

The Role of Activin A levels, Body Mass Index and Beta-Human Chorionic Gonadotropin in Ectopic Pregnancies and Missed Abortions – A Study on a Group of Iraqi Women

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Abstract

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Background: Activin A (ACV-A), a member of the transforming growth factor-beta (TGF-beta) superfamily that regulates follicular growth hormone (FSH) secretion and initiates intracellular signaling pathways, is essential to reproductive regulation. ACV-A is involved in regulating cellular proliferation, differentiation, apoptosis, and homeostasis, among other biological processes. The pituitary gland, the gonads, and other organs all secrete ACV-A, which is made up of two beta A (β A) subunits.

Objectives: To compare the serum concentrations of ACV-A in women diagnosed with missed abortion (MA) or ectopic pregnancy (EP) with those of healthy controls.

Methods: The study was conducted in the gynecology departments of the Medical City - Baghdad Teaching Hospital and Al-Kut Obstetrics and Gynecology Hospital from October 2023 to January 2024. A total of 120 women aged between 18 and 45 years participated in the study; An ectopic pregnancy was diagnosed in 30 of them, 30 had a missed miscarriage, and the remaining 60 were considered a control group. ACV-A and beta-human chorionic gonadotropin (β -HCG) levels were measured by the enzyme-linked immunosorbent assay (ELIZA) method.

Results: The control group had a significantly lower mean \pm SD of ACV-A (773.6 ± 130.26 pg/ml) in comparison to the EP group (1408.1 ± 219.02 pg/ml) and the MA group (1200.9 ± 199.31). In addition, patients in the ectopic group had a significantly lower mean \pm SD of ACV-A than patients in the missed abortion group.

Conclusion: Serum Activin A levels can be used as an indicator of ectopic pregnancy and missed abortions. A novel biomarker for evaluating women who have an ectopic pregnancy could be the level of HCG in their serum at a cutoff value of greater than 236 ng/ml.

Keywords: Activin A (ACV-A); BMI; Ectopic pregnancies; Missed abortions; β -HCG.

Introduction:

Ectopic pregnancy (EP) refers to fertilized eggs implanted outside of the uterus, typically in the Fallopian tubes (98%) (1). It may be linked to a genetic defect that results in an aberrant development (2). Women with an EP may experience vague symptoms like pain in the lower abdomen and vaginal bleeding. These symptoms frequently mimic the clinical presentation of trauma, kidney stones, and hepatitis (3). When a blastocyst embeds itself some place other than the coating of the uterus, this condition is known as an ectopic pregnancy (4). Vaginal infections, intrauterine devices (IUDs), assisted reproductive technologies (ARTs), and previous EP are additional established risk factors for EP (5). A "missed abortion" is the type of spontaneous abortion in which the embryo has already died but with a closed cervical ostium

(6). The known potential causes include infections, fetal rejection by the mother's immune system, and environmental factors (7). Defects in the embryonic chromosome have been identified as the most common cause of unsuccessful pregnancies (8). Identifying the cause of the (MA) can help in speeding up the diagnostic process, giving a precise estimate of the likelihood of a recurrence, and providing comfort and direction (9). Human chorionic gonadotropin beta, (β -HCG) is detected in the maternal blood two days after implantation (10), and together with transvaginal ultrasound (TVUS) have become standard procedures in the evaluation of difficulties connected with early pregnancy (11). ACV-A is a bi functional glycoprotein that belongs to a class of growth factors called transforming growth factor - β (TGF- β). ACV-A secretion has been demonstrated by many reproductive tissues, such as the ovaries, the uterine cavity, the testicles, the endometrium, and the pituitary gland (12).

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Predicting and diagnosing preeclampsia in the second and third trimesters of pregnancy has been made easier by ACV-A (13). Numerous biologic fluids (cerebrospinal fluid, cord blood, peripheral blood and urine) showed elevated ACV-A levels early in life in fetuses and newborns who had been subjected to chronic and acute oxygen deprivation, perinatal death by asphyxia, and cerebral bleeding (14). Thus the current study established to compare the serum concentrations of ACV-A in women diagnosed with missed abortion (MA) or ectopic pregnancy (EP) with those of healthy controls.

Patients and Methods:

A case-control study was carried out in the gynecological wards of the Medical City Teaching Hospital in Baghdad and Al-Kut Hospital for Gynecology and Obstetrics from October 2023 to January 2024. A total of 120 women between the ages of 18 and 45 years participated in the study. Thirty women had an ectopic pregnancy, 30 had missed abortions, and the remaining 60 were healthy pregnant controls. The concentration of serum activin A and β-HCG was measured at Al-Kut Hospital for obstetrics and gynecology using the ELISA method. The study questionnaire included demographic characteristics such as age and body

mass index classified according to the classification of the World Health Organization (15).

Blood samples were taken from the participants after obtaining their consent to the blood drawing procedure.

Laboratory tests were conducted in one of the private laboratories in Baghdad and in Al-Kut Hospital for Gynecology, where blood samples were drawn from the patients and serum ACV-A and β-HCG were measured using the ELISA method.

Statistical Analysis:

The data was analyzed using SPSS version 25.0 software. Frequencies, percentages, means and stander deviations were used to describe the data. Graphs were used to present the data. The Chi-square test was used to test associations between qualitative variables and the independent t test was used to test differences of mean between two quantitative variables.

Results:

The distribution of the cases and controls by age and BMI is shown in Table 1. The table shows that there were no statistically significant associations between these two variables in the study groups.

Table 1: Distribution of the study groups by age and BMI

Variables	Categories	Study Groups – No. (%)			Total No. (%)	p- value
		Controls	EP	MA		
Age (Years)	group ≤ 20	6 (10.0)	5 (16.7)	6 (20.0)	17 (14.2)	0.96
	21-35	48 (80.0)	21 (70.0)	18 (60.0)	87 (72.5)	
	> 35	6 (10.0)	4 (13.3)	6 (20.0)	16 (13.3)	
BMI (kg/m2)	Low	4 (6.7)	1 (3.3)	2 (6.7)	7 (5.8)	0.50
	Normal	36 (60.0)	19 (63.3)	15 (50.0)	70 (58.3)	
	Overweight	18 (30.0)	10 (33.3)	12 (40.0)	40 (33.3)	
	Obese	2 (3.3)	0 (0)	1 (3.3)	3 (2.5)	
Total (100.0%)		60	30	30	120	120

Table 2 shows the mean ± SD of Activin-A and β-HCG in the three study groups. The control group had a significantly lower mean ± SD of ACV-A compared to the EP group and the MA group. In addition, the mean of the EP group was significantly lower than that of the MA group. The mean ± SD of β-HCG was lowest in the EP group followed by the MA group and the controls.

Table 2: Mean± SD of ACV-A and β-HCG in the study groups

Mean ±SD	Study Groups			Total	p- value
	Controls	EP	MA		
ACV-A a, b, c	773.6 ±130.26 (16.18)	1408.06 ± 219.02 (39.98)	1848.24 ±222.37 (39.93)	1200.86 ±199.31 (36.38)	<0.001*
β-HCG ^{a, b, c}	382.0 ± 80.21 (13.26)	284.5 ± 40.65 (7.42)	329.7 ± 70.94 (12.95)	337.5 ± 78.41 (9.84)	< 0.001*

a: Controls and EP, b: Controls and MA c: EP and MA, *p-value is significant

Activin-A had the largest AUC (0.766) with a cut-off level of >236, with 100% sensitivity and 67% specificity, to help distinguish EP from the other categories. β- HCG had the lowest AUC (0.688) with a cut-off level of >1027, with 93% sensitivity and 69% specificity, as shown in Table 3.

Table 3: ROC test for biochemical markers in EP patients

Test Result Variables	AUC	Cut value	off p-value	Sensitivity	Specificity
ACV-A	0.688	>1027	0.002	100%	67%
β-HCG	0.766	>236	0.000	93%	69%

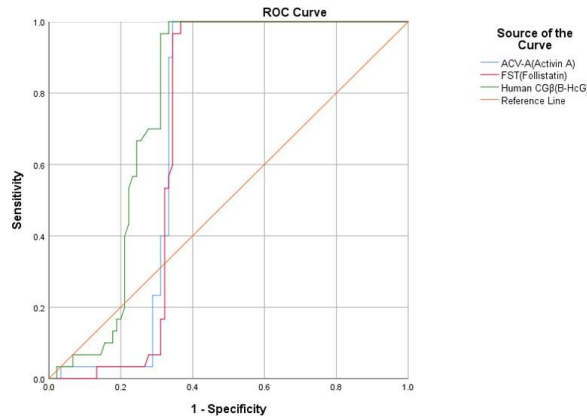


Figure 1: ROC curve for biochemical markers in the EP group

Activin-A had the largest AUC of 0.97 and a cutoff value of >1531, with 93% sensitivity and 92.2% specificity, with the objective of distinguishing patients who had MA from other patients, whereas β-HCG had the lowest AUC of 0.88 and a cutoff value of >261 and 93.3% sensitivity and 77% specificity, as shown in Table 4.

Table 4: ROC test for the biochemical markers in the MA group

Test Variables	Result Area	Cut value	off Sensitivity	Specificity	p-value
ACV-A	0.97	>1531	93%	92.2%	<0.001
β-HCG	0.88	>261	93.3%	77%	<0.001

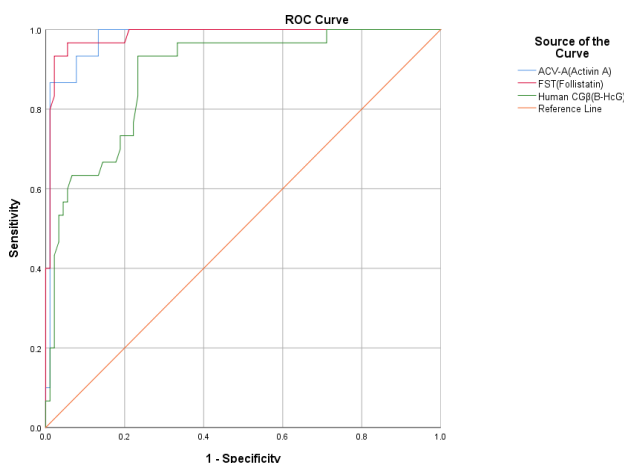


Figure 2: ROC curve for the biochemical markers in the MA group

Discussion:

The findings of the current study regarding the not-significant distribution of the three study groups by age and BMI are in agreement with that of Suliman

(16) who found that age is not significantly associated with the risk of EP. Salem (17) reported non-significant differences in patient’s age between controls and MA cases. In the current study the mean age of the MA group was higher than that of the controls. Zakira (18) reported a mean age of 28 years for the control group and 31 years for the MA group. Women between 25–29 years of age had the lowest chance of MA, while those 45 years old or over were the highest. The findings of the current study of the significant differences in mean ACV-A among the three groups are in agreement with those of Humadi (19) who reported that a successful pregnancy has considerably greater serum levels of ACV-A, than a failed pregnancy. It appears that cytotrophoblasts secrete ACV-A, and that aberrant decidualization with poorly implanted trophoblasts is typically seen during tubal pregnancy. Conversely, in heterogeneous ectopic pregnancies (one fetus inside the uterus), increased serum ACV-A may be detected. The current investigation found significant differences in the mean β-HCG among the three study groups. Lu (20) found that the only biomarker that is often and widely utilized in medical care is β-HCG. Although β-HCG is not sufficient to diagnose EP on its own, it can be useful in recognizing patients who need more frequent screening for early pregnancy loss. For an effective intrauterine pregnancy (IUP), there should be a minimum 53% increase in β-HCG over a period of 48 hours. But such a strategy involves multiple follow-ups over a few days for EPs, which prolongs the possibility of tubal rupture. On the other hand, the study of Daponte A (21) supports the idea that it is possible to distinguish between an IUP and a MA or EP with just one measurement of ACV-A at 6–8 weeks of gestation. More significantly, the current research shows that serum ACV-A can help to distinguish between an EP and an MA. However, there has been contradictory research looking into the use of serum ACV-A for this purpose. Serum ACV-A levels in pregnancy were shown to increase by 69-fold (with a broad range of values) from 700 ± 200 pg/mL at weeks 6-7 to a peak of 45,900 ± 54,000 pg/mL between weeks 38 and 39. It appears that this mechanism can be further impaired in EP and perhaps even more so in unsuccessful pregnancies. Lower levels of ACV-A in EPs have been compared to those in other failed pregnancies; it has been suggested that this could be because the ectopic trophoblast finds it difficult to implant correctly, which compromises the decidualization process. Additionally, some EPs may have more active trophoblasts and behave more like IUPs, while other EPs will be failing and behave more like failing MAs Daponte (21) discovered that there is a weak association between β-HCG and ACV-A in IUPs, suggesting a moderate but statistically significant association. Muttukrishna (22) found that in women with a subsequent miscarriage, there was a positive correlation between plasma ACV-A and

progesterone, estradiol, and HCG. To distinguish EP from other groups, β -HCG had the highest AUC, high sensitivity and moderate specificity. The most widely used serological marker of EP, β -HCG, is crucial for the early detection of EP. As per our experimental findings, low levels of β -HCG may raise suspicions about EP, however β -HCG by itself neither supports or disproves EP. On the other hand, Ray (23) found with a high sensitivity, specificity, and positive predictive value, ROC analyses showed that pre-treatment levels B-HcG of ≤ 4000 mIU/ml had a greater likelihood of successful outcome after medical management.

Receiver Operation Characteristic (ROC) and Area Under the Curve (AUC)

β -HCG is the most widely used serological biomarker of EP and is crucial for the identification of early EP. Although low levels of β -HCG can raise suspicions about EP, they do not definitively confirm or rule out the condition as suggested by Marion (24). A moderate sensitivity and specificity were obtained with the cutoff of β -HCG of 24,300 mIU/mL. Ray (23) also found a moderate sensitivity and specificity, a favorable positive predictive value of 90.3%, and a negative predictive value of 75%, ROC analyses indicated that a pre-treatment processes β -HCG levels.

Conclusions:

Serum Activin A levels can be used as an indicator of ectopic pregnancy and missed abortion. Serum β -HCG level at a cutoff value of >236 , ng/ml may be a novel biomarker for the assessment of women with ectopic pregnancy.

Authors' declaration:

We confirm that all the Figures and Tables in the manuscript belong to the current study. Besides, the Figures and images, which do not belong to the current study, have been given permission for republication attached to the manuscript. Authors sign on ethical consideration's Approval-Ethical Clearance: The project was approved by the local ethical committee in (Place where the research was conducted or samples collected and treated) according to the code number (43) on (20/ 05/ 2024).

Conflicts of Interest: None.

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Authors' Contributions:

Study conception & design: (Manal K Rasheed). Literature search: (Manal K Rasheed). Data acquisition: (Hussein Mohan Rafik & Farah Abdul Hussein Salih). Data analysis & interpretation: (Hussein Mohan Rafik & Farah Abdul Hussein Salih). Manuscript preparation: (Hussein Mohan Rafik). Manuscript editing & review: (Manal K Rasheed).

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في حالات الحمل خارج الرحم وحالات (β -HCG) وموجهة الغدد التناسلية المشيمية بيتا البشرية (BMI) ومؤشر كتلة الجسم A دراسة دور مستويات الأكتيفين الإجهاض الفائتة لدى مجموعة من النساء العراقيات

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الخلاصة

خلفية البحث: يعد Activin A (ACV-A)، وهو عضو في فصيلة عامل النمو المحول بيتا (TGF-beta) التي تنظم إفراز هرمون النمو الجريبي (FSH) ويبدأ مسارات الإشارات داخل الخلايا، ضروريًا لتنظيم التكاثر. يشارك ACV-A في تنظيم تكاثر الخلايا، والتمايز، وموت الخلايا المبرمج، والتوازن، من بين العمليات البيولوجية الأخرى. تفرز الغدة النخامية والغدد التناسلية والأعضاء الأخرى ACV-A، الذي يتكون من وحدتين فرعيتين β (بيتا A).

الأهداف: مقارنة تركيزات Activin A في مصل الدم في النساء اللاتي تم تشخيص إصابتهن بالإجهاض الفائت (MA) والحمل خارج الرحم (EP) مع تلك الموجودة في العينة الضابطة من السيدات الأصحاء اللاتي لا يعانين من أي من هذه الحالات.

الحالات والمنهجية: جريت الدراسة في أقسام أمراض النساء في مدينة الطب - مستشفى بغداد التعليمي ومستشفى الكوت لأمراض النساء والولادة في الفترة من أكتوبر 2023 إلى يناير 2024.

وشارك في الدراسة ما مجموعه 120 امرأة تتراوح أعمارهن بين 18 و45 عامًا؛ وتم تشخيص الحمل خارج الرحم في 30 منهن، و30 لديهن إجهاض مفقود، وكانت الـ 60 المتبقيات يعتبرن كمجموعة ضابطة. تم قياس مستويات ACV-A وموجهة الغدد التناسلية المشيمية بيتا البشرية (β -HCG) بواسطة طريقة مقايسة الامتصاص المناعي المرتبط بالإنزيم (ELIZA).

النتائج: كان لدى المجموعة الضابطة متوسط أقل بكثير \pm SD لـ ACV-A 130.26 ± 773.6 بيكوغرام / مل مقارنة بمجموعة EP 1408.1 ± 219.02 بيكوغرام / مل) ومجموعة MA 199.31 ± 1200.9 . بالإضافة إلى ذلك، كان لدى المرضى في مجموعة الإجهاض خارج الرحم

انخفاضًا ملحوظًا مقارنة بالمرضى في مجموعة الإجهاض الفائت.

الاستنتاجات: يمكن استخدام مستويات مصل Activin A كمؤشر على الحمل خارج الرحم والإجهاض الفائت. يمكن أن يكون مستوى HCG في مصل الدم من العلامات الحيوية الجديدة لتقييم النساء اللاتي يعانين من الحمل خارج الرحم عند قيمة قطع أكبر من 236 نانوغرام / مل.

مفتاح الكلمات: اكتفين أ، هرمون موجهة الغدد التناسلية المشيمية، مؤشر كتلة الجسم، الحمل خارج الرحم، الإجهاض الفائت.