Evaluating and managing ectopic pregnancy

While the incidence of ectopic pregnancy has increased dramatically over the past several decades, maternal mortality rates have steadily declined. Earlier detection and refinements in treatment account for most of this decline. Here, the authors outline current therapeutic options.

By VANESSA A. GIVENS, MD, and GARY H. LIPSCOMB, MD

Ectopic pregnancy is the leading cause of maternal death in the first trimester.[1] Fortunately, despite an almost 5-fold increase in the incidence of ectopic pregnancy in the United States since 1970, deaths have declined approximately 10-fold. The lower maternal mortality rates can be attributed to earlier diagnosis of the unruptured ectopic pregnancy, along with nonsurgical therapy and other alternatives to the traditional salpingectomy. On the other hand, the rising ectopic pregnancy rate is thought by many to be the result of an increased incidence of tubal disease due to gonorrhea and chlamydia infections, and tubal surgery.

The development of more sensitive and specific radioimmunoassays for progesterone and human chorionic gonadotropin (hCG), along with the widespread availability of laparoscopy and high-resolution transvaginal sonography, have made early diagnosis feasible. Diagnostic algorithms have been developed to simplify the management of suspected ectopic pregnancy. Initially, these algorithms relied on quantitative hCG titers and transabdominal ultrasound followed by diagnostic laparoscopy to confirm an ectopic pregnancy. But as the sensitivity and specificity of the diagnostic tests increased, the need for laparoscopy to confirm the diagnosis decreased. In a randomized clinical trial, Stovall and colleagues developed an algorithm that proved 100% accurate without the use of laparoscopy.[2] This algorithm was an extension of one then in use at the University of Tennessee, Memphis.

Dr. Givens is instructor and Dr. Lipscomb is professor and director, division of gynecologic specialties, department of OBG, at the University of Tennessee Health Science Center in Memphis.

Past treatment options

Prior to the development of surgical treatments, presumed ectopic pregnancies had a mortality rate of 67%.[3] In 1884, Tait examined a series of 5 patients treated with salpingectomy and reported a mortality rate of 5%.[4] Soon after, laparotomy with salpingectomy became the standard treatment for tubal pregnancy.

Approximately 80% of all patients receiving the single-dose protocol require only 1 treatment of methotrexate.

In 1887, the first case report of a tubal pregnancy removed by opening the tube, extracting the trophoblastic tissue, and suturing the tubal incision was published by Martin in the German literature.[5] However, salpingectomy remained the treatment of choice for almost a century following this report. In fact, it was not until 1953 that a similar procedure was reported in the English literature by Strome.[6]

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Success rates for systemic methotrexate in series with at least 35 patients*

TABLE 1

Author	Year	Number of patients	Type of protocol	Successfully treated (%)
Lipscomb[10,11]	1999	352	Single-dose IM	322/352 (91.5)
Stovall[12]	1991	100	Multiple-dose IM	96/100 (96)
Henry[27]	1994	61	Single-dose IM	52/61 (85.2)
Tawfig[28]	2000	60	Single-dose IM	44/60 (73)**
Hajenius[23]	1997	51	Multiple-dose IM	44/51 (86.3)
Thoen[29]	1997	50	Single-dose IM	43/47 (91.5)
Stika[30]	1996	50	Single-dose IM	39/50 (78)
Corsan[31]	1995	44	Single-dose IM	33/44 (75)
Schafer[32]	1994	40	Variable-dose IV	37/40 (92.5)
Saraj[24]	1998	38	Single-dose IM	36/38 (94.7)
Lecuru[33]	1998	37	Single-dose IM	34/37 (91.9)
Glock[34]	1994	35	Single-dose IM	30/35 (85.7)
TOTAL				810/915 (88.5)

* Only most recent series reported for multiple publications unless previous reports involved patients not included in more recent publications
** Surgery performed if not successful with 1 dose

In the early 1970s, laparoscopy replaced exploratory laparotomy as the definitive tool for the diagnosis of ectopic pregnancy. Initially, the laparoscope was used only to diagnose a patient with an ectopic pregnancy before committing to a laparotomy, but in 1973, Shapiro and Adler reported the first laparoscopic salpingectomy for the treatment of ectopic pregnancy.[7] In the 1980s, Bruhat and associates published their experience with laparoscopic salpingostomies.[8,9] Despite these advances, salpingectomy remains the most commonly performed procedure for ectopic pregnancy in the United States.

Researchers have found that hCG levels are the only significant predictor of methotrexate failure.

Nonsurgical treatment

The most recent development in the treatment of ectopic pregnancy is medical management. In a review of all studies involving more than 35 patients treated with systemic methotrexate, the nonsurgical alternative was successful in 810 of 915 women (88.5%) (*Table 1*).

Systemic methotrexate is administered in 1 of 2 ways: as a single-dose protocol or a multiple-dose protocol in which an injection is given every other day for at least 3 doses. The latter usually alternates with citrovorum rescue factor (leucovorin). Approximately 80% of all patients receiving the single-dose protocol require only 1 treatment of methotrexate. If subsequent doses of the agent are needed, they are administered on a weekly basis.

In the single-dose protocol, methotrexate is given intramuscularly (IM) (50 mg/m^2) based on actual body weight. The initial treatment day is considered day 1. Titers of hCG are repeated on days 4 and 7. (Levels of hCG frequently continue to rise until day 4.) If the hCG titer declines less than 15% between days 4 and 7, a second dose of methotrexate is given and the protocol restarted at a new day 1. If the hCG titer declines 15% or more between days 4 and 7, hCG titers are followed weekly until they reach less than 15 mIU/mL. If the hCG level declines less than 15% in any week, another dose of methotrexate is given, and the protocol is restarted. The mean time of reso-

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lution in successfully treated women is approximately 35 days, but resolution in individual patients may take as long as 109 days.[10]

In multiple-dose protocols, administer 1 mg/kg of methotrexate intramuscularly every other day with a minimum of 3 doses. A dosage of 0.1 mg/kg leucovorin also is given intramuscularly each day after a methotrexate injection. Once hCG levels have fallen 15%, patients are then monitored weekly. If hCG levels fail to fall appropriately, the protocol is restarted.

Salpingostomy is the procedure of choice, especially when the opposite tube is blocked or lost from a ruptured ectopic pregnancy.

Compared with multiple-dose protocols, single-dose methotrexate is less expensive, has fewer side effects, requires less intensive patient monitoring, has greater patient acceptance, and does not necessitate rescue with citrovorum. However, no randomized comparisons of success rates between multiple- and single-dose protocols are available. At our institution, the overall success rates were comparable between 100 patients treated with a multiple-dose protocol and 352 patients treated with single-dose methotrexate.[11,12] Those rates were 96% and 91.5%, respectively. Although they were slightly higher for the multiple-dose protocol, the difference was not statistically significant. However, in the single-dose group, treatment criteria were liberalized with respect to the size of the ectopic pregnancy. Only pregnancies less than 3 cm were treated with multiple-dose methotrexate, while 4 cm was the maximum size treated with the single-dose protocol.

Although the most commonly quoted predictors of success with methotrexate are hCG and progesterone levels, ectopic size, the presence of ectopic cardiac activity, and the presence of free peritoneal blood, there is no consensus on which are most reliable. Because of the small number of patients previously available for analysis, it has been difficult to determine the true effect of these parameters on success rates. In a recent review of 350 consecutive tubal pregnancies treated with single-dose methotrexate, logistic regression revealed hCG levels as the only significant predictor of failure.[11] Interestingly, ectopic size, hematoma volume, and free peritoneal blood confined to the pelvis were not significant risk factors for treatment failure. These data suggest that many previous relative contraindications for medical therapy may be invalid.

The success rates listed in Table 2 can be used to counsel patients considering single-dose methotrexate.

Comparing treatments

Although multiple options are now available for the treatment of ectopic pregnancy, the best way to minimize morbidity and mortality while maximizing tubal patency and fertility remains uncertain. That is because most of the available data come from nonrandomized trials. The most comprehensive review of randomized trials was published in the Cochrane Library.[13] The following is a comparison of the various practices.

Salpingostomy versus salpingectomy. No randomized prospective trials have compared fertility and/or recurrent ectopic pregnancy rates following salpingostomy versus salpingectomy. While a few small retrospective studies are available, the operations are lumped together and

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Single-dose methotrexate success rates by hCG levels — TABLE 2

hCG level*	Success**	Fail**	% Success
<1,000	118	2	98.3
1,000 to 1,999	40	3	93.0
2,000 to 4,999	90	8	91.8
5,000 to 9,999	39	6	86.7
10,000 to 14,999	18	4	81.8
>15,000	15	7	68.2

* hCG expressed as IU/L
** Number of patients

Salpingectomy versus salpingostomy

TABLE 3

	Salpingectomy		Salpingostomy	
	LBR	REP	LBR	REP
Paavonen[15]	20/39 (51.3%)	3/39 (7.7%)	18/34 (52.9%)	3/34 (8.8%)
DeCherney[14]	21/50 (42%)	6/50 (12%)	19/48 (39.6%)	9/48 (18.8%)
Swolin[16]	4/44 (9.1%)	7/44 (15.9%)	3/24 (12.5%)	4/24 (16.7%)
Timonen[17]				
Nullipara	46/160 (28.8%)	14/160 (8.8%)	9/34 (26.5%)	6/34 (17.6%)
Multipara	106/398 (26.6%)	39/398 (9.8%)	16/49 (32.7%)	4/49 (8.2%)

LBR=live birth rate; REP=repeat ectopic pregnancy

subsequent pregnancy outcomes are not specified. Presently, only 4 reports can be sufficiently analyzed.[14-17]

Overall, the data show a slight increase in live birth rates in patients who undergo salpingostomy (*Table 3*). They also show a consistently higher number of recurrent ectopic pregnancies, although neither difference is statistically significant. Generally, salpingostomy is the procedure of choice, especially when the opposite tube is blocked or lost from a ruptured ectopic pregnancy.

There also is a greater risk of persistent trophoblastic tissue with salpingostomy, ranging from 3% to 20%.[18] This outcome is rare with salpingectomy.

Laparoscopy versus laparotomy. Three prospective randomized trials involving 231 patients compared laparoscopy with laparotomy in hemodynamically stable patients.[19-21] In these trials, laparoscopic surgery proved to be superior to laparotomy with respect to blood loss, analgesic requirements, and duration of hospital stay (*Table 4*). It also resulted in cost savings of $1,200 to $1,500 (in 1992 dollars) per patient over laparotomy, primarily due to shorter hospital stays.

The rate of intrauterine pregnancy following laparoscopy and laparotomy was 61% and 53%, respectively, and the rate of recurrent ectopic pregnancy was 7% and 14%, respectively. In contrast, when salpingostomy was performed, laparoscopic surgery was less effective than laparotomy in preventing persistent trophoblastic disease.[13,22]

Laparoscopic salpingostomy versus systemic methotrexate. In a multicenter study, 100 hemodynamically stable women with laparoscopically confirmed unruptured ectopic pregnancy and no evidence of intra-abdominal bleeding were allocated to receive systemic methotrexate or undergo laparoscopic salpingostomy.[23] Of the 51 patients treated medically, who were given methotrexate alternating with leucovorin in a multidose regimen, 86% were treated successfully, although 4% required a second course of methotrexate. The remaining 14% required surgery.

Of the 49 women allocated to laparoscopic salpingostomy, 72% were successfully treated with laparoscopic salpingostomy alone, 8% required salpingectomy, and 20% needed methotrexate after salpingostomy for persistent trophoblast disease. Overall, the tube was preserved in 90% of the methotrexate group and 92% of the salpingostomy group. Of

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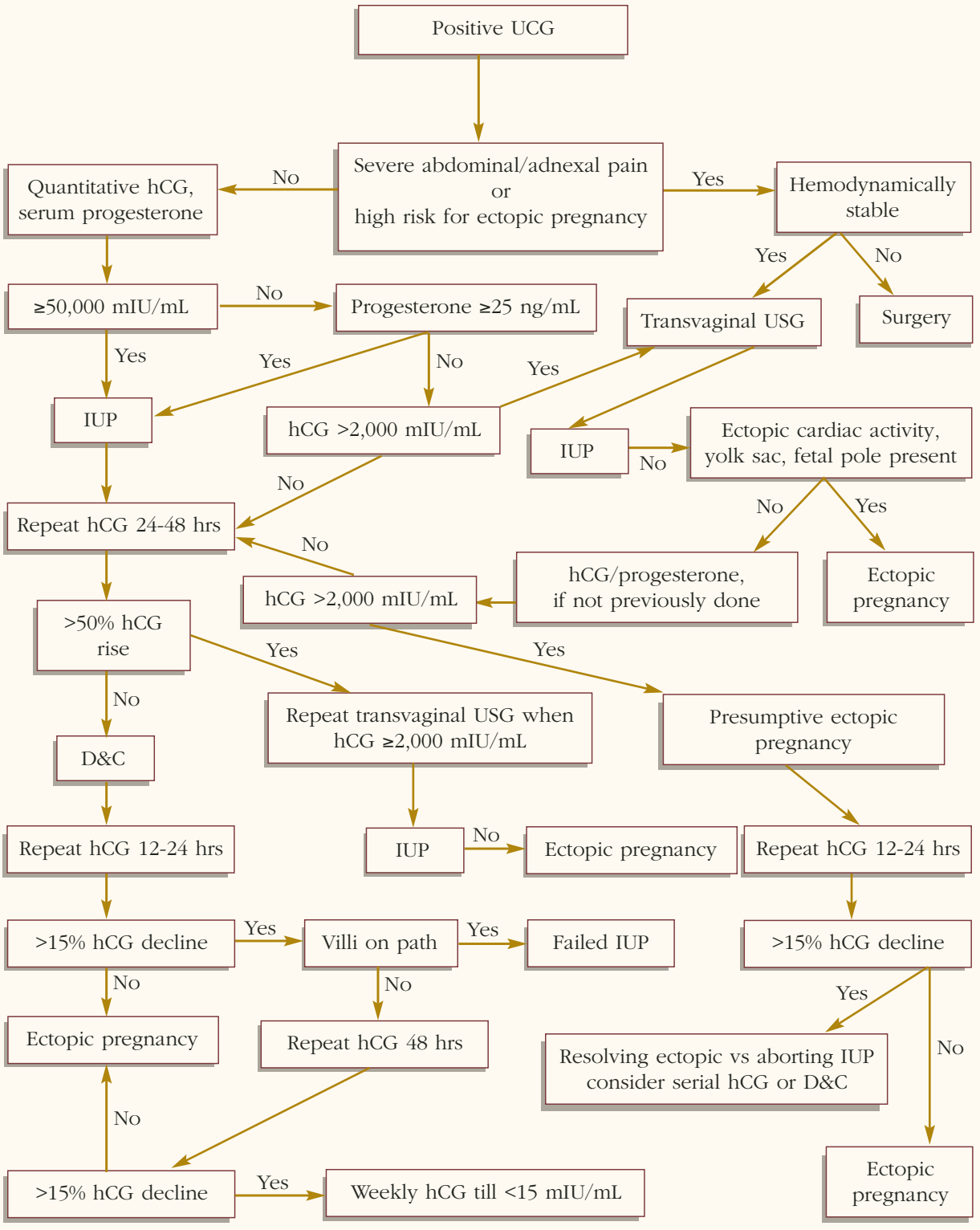
Laparoscopy versus laparotomy for treatment of ectopic pregnancy

TABLE 4

	Laparoscopy	Laparotomy
Blood loss (mL)	60 to 79	115 to 195
Analgesic requirements (mg morphine)	29 to 69	58 to 95
Hospital stay (days)	1.4 to 2.2	3.3 to 5.4

Diagnosing ectopic pregnancy



D&C=dilatation and curettage; hCG=human chorionic gonadotropin; IUP=intrauterine pregnancy; UCG=urinary chorionic gonadotropin; USG=ultrasonography

the 81 patients assessed for ipsilateral tubal patency following treatment, a patent tube was present in 55% of the methotrexate group and 59% of the salpingostomy group. In a later publication using the same database, the authors calculated that systemic methotrexate was less costly than laparoscopic salpingostomy only if it was performed in patients with hCG titers of less than 1,500 mIU/mL.[24] Data were calculated based on care rendered in the Dutch health-care system.

Methotrexate is best in patients with ectopic pregnancies less than 4 cm and hCG titers less than 10,000 to 15,000 mIU/mL.

Three randomized studies involving a total of 207 patients compared single-dose methotrexate to laparoscopic salpingostomy.[25-27] If failure of medical therapy was defined as a requirement of more than 1 dose of methotrexate, salpingostomy was significantly more successful in treating ectopic pregnancy. However, if success in the medically managed group was defined as avoidance of surgical intervention, the groups were equally successful.

Following treatment, ipsilateral tubal patency could be assessed in 77 patients. No significant differences were found between the 2 groups.[13] Subsequent intrauterine pregnancy and repeat ectopic pregnancy rates also were the same in both groups. In an analysis of direct costs, single-dose methotrexate proved to be less expensive than laparoscopy in patients with an initial hCG level of less than 1,500 mIU/mL.[27]

Key points

- Ectopic pregnancy is the leading cause of maternal death in the first trimester.
- More sensitive and specific radioimmunoassays for progesterone and hCG have made early diagnosis feasible.
- Persistent trophoblastic tissue is not uncommon after salpingostomy, but rare after salpingectomy.
- Studies have shown that laparoscopy is superior to laparotomy with respect to blood loss, analgesic requirements, and duration of hospital stay.

Conclusion

While the incidence of ectopic pregnancy has reached epidemic proportions in the United States, the mortality associated with this disease has steadily declined. This decrease is primarily due to diagnosis prior to rupture. In addition, numerous treatment options are now available, including nonsurgical therapy. It is hoped that future research will lead to even earlier diagnosis and provide data on prime candidates for each form of treatment.

In the meantime, it is our belief that single-dose methotrexate offers the best compromise between overall cost, morbidity, patient recovery, and future fertility in patients with ectopic pregnancies less than 4 cm and hCG titers less than 10,000 to 15,000 mIU/mL. Appropriate counseling of the overall risks and benefits, along with personal success rates of the treating practitioner should be considered. This will allow the patient to make an educated treatment decision. ■

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The authors report no financial relationship with any companies whose products are mentioned in this article.