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Ultrasonography for the prediction of extension of trophoblastic infiltration into the tubal wall in ampullary pregnancy

Ultrasonografia w przewidywaniu rozległości nacieku trofoblastu w obręb ściany jajowodu w ciąży bańkowej

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Abstract

Objective: *Predictive factors of damage to the Fallopian tube may guide the treatment for patients with tubal pregnancy. The purpose of this study was to evaluate the predictive value of ultrasonographic findings in patients affected by ampullary pregnancy for the determination of the depth of trophoblastic infiltration into the tubal wall on histological examination.*

Material and methods: *38 patients with ampullary pregnancy undergoing salpingectomy were enrolled into the study. The patients were divided into two subgroups depending on their transvaginal sonography (TVS) findings; either an ectopic gestational sac containing an embryo with cardiac activity or those with a tubal ring. The ampullary pregnancies were histologically classified according to the depth of infiltration of trophoblastic tissue into the tubal wall as follows: stage I: limited to mucosa; stage II: extension to the muscularis layer; stage III: complete infiltration of the tubal wall with or without rupture of the serosa. The association between findings on TVS and stage of trophoblastic invasion, serum beta-human chorionic gonodatropin (β-hCG) levels was evaluated.*

Results: *Although there was no significant difference among two groups in terms of histological stage of trophoblastic infiltration (p=0.257), patients in whom an embryo with cardiac activity had been identified were found to have higher percentage of stage II (47.8%) or stage III (8.7%) invasion. However, there was a significant difference in serum β-hCG levels on the day of surgery among the two groups (p=0.028).*

Conclusions: *Ultrasonographic aspect of ampullary pregnancy is associated with depth of trophoblastic infiltration into the tubal wall and serum β-hCG levels.*

Key words: **ampullary pregnancy** / **trophoblastic infiltration** / / **transvaginal sonography** /

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Streszczenie

Cel: *Czynniki predykcyjne zniszczenia jajowodu mogą być pomocne w leczeniu pacjentek z ciążą jajowodową. Celem badania była ocena wartości prognostycznej badania ultrasonograficznego u pacjentek z ciążą bańkową dla określenia rozległości naciekania trofoblastu w obręb ściany jajowodu potwierdzonego w badaniu histopatologicznym.*

Materiał i metoda: *Do badania włączono 38 pacjentek z ciążą bańkową, u których wykonano usunięcie jajowodu. Pacjentki podzielono na dwie podgrupy pod względem różnych obrazów ultrasonograficznych; jeden z widocznym pęcherzykiem ciążowym i z zarodkiem z czynnością serca, drugi z widocznym pierścieniem jajowodowym. Ciąże bańkowe podzielono na podstawie wyniku histopatologicznego, pod względem głębokości nacieku trofoblastu w ścianę jajowodu: stopień I: ograniczone do śluzówki, stopień II: przechodzące na mięśniówkę, stopień III: całkowite nacieczenie ściany jajowodu z /bez pęknięcia surowicówki. Oceniono związek pomiędzy obrazem ultrasonograficznym, stopniem nacieczenia ściany jajowodu oraz poziomem surowiczego beta hCG.*

Wyniki: *Nie znaleziono istotnych różnic pomiędzy badanymi grupami pod względem histologicznie ocenionego nacieku trofoblastu (p=0,257). Jednak kobiety, u których stwierdzano żywy zarodek częściej miały stopień II (47,8%) lub III (8,7%) inwazji trofoblastu. Znaleziono również istotną różnicę poziomu beta-hCG w dniu operacji pomiędzy dwoma grupami (p=0,028).*

Wnioski: *Pewne ultrasonograficzne aspekty ciąży bańkowej są związane z głębokością inwazji trofoblastu w ścianę jajowodu oraz surowiczym beta-hCG.*

Słowa kluczowe: **ciąża bańkowa** / **inwazja trofoblastu** /
/ **ultrasonografia przezpochwowa** /

Introduction

Ectopic pregnancy (EP) occurs when the developing blastocyst implants outside the endometrial cavity. Implantation may occur anywhere along the reproductive tract with the most common implantation site being the fallopian tube. The incidence of ectopic pregnancy is approximately 1% of pregnant women, and may seriously compromise women's health and future fertility [1]. Risk factors for developing an EP include history of previous EP, pelvic inflammatory disease and other sexually transmitted diseases, previous tubal surgery, use of assisted reproduction technology, and current use of an intrauterine device [2].

Early diagnosis can reduce the mortality and morbidity associated with ectopic pregnancy. Most important diagnostic tests in evaluating for an ectopic pregnancy are transvaginal ultrasonography (TVS) and a serum human chorionic gonodatropin (hCG) level. The sensitivity and specificity of combining these tests has been reported to range from 95% to 100% [3, 4]. Ultrasonography is used not only to diagnose ectopic pregnancy but also to triage patients into the most appropriate surgical or nonsurgical management, to guide for percutaneous treatments of ectopic pregnancy, and to follow-up patients when medical or expectant management protocols are used. Ultrasonographic features of EP include;

1. tubal ring (bagel sign) - paraovarian anechoic mass surrounded by a peripheral hyperechogenic halo similar to a gestational sac that does not contain a viable embryo;
2. solid or complex inhomogenous mass (blob sign) -paraovarian irregularly boarded image suggestive of haematosalpinx or pelvic haematoma;
3. ectopic gestational sac containing an embryo with cardiac activity. The most specific ultrasonographic finding of an ectopic pregnancy is an extrauterine live embryo (100% specificity). Other ultrasonographic aspects (tubal ring or a solid-complex inhomogenous adnexal mass) have a lower specificity [5].

In clinicopathological studies, morphological and functional alterations such as diverticula, persistent foci of decidual transformation, or postinflammatory changes have been observed in tubes with EP [6, 7]. Further impairment of tubal function might occur as a result of the pregnancy implantation and may depend on the degree of trophoblastic infiltration into the tubal wall [8, 9]. The extension of the implantation site varies among cases, ranging from superficial involvement of the mucosal area to involvement of the total transmural location [10, 11].

Objectives

There are still no validated criteria for the prediction of the depth of trophoblastic infiltration into the tubal wall in EP. The main objective of this study was to evaluate the predictive value of ultrasonographic findings in patients affected by ampullary pregnancy for the determination of the depth of trophoblastic infiltration into the tubal wall.

Material and methods

A cross-sectional study was conducted on patients with a diagnosis of tubal pregnancy in the ampullary region who underwent salpingectomy between January 2008 and December 2013 at Antalya Training and Research Hospital. The Ethics Committee of the institution approved the study, and the patients who agreed to participate provided signed informed consent.

Inclusion criteria in the study were diagnosis of tubal pregnancy in the ampullary region, radical surgical treatment (salpingectomy) by laparotomy or laparoscopy, measurement of serum β-hCG levels on the day of surgery, and description of the ectopic mass by on TVS that fitted one of the following two categories: either an ectopic gestational sac containing an embryo with cardiac activity or a tubal ring. Exclusion criteria were cases with inconclusive postoperative or histological findings regarding the location of the pregnancy and an uncertain last menstrual date of the patients.

The treatment choice (salpingectomy) was based on the clinical state, ultrasonographic findings, gross characteristics of the tube (bleeding, rupture of the tubal wall with peritubal adhesions or haematoma), the condition of the contralateral tube, serum β-hCG level of the patients, and on the patient's future reproductive intent. Assessment of gestational age was based on the last menstrual period.

TVS examinations were performed using a 7.5-MHz transvaginal probe (Logic5 Pro; GE Medical Systems, Milwaukee, WI, USA). The size of the ectopic mass was determined by measuring its longer axis. The patients were divided into two subgroups depending on their TVS findings: (1) ectopic gestational sac containing an embryo with cardiac activity (Figure 1A) and (2) those with a tubal ring (Figure 1B).

Serum β-hCG levels were quantified with a two-site chemiluminescence immunoassay based on the direct sandwich technique (Access UniCel® DxI 800 Immunoassay System; The Access Total β-hCG Assay; Beckman Coulter Diagnostics, Munich, Germany). The inter- and intra-assay coefficients of variation were 4.1% and 1.3%, respectively.

Following salpingectomy, the samples removed were fixed in 10% formalin and sectioned serially for light microscopic analysis. An average of eight sections stained with haematoxylin-eosin was analysed. Histological assessment was performed by a single experienced pathologist who was unaware of the clinical, laboratory and imaging characteristics of the patients. Ampullary pregnancies were classified histologically according to the depth of trophoblastic infiltration into the tubal wall as follows [12]: Stage I, trophoblastic infiltration limited to the tubal mucosa (Figure 2A); Stage II, trophoblastic infiltration extended to the tubal muscularis (Figure 2B); Stage III, complete infiltration of the tubal wall with or without rupture of the serosa (Figure 2C).

The association between the findings on TVS, either a tubal ring or an embryo with cardiac activity, and the stage of trophoblastic infiltration was evaluated. Data were summarised using the mean, standard deviation, median, minimum, maximum and percentages values for numerical values. Student's *t*-test was used to evaluate any difference in maternal age between the groups. Pearson Chi-Square test and Mann-Whitney U test were used for comparison of proportions. Statistical analysis was performed using the SPSS statistical package for Windows, ver. 18.0 (SPSS Inc., Chicago, IL, USA). The result was considered statistically significant when the *p* value was less than 0.05.

Results

A total of 296 consecutive cases of EP were recorded during the study period. Of these, 258 patients were not included in the analysis for the following reasons: 10 cases were not tubal pregnancies; 6 cases were tubal but not ampullary pregnancies; 15 patients were treated by salpingostomy; 104 patients received methotrexate; 20 other patients were managed expectantly; 35 patients did not know the exact date of their last menstrual period, in 58 cases TVS findings were described as showing a solid or complex irregularly boarded mass which resembles a haematosalpinx or pelvic haematoma around the paraovarian region, in 10 cases pathologic preparations were inappropriate, thus exact site of trophoblastic infiltration into the tubal wall could not be confirmed. Thirty-eight patients fulfilled the inclusion criteria and were selected to participate in the study.

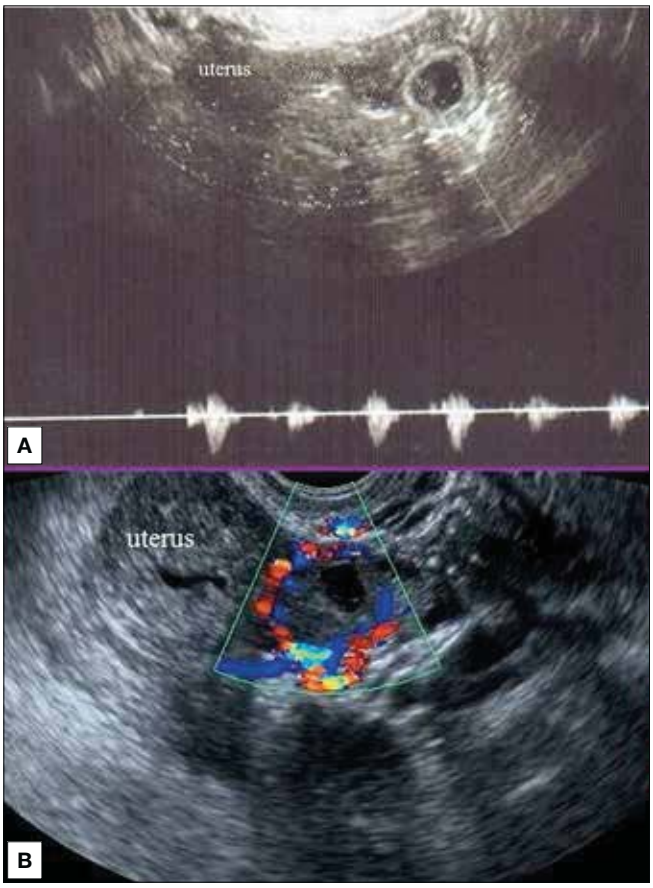

Figure 1. Ultrasonographic aspects of tubal pregnancy. **A** – An ectopic gestational sac containing an embryo with cardiac activity. **B** – Tubal ring with peritrophoblastic flow.

The mean age of the patients was 31.7± 5.1 years (range, 23-45 years) and the mean gestational age at the time of hospitalization was 43.7± 12.6 days (range, 25-91 days) in the entire study population. Regarding ultrasonographic aspects of the ectopic mass, 15 (39.4%) cases showed a tubal ring, in remaining 23 (60.6%) cases an embryo with cardiac activity was detected. The demographic features of two groups are presented in Table I. No significant differences were found in terms of maternal age, obstetric history, gestational age, and ectopic mass size, nevertheless there was a significant differences in serum β-hCG levels on the day of surgery among the two groups (p=0.028).

After histologic evaluation, 20 patients (52.6%) showed stage I infiltration, 16 (42.1%) had stage II, and 2 (5.3%) had stage III. Patients in whom a tubal ring had been identified were found to have higher percentage (66.7%) of stage I infiltration, whereas in those patients who showed an embryo with cardiac activity on TVS stage II (47.8%) was the most frequent finding. Nevertheless, no significant difference was found among the two groups in terms of histological stage of trophoblastic infiltration (Table II).

Discussion

Although surgical intervention has long been the gold standard of EP treatment, conservative management has emerged as a safe and effective alternative [13]. Prompt diagnosis and proper treatment may also play a role in the preservation of fertility and avoidance of catastrophic outcomes including tubal rupture.

Table I. Comparison of demographic features, gestational age, ectopic mass size and serum-hCG level among study groups.

Characteristic	Tubal ring (n=15)	Embryo with cardiac activity (n=23)	*p* value
Age (years)[a]	31.33±5.29	32.0±4.96	0.696
Gravidia[b]	2 (0-6)	2 (0-5)	0.755
Parity[b]	2 (0-3)	1 (0-3)	0.177
Gestational age (days)[b]	42 (25-56)	43 (27-91)	0.611
Ectopic mass size (mm)[b]	35 (20-55)	35 (20-100)	0.740
Sereum β-hCG level (mIU/ml)[b]	3150 (115-27227)	12800 (2240-67280)	0.028*

[a] – Mean values with standart deviations (SD); [b] – Values are given as median (range), Mann-Whitney U test was used;
* – Statistically significant

Table II. Histological stage according to ultrasonographic aspects of ectopic mass. Data are given as number (percentage), Pearson Chi-Square test was used.

Histological stage	Tubal ring (n=15)	Embryo with cardiac activity (n=23)	*p* value
I	10 (66.7)	10 (43.5)	0.257
II	5 (33.3)	11 (47.8)	
III	–	2 (8.7)	

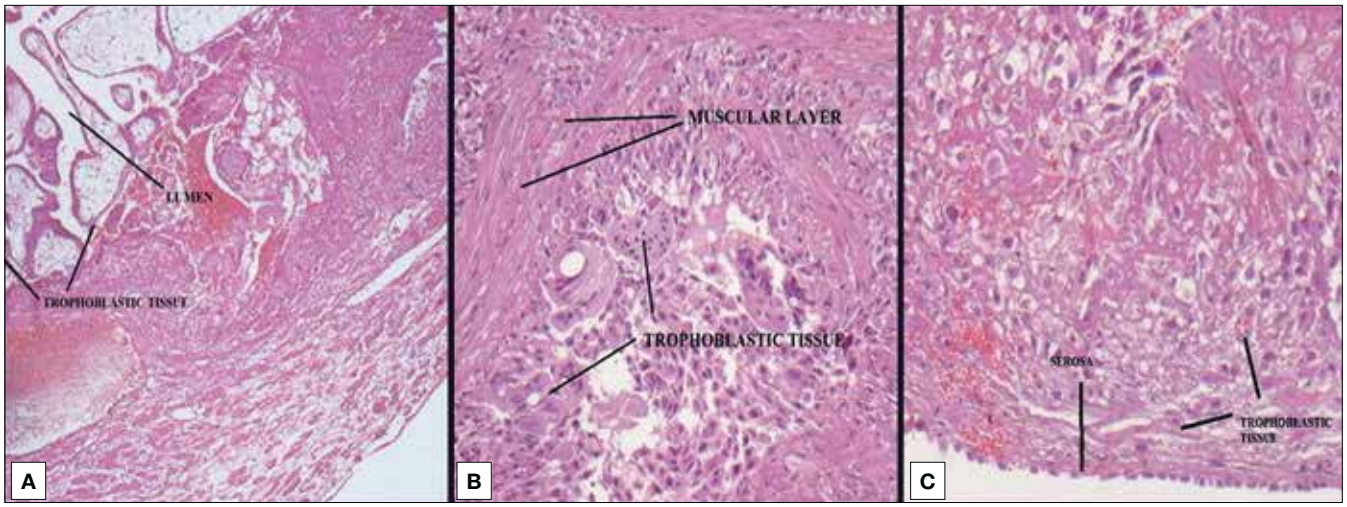

Figure 2. Histopathologic photomicrographs of the fallopian tube affected by ectopic pregnancy and classification according to the depth of infiltration of the trophoblastic tissue. **A** – Stage I, trophoblastic invasion limited to the tubal mucosa. Magnification x 100; hematoxylin-eosin (HE). **B** – Stage II, trophoblastic tissue extends to the tubal muscularis. Magnification x 200; HE. **C** – Stage III, Complete tubal wall infiltration. Magnification x 200; HE.

Many factors have been considered as potential determinants for tubal damage, degree of trophoblastic invasion into tubal wall and selection of patients who will benefit from a conservative approach in EP: physical examination, findings on TVS (presence of embryo with cardiac activity, ectopic mass size and fluid in the pouch of Douglas), serum β-hCG level, gestational age and vascular endothelial growth factor. Some of these factors can be used to predict the presence of microscopic lesions in the Fallopian tube [14, 15].

One of the most important variables in the reproductive prognosis of a woman with tubal pregnancy is the condition of the tube. In medical therapy or expectant management of EP, intraoperative information on the condition of the tube is lacking.

As implantation of trophoblastic tissue into the tubal wall may impair oviductal function, some authors have correlated gestational age, ectopic mass size as evaluated by TVS, and serum β-hCG level with the depth of trophoblastic invasion into the tubal wall [9, 16]. Gestational age and ectopic mass size are proportional to the duration of exposure to trophoblast-mediated erosive event and extent of the tubal disruption. Serum β-hCG level is an accurate marker of trophoblast activity and reflects its ability to penetrate the tubal wall. The deeper invasion of the tubal wall might impair the complete removal of trophoblastic tissue and predispose the recurrence of EP if a conservative therapeutic approach is used.

TVS is now the imaging modality of choice for the diagnosis of ectopic pregnancy. More than 90% of ectopic pregnancies should be visualized on TVS prior to treatment [17]. The precise relationship between the appearance of a tubal ectopic pregnancy on TVS, the size of the mass and serum hCG levels is uncertain. In their study on 120 women with ectopic pregnancies, Cacciatore et al. [18] found that serum hCG levels correlated with the size of ectopic gestational sacs but not with the diameter of inhomogeneous adnexal masses. In addition, the authors stated that the presence of a tubal ring was associated with tubal integrity and that such cases can be managed conservatively, whereas the identification of a heterogeneous adnexal mass was related to rupture of the Fallopian tube in 22% of the cases. It has been suggested that visualization of an inhomogeneous mass may represent either an early developing ectopic pregnancy (before a gestational sac is visualized) or a failing ectopic pregnancy [19]. Pereira et al. [20] reported that sonographic detection of an embryo with cardiac activity was strongly correlated with stage III infiltration. Other studies, that included patients with unspecific TVS findings such as a heterogeneous adnexal mass, have corroborated this finding and emphasised that the presence of an embryo with cardiac activity on TVS may indicate the possible occurrence of greater tubal damage [12, 21]. Our findings are in accordance with previous reports of a higher percentage of embryo with cardiac activity on TVS in patients with stage II infiltration compared with those with stage I infiltration. In addition, a tubal ring was the most frequent finding in patients with stage I infiltration. In contrast to previous studies, embryo with cardiac activity was identified in patients with superficial trophoblastic invasion (stage I). No other study to date has reported this finding.

In this study we recruited only ampullary pregnancies, which represent the main extrauterine site of trophoblast implantation. Considering that different anatomic segments of the fallopian tube are histologically distinct, trophoblast penetration might be different in each tubal portion. In addition, we decided to compare only two specific TVS findings of tubal pregnancy, either a tubal ring or a embryo with cardiac activity. This is the limitation of our study, since solid or complex inhomogenous mass is the commonest presentation of tubal pregnancy on ultrasonographic examination.

Conclusions

Despite the small sample size, the results of this study reinforce the association between serum β-hCG levels and findings on TVS in EP. We infer that high serum levels of β-hCG and embryo with cardiac activity on TVS may indicate the possible occurrence of greater tubal damage, thus surgery must be considered in these situations.

Authors' contribution:

1. Onur Erol – analysis, assumptions, study design, interpretation of data, corresponding author.
2. Dinc Suren – he played role in material and methods, he made histochemical analysis and revised article critically.
3. Mehmet Karaca – he played role in acquisition of data and interpretation of data.
4. Cem Sezer – he played role in revising article critically.

Authors' statement

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