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ECTOPIC PREGNANCY (E.P) RISK FACTORS , DIAGNOSIS AND MANAGEMENT

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INTRODUCTION

Ectopic pregnancy, which is any pregnancy implanted outside the uterinecavity, remains the leading cause of pregnancy-related first-trimester deathamong women in the Iraq. Fertilization of the ovum occurs inthe fallopian tube. As the zygote divides, it becomes first a morula andthen a blastocyst, normally arriving in the uterine cavity and beginning implantationon day 6 after fertilization. Anything that delays or impedestubal transport may allow implantation to begin while the blastocyst is stillin the tube; approximately 97% of ectopic pregnancies are tubal in location.Ectopic pregnancies represent approximately 2% of all pregnancies [1,2].This estimate is conservative, as the analysis did not include patients whosecondition was diagnosed and managed exclusively as outpatients. While theincidence of ectopic pregnancy has continued to increase, the case fatalityrate has dropped from 69% in 1876 [3], to 0.35% in 1970, and to 0.05%in 1986. The death rate for African American and other minority womenremains over double that for white women, and the highest death rate occursin the 15- to 19-year-old age group [4].With documented intrauterine pregnancy, the risk of coexisting ectopic(heterotopic pregnancy) is approximated at 1 case in 10,000 patients to 1 casein 30,000 [5,6]. This risk increases to approximately 1 case in 100 patientsif the woman is being treated for infertility [7].

Keyword: CPK(creatine Phosphokinase), β human chorionic gonadotropin,, methotrexate, Ectopic Pregnancy (E.P).

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EPIDEMIOLOGY

It has been reported that 1.3–2.4% of all pregnancies are extrauterine. The true frequency cannot be estimated any more accurately than this, because statistics generally reflect only cases treated in the hospital and with surgery (4). In the mid-twentieth century, it was
estimated that 0.4% of all pregnancies in the USA were extrauterine; recent data show a current figure higher than 1.4% (1). In Germany today, there are an estimated 20 extrauterine pregnancies for every 1000 live births (4). The rising frequency of (diagnosed) extrauterine pregnancies is due to a number of factors, including:

- the increased utilization of assisted reproductive technology,
- the increasing number of operations performed on the fallopian tubes,
- rising maternal age, and more sensitive diagnosis (2).

PATHOGENESIS

Extrauterine pregnancy is of multifactorial origin. Up to half of all women with an extrauterine pregnancy have no recognized risk factors for it (5). The postulated mechanisms include anatomical and/or functional tubal obstruction, impaired tubular motility and ciliary dysfunction, and molecular chemotactic factors that stimulate and promote tubal implantation (5).

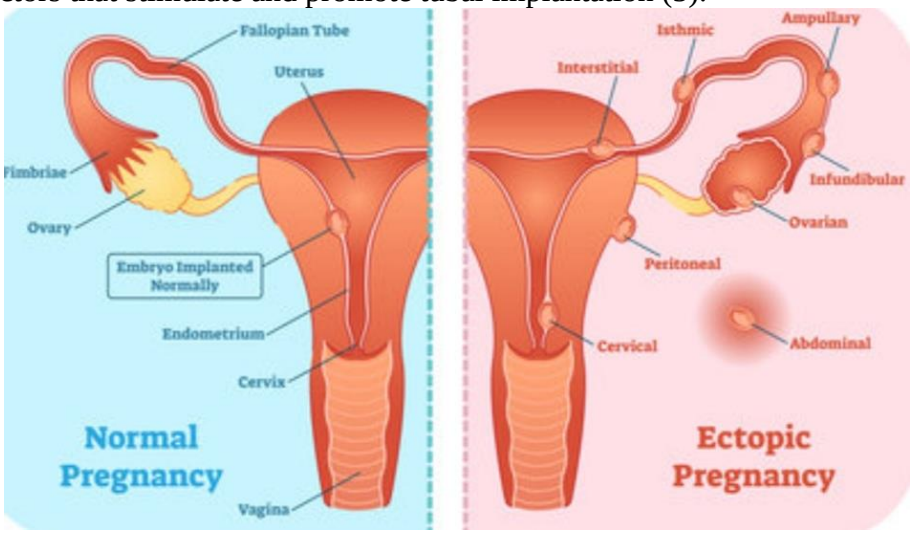


Fig. 1Ectopic pregnancy

RISK FACTORS

Factors conferring a high risk [odds ratio (OR) > 4.0]

Prior tubal surgery or a prior tubal pregnancy are the most important risk factors for tubal pregnancy (6, 7) *(Table 1)*. Sterilization is a very effective method of
contraception; nevertheless, if a woman becomes pregnant despite having undergone a putatively sterilizing procedure, extrauterine pregnancy must be considered as a possibility, as about 30% of pregnancies after sterilization are extrauterine (8). The cumulative 15-year risk of tubal pregnancy is 2.9 per 1000 sterilizations (9). The risk of tubal pregnancy is higher after electrocoagulation of the fallopian tubes, because
of tubal recanalization and/or the formation of a utero-/ tuboperitoneal fistula (8).
Women who use an intrauterine device are at lower risk of ectopic pregnancy than those who use no contraception. If woman using an intrauterine device is
nonetheless found to be pregnant, extrauterine pregnancy should be ruled out, as 50% of such pregnancies are extrauterine (5, 10).

Factors conferring a moderately elevated risk (OR > 2.0)

Elevated rates of extrauterine pregnancy have been found among women taking hormones (clomifene) to treat infertility, although the increased prevalence of
tubal pathology and prior surgical treatments in this population are obvious confounding variables (1). Assisted reproductive technology (ART) has also been
reported to elevate the risk of an extrauterine pregnancy from 0.025% (the value in the general population) to 1% among women who have undergone in vitro fertilization (11). The incidence of extrauterine pregnancy after ART
seems to have fallen somewhat in recent years (12). Women with an active or prior ascending infection with *Chlamydia trachomatis* or *Neisseria gonorrhoeae*
are at an elevated risk of extrauterine pregnancy. Other types of intra-abdominal infection, e.g., appendicitis, can also raise the risk (13).

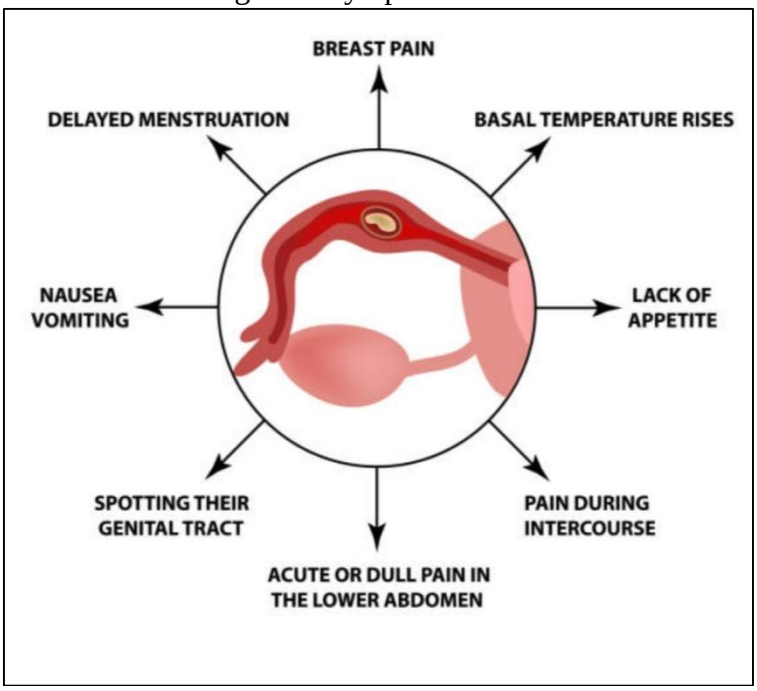
Factors conferring a mildly elevated risk (OR < 2.0)

The highest incidence of extrauterine pregnancy is between the ages of 35 and 45, perhaps because of the cumulative effect of multiple risk factors over time (5).

Clinical features, course, and differential diagnosis

Extrauterine pregnancy may be wholly asymptomatic (intacttubal pregnancy [intact fallopian tube and embryo perhaps with discernible cardiac function]), or it may present with pelvic pain that is worse on one side (tubalabortion) or with severe hemorrhagic shock (tubal rupture). Extrauterine pregnancies are most commonly diagnosed in the 6th through 9th week of gestation; mostpatients present with nonspecific complaints (2). The symptom triad of mild vaginal spotting in the first trimester, aching pelvic pain, and secondary amenorrheamay indicate extrauterine pregnancy but can also arise in an intact intrauterine pregnancy or as a consequence of early miscarriage (2). Further suggestivemanifestations include abdominal pain radiating to the shoulder(s), abdominal guarding or an acute abdomen, pain on displacement of the vaginal portion ofthe cervix, hemorrhagic shock/hemodynamic instability (dyspnea, hypotension, tachycardia), and syncope. The adnexum on the affected side is often enlarged andtender (8). In view of the complexity of the associated findings, various other entities in the differential diagnosis need to be ruled out whenever an extrauterinepregnancy is suspected: cystic or solid adnexal tumors causing peritoneal irritation (especially by torsion or rupture), adnexal infection (e.g., tubo-ovarian abscess),appendicitis, or ovarian hyperstimulation syndrome

figure 2. symptom of E.P



with ascites perhaps with discernible cardiac function]), or it maypresent with pelvic pain that is worse on one side (tubal abortion) or with severe hemorrhagic shock (tubal rupture). Extrauterine pregnancies are most commonlydiagnosed in the 6th through 9th week of gestation; most patients present with nonspecific complaints (2). The symptom triad of mild vaginal spotting in thefirst trimester, aching pelvic pain, and secondary amenorrhea may indicate extrauterine pregnancy but can also arise in an intact intrauterine pregnancy or as aconsequence of early miscarriage (2). Further suggestive manifestations include abdominal pain radiating to the shoulder(s), abdominal guarding or an acute abdomen, pain on displacement of the vaginal portion of the cervix, hemorrhagic shock/hemodynamic instability (dyspnea, hypotension, tachycardia), and syncope.The adnexum on the affected side is often enlarged and tender (8). In view of the complexity of the associated findings, various other entities in the differential diagnosis need to be ruled out whenever an extrauterine pregnancy is suspected: cystic or solid adnexal tumors causing peritoneal irritation (especially by torsion orrupture), adnexal infection (e.g., tubo-ovarian abscess), appendicitis, or ovarian hyperstimulation syndrome with ascites.

Table,1.Risk factors for extrauterine pregnancy (6, 7)*

Factors		
Mildly elevated risk	**Moderately elevated risk**	**High risk**
(OR < 2.0)	**(OR > 2.0)**	**(OR > 4.0)**
– age over 40 years	**– sterility**	**– prior tubal surgery**
(OR: 1.4–6.1)	**adjusted OR: 2.1–2.7; OR: 2.5–21.0**	**adjusted OR: 4.0 (2.6–6.1); OR: 4.7–21.0**
	– current or prior ascending infection	**– prior tubal surgery**
	adjusted OR: 3.4 (2.4–5.0); OR: 2.5–3.7	**adjusted OR: 4.0 (2.6–6.1); OR: 4.7–21.0**
	– cigarette smoking	**– sterilization**
	adjusted OR: 1.5 (1.1–2.2); OR: 2.3–2.5	**(OR: 4.9–18.0)**
	– more than one sexual partner (OR: 2.1–2.5)	**– use of intrauterine device**
		adjusted OR: 2.4 (1.2–4.9); OR: 4.2–45.0
	– tubal pathology	**– intrauterine exposure to diethylstilbestrol**
	adjusted OR: 3.7 (1.2–4.8); OR: 2.5–3.5	**(OR: 2.4–13.0)**

*adjusted for prior ascending infection, cigarette smoking, educational level, and region of origin; OR, odds ratio.

DIAGNOSIS

1.Historical features and physical findings

Ectopic pregnancy is usually diagnosed in the first trimester of pregnancy. The most common gestational age at diagnosis is 6 to 10 weeks, but fetal viability can be discovered
until the time of delivery.Ectopic pregnancy has about the same frequency across a wide range of maternal ages and ethnic origins.

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2.Use of β□□human chorionic gonadotropin measurement

It is important to confirm pregnancy. In the emergency department, pregnancy is diagnosed by determining the urine or serum concentration of β□□human chorionic gonadotropin (β-hCG). This hormone is detectable in urine and blood as early as 1 week before an expected menstrual period. Serum testing detects levels as low as 5 IU/L,
whereas urine testing detects levels as low as 20–50 IU/L.22 In most cases.

3.Use of progesterone measurement

Measurement of the serum concentration of progesterone
has been investigated as a potentially useful adjunct
to serum β -hCG measurement, since progesterone levels
are stable and independent of gestational age in the first trimester.

4.Ultrasound imaging

Transvaginal ultrasonography has transformed the assessment of women with problematic early pregnancy, allowing earlier, clearer visualization of both normally developing
embryos and abnormalities. A normal gestational sac, an ovoid collection of fluid adjacent to the endometrial stripe, can be visualized by means of the transvaginal probe
at a gestational age of about 5 weeks. It can often be seen when 2 or 3 mm in diameter and should be consistently seen at 5 mm. Since the hormonal environment in ectopic
pregnancy can produce an intrauterine fluid collection that mimics a gestational sac

Management

1. Surgical management

This involves having an operation to remove the ectopic pregnancy. It is the most common treatment. You will have a general anaesthetic so you will be completely asleep.

We recommend that you have surgery if:

• we find internal bleeding on your scan
• you have an ectopic pregnancy with a heart beat
• you are in severe pain
• expectant management or medical management fail.

You usually have a type of keyhole surgery called a laparoscopy, which allows you to go home sooner. This is where the surgeon makes a cut close to your belly button through which they will insert a slim probe with a tiny camera on the end. They will also make two small cuts in your lower abdomen through which they will put surgical instruments.

If you have heavy internal bleeding or lots of scar tissue, you may have a type of open surgery called a laparotomy. This is where we make an 'open' cut in your lower abdomen.

• We may remove the affected fallopian tube if the other tube looks healthy. This is called a salpingectomy.
• If the other fallopian tube looks scarred, we will try to remove the ectopic pregnancy only. This is called a salpingotomy.

2. Expectant management

This involves monitoring you closely to see if the ectopic pregnancy is a failing pregnancy and will resolve naturally without you needing any treatment.

3. Medical management

This involves injecting you with a drug called methotrexate. This stops placental tissue growing and so stops the ectopic pregnancy developing.

Table 2. The surgical and medical treatment*1, 2 of extrauterine pregnancy, modified from Pisarska et al. (8)

Surgical treatment	Medical treatment (methotrexate)
Indications - rupture - hemodynamic instability - symptoms (eg., pain) - diagnostic laparoscopy - suspected heterotopic pregnancy	**Indications** -hCG< 5000 IUIL - rising hCG level in 48 hours - normal: hemoglobin, leukocytes, platelets, liver enzymes - diameter of gestational sac <4 cm **Absolute contraindications** - intrauterine pregnancy - immune suppression - hypersensitivity to methotrexate -active lung disease - active peptic ulcer disease - clinically significant renal or hepatic dysfunction - breastfeeding - ruptured extrauterine pregnancy - hemodynamic instability **Relative contraindications** -hCG > 5000 IUL - objection to blood transfusions - follow-up not possible
Surgical procedure organ- (tube-) preserving surgery - salpingotomy - segmental resection (partial salpingectomy) - transampullary expression ('milk-out) indications for an ablative procedure (salpingectomy) - uncontrollable bleeding - marked tubal destruction - ipsilateral recurrence - prior ipsilateral sterilization	
Follow-up - weekly hCG measurement until normalization - persistent extrauterine pregnancy/trophoblastic tissue: - re-laparoscopy - drug therapy (methotrexate) when indicated	**Follow-up** - weekly hCG measurement until normalization - persistent extrauterine pregnancy/trophoblastic tissue: -repeat methotrexate administration - surgery when indicated

METHODS

This was an observational comparative three group clinical study, conducted in the department of Obstetrics and Gynecology Hospital, **No. of patients (n=20)** between the May 2017 to January 2020. Women in the first trimester who presented to the emergency room with complaints of period of amenorrhea, vaginal bleeding, abdominal pain with or without syncope were enrolled for the study

and followed up longitudinally. Study included consecutive patients with documented tubal pregnancy, 40 consecutive

A detailed history with thorough clinical examination along with routine investigations and ultrasonography of pelvic organs was done. History included period of amenorrhea, pelvic and abdominal pain, vaginal bleeding or spotting, vasomotor disturbances like vertigo or syncope. Meticulous physical examination included general physical examination, per abdominal and per vaginal examination. Before any invasive procedure maternal venous samples were collected for CPK, B-HCG, in addition to other investigations required for surgical or medical intervention. CPK (creatine Phosphokinase**)** level was determined by NAC activated with Beckman Coulter AU480.

Statistical analysis

Data was analysed using the Statistical software namely SAS 9.2, SPSS 15.0 and R environment ver.2.11.1.

RESULTS

Table 1: **Clinical parameters in the studied population.**

Demographic details	Normal pregnancy	Abortive pregnancy	Ectopic pregnancy
Parity			
Primi	11 (57.5%)	10 (47.5%)	8 (42.5%)
Multi	8 (42.5%)	11 (52.5%)	12 (57.5%)
Age in years			
<20	1 (2.5%)	0 (0%)	0 (0%)
20-30	15 (75%)	16 (77.5%)	16 (77.5%)
31-40	5 (22.5%)	5 (22.5%)	5 (22.5%)
3-5 weeks	5 (22.5%)	2 (10%)	11 (57.5%)
6-10 weeks	16 (77.5%)	17(82.5%)	8 (42.5%)
>10 weeks	0 (0%)	2 (7.5%)	0 (0%)

Table 2: Clinical features of patients who presented with ectopic pregnancy

Clinical presentation	Ectopic pregnancy	P value
Pain abdomen		
Absent	2 (7.5%)	<0.001
Present	18 (92.5%) <0.001	
Amenorrhoea		
Absent	7 (32.5%)	<0.001
Present		
	Shock	13 (67.5%)
Absent	16 (80%)	<0.001
Present	4 (20%)	
Absent	14 (70%)	<0.001
Present		6 (30%)
Bleeding P/V		
Absent	14 (70%)	<0.001
Present		6 (30%)

Table 3: CPK distribution in three groups of patients studied.

CPK	Normal pregnancy	Abortive pregnancy	Ectopic pregnancy
<50	18 (94.9%)	15 (75%)	0 (0%)
50-100	2 (5.1%)	5 (25%)	12 (70%)
>100	0 (0%)	0 (0%)	6 (30%)
Total	20 (100%)	20 (100%)	20 (100%)

Table 4: Management in ectopic surgery

Management	No. of patients (n=20)	%
Medical Rx	8	40
Laparoscopy	10	50
Laparotomy	1	7.5
D/e	1	2.5

Table 5: CPK levels in relation to ruptured and unruptured ectopic pregnancy

CPK	Ectopic pregnancy	Ectopic pregnancy	
	Ruptured	Unruptured	
<80	2 (17.4%)	5 (64.7%)	8 (37.5%)
80-120	8 (65.2%)	2 (23.5%)	10 (47.5%)
>120	2 (17.4%)	1 (11.8%)	3 (15%)
Total	12 (100%)	8 (100%)	20 (100%)

Table 6: Comparison of mean CPK values in relation to ruptured and unruptured in Ectopic pregnancy

Variables	Ectopic pregnancy		P value
	Ruptured	Unruptured	
Mean CPK	97.26±25.97	63.82±34.92	0.015

DISCUSSION

Ectopic pregnancy remains a leading cause of maternal mortality and accounts for a sizeable proportion of infertility and ectopic recurrence.8 Ectopic pregnancy is still a diagnostic challenge, presenting with various complaints. Though it can be easily treated, early detection is absolutely necessary to prevent fatal consequences. Despite all the advancement 40-50% of EP is missed at the first assessment The commonest presenting complaint was abdominal pain (92.5%) and period of amenorrhea (67.5%) which was similar to the results reported by Shetty et al and Porwal et al Ectopic pregnancy in developing countries is a serious threat, just because of poor medical facility so that a significant morbidity rate and the potential for maternal deathgenerally are seen. Many patients have no documented risk factors and no physical indications of EP, yet they suffer from the complication. On the other hand, in developedcountries, it is now not so threatening as in past because they have advanced technique of diagnosis and women are much more aware of their health. Management is dictatedby the clinical presentation, serum b-hCG levels and TVS findings. Expert consultation with radiologists and gynecologists is recommended whenever ectopic pregnancy issuspected. The use of MTX for treatment of early unruptured EP reported to be safe and effective. Surgical treatment is particularly appropriate for women who arehemodynamically unstable or unlikely to be compliant with post treatment monitoring and those who do not have immediate access to medical care. The

choice of treatmentshould be guided by the patient's preference, after a detailed discussion about monitoring, outcome, risks, and benefits of the approaches. The radiologists and gynecologistsshould have been firstly the identification of clinical features or biomarkers predictive of MTX success and the secondly is the use of additional medical treatments or novel adjuncts that reduce treatment failures. The current analysis of EP would suggest declining trends over time.However, this reflects a decrease in surgical treatment and not an actual decline in EP occurrence.

CONCLUSIONS

Ectopic pregnancy is a common and serious problem, with a significant morbidity rate and the potential for maternal death. Many patients have no documented risk factorsand no physical indications of ectopic pregnancy. Ultrasonography (either formal or ED-based) is the initial investigation that should be done in an ED patient with1st-trimester bleeding or pain; indeterminate results may be clarified by measurement (single or serial) of the serum β□□-hCG and progesterone concentrations. Expert consultationwith radiologists and gynecologists is recommended whenever ectopic pregnancy is suspected. Management is dictated by the clinical presentation, serum β□□-hCG levels and transvaginal ultrasound findings. MTX, as a single intramuscular injection, can be given towomen who are hemodynamically stable and compliant and have an initial serum □-hCG concentration of less than 5000 IU/L and no ultrasound evidence of fetal cardiac activity.Patients who do not meet these criteria should be treated surgically, in most cases by laparoscopy. Surgical treatment is particularly appropriate for women who arehemodynamically unstable or unlikely to be compliant with post-treatment monitoring and those who do not have immediate access to medical care. The choice of treatmentshould be guided by the patient's preference, after a detailed discussion about monitoring, outcome, risks, and benefits of the 2 approaches

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