

Histopathologic Evaluation of Endometrium in Patients with Ectopic Pregnancy

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OBJECTIVE: To evaluate the endometrial changes in patients with proven ectopic pregnancies and the value of endometrial histopathology in diagnosis of ectopic pregnancies.

STUDY DESIGN: Medical records of 71 patients with proven ectopic pregnancies and who had endometrial curettage results were reviewed. Ectopic pregnancy was confirmed either at operation or at transvaginal ultrasound evaluation with clearly visualized characteristic adnexal mass in the presence of an empty uterus and serum beta-subunit human chorionic gonadotropin level above the discriminatory zone. Histopathologic findings of the endometrial curettage materials were evaluated.

RESULTS: The mean age of the patients was 30±5.9 years. The mean gestational age (by date of last menstrual period) at presentation was 36.9 days. The most common symptoms at presentation were both vaginal bleeding and missed menstruation. Review of the endometrial curettages revealed that the most common type of endometrium associated with ectopic pregnancy was secretory (52.2%) followed by decidual reaction (15.5%), proliferative endometrium (14.1%), Arias-Stella reaction (11.2%), and endometrial fragments (7%).

CONCLUSION: Since ectopic pregnancy is associated with various types of endometrial histopathology, it is not valuable in the diagnosis and should be performed in selected patients for differential diagnosis when TVUS, serial serum b-HCG levels are inconclusive.
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Key Words: Curettage, Ectopic Pregnancy, Endometrium, Histopathology

The incidence of ectopic pregnancy (EP) has increased from 0.45% to 1.97% within the last two decades. This may be due to increased incidence of salpingitis, ovulation induction and surgical tubal sterilization.¹ However, at the same time mortality rate decreased from 35.5 to 3.4 per 10,000 EP. Whilst the risk of death from an EP is still 10 times greater than the deaths of legal abortion related complications², it is the leading cause of pregnancy related death in the first trimester and accounts for 9% of all pregnancy related deaths.¹ One of the major reasons of mortality related with EP is the delay in diagnosis either because of a lack of suspicion or an improper reassurance from the assessment of information available.²

Management of EP has changed dramatically within the last years and results of conservative treatment are encouraging. For conservative approach, however early accurate diagnosis of EP is essential.³ Presently there is no single non-invasive test to confirm the presence of an ectopic pregnancy definitively and diagnosis requires the exclusion of an

intrauterine pregnancy. When the beta-subunit human chorionic gonadotropin (b-HCG) level is above the discriminatory zone (2000 mIU/mL), the sensitivity of transvaginal ultrasound (TVUS) scanning to detect a normally developing intrauterine pregnancy approaches 100%.⁴ Therefore, when an intrauterine pregnancy is not identified by TVUS scanning and the b-HCG level is above the discriminatory zone, a nonviable pregnancy is diagnosed. Similarly, when serial b-HCG values do not show a proper rise or fall, there is a query of abnormal gestation.⁵ Currently, the only definitive way to differentiate between an impending miscarriage and an EP is curettage however there is conflicting information about the role of endometrial curettage in clinical diagnosis of EP.^{2,5,8} In this study we aimed to evaluate the endometrial changes in patients with proven EP in order to determine its prognostic value in diagnosis of EP.

Materials and Methods

The medical records of all patients with proven EP who were hospitalized within the year 2003 at Ankara Etlik Maternity and Women's Health Teaching Hospital, were reviewed. Institutional ethics committee approval was obtained and curettage findings of the seventy-one proven EP cases were evaluated. EP was confirmed either at the time of operation or at TVUS with clearly visualized characteristic adnexal mass in the presence of an empty uterus and serial serum b-HCG levels that were above the discriminatory zone and not doubled within 48 hours. In this study, a cut off level of 1,500 mIU/ml was accepted as the discriminatory zone.^{7,8} Demographic characteristics, significant risk factors such as

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Table 2. Management of 71 ectopic pregnancies

		n	%
Surgery	Salpingectomy	24	34
	Laparoscopic salpingostomy	5	7
MTX	Surgery after MTX	9	13
	One dose	26	37
	Second dose	15	21
Expectant management		10	14

Evaluation of 71 endometrial curettages revealed that the most common type of endometrium associated with EP was secretory (52.2%) followed by decidual reaction (15.5%) and proliferative endometrium (14.1%). Arias-Stella and decidual reaction which have been highly suggestive for EP, were seen only in 8 (11.2%), and 11 (15.5%) of the cases respectively (Table 3).

Table 3. Histopathologic diagnosis of 71 patients

Histopathologic findings	n	%
Secretory endometrium	37	52.2
Decidual reaction	11	15.5
Proliferative endometrium	10	14.1
Arias-Stella reaction	8	11.2
Endometrial fragments	5	7.0

Discussion

The diagnosis of the unruptured, asymptomatic EP remains as one of the most challenging problems for the gynaecologist.⁹ Diagnosis of EP at a very early stage prevents the rupture of fallopian tube and related to this, reduces maternal mortality and improves the future conception rates.¹⁰⁻¹¹ It is sometimes difficult to distinguish an early spontaneous abortion from an EP and in some cases histopathologic diagnosis of the curettage material may be the first indication to suggest the possibility of an EP.¹²

Various histopathological findings that are thought to be clues of EP are: absence of placental or fetal parts and presence of well-developed decidua, hypersecretory endometrium and/or the Arias-Stella reaction.⁹ Decidual and Arias-Stella reactions are the earliest endometrial changes expected to occur during pregnancy, including ectopic.¹³ Although highly suggestive, the Arias-Stella reaction is not pathognomonic of EP since it has been seen also in hydatidiform mole, choriocarcinoma, chorioepithelioma, as a reaction of clomiphene citrate treatment and contraceptive pills. In the literature, it is claimed that the accuracy of histopathological evaluation in diagnosis of ectopic pregnancy varies from 40 to 76%.¹⁴ In our study, we found a variety of histological changes associated with proven EP. The endometrial changes classically thought to be suggestive of EP are found only in 19 (26.7%) of the cases. Surprisingly, 10 (14.1%) of the patients had proliferative endometrium, that is more common than Arias-Stella reaction. Our finding is consistent with the

history of a pelvic inflammatory disease and previous EP, symptoms at admission, presence of an intrauterine device (IUD) as a method of contraception, TVUS reports and serum b-HCG levels were recorded. All the TVUS examinations were performed by 6-7.5 MHz vaginal probes (Aloka SSD 5500) and serum b-HCG levels were studied by radioimmunoassay (RADIM SpA; Italia) using an assay with a sensitivity of 2.0 mIU/mL. Endometrial curettage was performed by using Karman cannula either under general (during operation) or local anaesthesia (at clinic) before treatment. Consent forms for operation, medical treatment and endometrial curettage were signed by all the patients after counselling.

Results

The mean age of the patients was 30±5.9 years (range 20-43 years). The mean gestational age (by date of last menstrual period) at presentation was 36.9 days. Most common symptom recorded at presentation was vaginal bleeding accompanied by missed menstrual period (52.2%). Vaginal bleeding, abdominal pain, and missed menstrual period were recorded alone in 20.3%, 18.8%, and 7.2% of the patients, respectively. One patient (1.4%) had no symptoms. Five (7%) patients had a history of EP, and three (4.2%) had a history of pelvic inflammatory disease. Twelve patients (16.9%) were IUD users at admission. All patients had conceived in natural cycles (Table 1).

Table 1. Baseline characteristics

Characteristic†	Patients(n=71)
Age (y)	30±5.9
Gestational age (day)	36.9±17.5
Parity (Median, range)	1 (0-5)
Mean systolic arterial pressure at admission (mmHg)	105.9±8.7
Mean diastolic arterial pressure at admission (mmHg)	67.6±7.5
Initial serum HCG level (mIU/mL)	4814±10085
Endometrial thickness at admission (mm)	8.6±4.6

†Results are expressed as means±SDs except parity

Mean b-HCG level at admission was 4814±10085 mIU/mL. The mean endometrial thickness was 8.6 ± 4.6 mm at TVUS evaluation. In one patient (1.4%) fetal cardiac activity was observed by TVUS. Remaining 70 patients had adnexal masses with a diameter of 8-15 mm without cardiac activity. Twenty-nine (40.9%) patients underwent surgery including nine patients (12.7%) who had either continuously rising b-HCG levels or tubal rupture despite methotrexate (MTX) treatment. Five women (7%) underwent laparoscopic salpingostomy and 24 (34%) had salpingectomy via laparotomy. Ten patients (14.1%) were followed by expectant management and all of them resolved spontaneously. Forty-one (57.8%) of 71, hemodynamically stable patients were medically managed with methotrexate (50 mg/m²) intramuscularly and 32 (45%) of them had uneventful resolution. Fifteen patients (21%) required a second dose of MTX (Table 2).

results of Ollendorff and coworkers.² In their study, 19% of the patients had proliferative endometrium and these false negative results could lead to a delay in the diagnosis of EP. These investigators also concluded that neither the absence of decidual reaction or an Arias-Stella reaction nor the presence of proliferative endometrium should lower the clinician's level of suspicion about the potential presence of an EP. Since the presence of secretory, decidual or Arias-Stella changes and even a mixture of these changes with proliferative ones would suggest continuing progesterone activity, and conversely, proliferative endometrial signs and symptoms should theoretically reflect the absence of a progestational impact, further studies correlating the histopathologic patterns with serum b-HCG, estradiol and progesterone levels are needed.¹⁵

There is conflicting information about necessity of D&C in clinical diagnosis of EP. It was reported that the effort on the part of the pathology department to exclude intrauterine pregnancy by thorough examination of endometrial material was a fruitless exercise and also unnecessarily raised medical costs.¹³ In line with this report, Novak and Woodruff did not consider endometrial curetting diagnostically helpful. This was especially the case when bleeding occurred before curetting.⁶ According to Barnhart, histopathologic evaluation of endometrium is necessary in order to avoid misdiagnosis and improper treatment of EP, while Goldstein claims that many women currently eligible for biopsy will get MTX anyway so it may have a role particularly in patients with contraindications to systemic MTX administration.¹⁶ In early publications about MTX therapy, Stovall and co-workers used biopsy and laparoscopy as an integral part of the diagnostic work out.¹⁷ The most recent MTX protocols do not recommend histopathologic evaluation of an intrauterine gestation via endometrial curetting if the serum b-HCG level is greater than 2,000 mIU/mL and no intrauterine pregnancy is seen on TVUS.¹⁸ Goldstein stated that if the patient has experienced any bleeding prior to the intervention, failure to find chorionic villi is compatible with complete abortion or ongoing EP and only serial serum bHCG measurements can help to distinguish these from each other.¹⁹

In conclusion, various types of endometrial histopathologies may be associated with EP and the lack of decidual reaction or Arias-Stella phenomenon should not alone lower the clinician's index of suspicion. In the light of literature, it can be recommended that endometrial curetting should only be performed when TVUS and serial serum b-HCG levels are inconclusive, in order to rule out the intrauterine pregnancy whilst it has no diagnostic value in cases with proven EP.

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