Review Article

A review search about Ectopic Pregnancy; Incidents, Environmental Causes and Consequences in Diyala Province

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Abstract

Background: It was founded that numbers of pathological cases occur two or three months after marriage, or even for married women who have given birth previously, which reflect the symptoms of an ectopic pregnancy, and the cases are proven by conducting an analysis and Doppler sonar to show that the pregnancy is outside the uterus and thus the result will be an explosion of the Fallopian tubes and severe bleeding, and thus may require surgical intervention, and one of the fallopian tubes may need to be removed or the other healthy tube may remain. Which raised our desire to search for this topic, to find out more details about ectopic pregnancy, its types, how it was diagnosed previously and recently, the physical and environmental and body circumstances of these cases and the reasons that may lead to an ectopic pregnancy. Perhaps the research will come out with recommendations that may contribute to reducing such cases in Diyala Governorate.

The aim of the study : The purpose of the was obtaining the different type and to learn about the causes and circumstances that may play a role in the occurrence of an ectopic pregnancy and the consequences of that. Perhaps the research will come out with results and recommendations that may help in reducing or prevention of such cases.

Objectives:

1. Review about ectopic pregnancy what it is, types and how can be diagnosed nowadays.
2. Follow the environment and expected related body factors from may be aggravated the occurrence.
3. Obtain the related risk factors like other diseases the patients suffered from.
4. Obtain of any blood, hormonal and other analysis related to EP.

Key Words: Ectopic pregnancy, Uterine tube inflammation, Metritis, Infertility.

Methods : The current study adopted a reviewed the different information's about EP from different references and sources as articles, text books, Websites to find out different type of EP, Diagnosis, Surgical international interference, and consequences, the circumstances and causes related to the occurrence of an ectopic pregnancy.

Introduction

Ectopic pregnancy (EP) is the result of implantation and maturation of the conceptus outside the endometrial cavity, which ultimately ends in the death of the fetus. Without timely diagnosis and treatment, EP can become a life-threating situation [1]. It is accepted from the Greek word “ektopos,” meaning out of place [2], referring to the blastocyst implantation outside the endometrial cavity with over 95.5% implanting in the Fallopian tube [3–7], where the fetus or embryo is absent or stops growing. The EP presents a major health problem for women of child-bearing age, constituting 1.2–1.4% of all reported pregnancies. Most specified risk factors are of maternal origin: pelvic inflammatory disease, Chlamydia trachomatis infection, smoking, tubal surgery, induced conception cycle as well as endometriosis [8]. During the past 40 years, its incidence has been steadily increasing concomitant with increased sexually transmitted disease (STD) rates and associated salpingitis (inflammation of the Fallopian tubes). The most

common site of ectopic implantation is the Fallopian tube. Other sites such as the abdomen, ovary or cervix are far less common but are associated with higher mortality. This higher mortality is due to greater detection difficulty and to massive bleeding that can result if rupture occurs at these sites [9]. Ectopic pregnancy, which is any pregnancy, implanted outside the uterine Cavity remains the leading cause of pregnancy-related first-trimester death among women in the United States. Fertilization of the ovum occurs in the fallopian tube. As the zygote divides, it becomes first a morula and then a blastocyst, normally arriving in the uterine cavity and beginning implantation on day 6 after fertilization. Anything that delays or impedes tubal transport may allow implantation to begin while the blastocyst is still in the tube; approximately 97% of ectopic pregnancies are tubal in location. Ectopic pregnancies represent approximately 2% of all pregnancies [10, 11]. This estimate is conservative, as the analysis did not include patients whose condition was diagnosed and managed exclusively as outpatients. While the incidence of ectopic pregnancy has continued to increase, the case fatality rate has dropped from 69% in 1876 [12], to 0.35% in 1970, and to 0.05% in 1986. The death rate for African American and other minority women remains over double that for white women and the highest death rate occur in the 15- to 19-year-old age group [13]. With documented intrauterine pregnancy, the risk of coexisting ectopic (heterotopic pregnancy) is approximated at 1 case in 10,000 patients to 1 case in 30,000 [14,15]. This risk increases to approximately 1 case in 100 patients if the woman is being treated for infertility [16].

The patient history, physical examination, and imaging with transvaginal ultrasonography can usually confirm the diagnosis. When ultrasonography does not clearly identify the pregnancy location, the physician must determine whether the pregnancy is intrauterine (either viable or failing) or ectopic. Use of the beta subunit of human chorionic gonadotropin (β-hCG) discriminatory level, the β-hCG value above which an intrauterine pregnancy should be visualized by transvaginal ultrasonography, may be helpful. Failure to visualize an intrauterine pregnancy when β-hCG is above the discriminatory level suggests ectopic pregnancy. In addition to single measurements of β-hCG levels, serial levels can be monitored to detect changes. β-hCG values in approximately 99% of viable intrauterine pregnancies increase by about 50% in 48 hours. The remaining 1% of patients have a slower rate of increase; these patients may have pregnancies that are misdiagnosed as nonviable intrauterine or ectopic. After an ectopic pregnancy has been confirmed, treatment options include medical, surgical, or expectant management. For patients who are medically unstable or experiencing life-threatening hemorrhage, a surgical approach is indicated. For others, management should be based on patient preference after discussion of the risks, benefits, and monitoring requirements of all approaches [17].

Types of ectopic pregnancy

The Fallopian tube is the common site in most cases of tubal EP [18]. About 75–80% of EPs occur in ampullary portion, 10–15% in isthmic portion, and about 5% in the fimbrial end of the Fallopian tube [19]. The tubal EP can be diagnosed by a transvaginal ultrasound scan (TVS) and implies an intact Fallopian tube with a pregnancy that is likely to be growing and visualized as an inhomogeneous mass that might well be a collapsed sac, which contains trophoblastic tissue [20]. Cervical EP is rare and represents only 0.15% of all EPs [21]. It can be defined as the implantation of the blastocyst in the endocervix, blowing the internal orifice. It is associated with a high morbidity and mortality potential. Timely intervention is required to preserve fertility and avoid the need for a hysterectomy [22]. It can be diagnosed by ultrasonography according to the criteria described by Hofmann and Timor-Tritsch. In true EP, Doppler investigations observed characteristic patterns of trophoblast with high flow velocity and low impedance [23]. Ovarian EP is one of the rarest variants, and incidence is estimated to be 0.15–3% of all diagnosed EPs. One of the important

risk factors for ovarian pregnancy is in the use of intrauterine devices (IUDs). IUD is one of the contraceptive methods that prevent intrauterine implantation in 99.5%; if implant occurs with IUD, it is tubal implantation in 95% of cases, and it is very rare in other places such as ovary [24]. One in every nine ectopic pregnancies among intrauterine device (IUD) users is an ovarian pregnancy. The diagnosis is intricate and based on surgical and histopathological observations. Early diagnosis is necessary to avoid more serious complications and emergency invasive procedures. However, Panda et al. noticed that its preoperative diagnosis remains a challenge, and it cannot be diagnosed early [25].

Location

The most common location for an ectopic pregnancy is in the fallopian tube. Other less common sites include the abdomen, ovary, cervix, and the interstitial portion of the fallopian tube. In one study, over 95% occurred in the fallopian tube in the following locations: ampulla (70%), isthmus (12%), fimbria (11.1%), and interstitium/cornua (2.4%). The remaining sites of ectopic pregnancies were ovarian (3.2%), abdominal (1.3%), and cervical (1%). Identifying the location of an ectopic is important for therapy, but may be very challenging. Ultrasound remains the best method to diagnose location. The location of an ectopic pregnancy may alter the approach to treatment and subsequent follow-up. Depending on location, a combination of medical and surgical treatment may need to be employed [26].

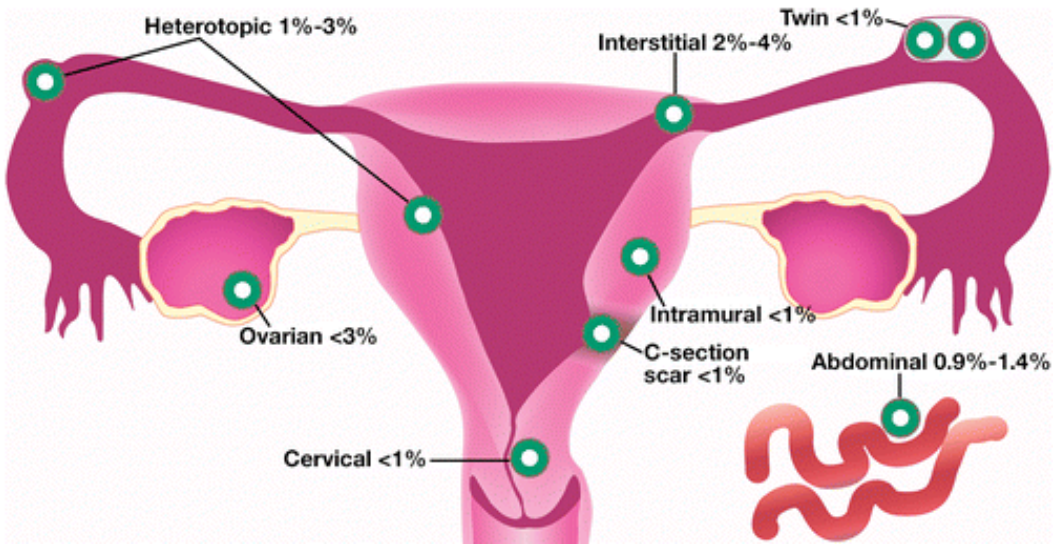

Figure١ : Different sites of ectopic pregnancy

Presentation

The classic triad of abdominal pain, amenorrhea, and vaginal bleeding should always alert the clinician to evaluate for an ectopic pregnancy. Unfortunately The diagnosis may be quite challenging because the presentation of an ectopic pregnancy can vary significantly. In one study, the percentage of patients who presented with ectopic pregnancy with abdominal pain was98.6%, amenorrhea 74.1%, and irregular vaginal bleeding 56.4%. Abdominal tenderness (97.3%) and adnexal tenderness (98%) were the most common physical findings. Barnhart and colleagues reported an increased odds ratio for ectopic pregnancy in patients presenting with first-trimester symptoms if moderate to severe bleeding (odds ratio 1.42; 95% CI, 1.04–1.93) and pain (odds ratio 1.42; 95% CI, 1.06–1.92) were present [27].

Symptoms of acute and chronic ectopic pregnancy

The symptoms of EP could be acute, like short period of amenorrhea (5–8 weeks), intermittent scanty vaginal bleeding of dark blood (spotting) and abdominal and shoulder-tip pain. The chronic symptoms including those recovered from previous attack of acute pain, amenorrhea, dull aching lower abdominal pain, vaginal bleeding, dysuria, frequency of micturition or retention of urine and rectal tenesmus. Acute EP is a common clinical problem, diagnosed by a combination of clinical, sonographic and laboratory findings. Chronic

EP is a more usual situation and is thought to result from minor repeated ruptures of tubal pregnancy that develop into a hematocele containing blood, clots and trophoblastic tissue that can be active or inactive [28]. The hematocele is surrounded by adhesion and induces an inflammatory response. Other findings reported that women who presented acutely or chronically had similar presenting medical and surgical histories. In particular, the two groups did not differ in terms of the putative risk factors for EP; they had similar history of pelvic surgeries, tubal ligation, sexually transmitted diseases or pelvic infection [29].

Risk Factors

Transport of the fertilized ovum through the fallopian tube is controlled by a combination of smooth muscle contractions and ciliary beating. Conditions that damage the integrity of the tube and impair these functions are risk factors for ectopic pregnancy **(Table 1)** [30, 31].

Table 1. Risk Factors for Ectopic Pregnancy

Risk factor	*Odds ratio*	*95% confidence interval*
Previous tubal surgery[5]	21.0	9.3 to 47
Sterilization[6]	9.3	4.9 to 18
Previous ectopic pregnancy[5]	8.3	6.0 to 11.5
In utero exposure to diethylstilbestrol[5]	5.6	2.4 to 13
Current use of intrauterine device[7]*	5.0	1.1 to 2.8
History of pelvic inflammatory disease[8]	3.4	2.4 to 5.0
Infertility for two years or longer[8]	2.7	1.8 to 4.2
Advanced maternal age[8]		
≥ 40 years	2.9	1.4 to 6.1
35 to 39 years	1.4	1.0 to 2.0
Smoking[8]		
≥ 20 cigarettes per day	3.9	2.6 to 5.9
10 to 19 cigarettes per day	3.1	2.2 to 4.3
1 to 9 cigarettes per day	1.7	1.2 to 2.4
Past smoker	1.5	1.1 to 2.0

Diagnosis of ectopic pregnancy

In the past, EP was diagnosed on clinical symptoms such as vaginal bleeding and lower abdominal pain, but it imposed constraints on early detection [32]. It is worthy to mention that the initial diagnosis of first-trimester hemorrhage presents a crucial challenge. Recently, detection of EP is possible through serum beta-human chorionic gonadotropin (β-hCG) and progesterone levels as well as vaginal ultrasonography techniques [33, 34]. Blood test alone cannot tell where the pregnancy is developing, but it can help doctors monitor patients who might have a growing EP.

Serum β-hCG concentration

In early pregnancy, the level of β-hCG should double roughly every 48 hours. After a miscarriage, it drops quite quickly. If it rises slowly, or stays around the same level over this time, this can mean a pregnancy is failing or EP. A single serum measurement of β-hCG concentration may not show the location of gestational sac [35,36]. Demonstration of normal doubling of serum levels over 48 hours supports a diagnosis of fetal viability but does not rule out EP. Failing levels on raising the level of β-hCG concentration to reach 50% confirm nonviability suggesting occurrence of EP [37]. Moreover, it was noticed that β-hCG cutoff values on day 12 after embryo transfer are useful to predict the final type of clinical pregnancy. Cutoff values were found at 91 IU/L for EP (sensitivity 82.7%, specificity 71.1%) [38]. In a study of 287 patients with pain or bleeding, the minimum rise in β-hCG for a viable IUP was 24% at 24 hours and 53% at 48 hours [39]. Seeber et al. [40] produced data with a 99% CI that suggested a more conservative minimum rise of 35% over 2 days.

In current practice, most units use a minimum value of between 50 and 66% for the acceptable 48-hour increase in βhCG in a normal pregnancy [41].

Serum progesterone concentration

Patients with normal intrauterine pregnancies had serum progesterone levels greater than 20 ng/ml (mean = 30.9 ng/ml), while all patients with ectopic pregnancies had progesterone levels less than 15 ng/ml (mean = 5.7 ng/ml) [42]. In contrast to β-hCG concentrations, serum progesterone levels are stable for first 8–10 weeks of gestation. [43] demonstrated that patients that have serum progesterone concentration below 10 ng/ml (31.8 nmol/L) and β-hCG levels below 1500 mIU/L are more likely to have a spontaneous EP. Similarly, [44] reported that the mean progesterone for normal pregnancies was 32.8- 4.25 ng/ml (n = 49), for ectopic pregnancies 7.8 -0.79 ng/ml (n = 51), and pregnancies that spontaneously aborted 8.1 - 0.91 ng/ml (n = 74). This test may be useful in selected patients when the diagnosis is unsure after β-hCG and transvaginal ultrasound have been performed.

Serum vascular endothelial growth factor (VEGF) concentration

Vascular endothelial growth factor (VEGF) is a potent angiogenic factor that acts as a modulator of vascular growth, remodeling and permeability in the endometrium, decidua and trophoblast, as well as during vascular development in the embryo, all of which are crucial processes related to the normal implantation and placentation [45]. Serum values of VEGF were increased in EP. Daponte et al. [54] described greater serum VEGF concentrations in women with EP (227.2 pg/ml) than with abnormal intrauterine pregnancy (107.2 pg/ml). They subsequently concluded that VEGF serum concentrations might be a good marker for EP and suggested 174 pg/ml as the cutoff value for EP diagnosis.

Serum creatine kinase (CK) concentration

Obvious evidence suggests elevated creatine kinase (CK) as a tool for diagnosis of EP. The trophoblast usually invades the muscle layer and maternal blood vessels are eroded, allowing muscle cell products such as CK to enter the circulation [46]. Consequently, increased serum CK activity is normal during EP. [47] carried out a study involving 40 women, and the total serum CK activity was found to be greater in the EP group compared to the controls, suggesting that this test might be an indicator for EP. Similarly [48] studied 40 women with EP cases and concluded that women with EP had significantly greater CK activity as compared to the women with intrauterine abortive pregnancies and controls, suggesting that CK could be a crucial predictive tool for EP.

Transvaginal sonography

Transvaginal sonography (TVS) is the imaging modality of choice for the diagnosis of EP of sensitivity less than 90%. Diagnosis is based on the visualization of an ectopic mass rather than the inability to visualize an intrauterine pregnancy. A diagnosis of EP should be made on the basis of the positive visualization of an extrauterine pregnancy. If neither extrauterine nor intrauterine pregnancy is visualized on TVS, the woman should be classified as having a “pregnancy of unknown location” and then followed up until the final pregnancy outcome is known [49]. A number of findings may suggest the presence of EP, but are not diagnostic. There may be anechoic or echogenic-free fluid within the pouch of Douglas. Echogenic fluid within the pouch of Douglas may suggest hemoperitoneum secondary to a ruptured EP or tubal miscarriage, but it may also be noticed with the rupture of hemorrhagic ovarian cyst (Figure 2). The precise relationship between the appearance of tubal EP on TVS, the size of the mass and serum hCG levels is uncertain. In their study on 120 women with EP, Cacciatore [50] found that hCG levels correlated with the size of ectopic gestational sacs but not with the diameter of inhomogeneous adnexal mass. They also found that in women with ectopic gestational sacs, the majority of serum hCG levels were high and

increasing, while in those with an inhomogeneous mass, the serum hCG levels were significantly lower and most were decreasing.

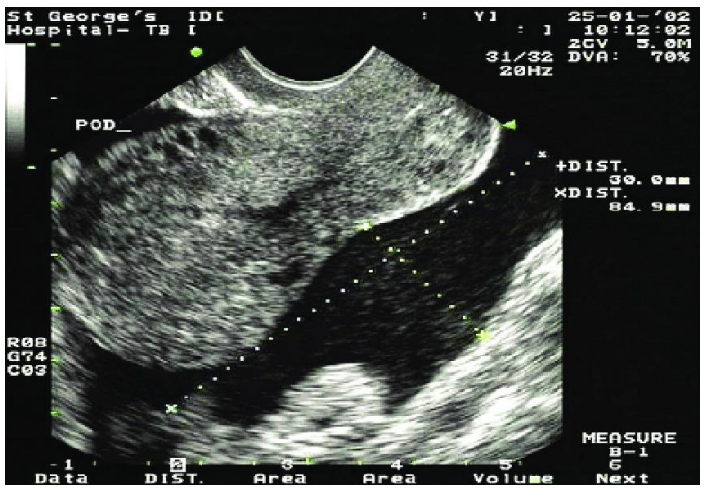

Figure٢ TVS image of echogenic fluid in the pouch of Douglas, suggestive of hemoperitoneum following rupture of EP

Recommendations

From the above sources we can recommend:

1-In general, women cannot prevent EP, but they can prevent serious complications with early diagnosis and treatment. If they have one or more risk factors for EP, women and their physician can closely monitor the first weeks of a pregnancy. Reducing the risk of sexually transmitted infections (STIs), such as gonorrhea or chlamydia, may increase a woman's chances of having an ectopic pregnancy. If a woman reduces her risk of contracting one of these diseases, she may reduce her risk of having an ectopic pregnancy as well .

2- Moreover, if women do get STIs, it is important to get treatment right away. The sooner those women are treated, the less likely they will develop inflammation that may damage the reproductive system and increase the risk of developing EP. Common symptoms of STIs include abdominal pain, painful urination, vaginal discharge, abnormal vaginal bleeding, vaginal odor and pain during sex. On the other hand, smoking may increase the risk of having EP. Women should quit smoking before trying to conceive in order to reduce the risk .

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