ovarian cyst, Polycystic ovary syndrome, Ovarian hyperstimulation syndrome, Rheumatoid arthritis, Ischemic heart disease, Angiosarcoma, Heterotopic pregnancy.

A questionnaire had been applied to all study patients to collect needed information. General examination BMI was done for the patients. The studied groups investigated and examined for the following: Full blood count, blood group and cross match, Beta HCG titer, Transvaginal ultrasound for site, size of the gestational sac and free fluid collection was done at time of admission and verified then by senior specialist of radiology, Patients who undergone surgery their specimen sent for histopathology, Serum VEGF concentration .

RESULTS

The total number of participants in this study were 90 pregnant women , 30 were diagnosed with normal intrauterine pregnancy, 30 were diagnosed with arrested IUP, and 30 diagnosed with ectopic pregnancy , all ectopics was tubal ectopic pregnancy and they undergone laparotomy. The mean age across ectopic group 27.1, across arrested IUP group was 27.07, across normal IUP group was 27.3, and the difference in age was not significant among groups ($p=0.46$). There were 12 (13.3%) patients their age was less than 20 years old, 13 (14.4%) patients their age was between 21 – 25 years, 52 (57.8%) patients their age was range between 26 – 30 years, and 13 (14.4%) patients their age was above 30 years old as shown in[table1].

The mean BMI did not show statistically significant difference among Ectopic, Arrested IUP and Normal IUP ($p=0.57$) as shown in[table 1].

Table1: Descriptive statistics of mean Age and BMI across all groups

		Ectopic	Arrested IUP	Normal IUP	P value*
Age	Mean	27.1	27.07	27.3	
	SD	4.4	4.7	4.6	0.46
	Maximum	33	34	33	
	Minimum	18	16	18	
BMI	Mean	23.71	22.68	25.73	
	SD	3.21	3.11	4.2	
	Maximum	30.0	30.0	30.0	0.574
	Minimum	17	17.9	17.9	

***AVONA test**

The mean VEGF across ectopic pregnancy group was 300 ± 15.7 pg/ml , the mean across arrested IUP group 173 ± 14.4 pg/ml, and the mean across control normal IUP group was 26.8 ± 2.2 pg/ml . There was significant higher mean of VEGF among Arrested IUP group in comparison to Normal IUP group ($p=0.001$), and the mean of VEGF among Ectopic group was significantly higher in comparison to Arrested IUP and Normal IUP ($P=0.001$) as shown in [table 2, figure 1].

Table 2: Descriptive statistics of VEGF across study groups

Cases	Mean	Std. Deviation	Maximum	Minimum
Ectopic	300.7	15.79	332.7	275.3
Arrested IUP	173.0	14.49	198.0	140.3
Normal IUP	26.8	2.28	31.0	22.0

P=0.001 (ANOVA test)

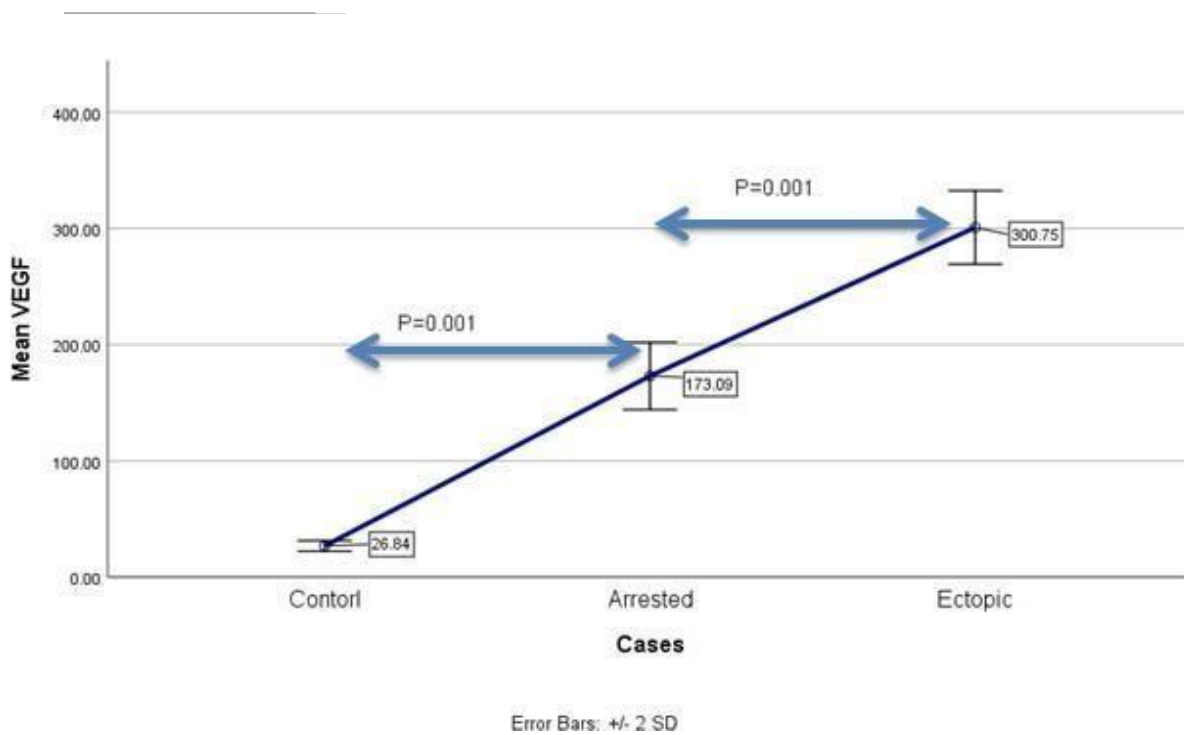


Figure1: Mean VEGF across group. P value = 0.001 (Independent sample T test)

The serum BhCG concentrations were significantly higher in women with Normal IUP than Arrested IUP and Ectopic pregnancy while The serum concentration of VEGF among women

with ectopic pregnancy were significantly higher than in those with Normal IUP and Arrested IUP as shown in [table 3] .

Table 3: Comparison between study groups for BhCG and VEGF

	BhCG Mean ± SD	VEGF* Mean ± SD
Ectopic	1285.13 ± 1314.32	300.75 ± 15.79
Arrested	1930.20 ± 2389.35	173.09 ± 14.49
control	3331.33 ± 1546.06	26.84 ± 2.28

*P value <0.0001 comparison between Ectopic and other groups

*P=0.001 between Arrested and Normal IUP group

The ROC showed the cutoff value of VEGF of ≥ 200 pg/ml was associated with 98% sensitivity and 96.3% specificity to detect the ectopic pregnancy which is higher when compared with sensitivity and specificity of BhCG [Figure 2].

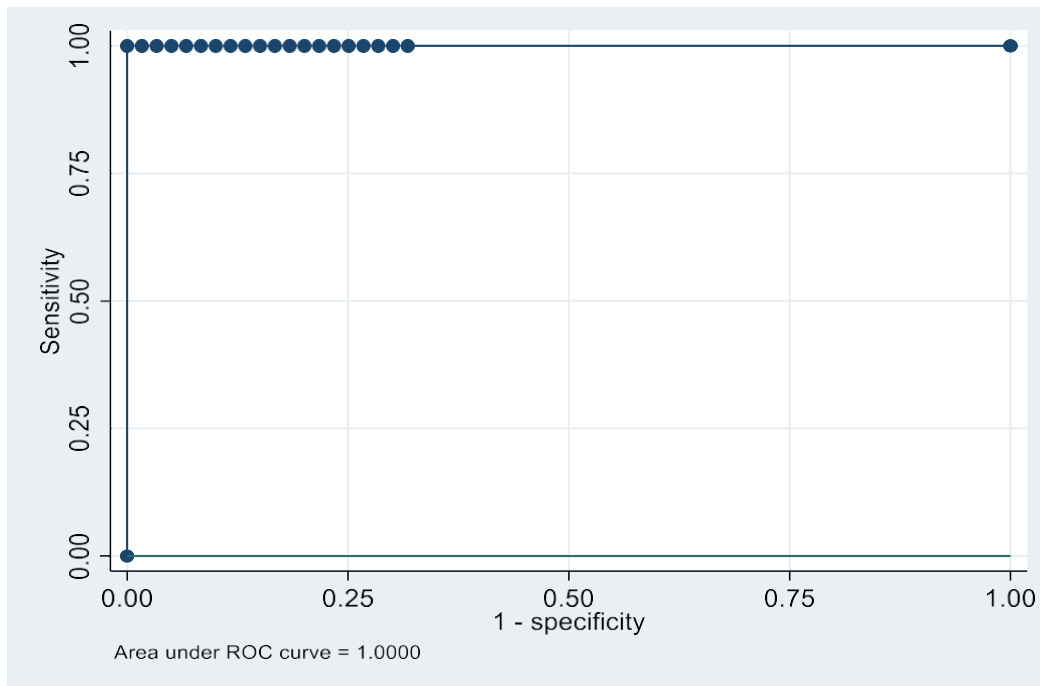


Figure2. Receiver operating characteristic curve analysis of VEGF

DISCUSSION

Ectopic pregnancy (EP) is a well-known issue that has overgrown over the last thirty years, however, it has recently stabilized off at about 2% of all pregnancies. Because EP care has shifted to a more conservative strategy over time, earlier diagnosis is critical to allowing conventional treatment possibilities. Implantation and placentation are the earliest and essential steps of creating a viable pregnancy. They are associated with angiogenesis, for which vascular endothelial growth factor (VEGF) is primarily responsible and performs a significant influence. EP can be detected as early as 4–5 weeks of gestation. However, despite high-resolution vaginal ultrasonography and sensitive, quantitative β -hCG tests, almost 40%–50% of EP patients are initially misdiagnosed. As a result, numerous indicators have been

investigated for the diagnosis of EP, in addition to non-invasive procedures, such as maternal serum creatine kinase levels, fetal fibronectin levels from cervico-vaginal swabs, and serum VEGF levels^[10]. Daniel et al first reported that there is a difference in serum VEGF concentrations in women with IUP, women with EP and women with abnormal IUP. They postulated that this could be due to increased production of VEGF originating from the hypoxic condition of the tube and/or from altered production of VEGF binding protein in abnormal pregnancies^[9]. The main hypothesis behind present study is that maternal serum vascular endothelial growth factor differ between ectopic pregnancy , arrested IUP , and normal IUP , since Vascular endothelial growth factor (VEGF) is an angiogenic factor that participates in the processes of vascular development in the embryo and implantation and placentation , for that reason we aimed to evaluate the VEGF levels in ectopic pregnancy ,arrested IUP ,and normal IUP and determine whether it can serve as a marker for diagnose of ectopic (EP) pregnancy.

Analysis of age result in present study revealed no statistically significant difference in mean age among studied groups. Although Correa et al^[11] stated maternal age of ≥ 35 years is associated with a four- to eight-fold increased risk of ectopic pregnancy. Nybo Andersen et al^[12] also demonstrated higher maternal age was associated with increased risks for ectopic pregnancy. But the same result no stated in present study, this is may be due to similarity in the ages of the study participants allowed the exclusion of the effect of age on abnormal pregnancy.

Regarding BMI present study did not show statistically significant difference in mean of BMI between study groups. These findings are in agreement with Grazi et al ^[13] that documented miscarriage, ongoing pregnancy, or ectopic pregnancy in singleton gestations in the first trimester, was not affected by BMI. Although, BMI did not show significant difference in mean between study groups, Caval cante et al^[14] study stated the higher BMI have been shown to be associated with higher rate of miscarriage . Another study by Ghimire et al ^[15] stated an increase in the risk of miscarriage with increased BMI among reproductive aged women. Nlome et al^[57] showed that there was increase in rate of ectopic pregnancy among obese women after IVF. Hence, the role of BMI in ectopic pregnancy still controversy and more studies needed to roll out the effect of BMI on ectopic pregnancy.

The mean BhCG was significantly higher among normal IUP group in comparison to other groups (Ectopic and Arrested IUP).However in Ectopic pregnancy and Arrested IUP the level of human chorionic gonadotropin is subnormal. Tenore et al^[16] study stated , the lack of a 48 –hour doubling indicates the presence of abnormal pregnancy .This finding coincides with reports of Michael A Kohn et al ^[17] which stated that in women with abdominal pain or bleeding and serum beta-hCG levels less than 1500 mIU/mL, the risk of ectopic pregnancy is substantially increased, while the likelihood of normal intrauterine pregnancy is low.

However no statistically difference was found in current study between the concentrations in women with Ectopic and Arrested IUP. This was consistent with the finding of Silva et al ^[18] which found the number of women with ectopic pregnancy who experience an increase in hCG values is approximately equal to the number of those who experience a decrease, and the

hCG profile in women with ectopic pregnancy can mimic that of an intrauterine pregnancy or a arrested IUP in approximately 29% of cases. Moreover present study showed the cutoff value of BhCG of ≥ 877.8 pg/ml was associated with 91.5% sensitivity and 58% specificity to distinguish the Ectopic pregnancy from Arrested IUP and Normal IUP.

The mean VEGF across control group was 26.8 ± 2.2 pg/ml, the mean across arrested group 173 ± 14.4 pg/ml, and the mean across ectopic pregnancy group was 300 ± 15.7 pg/ml. There was significant higher mean of VEGF among arrested group in comparison to control group ($p=0.001$), and the mean of VEGF among ectopic group was significantly higher in comparison to other groups ($P=0.001$), which was comparable to Felemban et al^[19] study that showed there was a significant difference in VEGF concentrations among women with EP, arrested IUP and normal IUP in which it was higher among EP in comparison to other groups and they concluded that VEGF is a potential marker for EP and its concentrations in women with EP are higher than in those with normal and arrested IUP. Another study by Silva et al^[20] showed that serum VEGF concentrations could discriminate a normal intrauterine pregnancy from an unviable pregnancy. These result also show agreement with Zou et al^[21] study which published in 2013 showed that Individual measurements of serum VEGF levels is strongly related to early pregnancy outcomes for women with IUP and EP, and pregnancy associated VEGF level provide diagnostic accuracy for the presence of tubal EP. Furthermore, , Cabar et al^[22] study which conducted in 2013 in Brazil and included 34 patients with an ampullary ectopic pregnancy showed an increase in the depth of trophoblastic penetration into the tubal wall associated with increasing maternal serum VEGF concentration. Flora Saghafi et al^[23]

study also showed agreement with present study which found serum VEGF levels could be of great help in differentiating tubal pregnancy from normal pregnancy with appropriate sensitivity and specificity.

When cut-off concentrations of 200 pg/ml for VEGF were used, normal IUP could be distinguished from EP with a sensitivity of 98%, and a specificity of 96.3% .This result coincides with results of Daniel et al^[24] study which found Women with EP had higher serum levels of VEGF than women with normal intrauterine pregnancy and women with abnormal intrauterine pregnancy and with a cut-off level of 200 pg/mL, serum VEGF could distinguish intrauterine from extrauterine pregnancy. Felemban et al^[19] study result showed serum VEGF could distinguish normal IUP from EP with a sensitivity of 88%, a specificity of 100% and a positive predictive value of 100% with a cut-off concentration 200pg\ml .Another study by Saghafi Flora et al ^[23]also shows similar result to our present study when threshold concentrations of a serum VEGF level > 280 pg/ml were used, and demonstrated that tubal pregnancy could be distinguished from normal pregnancy with a sensitivity of 86%, specificity of 67.9%, positive predictive value of 99.6%.In present study the finding that VEGF concentrations in women with ectopic pregnancy are different from those in arrested IUP is important .Unlike progesterone and HCG concentration, it might be possible to distinguish between EP and arrested IUP, this finding shows agreement with Kucera et al^[10] found VEGF could distinguish EP from abnormal intrauterine pregnancy with a cut-off value 200 pg\ml at 6 weeks gestation .Despite the difference between studies in cut off value for VEGF, the VEGF considered a strong predictor marker for ectopic pregnancy. Finally if our

results can be confirmed in a larger study , VEGF may be useful in detecting an early EP ,this will allow early and successful medical treatment .

CONCLUSION

- Based on study results, we concluded:
 1. Vascular endothelial cell growth factor (VEGF) is useful marker in detecting an early Ep at a cutoff value ≥ 200 pg/ml .
 2. There was significant difference in the mean of VEGF in women with EP , Arrested IUP , and Normal IUP .
 3. Vascular endothelial growth factor is more sensitive and specific than BhCG in detecting early ectopic pregnancy .
 4. Mean level of VEGF was significantly different between Arrested IUP and Normal IUP .

RECOMMENDATION

- Larger multicenter prospective studies with large number of patients needed to determine the following :
 - Potential use of VEGF as a marker for diagnosis of early ectopic pregnancy.
 - Investigate and correlate of VEGF with BhCG and TVS in early prediction of ectopic pregnancy .

- Utilization of VEGF in women with high risk of ectopic pregnancy especially in cases of assisted reproductive technology and previous pelvic surgery.

The study is self-funded

There is no conflict of interest

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