Ectopic pregnancy: how the diagnostic and therapeutic management has changed

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Nowadays ectopic pregnancy often can be diagnosed before the woman’s condition has deteriorated, which has altered the former clinical picture of a life-threatening disease into a more benign condition. This review describes the historical developments in the diagnostic and therapeutic management of ectopic pregnancy leading up to current clinical practice.

The first attempts to diagnose ectopic pregnancy originate from the beginning of the 20th century. (Fertil Steril 2012;98:1066–73. ©2012 by American Society for Reproductive Medicine.)

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Ectopic pregnancy is an early pregnancy complication in which a fertilized ovum implants outside the uterine cavity. Implantation may occur anywhere along the reproductive tract with the most common implantation site being the fallopian tube. The incidence of ectopic pregnancy is ~1% of pregnant women, and may seriously compromise women’s health and future fertility (1). Currently, ectopic pregnancy can be often diagnosed before the woman’s condition has deteriorated, which has altered the former clinical picture of a life-threatening disease into a more benign condition in frequently asymptomatic women. This paper reviews historic changes in the diagnostic and therapeutic management of ectopic pregnancies from the 19th century until today.

**DIAGNOSIS OF ECTOPIC PREGNANCY**

Towards the end of the 19th century the first diagnostic strategies for ectopic pregnancy were reported, occasionally with successful outcome for the women (2). The diagnosis ectopic pregnancy was based on criteria of gastric and mammary symptoms of pregnancy, cessation of the menstrual cycle, palpation of a tumor next to an enlarged uterus, ballottement in the tumor and purple discoloration of the vagina. At that time the pre-operative diagnosis of a ruptured ectopic pregnancy was false in about 20% of women, while the diagnosis of an unruptured ectopic pregnancy was virtually impossible (3).

**Laparoscopy**

The use of a laparoscope in the diagnostic management of ectopic pregnancies was suggested in 1937 by Hope in the United States (4). The first use of this device was described in 1910 in patients with liver disease and ascites (5). It took the best part of the 20th century before technical development allowed the introduction of laparoscopy in general practice. It is said that the introduction of laparoscopy was hampered by some skeptical opinions on its success and safety being dependent on the experience of the surgeon (6). From the late 1960s onward, laparoscopy was more and more used in the diagnostic management of ectopic pregnancy. This technique solved the dilemma of prolonged clinical observation, the risk of performing an unnecessary laparotomy and resulted in an earlier diagnosis of ectopic pregnancy (7, 8). Laparoscopy remained the most reliable method for diagnosing or excluding ectopic pregnancy until well into the 1980s.

**Ultrasoundography**

Further technological progress led to the introduction of ultrasoundography. Towards the end of the 1960s, ultrasoundography was shown to improve the likelihood of an ectopic pregnancy in
the absence of a visualized intra uterine pregnancy. Ultrasound diagnosis of ectopic pregnancy was hoped to be a non invasive alternative for laparoscopy. The first large cohort study dates from 1980. In this study, performed between 1966 and 1976, women suspected of ectopic pregnancy were scanned with abdominal ultrasound. Data from 342 women showed a moderate reliability with a sensitivity of 81% and specificity of 77% (9). Technical developments enabled the construction of smaller ultrasound transducers compared to the older bulky type of probes, thus meeting the requirements for vaginal insertion. This strongly reduced the distance between the probe and its target area, thereby overcoming the limitations of the physical properties of high frequency ultrasound, i.e. the trade off between better image resolution and diminished tissue penetration. From then on much smaller intruterine and ectopic pregnancies could be visualized with the improved resolution of high frequency transvaginal inserted ultrasound probes (10).

Over the last decades, transvaginal ultrasound has become the first step in the diagnosis of ectopic pregnancy. Between 87% and 99% of tubal pregnancies can now be diagnosed reliably using transvaginal ultrasound. Sensitivity of transvaginal ultrasound as a single test in the diagnosis of ectopic pregnancy is 74% (95% CI: 65.1–81.6) with a specificity of 99.9% (95% CI: 99.8–100) (11). Approximately 60% of ectopic pregnancies are seen as an inhomogeneous mass (“blob sign”) adjacent to the ovary, 20% appear as a hypeechoic ring (bagel sign) and 13% have an obvious gestational sac with a fetal pole, with or without fetal cardiac activity.

Nowadays, the ultrasound diagnosis of an ectopic pregnancy has changed to the positive identification of an adnexal mass rather than on the absence of an intruterine gestational sac. Some experts state that transvaginal ultrasound is becoming the gold standard for diagnosing all types of ectopic pregnancies and that laparoscopy should only be seen as part of a therapeutic intervention (12).

Only a small proportion of women will have a positive pregnancy test and an inconclusive scan, e.g. no intrauterine or ectopic pregnancy or retained products of conception seen at transvaginal ultrasound. These women are categorized as a pregnancy of unknown location (PUL). This is a descriptive term rather than a pathologic entity.

Human Chorionic Gonadotropin

The third important element in the history of diagnosing ectopic pregnancy was measurement of concentrations of human chorionic gonadotropin (hCG). In the 1960s, the production of an immunologic test specific for the beta subunit of hCG in urine led to a clinical application of the pregnancy test. The sensitivity improved from 20,000 IU/L to 1,000 IU/L and the detection time up to five minutes which greatly attributed to its applicability in the diagnosis of early ectopic pregnancy (13). However these immunological urine pregnancy tests were still negative in around 20% of ectopic pregnancies. This was probably due to detection limits and to the fact that ectopic pregnancies have lower hCG levels compared to normal intra uterine pregnancies. The use of quantitative serum hCG concentrations in diagnosing ectopic pregnancies was introduced in 1973 by Kosasa et al. (14). They developed a radioimmunoassay that was capable of detecting serum hCG levels of 15 mIU/mL within 36 hours. Together with the improvement of the sensitivity of the serum hCG test and improvement in detection time up to one hour, the concept of serial hCG measurements was introduced based upon the observation that ectopic pregnancies generally have a slower increase in serum hCG compared to normal intra uterine pregnancies which doubles in two days. In clinically stable women with a non diagnostic ultrasound scan (pregnancy of unknown location) serial hCG measurements taken 48 hours apart showed that if the increase of hCG was less than 66% an ectopic pregnancy was more likely. In this strategy using serial hCG 13% of ectopic pregnancies would not have been diagnosed and 15% of normal intra uterine pregnancies fell into the abnormal increase group (15).

Discriminatory Serum hCG Zone

The importance of combining ultrasound findings with serum hCG concentrations was first recognized by Kadar et al. (16), who introduced the concept of the discriminatory serum hCG zone in 1980. According to this concept, the diagnosis of ectopic pregnancy was most likely whenever an intrauterine pregnancy was not detectable by (abdominal) ultrasound at serum hCG concentrations above a threshold of 6,500 IU/L. However, the clinical value was limited since many women with ectopic pregnancies showed serum hCG concentrations well below 6,500 IU/L. The more sensitive and rapid serum hCG tests and the vaginal ultrasound probes with high resolution brought the optimal serum hCG cut-off value of the discriminatory zone concept down to between 1,000 and 2,000 IU/L for women with inconclusive vaginal ultrasonographic findings. From a prospective diagnostic study including 354 women with suspected ectopic pregnancy and inconclusive transvaginal ultrasound findings the diagnosis ectopic pregnancy could be excluded with a specificity of 86% for a cut off serum hCG below 1,000 IU/L and a specificity of 98% using a serum hCG cut off below 2,000 IU/L. The sensitivity using this discriminatory zone principle was rather low around 40% (17).

Serum Progesterone

Serum progesterone levels have long been considered as a diagnostic tool in conjunction with serum hCG concentrations (18). A metaanalysis of 26 studies concluded that a single serum progesterone measurement can identify women at risk for ectopic pregnancy who need further evaluation, but that its discriminative capacity is insufficient to diagnose ectopic pregnancy with certainty (19). A more recent meta-analysis was published focusing on the accuracy of a single progesterone measurement in early pregnancy to discriminate between a viable and non-viable pregnancy. The results of 26 studies showed that a single progesterone measurement is useful in predicting non-viable pregnancies in women with abdominal pain or vaginal bleeding when ultrasound is inconclusive. A low level of progesterone (<3.2 ng/ml to 6 ng/ml) in these women rules out a viable pregnancy in 99%. However, the
test cannot distinguish women with an ectopic pregnancy from those with an early normal pregnancy or a miscarriage and should not be used for this purpose (20).

**International Consensus Statement**

In the diagnosis of ectopic pregnancy comparative studies are not available and there is a large clinical heterogeneity in populations studied and final pregnancy outcome definitions. To improve the objective comparison of research outcomes in the diagnosis of ectopic pregnancy and to reduce clinical heterogeneity, a recent international consensus statement proposes uniformity in definitions of population, target disease and final outcome of women with a PUL (21). Adopting this consensus statement will hopefully lead to improved clinical care.

**Diagnostic Algorithms**

In women with PUL various diagnostic algorithms have become available integrating history, clinical examination, repeated transvaginal ultrasound, (repeated) serum hCG concentrations, serum progesterone concentration, and histology of an uterine curettage to predict the final location and viability of the early pregnancy (22–26). As an example, two diagnostic algorithms for clinical practice recommended by the national guidelines in the United States and the United Kingdom are shown in Figure 1 (27, 28). To date no prospective comparative studies have been performed to determine the best strategy. Serial hCG measurements have become a standard of care. The role of uterine curettage is still under debate.

**Spontaneous Resolving Ectopic Pregnancies**

Due to the non-invasive diagnostic approach and close follow up of women with suspected ectopic pregnancy, more insight was obtained on the pathophysiology of ectopic pregnancies. A subgroup of ectopic pregnancies was identified being self-limiting and with spontaneous resolution without the need for an intervention. This new diagnostic category of women was defined as having trophoblast in regression (TIR) (29). These women with a positive pregnancy test but inconclusive transvaginal ultrasound findings had spontaneously declining serum hCG concentrations to undetectable levels during follow up without the exact location of the pregnancy ever having been clarified.

**Pregnancy of Unknown Location**

In 1999, the currently used term PUL was introduced for women with a positive pregnancy test and an inconclusive transvaginal ultrasound (30). From cohort studies it became apparent that PUL occurs in 7 to 30% of women presenting with complaints in early pregnancy (31). The majority of women with PUL (50%–70%) have a spontaneously resolving pregnancy with serum hCG levels declining to undetectable levels, the so-called failed PUL. Such a pregnancy can either be a failed intrauterine pregnancy or a spontaneously resolved ectopic pregnancy, as the location of the pregnancy remains undetermined. In some women the pregnancy duration is simply too short to allow its visualization on the initial scan. Follow-up scans in combination with rising serum hCG concentrations, will eventually demonstrate an intrauterine pregnancy. In 7%–20% of women with a PUL, an ectopic pregnancy is eventually diagnosed and these women are eligible for treatment. A minority of women will have a persisting PUL, defined as an inconclusive transvaginal scan in combination with a rise or plateau in serial serum hCG concentrations. Women with persisting PUL are usually regarded as cases of ectopic pregnancy. A recent systematic review and meta-analysis, which analyzed the diagnostic accuracy of various serum hCG strategies in women with PUL, concluded that those diagnostic strategies using serum hCG ratios, either alone or in logistic regression models, had the best performance in diagnosing ectopic pregnancy (32).

**Current Clinical Practice**

As a result of the more sensitive diagnostic tools, together with an increased awareness among both the public and health care providers which resulted from the world-wide epidemic of ectopic pregnancies during 1980s the former clinical picture of ectopic pregnancy as a life-threatening disease has changed into a more benign condition in women who are frequently asymptomatic or show a mild clinical picture dominated by vaginal bleeding and/or slight abdominal discomfort (33, 34). Transvaginal ultrasound is the first diagnostic step in women with a positive urine pregnancy test. In case of an inconclusive ultrasound, (serial) serum hCG measurement with or without progesterone measurement in a regular follow up scheme has allowed to distinguish early intra-uterine from ectopic pregnancies.

For clinical practice, algorithms are available based on diagnostic strategies using serum hCG ratios within 48 hours, either alone or in logistic regression models. The specific serum hCG cut off levels used for local protocols should be based on the capacity of correctly identifying ectopic pregnancies by transvaginal ultrasound, mostly depending on the expertise of the ultrasonographer. It should be noted that when using diagnostic algorithms false positive diagnoses of ectopic pregnancy may occur in case of a miscarriage, molar pregnancies, multiple pregnancies due to higher serum hCG concentrations and in case of heterotopic pregnancies due to false reassurance by the ultrasound result.

Diagnostic laparoscopy is now reserved for situations that do not allow any delay, e.g. in women with a positive urine pregnancy test, rebound tenderness and/or with hemodynamic instability thus necessitating direct (laparoscopic) operative intervention.

**TREATMENT OF ECTOPIC PREGNANCY**

**Laparotomy**

In 1849, W.W. Harbert of Louisville was the first to perform surgery early enough to stop fatal bleeding (35). Robert Lawson Tait in London, after having performed autopsies on several women, recognized that appropriate dissection and ligation of bleeding vessels would be effective in the treatment of ectopic pregnancy. He successfully performed
(A) Diagnostic algorithm for ectopic pregnancy derived from ACOG Clinical Management Guideline, No. 94, June 2008 (27). (B) Diagnostic algorithm for early pregnancy loss derived from RCOG Green Top Guideline, No. 25, October 2006 (28). D&C = dilation and curettage. *Discriminatory Zone cutoff of 1,500–2,500 IU/L should be set by each institution based on that hospital’s success in correctly identifying ectopic pregnancies, based mostly on equipment used and expertise of the sonographers. **Abnormal rise or fall if the hCG does not fall 21%–35% in 2 days (depending on the initial value). ***Normal fall is a rapid decline in hCG value, consistent with a miscarriage that may resolve spontaneously.

a laparotomy to ligate the broad ligament and removed a ruptured tube. By 1885, Tait had accumulated a relatively large number of successful cases of laparotomic salpingectomies (36, 37). The diagnosis of an ectopic pregnancy was difficult, but if recognized, the procedure of choice was a laparotomy before rupture. In 1913 it is stated in Hartmann’s textbook that: “every ectopic when diagnosed should be operated upon”. Expectant management led in 86% of women to death, but surgery saved 85% of women (38).

In the first decades of the 20th century the introduction of asepsis, anesthesia, antibiotics and blood transfusions saved the lives of many women with ectopic pregnancy. Still, the maternal mortality rate in the United States ranged from 200 to 400 per 10,000 cases of ectopic pregnancies (39). Salpingectomy via laparotomy remained the standard procedure for decades.

Salpingotomy
In 1920 Beckwith Whitehouse from the United Kingdom raised the question as to whether sacrificing the tube on all occasions was justified. He performed a salpingotomy first in fresh specimens after salpingectomy. Thereafter he introduced the method on five occasions and reported these to be successful in 1921. He stated, “Time, of course, must prove whether the adoption of such a procedure is followed by other complications such as the recurrence of the accident, the development of hydrosalpinx, or, perchance the incidence of a tubal chorion-epithelioma” (40). He did not mention future fertility. The first instance of conservative surgical treatment, i.e., salpingotomy, which appeared in the English literature was published in 1953 (41). The argument in favor of conservative surgery was preservation of the childbearing function confirmed by subsequent successful pregnancies. The downside of the conservative surgical approach was persistent ectopic pregnancy, i.e., the continued proliferation of the trophoblast after the conservative surgical treatment for which at that time additional surgical treatment (salpingectomy) was necessary (10). To date, methotrexate is available as a non surgical treatment alternative for persistent trophoblast. Combined results of two randomized studies showed that salpingotomy alone was significantly less successful than when combined with a prophylactic single dose of systemic methotrexate to prevent persistent trophoblast (42). However to prevent one case of persistent trophoblast the number needed to treat was 10. Serum hCG monitoring post-operatively seems a better option for detection and treatment of persistent trophoblast after salpingotomy.

Laparoscopic Treatment
During the 1970s and 1980s laparotomy was gradually replaced by operative laparoscopic options. Shapiro and Adler (43) reported laparoscopic salpingectomy using electrocoagulation followed by excision for an ectopic pregnancy in 1973. Salpingotomy by laparoscopy was first reported using multiple punctures in 1980 (44). Linear salpingotomy with a cutting current was described by DeCherney et al. in 1981 (45). To date, if skills and equipment are available, laparoscopic surgery is the preferred treatment option. It is feasible in nearly all patients, safe, and less costly than open surgery because of reduced morbidity and shorter hospital stay (42). Whether laparoscopic treatment should be performed conservatively (salpingotomy) or radically (salpingectomy) in women wishing to preserve their reproductive capacity, has long been subject of debate. The result of a randomized controlled trial on salpingotomy versus salpingectomy in 454 women with a tubal pregnancy without contra lateral tubal pathology showed that salpingotomy does not improve time to spontaneous ongoing pregnancy and leads more often to persistent trophoblast (46). In women with desire for future pregnancy and with a tubal ectopic pregnancy in a solitary tube or in the presence of contra lateral tubal pathology, salpingotomy is the treatment of choice (47, 48). In case salpingectomy is performed due to a failed salpingotomy or other surgical difficulties, IVF is the appropriate treatment option for the loss of fertility.

Medical Treatment
The most commonly and successfully used drug in clinical practice by far is methotrexate, a folic acid antagonist which interferes with DNA synthesis and cell proliferation. It affects highly proliferative tissues such as trophoblast. Methotrexate has a strong dose-related potential for toxicity. Side effects include stomatitis, conjunctivitis, gastritis-enteritis, impaired liver function, bone marrow depression, and photosensitivity. In 1985 Chotiner was the first in English literature to describe a patient with tubal pregnancy treated successfully with systemic methotrexate (49).

When methotrexate is administered systemically, it can either be given in a fixed multiple dose intramuscular regimen or in a variable dose intramuscular regimen. The fixed multiple dose regimen is derived from the treatment of gestational trophoblastic disease and is combined with folinic acid (citrovorum/leucovorin rescue) to reduce chemotherapy toxicity (50, 51). In 1991, Stovall et al. individualized the methotrexate dosage to improve patient compliance, to minimize side effects, and to reduce overall costs, which ultimately led to a single dose regimen of 50 mg/m2 body surface area given intramuscularly without folinic acid (52–54). Treatment with methotrexate in a multiple dose regimen has been proven to be effective compared to laparoscopic salpingotomy in women with serum hCG levels below 3,000 IU/L (42). Furthermore, it was shown that methotrexate is safe with no adverse effects reported on reproductive outcome (55). Single dose methotrexate, if necessary with additional methotrexate injections, has been shown to be cost effective compared to laparoscopic salpingotomy in women with hCG <1,500 IU/L (56). Data on the fixed multiple dose methotrexate regimen versus a single dose regimen is limited. One randomized clinical trial has shown that treatment effect of a multiple dose methotrexate regimen (90%) was not more effective than a single dose (81%) for the treatment of unruptured tubal ectopic pregnancy, with mean hCG levels ~2,000 IU/L. The multiple dose regimen caused more side-effects, but the
time for serum hCG concentrations to fall below 5 mU/mL was shorter (18 versus 22 days) [57].

Criteria for treatment success with methotrexate are the size of the ectopic pregnancy, absence of fetal cardiac activity on transvaginal ultrasonography, and low hCG concentrations [58]. Close serum hCG monitoring is mandatory to detect treatment failure and inadequately declining serum hCG concentrations after treatment with methotrexate [59–61].

Expectant Management

In 1955, Lund [62] was the first to practice expectant management in patients suspected of having an ectopic pregnancy who were not distressed on admission. In 1982, Mashiach et al. [63] advocated expectant management based on the knowledge that the natural course of many early ectopic pregnancies is self-limiting, ultimately resulting in tubal abortion or reabsorption. Since the work of these pioneers, only a few studies have been published describing expectant management in selected patients with small ectopic pregnancies without fetal cardiac activity, an upper limit for serum hCG concentration that continues to decline and/or a low serum progesterone concentration [64, 65]. A placebo-controlled randomized trial has been published evaluating expectant management compared to oral methotrexate (2.5mg daily for five days) [66]. The surgical intervention rate amongst the 60 women randomized was 23% in each group. However, the mean serum hCG concentrations in both treatment groups were extremely low (211 IU/L in the placebo group and 395 IU/L in the treatment group), and the dose of methotrexate used unlikely to have had any treatment effect. A randomized controlled trial comparing systemic methotrexate with expectant management in 73 women with an ectopic pregnancy or a PUL and low and plateauing serum hCG concentrations showed no difference in treatment success (uneventful decline of serum hCG). Sixty percent of women after expectant management compared to 76% in the methotrexate group (RR 1.3 95%CI 0.9 to 1.8) had an uneventful clinical course with steadily declining serum hCG levels without any intervention. The surgical intervention rate was 2% in the methotrexate group and 13% in the expectant management group (RR 0.2 95%CI 0.02 to 1.7), all after experiencing abdominal pain within the first week of follow up. The mean serum hCG concentration was 535 IU/L in the methotrexate group and 708 IU/L in the expectant group. This may indicate that methotrexate, a potentially harmful drug, can be withheld in this subgroup of women [67]. Currently, two randomized controlled trials are still ongoing comparing expectant management with single dose methotrexate [68, 69]. In the near future, meta-analysis of the results of these trials may provide guidance on the present management dilemmas in women with ectopic pregnancy with low and plateauing serum hCG concentrations.

Although many ectopic pregnancies may resolve spontaneously, the risk of morbidity remains in those patients who fail to resolve, and careful consideration is thus warranted when offering expectant management.

SUMMARY

From this historical overview we learn that the first attempts to diagnose ectopic pregnancy originate from the beginning of the 20th century. The first diagnostic tool was surgery—initially laparotomy and later laparoscopy. With the entry of laparoscopy into mainstream gynecology decades later, it became easier to make the diagnosis in a timelier and less morbid manner. It has taken up to the 1970s until a nonsurgical diagnostic strategy for ectopic pregnancies was developed using a combination of high resolution ultrasonography and sensitive serum hCG assays. Further development of these diagnostic methods has led to an expansion of the diagnosis ectopic pregnancy into multiple categories related to their appearance on ultrasonography (viable ectopic pregnancy, ectopic mass and pregnancy of unknown location).

Treatment options in the beginning of the 20th century were installed mostly in symptomatic women and comprised salpingectomy by laparotomy. From the seventies, laparoscopy was more generally used in the surgical treatment of tubal ectopic pregnancies, either by salpingectomy or by salpingotomy. Systemic methotrexate is an alternative nonsurgical treatment option in women with an ectopic pregnancy and no signs of active bleeding presenting with low initial serum hCG concentrations. Expectant management may be considered in women with low and plateauing serum hCG.

The diagnosis ectopic pregnancy is now guided by national guidelines and local protocols, using the concept of transvaginal ultrasound and serial hCG measurements. The severity of ectopic pregnancies has not changed, but the tools to diagnose ectopic pregnancy have enabled earlier diagnosis and treatment.

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