Review Article

Management Options of Tubal Ectopic Pregnancy and Recent Advances

Arzoo S[1], Akter MS[2], Begum SA[3], Abedin F[4], Afroz S[5], Ammar MR[6], Khan SI[7]

Abstract:
Ectopic pregnancy occurs in approximately 1.5-2% of all pregnancies. It presents a major health problem for women of child-bearing age. The morbidity and mortality associated with ectopic pregnancy has decreased dramatically, mainly because of earlier diagnosis with transvaginal ultrasound and b-hCG levels and subsequent treatment before rupture. Treatment options include surgical, medical and expectant management. Surgery, salpingectomy or salpingotomy is performed laparoscopically or by open surgery. The most commonly used drug for the medical treatment of ectopic pregnancies is methotrexate. This can be administered either systemically or locally or both. It was concluded that review data reflect a decrease in surgical treatment and not an actual decline in ectopic pregnancy occurrence so that further new avenues are needed to explore early detection of the ectopic pregnancy.

Keywords: Ectopic pregnancy (EP), Methotrexate (MTX), Transvaginal sonography (TVS), b-hCG

Introduction:
In the developed world between 1% and 2% of all reported pregnancies are ectopic pregnancies[1]. It seriously compromise women's health and future fertility. Currently ectopic pregnancy diagnosed before the patient condition has deteriorated. Currently diagnosis relies on a combination of ultrasound scanning and serial serum beta-Human chorionic gonadotrophin (b-hCG) measurements[2]. Timely diagnosis allows the clinician to consider the full range of treatment options. This is important for treatment success and retaining optimal fertility for those women desiring future pregnancy. The etiology of ectopic pregnancy remains uncertain although a number of risk factors have been identified. Its diagnosis can be difficult. The risk factors are maternal: pelvic inflammatory disease, *Chlamydia trachomatis* infection, smoking, tubal surgery, induced conception cycle and endometriosis. The annual incidence of ectopic pregnancy has increased over the past 30 year[3]. In the western world 4-10% of pregnancy related deaths have been observed from this issue and now it is growing problem in developing countries also[4].

The treatment options are expectant management, medical treatment or surgery. In surgery laparoscopy is now the accepted approach to perform salpingostomy or salpingectomy. Concerning medical treatment, systemic administration of methotrexate (MTX) has gained acceptance in selected patients. It is given intramuscularly either in a fixed multiple dose regimen alternated with folinic acid or in a single dose regimen without folinic acid. Expectant management has been advocated based on the knowledge that the natural course of many early ectopic pregnancy is a self-limiting process, ultimately resulting in tubal abortion or re-absorption.

Types of Ectopic pregnancy:
The fallopian tube is the dominant site in the majority cases of EP[5]. 75-80% of EPs occur in ampullary portion, 10-15% EPs occur in the isthmic portion and about 5% of EP is in the fimbrial end of the fallopian tube[6]. Cervical EP is rare and represents only 0.15% of all EP[7]. Ovarian EP is one of the rarest variants, and incidence is estimated to be 0.15-3% of all ectopic pregnancy[8]. Caesarean scar EP is another rarest form of EP with an incidence of 1:1800 pregnancies due to increase number of caesarean

[1]Dr. Shabera Arzoo, Assistant Professor, Dept. of Gynaecology & Obstetrics, EMCH.
[2]Dr. Musammat Shamima Akter, Associate Professor, Dept. of Gynaecology & Obstetrics, EMCH.
[3]Dr. Sayeda Anwara Begum, Registrar, Dept. of Gynaecology & Obstetrics, EMCH.
[4]Dr. Forhad Abedin, Resident Physician, CoMCH.
[5]Dr. Saima Afroz, Associate professor, Dept. of Gynaecology & Obstetrics, EMCH.
[6]Dr. Mahbubur Rahman Ammar, Intern Doctor, EMCH.
[7]Dr. Shahriar Inam Khan, Intern Doctor, EMCH.

Address of Correspondence: Dr. Shabera Arzoo, Assistant Professor, Dept. of Gynaecology & Obstetrics, Eastern Medical College and Hospital. Mobile: +8801711385778, Email: shaberaarzoo123@gmail.com

deliveries over the last 30 years[9]. Abdominal EP with 1.3% of cases are diagnosed at a rate of 1:10,000 births and is an extremely rare and serious form of extrauterine gestation[10]. A heterotopic EP is diagnosed when women have any of the above said EP in conjunction with an intrauterine pregnancy. It is also more common (1-3%) in in vitro fertilization and fertility treatments involved super ovulatory drugs[11].

Etiology:

The exact etiology of EP is unknown. However, it is thought that tubal implantation occurs as a result of a combination of arrest of the embryo in the fallopian tube and changes in the tubal micro environment that allow early implantation to occur[12]. Inflammation within the tube, resulting from infection or smoking, may effect embryo-tubal transport by disrupting smooth muscle contractility and ciliary beat activity.

Clinical Presentation:

Patients with an EP commonly present with pain and vaginal bleeding between 6 and 10 weeks of gestation[13]. However, these are common symptoms in early pregnancy, with one third of women experiencing some pain and/or bleeding[14]. Shoulder tip pain, syncope and shock occur in up to 20% of women and abdominal tenderness in more than 75%. Cervical motion tenderness has been reported in up to 67% of cases, and a palpable adnexal mass in about 50%[15]. In 2006-2008 Center for Maternal and Child Enquiries (CMACE) report, four of the six women who died from EP complained of diarrhea, dizziness or vomiting as early symptoms, without triggering any consideration of extrauterine pregnancy by their medical attendants[16]. However, it remains difficult to diagnose an EP from risk factors, history and examination alone.

Diagnosis:

Initial diagnosis of first trimester hemorrhage presents an important challenge[17]. Recently, detection of EP is determined through serum b-hCG levels and vaginal ultrasonography technique[18]. A single serum measurement of the b-hCG concentration may not show the location of gestational sac. 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 b-hCG concentration to reach 50% of confirm non-viability suggesting EP. In contrast with b-hCG concentrations, serum progesterone levels are stable for first 8-10 weeks of gestation. Investigate that sensitivity ranged of progesterone from 45-100% depending on the threshold. Both high (>22 ng/ml) and low (≤5 ng/ml) cutoff points have been assessed for their ability to correctly identify non-viable and ectopic pregnancies; serum progesterone levels ≤5 ng/ml could apparently be used to predict EP with 70-90% sensitivity and 30-90% specificity[19]. If patient have serum progesterone measurement below 10ng/ml and b-hCG level below 1500 mIU/L are more likely to demonstrate spontaneous resolution of EP. Transvaginal ultrasound scan (TVS) is very popular from 1980, and by the mid 1990 sensitivity and specificity were calculated at 84.4 and 98.9% respectively it remains the gold standard for diagnosis of EP[20].

Management:

The treatment option of tubal EP involves surgical treatment by laparotomy or laparoscopy, and medical treatment is usually systemic or through local route, or by expectant treatment.

Expectant Treatment:

Expectant management can be applied in a selected population of the patients with self-limiting EP. According to the most recent guideline, published by the American College of Obstetrician and Gyanecologists, there may be a role for expectant management when the b-hCG level is <200 IU/ml and which is further in decline phase. It should only be offered when TVS remains non-diagnostic and b-hCG levels continue to decline. Successful expectant management occurs in 98% of cases for bhCG <200 IU/L, in 73% for b-hCG <500 IU/L and in 25% for b-hCG <2,000 IU/L. If initial serum b-hCG <1,000IU/L then successful expectant management might occur in most patients (88%) with an EP size of <4 cm, without a fetal heart beat on transvaginal sonography; followed by haemoperitonium <50 ml. Evidence of ectopic resolution on scan is another way to diagnosis. A decrease in EP size on day 7 had a sensitivity of 84% and specificity of 100% in predicting spontaneous resolution[21].

Medical Treatment:

Medical treatment of EP is quite less expensive than surgery[22]. Many different agent have been used to treat EP including systemic and local Methotrexate (MTX), local potassium chloride, hyperosmolar glucose, prostaglandins, danazol, etoposide and mifepristone[23]. Current therapies focus primarily on MTX treatments. Methotrexate (MTX) is a drug that inhibits the action of dihydrofolate reductase, thereby inhibiting DNA synthesis MTX affects actively proliferating tissues such as bone marrow, intestinal mucosa, malignant cells and trophoblastic tissue. MTX is contraindicated when embryonic cardiac motion or the presence of a gestational sac larger than 3.5 cm due to higher rate of treatment failure.

There are three different regimens for giving MTX: single dose, two-dose, and a fixed multidose protocol. The single 50 mg/m^2 dose of MTX is most

commonly used, given as an intramuscular injection. βhCG levels are measured at 4 and 7 days post treatment with an expected 15% decrease from day 4 to day 7. Weekly βhCG levels are then checked until zero. If βhCG levels do not drop appropriately, a second MTX dose or surgical intervention is advised. Multidose regimen for MTX is available (MTX 1.0 mg/kg I/M daily; days 0,2,4 and 6 alternated with folinic acid 0.1 mg/kg orally on days 1,3,5,7)[24]. This treatment more appropriate for patient who present with a large adnexal mass and greater initial b-hCG level (5000 IU).

Surgical Treatment:

Once the mainstay of therapy of EP, surgical treatment is now mainly reserved for patients with contraindication to medical management and for those with evidence of tubal rupture. Despite declining rates of surgical management, surgery remains the most definitive treatment of ectopic pregnancies. A laparoscopic approach is preferable to an open approach in a patient which haemodynamically stable. Laparoscopic procedure are associated with shorter operative times, less intraoperative blood loss, shorter hospital stays and lower analgesia requirements. Laparotomy should be reserved for patients who present with rupture and are in a state of hypovolaemic shock and compromise. Two techniques are described to remove the EP from the fallopian tube—1) Salpingectomy: The pregnancy is removed en bloc with the tube, 2) Salpingostomy: An incision is made on the fallopian tube over the swelling, the EP carefully removed with the forceps or irrigation and the incision should be either closed or let to heal by secondary intention. The success rate of salpingostomy is 92% and failure cases can be managed with MTX. Serial b-hCG measurement should be taken until undetectable to be certain that there is no persistence of trophoblastic tissue. Sometimes a prophylactic dose of MTX is given with salpingostomy[25].

Literature Review:

Gabbur et al. reported that on its retrospective analysis of stable women with small unruptured EP treated with single dose intramuscular MTX concluded that day 4 post treatmen b-hCG levels do not predict successful treatment or need for surgery[26]. Only day 7 b-hCG levels were associated with successful single dose MTX treatment[26].

Barnhart et al. investigated in there meta-analysis of both regimens (single and multi-dose) and concluded that the multi dose regimen was more effective than single dose regimen, with success rate reported as 93% for multi dose regimen and 88% for the single dose regimen[27].

Barnhart et al. was attempted by the challenge to develop an optimum regimen that balances efficacy and safety on the one hand and convenience on the other hand and it first described what is called the “double-dose-protocol”. In a study that included 101 patients, two doses of MTX were administered on days 0 and 4 without measuring b-hCG between doses. The authors reported a success rate of 76% after two doses and 87% after a further two doses[28].

MTX treatment is very successful for small stable ectopic pregnancies. A meta-analysis of non-randomized studies showed success rate of 93% (95% CI 89-96%) for multi dose protocols and 88% (95% CI 89-96%) for single dose therapy[29].

In one randomized controlled trial of laparoscopic surgery, prophylactic MTX lower the rate of persistent ectopic pregnancy 14.5-1.9%. The major benefit was in the shorter duration of post-operative monitoring[30].

Several studies done to see the subsequent pregnancies after ectopic pregnancy. Studies suggest that around 60% of women affected by an EP go on to have a viable IUP. This figure includes those who do not plant to have another pregnancy and so the proportion will be higher if further pregnancy is planned. There is thought to be a 5-20% risk of a recurrence of EP with one previous EP and a risk of 32% or more following more than one previous ectopic. However the risk is reduced after each subsequent IUP.

Recent Advance:

Previously ectopic pregnancy was diagnosed on clinical symptom, TVS and by measuring b-hCG, but now-a-days some new advancement arrived for diagnostic purpose.

VEGF is a potent angiogenic factor that acts as a vascular growth, remodeling and permeability in the endomertium, decidua and trophoblast. Daponte et al. described higher serum VEGF concentrations in women with EP (medium 227.2 pg/ml) than with abnormal intrauterine pregnancy (median 107.2 pg/ml) (p<0.001) and it concluded that VEGF serum concentrations might be a useful marker for-EP and suggested 174 pg/ml as the cut-off value for EP diagnosis[31].

Existing evidence suggests elevated creatine kinase (CK) as a tool for diagnosis of EP. The trophoblast usually invades the muscular layer and maternal blood vessels are eroded, allowing muscle cell products such a CK to enter the circulation; therefore, increased serum CK levels are normal during EP[32].

Conclusion:
EP in developing countries is a serious threat, just because of poor medical facilities so that a significant morbidity rate and the potential for maternal death generally are seen. Management is dictated by the clinical presentation, serum b-hCG levels and TVS findings. Expert consultation with radiologists and gynecologists are recommended whenever EP is suspected. The use of MTX for treatment of early unruptured EP reported to be safe and effective. Surgical treatment is appropriate for women who are haemodynamically unstable or unlikely to be complained with post treatment monitoring and those who do not have immediate access to medical care. The preferred method of surgical treatment of EP today is diagnostic laparoscopy with salpingostomy and tubal conservation followed by prophylactic dose of MTX. Existing evidence suggests elevated vascular endothelial growth factor (VEGF) and creatine kinase (CK) as a tool for diagnosis of EP. Further new avenues are needed to explore less side effects of medication of EP.

Reference:

1. Goldner TE, Lawson HW, Xia Z, et al. Surveillance for ectopic pregnancy - United States, 1970-1989. MMWR CDC Surveill Summ 1993; 42(6): 73–85.

2. Horne AW, Duncan WC, Critchley HO. The need for serum biomarker development for diagnosing and excluding tubal ectopic pregnancy. Acta Obstet Gynecol Scand 2010; 89: 299–301.

3. Gamzu R, Almog B, Levin Y, Avni A, Jaffa A, Lessing J. Ef cacy of methotrexate treatment in extrauterine pregnancies de ned by stable or increasing human chorionic gonadotropin concentrations. Fertil Steril 2002; 77: 761–5.

4. Wedderburn CJ, Warner P, Graham B, Duncan WC, Critchley HO, Horne AW. Economic evaluation of diagnosing andexcluding ectopic pregnancy. Hum Reprod 2010; 25: 328–33.

5. Condous G. The management of early pregnancy com-plications. Best Pract Res Clin Obstet Gynaecol 2004; 18: 37–57.

6. Ackerman TE, Levi CS, Dashefsky SM. Interstitial line: sonographic nding in interstitial (cornual) ectopic pregnancy. Radiology 1993; 189: 83–7.

7. Webb EM, Green GE, Scoutt LM. Adnexal mass withpelvic pain. Radiol Clin North Am 2004; 42: 329–48.

8. Gon S. Two cases of primary ectopic ovarian pregnancy. OJHAS 2011; 10(1): 26.

9. Rotas MA, Haberman S, Levgur M. Cesarean scar ectopic pregnancies: etiology, diagnosis, and management. Obstet Gynecol 2006; 107: 1373–81.

10. Yildizhan R, Kurdoglu M, Kolusari A, Erten R. Primary omental pregnancy. Saudi Med J 2008; 9: 606–9.

11. Condous G, Okaro E, Bourne T. The conservative man-agement of early pregnancy complications: a review of the lit-erature. Ultrasound Obstet Gynecol 2003; 22: 420–30.

12. Shaw JL, Dey SK, Critchley HO, et al. Current knowledge of the aetiology of human tubal ectopic pregnancy. Hum Reprod Update 2010; 16: 432–44.

13. Walker JJ. Ectopic pregnancy. Clin Obstet Gynecol 2007; 50: 89–99.

14. Chez RA, Moore JG. Diagnostic errors in the management of ectopic pregnancy. Surg Gynecol Obstet. 1963; 117: 589–96.

15. Tay JI, Moore J, Walker JJ. Ectopic pregnancy. BMJ 2000; 320: 916–9.

16. Robson SJ, O'Shea RT. Undiagnosed ectopic pregnancy: a retrospective analysis of 31 'missed' ectopic pregnancies at a teaching hospital. Aust N Z J Obstet Gynaecol 1996; 36:182–5.

17. Daponte A, Pournaras S, Zintzaras E, Kallitsaris A, Lialios G, Maniatis AN. The value of a single combined measure-ment of VEGF, glycodelin, progesterone, PAPP-A, HPL and LIF for differentiating between ectopic and abnormal intra-uterine pregnancy. Hum Reprod 2005; 20: 3163–6.

18. Felemban A, Sammour A, Tulandi T. Serum vascular endothelial growth factor as a possible marker for early ectopicpregnancy. Hum Reprod 2002; 17: 490–2.

19. Dart R, Ramanujam P, Dart L. Progesterone as a predictor of ectopic pregnancy when the ultrasound is indeterminate. AmJ Emerg Med 2002; 20: 575–9.

20. Condous G. Ectopic pregnancy—risk factors and diag-nosis. Aust Fam Physician 2006; 35: 854–7.

21. Rajesh V, Lawrence M. Evidence-based management ofectopic pregnancy. Curr Obstet Gynaecol 2002; 12: 191–9.

22. Rodrigues SP, de Burlet KJ, Hiemstra E, Twijnstra AR, vanZwet EW, Trimbos-Kemper TC, Jansen FW. Ectopicpregnancy: when is expectant management safe? Gynecol Surg 2012; 9: 421–6.

23. van Mello NM, Mol F, Mol BW, Hajenius PJ. Conser-vative management of tubal ectopic pregnancy. Best Pract Res 2009; 23: 509–518.

24. Condous G, Okaro E, Khalid A, Lu C, Van HS, Timmerman D. A prospective valuation of a single-visit strategy tomanage pregnancies of unknown location. Hum Reprod 2005; 20: 1398–1403.

25. Seeber BE, Barnhart KT. Suspected ectopic pregnancy. Obstet Gynecol 2006; 107: 399–413.

26. Gabbur N, Sherer DM, Hellmann M. Do serum beta-human chorionic gonadotropin levels on day 4 following methotrexate treatment of patients with ectopic pregnancy pre-dict successful single-dose therapy? Am J Perinatol 2006; 23:193–6.

27. Barnhart KT, Gosman G, Ashby R, Sammel M. Themedical management of ectopic pregnancy: a meta-analysiscomparing ‘‘single dose’’ and ‘‘multidose’’ regimens. Obstet Gynecol 2003; 101: 778–84.

28. Barnhart K, Hummel AC, Sammel MD, Menon S, Jain J, Cha-khtoura N. Use of ‘‘2-dose’’ regimen of methotrexate totreat ectopic pregnancy. Fertil Steril 2007; 87: 250–6.

29. Horne AW, van den Driesche S, King AE, et al. Endometrial inhibin/activin beta-B subunit expression is related to decidualization and is reduced in tubal ectopic pregnancy. J Clin Endocrinol Metab 2008; 93: 2375–82.

30. Graczykowski JW, Mishell DR. Methotrexate prophy-laxis for persistent ectopic pregnancy after conservative treat-ment by salpingostomy. Obstet Gynecol 1997; 89: 118–22.

31. Daponte A, Pournaras S, Zintzaras E, Kallitsaris A, Lialios G, Maniatis AN. The value of a single combined measure-ment of VEGF, glycodelin, progesterone, PAPP-A, HPL and LIF for differentiating between ectopic and abnormal intra-uterine pregnancy. Hum Reprod 2005; 20: 3163–6.

32. Chandra L, Jain A. Maternal serum creatine kinase as a biochemical marker of tubal pregnancy. Int J Gynaecol Obstet 1995; 49: 21–3.