An Overview of Ectopic Pregnancy Diagnosis and Management Approach

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ABSTRACT

Background: Ectopic pregnancy (EP) is a result of blastocyst implantation away from the endometrium of the uterine cavity. The preferred site of EP is the fallopian tubes, however other locations can succumb to it as well. The presentation of EP patients can be quite silent or as extreme hemodynamic instability sequelae to the rupture. The etiology of the disease is extensive, whereas the risk factors can be documented and anticipated to some extent. Treatment options include medical (methotrexate), surgery, or expectant management in milder cases. **Objectives:** We aimed to review the literature reviewing the etiology of ectopic pregnancy, risk factors, clinical presentation, diagnosis, and management of this disease. **Methodology:** PubMed database was used for article selection, gathered papers underwent a thorough review. **Conclusion:** Accurate early diagnosis of ectopic pregnancy is the key to keep the intervention as minimum as possible while maximizing the outcomes. Transvaginal ultrasonography provides the maximum sensitivity and specificity, in detecting the ectopic pregnancy, when the β-hCG surpasses the discriminatory zone. Considering the patient's specific medical history results in a better overall management plan, treatment choice, and follow up.

Key Words: *Ectopic, Pregnancy, Diagnosis, Differential, Female, Diagnosis, Risk Factors, Diagnosis*

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INTRODUCTION

Ectopic pregnancy (EP) can be defined as any blastocyst implantation not confined within the endometrium of the uterine cavity [1, 2]. While the vast majority of ectopic pregnancies are localized in the fallopian tubes, nearly 10% tend to target extra-tubal sites such as the ovary, abdomen, a scar from a cesarean section, or even as rare as the cervix. [3, 4] The incidence of EP varies between countries, Unites States had recorded 12.3 ectopic pregnancies per 1000 live births between 2006-2013, whereas Saudi Arabia's incidence was as low as 5 ectopic pregnancies per 1000 live births in the period between 1980—2013. [5, 6] The discrepancies between regions can be explained by the multifactorial model where the risk factors play the leading role along with accurate diagnosis and reporting. The aim of this paper is to shed light on the ongoing issue by addressing its etiology, risk factors, clinical presentation, diagnosis, and management.

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METHODOLOGY

PubMed database was used for the selection process of relevant articles, and the following keys used in the mesh ((“Ectopic pregnancy"[Mesh]) AND (“Diagnosis"[Mesh] OR "Management"[Mesh] OR "Risk factors"[Mesh])). For the inclusion criteria, the articles were selected based on including one of the following: ectopic pregnancy or ectopic pregnancy risk factors, evaluation, management, and diagnosis. Exclusion criteria were all other articles that did not meet the criteria by not having any of the inclusion criteria results’ in their topic.

Etiology and Risk Factors

Ectopic pregnancy is a result of fertilized ovum mispositioning, where its natural destination is the uterine cavity, which can be justified by different underlying causes [7]. Mainly anything that hinders the function of the fallopian tube would result in unwanted outcomes. A positive history of pelvic inflammatory disease (PID), infection caused by *chlamydia trachomatis*, is associated with a high risk of developing ectopic pregnancy [8]. That can be explained by the end result of PID in untreated cases; adhesions formation especially in fallopian tubes. [9, 10] Progesterone-only contraceptive methods change the uterine environment and that includes, but not limited to, the motility of fallopian tubes, hence results in migration failure of blastocyst if the pregnancy ever occurred [11]. Moreover, smoking and alcohol intake of ≥10 g/day, shall be considered as risk factors. Both of them work by the same mechanism of action; reducing the tubal motility. [12] The established relationship between assisted reproductive technology (ART) and ectopic pregnancy is better explained by tubal factor infertility rather than the procedures themselves. [13] Apart from all exogenous and endogenous risk factors of developing ectopic pregnancy, once the lady experience it, she would have a higher reoccurring chance of 10%. [14, 15]

Clinical Presentation

The presentation of ectopic pregnancy takes the form of a wide range. A typical presentation would be a triad consists of amenorrhea, bleeding, and pain between the 6th and 10th weeks of gestation. As 30% of the cases exhibit no clinical symptoms, as well as 9% do not experience any symptoms, the luxury of a spot-on diagnosis cannot be always present. The pain usually comes with a severe intensity that is localized unilaterally, nevertheless, it can be mistaken for ovarian corpus luteum cyst. Syncope, shock, and shoulder tip pain are experienced by up to 20% of women, and abdominal tenderness in more than 75%. Bimanual examination, if performed, would be positive for cervical motion tenderness in up to 67% of cases, while palpable adnexal mass would be only present in nearly 50%. [16, 17] The extreme presentation of ruptured ectopic pregnancy takes the form of a hemodynamically unstable woman who should be treated as an emergency case. [18]

Diagnosis

As the clinical presentation may be prone to misinterpretation with other first trimester bleeding causes, the reliance on other modalities is preferred. Transvaginal ultrasonography (TVU) hand by hand with serum human chorionic gonadotrophin (β-hCG) level measurements would accurately diagnose ectopic pregnancy in most of cases. β-hCG acceptable pattern of increase lies between 50 – 66% over 48 hours in viable pregnancies. A failure to maintain such surge is highly indicative of pregnancy abnormalities. [19] On the other hand, a rapid decrease of β-hCG by 21-35% is suggestive of spontaneous abortion or resolving ectopic pregnancy. 71% of ectopic pregnancy patients show either suboptimal increase, that does not match the viable pregnancy, or decrease, that does not match the spontaneous abortion. [20, 21] The minimal level (discriminatory zone) of β-hCG in order the TVU be able to detect the gestational sac is 1500 IU/liter. [22]

Transvaginal ultrasonography can 100% accurately identify healthy intrauterine pregnancy (IUP) at 5.5 weeks of gestation, hence can promptly recognize otherwise. [23] The identification of viable IUB requires visualizing all of the following: a yolk sac or embryo in addition to a gestation sac, as the recognizing of an only gestational sac in the uterus, can be misread of the pseudo sac, a fluid collection produced by decidualized endometrium disintegration. [24-26] The presence of a non-cystic adnexal mass in addition to an empty uterus has a sensitivity of 84–90% and a specificity of 94–99% for ectopic pregnancy diagnosis. [27] Moreover, other literatures suggest even higher sensitivity and specificity of 90.9% and 99.9% respectively. [28] Tubal ectopic pregnancy TVU findings are illustrated in Table 1.

Table 1: Transvaginal ultrasonography findings in a tubal ectopic pregnancy [22]

Indicative signs	
	An adnexal mass, comprising a gestational sac containing a yolk sac, that moves separately from the ovary.
	An adnexal mass, comprising a gestational sac and fetal pole (with or without fetal heartbeat), that moves separately from the ovary.
Probable signs	
	An adnexal mass, comprising an empty gestational (bagel sign), that moves separately from the ovary.
	A complex-inhomogeneous adnexal mass, that moves separately from the ovary.
Possible signs	
	An empty uterus.

	A fluid collection within the uterine cavity, pseudo sac.

Management

A systemic scheme was developed to determine the outlines of ectopic pregnancy management. With three major options: expectant, medical (systematic methotrexate), or surgical interventions. Consequently, dealing with every case as a standalone situation by considering the patient's special circumstances is highly suggested. Heterotopic pregnancy, two embryos one located in the uterine cavity while the other is ectopic, has been more prevalent due to assisted reproductive techniques; 1 in 3900 compared to 1 in 30000 of spontaneous conception. [29] This special condition necessitates a different approach where avoidance of methotrexate is essential. All absolute contraindications of methotrexate are enlisted in Box 1. The patient's previous history of ectopic pregnancy also shall be put into consideration as the subsequent failure of medical treatment is evident. [30] Table 2 summarizes all of the three options' indications. Following up the efficacy of treatment rely on multiple readings of β-hCG, expectant plan would include three initial readings on the 2nd, 4th, and 7th day since the original reading, the anticipated result is a decrease of 15% or greater in each sitting. Medical/methotrexate plan would compose of 2 initial readings on 4th and 7th day while for surgery only one initial reading is recommended on 7th day post-surgical. Except for the initial readings, all the three plans share the same pathway of follow up after the first week as once weekly until β-hCG drop below 20 IU/L. [22]

Table 2: Indications of ectopic pregnancy management. [22]

Expectant Management*	**Methotrexate[1]**	**Methotrexate or Surgery[1]**	**Surgery[2]**
Clinically stable and pain-free.	No significant pain	No significant pain	Ectopic pregnancy and significant pain
Tubal ectopic pregnancy measuring < 35 mm + no visible heartbeat on TVU.	An unruptured tubal ectopic pregnancy with measuring < 35 mm + no visible heartbeat on TVU.	An unruptured tubal ectopic pregnancy with measuring < 35 mm + no visible heartbeat on TVU.	Tubal ectopic pregnancy measuring ≥ 35 mm.
Serum β-hCG levels of ≤1,000 IU/L.[3]	Serum β-hCG levels of < 1,500 IU/liter.	Serum β-hCG levels between 1500 – 5000 IU/L.	Ectopic pregnancy with a fetal heartbeat visible on a TVU.
	No viable intrauterine pregnancy.	No viable intrauterine pregnancy.	An ectopic pregnancy and serum β-hCG levels of ≥ 5,000 IU/liter,
Able to return for follow-up.	Able to return for follow-up.	Able to return for follow-up.	

Box 1.

Absolute Contraindications to Methotrexate

- Intrauterine pregnancy
- Evidence of immunodeficiency
- Moderate to severe anemia, leukopenia, or thrombocytopenia
- Sensitivity to methotrexate
- Active pulmonary disease
- Active peptic ulcer disease
- Clinically important hepatic or renal dysfunction
- Breastfeeding
- Ruptured ectopic pregnancy
- Hemodynamically unstable patient
- Inability to participate in follow-up

CONCLUSION

In conclusion, ectopic pregnancy should be considered on the top of differential diagnoses for every woman of child-bearing age who presents with the first trimester bleeding.

[1] All criterion should be fulfilled
[2] Any criterion is sufficient to indicate surgery
[3] If the patient fulfilled all other criterion consider expectant management if have serum β-hCG levels between 1000 – 1500 IU/L

As the diagnosis can be tricky on some occasions, a thorough history taking, proper examination with adjuvant laboratory and ultrasound testing are recommended. Clinical judgment with evidence that may determine the suitable plan of managing the patient would be followed; with options ranging from expectant, medical, or surgical interventions. Finally, and most importantly, patient autonomy must be kept at the highest priority when considering all the options.

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