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Current status of surgical and nonsurgical management of ectopic pregnancy

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Objectives: To review the efficacy, safety, costs, and subsequent reproductive outcome of surgical and nonsurgical management of ectopic pregnancy (EP).

Design: Pertinent studies were identified through computer Medline search. The rates of intrauterine pregnancy (IUP) and EP were calculated from the raw data in the original publications so that the denominator would be consistent.

Result(s): The efficacy of laparoscopic treatment of EP is similar to that by laparotomy. The rate of persistent EP after conservative surgery ranges from 3% to 20%. Based on a review of 1,514 patients attempting to conceive after linear salpingostomy, the IUP and recurrent EP rates were 61.4% and 15.4%, respectively, among patients who had laparotomy, and 61% and 15.5%, respectively, among patients who had laparoscopic procedure. Of 3,584 patients who had partial or total salpingectomy, the subsequent IUP rate was 38.1% and the recurrent EP rate was 9.8%. Of 540 patients treated with a single-dose methotrexate, 84% did not require further treatment and, among 215 patients who attempted to conceive, 54% had subsequent IUP and 8% had recurrent EP. The success rate of expectant management was 69.2% in 347 patients reviewed.

Conclusion(s): There is no difference in the reproductive outcome after treatment of EP by laparotomy and by laparoscopy. Salpingostomy is associated with higher subsequent IUP and recurrent EP rates compared with salpingectomy. Methotrexate is a viable alternative to laparoscopic salpingostomy for a selected group of patients. Fertil Steril® 1997;67:421–33

Key Words: Ectopic pregnancy, salpingotomy, salpingectomy, laparotomy, laparoscopy, methotrexate, expectant management, intrauterine pregnancy rate, recurrent ectopic pregnancy rate

Ectopic pregnancy (EP) is a potentially fatal condition. In 1992, there was an estimated 108,800 EPs in the United States, reaching 2% of reported pregnancies. Ectopic pregnancy accounted for 9% of all pregnancy-related deaths and remained a leading cause of pregnancy-related death in the first trimester. Increased sensitivity of serum β-hCG immunoassay and improved quality of transvaginal ultrasounds (US) allow early detection and conservative management of EP.

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Many protocols have been described for the diagnosis of EP. The advent of RIA and specific antiserum to the β-subunit of hCG allowed sensitive and specific detection. Abnormal pregnancies are associated with an increase of hCG at a rate < 66% in 48 hours, but 15% of normal pregnancies may have an abnormal hCG rise; further, abnormal rise did not differentiate between spontaneous abortion and EP. The same problems hold true when using single serum P in diagnosing EP. The optimal range of serum progesterone (9 to 14 ng/mL; conversion factor to SI unit, 3.18) discriminates between abnormal and normal pregnancies to a test efficiency of only 80%, and, again, spontaneous and EPs could not be distinguished.

Barnhart et al. (1) described a diagnostic algo-

rithm consisting of clinical examination, quantitative serum β-hCG, and transvaginal US (1). This protocol diagnosed EPs with a sensitivity of 100% and a specificity of 99%. This algorithm, similar to the one used at our center, obviated the need for diagnostic laparoscopy or diagnostic dilatation and curettage. Once the diagnosis of an EP is made, the mode of treatment can be selected.

The traditional treatment of EP is laparotomy and salpingectomy. The conservative approach includes surgical and nonsurgical management. The surgical approach is usually linear salpingostomy, which allows the fallopian tube to be preserved. Among medical treatments, the most popular is IM methotrexate injection. Local injection of various substances, including methotrexate, prostaglandins, hyperosmolar glucose, potassium chloride, and RU486 also have been attempted. Finally, expectant management that involves follow-up with serial serum hCG levels and USs is another option.

The assessment of these relatively new and conservative approaches is difficult for several reasons. The selection of patients is based on criteria that vary from one study to another. The definition of successful treatment varies and is sometimes not stated explicitly. Varying dosage schedules are used in different studies. Finally, the reports of fertility outcomes are only meaningful if there is adequate follow-up and the number of women attempting to conceive also is reported. It is difficult to compare the rates of subsequent intrauterine pregnancy (IUP) and EP among the different studies because the denominator often is inconsistent. In this review, we report these rates based on the denominator being the number of women who attempted to conceive and were followed up. We also define success as decline of serum hCG to undetectable levels with no need for further medical or surgical treatment. This review will focus on the efficacy, safety, costs, and fertility outcomes of surgical and nonsurgical management of EP.

SURGICAL MANAGEMENT

Laparotomy Versus Laparoscopy

Three prospective, randomized trials involving a total of 231 patients have shown definitively that laparoscopic surgery is superior to laparotomy in hemodynamically stable patients (Table 1). In the laparoscopic approach, there is less blood loss (3), less analgesia requirement (2), and shorter duration of hospital stay (3, 4, 6). All three studies demonstrated tremendous cost savings per patient. One study (4) found no difference in the rate of persistent EP, whereas two others (3, 6) revealed higher rates of persistent EP in the laparoscopy group. This could have occurred during the learning curve of the laparoscopists. In two studies, all persistent EPs in the laparoscopy group (3, 4) had successful medical treatment. In another (6), eight patients with persistent EP in the laparoscopy group were treated by laparotomy (five patients), by repeat laparoscopy (two patients), and by methotrexate injection (one patient). The only patient with persistent EP in the laparotomy group was treated with repeat laparotomy.

In those three studies combined, 69 patients desired pregnancy in the laparoscopy groups and 76 patients in the laparotomy groups. The rates of subsequent IUP were 61% and 53%, and the rates of EP were 7% and 14%, respectively. It appears that there is no difference in the reproductive outcome after salpingostomy by laparoscopy and by laparotomy.

Persistent EP After Conservative Surgical Treatment

The conservative surgical approach has a high success rate, with a reported failure rate or rate of persistent EP ranging from 3% (4) to 20% (9). Table 2 summarizes the rate of persistent ectopics reported in 10 studies (3, 4, 6, 9–15). Persistent EP was encountered in 58 of 699 patients treated by laparoscopic salpingostomy (8.3%) and in 9 of 230 patients treated by a similar procedure by laparotomy (3.9%). Many authors recommend weekly serum β-hCG measurements as a follow-up after surgery. In our practice, we measure serum β-hCG once approximately 1 week after laparoscopic salpingostomy. If the level remains high, a single dose of methotrexate is administered IM. Treatment of persistent ectopics with methotrexate is successful in 62 of 64 reported cases whereas expectant management is successful in all 7 selected cases (Table 3).

The reproductive outcome after treatment of persistent EP was reviewed in 50 cases. At 36 months follow-up, there were 19 (59%) IUPs in 32 women who attempted to conceive. There were no recurrent EPs. It is encouraging that the pregnancy rate does not seem to be decreased after persistent EP (16).

Persistent trophoblast tends to be found in the proximal portion of the tube; therefore, attention should given to this area. The use of a suction irrigation under pressure to flush the gestational products out of the tube is recommended at the initial surgery. Its removal piecemeal with forceps is not advisable.

Reproductive Outcome

Table 4 describes nine studies that retrospectively (one study used prospective cohorts) compared the

Table 1 A Summary of Three Prospective, Randomized Trials Comparing Laparoscopic Surgery With Laparotomy for the Treatment of Ectopic Pregnancy*

	Murphy et al. (2)		Vermesh et al. (3,4)		Lundorff et al. (5–7)	
	Laparoscopy	Laparotomy	Laparoscopy	Laparotomy	Laparoscopy	Laparotomy
Total no. of patients	26	36	30	30	52	57
Estimated blood loss (mL)	60 ± 61†	115 ± 115	79 ± 18†	195 ± 24	N/A‡	N/A
Analgesia (mg of morphine)	26 ± 43§	58 ± 37	N/A	N/A	N/A	N/A
Hospital stay (h)	26 ± 19§	634 ± 17	N/A	N/A	N/A	N/A
Hospital stay (d)	N/A	N/A	1.4 ± 0.1†	3.3 ± 0.2	2.2 ± 0.1†	5.4 ± 0.2
Time to normal activity (d)	17 ± 9‡	62 ± 49	N/A	N/A	10.9 ± 0.9†	24.1 ± 0.9
Direct cost (average saivngs per patient in U.S. dollars)	$1,200‡		$1,500†		SEK 4,641‖¶	
Complications						
Converted to laparotomy	0	N/A	2	N/A	2	N/A
Persistent ectopic	3/17 (18)	0	1/30 (3.3)	1/30 (3.3)	8/52 (15.4)	1/57 (1.8)
Blood transfusion	1	2	0	0	0	0
Gonococcal endometritis	1	0	0	0	0	0
Febrile morbidity	0	3	1	1	0	0
Wound infection	0	1	0	2	0	0
Subsequent laparotomy	0	0	0	0	5**	2††
Subsequent repeat laparoscopy	0	0	0	0	2**	1**
Oral methotrexate	0	0	0	0	1**	0
Subsequent fertility						
No. desiring conception	8	10	19	21	42	45
No. of IVPs	7 (88)	5 (50)	13 (68)	15 (71)	22 (52)	20 (44)
No. of recurrent EP	0	2 (20)	1 (5)	4 (19)	4 (10)	5 (11)

* Adapted from the IX World Congress on Human Reproduction Proceedings (2), with the permission of the publisher.
† $P < 0.001$.
‡ N/A, not applicable or not available.
§ $P < 0.005$.
‖ $P < 0.05$.
¶ Values in Swedish Krona.
** For persistent EP.
†† One subfascial hemotoma and one hematosalpinx with ovarian torsion.

reproductive outcome of conservative versus radical procedures (17–25). Among the 2,635 total patients, 528 in the conservative group and 1,246 in the radical group desired fertility. The rate of subsequent IUP was 53.0% in the conservative group and 49.3% in the salpingectomy group. The recurrent EP rates were 14.8% and 9.9%, respectively. One study (18) compared prospective cohorts of patients after conservative versus radical laparoscopic procedure. Among 86 women attempting to conceive, the IUP rates were 60% and 53.8%, whereas the recurrent ectopic rates were 18.3% and 7.7%, in the conservative and radical groups, respectively.

Table 5 depicts the fertility outcome after linear salpingostomy by laparoscopy and laparotomy (5, 7, 15, 17–41). Among 811 patients attempting to con-

Table 2 Rate of Persistent EP After Conservative Surgery by Salpingostomy*

		Laparoscopy			Laparotomy		
Author	Year	Total no.	No. of persistent EP		Total no.	No. of persistent EP	
				%			%
Hoppe et al. (10)	1994	101	13	(12.9)	53	6	(11.3)
Seifer et al. (11)	1993	103	16	(15.5)	54	1	(1.9)
Murphy et al. (3)	1992	26	3	(11.5)	36	0	(0.0)
Lundorff et al. (6); Gray et al. (8)	1991; 1995	52	8	(15.4)	57	1	(1.8)
Keckstein et al. (12)	1990	22	1	(4.5)	N/A	N/A	(N/A)
Henderson (9)	1989	15	3	(20.0)	N/A	N/A	(N/A)
Vermesh et al. (4)	1989	30	1	(3.3)	30	1	(3.3)
Brumsted et al. (13)	1988	25	1	(4.0)	N/A	N/A	(N/A)
Silva (14)	1988	8	1	(12.5)	N/A	N/A	(N/A)
Pouly et al. (15)	1986	317	11	(3.5)	N/A	N/A	(N/A)
Total		699	58	8.3	230	9	3.9

* Values in parentheses are percentages. N/A, not applicable or not available.

Table 3 Reported Cases of Persistent EP Treated Nonsurgically and Their Treatment Outcomes*

Author	Year	Successful cases	Total no. cases	Methotrexate use
Methotrexate				
Hoppe et al. (10)	1994	19	19	IM
Seifer et al. (11)	1993	3	3	IM
Bengtsson et al.	1992	14	15	Oral
Murphy et al. (3)	1992	1	1	IM
Dumesic et al.	1991	0	1	IM
Rose et al.	1990	3	3	IV + citrovorum
Cairns et al.	1989	1	1	Oral
Donnez et al.	1989	15	15	IM
Hill et al.	1989	2	2	Not specified
Pastner et al.	1988	1	1	Oral
Kenigsberg et al.	1987	1	1	Not specified
Cowan et al.	1986	1	1	IM
Higgins et al.	1986	1	1	Oral
Subtotal		62	64	
Expectant management				
Letterie et al.	1989	1	1	
Vermesh et al.	1988	2	2	
DiMarchi et al.	1987	1	1	
Cartwright et al.	1986	2	2	
Kanrava et al.	1983	1	1	
Subtotal		7	7	
Total		69	71	

* References for these case reports are available upon request.

ceive after the laparotomy approach, the IUP rate was 61.4% and the recurrent EP rate was 15.4%. Very similar intrauterine and recurrent EP rates (61.0% and 15.5%, respectively) were obtained in 703 patients attempting to conceive after the same surgery by laparoscopy.

The reproductive outcome after total or partial salpingectomy is depicted in Table 6 (17–21, 23–25, 42–51). Among 3,584 patients desiring fertility, the overall IUP rate was 38.1% and the recurrent ectopic rate was 9.8%. For reasons cited previously, strict comparison of these studies is not possible, therefore, one can conclude only that conservative surgery may provide a subsequent IUP rate that is at least comparable to or possibly higher than that after radical surgery. Unfortunately, the recurrent EP rate also may be higher after conservative surgery. In a randomized trial of 34 women, Tulandi and Guralnick (52) found there to be no difference in subsequent fertility or adhesion formation between salpingotomy with and without tubal suturing.

Studies that specifically reported reproductive outcome after conservative surgery in women with a solitary patent tube were reviewed (15, 25, 27, 29, 33, 41, 49, 53–63) (Table 7). Among the 176 total women attempting to conceive, there were 96 (54.5%) IUPs and 36 (20.5%) recurrent EPs. With an IUP rate of 54.5%, preserving the tube in these women is justified, providing the patient understands the risk of recurrent EP and the alternate option of IVF.

Many other factors influence the subsequent fertility rate, perhaps to a greater extent, than the type of surgical approach alone. A history of prior infertility was found to be associated with a decreased fertility rate (15, 21, 35). In fact, Ory et al. (17) found this factor to be the most important for subsequent fertility, and Sultana et al. (64) reported that the pregnancy rate was four times lower in patients with a history of infertility. Others have found that the status of the contralateral tube at the time of surgery is related directly to the subsequent fertility, regardless of the surgical modality used (7, 15, 19, 21, 27, 35, 65). Pouly et al. (35) found three factors that

Table 4 Reproductive Performance After Conservative Versus Radical Surgery for EP*

			Conservative				Radical		
Author	Year	Duration of follow-up	Total no. of patients treated†	No. of patients attempting to conceive	No. of IUPs§	No. of EPs§	n	No. of IUPs§	No. of EPs§
Ory et al. (17)‖¶	1993	3 y	188	38	19 (50.0)	8 (21.1)	50	29 (58.0)	4 (8.0)
Silva et al. (18)‖**	1993	N/A††	143	60	36 (60.0)	11 (18.3)	26	14 (53.8)	2 (7.7)
Tuomivaara and Kauppila (19)‖¶	1988	1 to 11 y; m = 5 y	523	86	59 (68.6)	10 (11.6)	237	169 (71.3)	25 (10.5)
Badawy et al. (20)‖‡‡	1986	N/A	37	12	7 (58.3)	0 (0.0)	7	5 (71.4)	0 (0.0)
Sherman et al. (21)‖¶§§	1982	3 mths-11 yrs	250	47	39 (83.0)	3 (6.4)	104	75 (72.1)	6 (5.8)
DeCherney and Kase (22)‖‖	1979	1 to 4 yrs	98	48	19 (39.6)	9 (18.8)	50	21 (42.0)	6 (12.0)
Kucera et al. (23)‖‡‡	1969	N/A	135	21	8 (38.1)	3 (14.3)	53	20 (37.7)	5 (9.4)
Timonen and Nieminen (24)‖¶¶	1967	N/A	1,067	185	76 (41.1)	29 (15.7)	558	222 (39.8)	64 (11.5)
Ploman and Wicksell (25)	1960	3 to 15 yrs	194	31	17 (54.8)	5 (16.1)	161	59 (36.6)	11 (6.8)
Total			2,635	528	280 (53.0)	78 (14.8)	1,246	614 (49.3)	123 (9.9)

* All the studies in this table were by laparotomy except Silva et al. (17), which was done by laparoscopy.
† Includes all types of surgical treatment.
‡ After that specific treatment of EP.
§ Values in parentheses are percentages.
‖ Conservative group includes salpingostomy.
¶ Conservative group includes cases of fimbrial expression.
** Prospective.
†† N/A, not applicable or not available.
‡‡ No description of procedures provided in the conservative group.
§§ Conservative group includes cases of ovarian ectopics.
‖‖ Retrospective, case-control.
¶¶ Conservative group includes cases of tubo-utero implantations.

Table 5 Reproductive Performance After Treatment of Ectopic Pregnancy by Salpingostomy

Author	Year	Duration of follow-up	Total no. of patients treated*	No. of patients attempting to conceive†	No. of IUPs‡	No. of EPs‡
Laparotomy						
Ory et al. (17)	1993	3 y	188	33	17 (51.5)	8 (24.2)
Vermesh and Presser (5)§	1992	3 y	30	21	15 (71.4)	4 (19.0)
Lundorff et al. (7)§	1992	1 y	57	45	20 (44.4)	5 (11.1)
Langer et al. (26)‖	1990	m = 7.2 y	496	85	63 (74.1)	15 (17.6)
Tuomivaara and Kauppila (19)¶	1988	1 to 11 y, m = 5 y	523	86	59 (68.6)	10 (11.6)
Badawy et al. (20)	1986	N/A	37	12	7 (58.3)	0 (0.0)
Oelsner et al. (27)	1987	N/A	58	38	19 (50.0)	9 (23.7)
Hallat (28)	1986	N/A	1,152	144	108 (75.0)	29 (20.1)
Sherman et al. (21)	1982	3 mo to 11 y	250	47	39 (83.0)	3 (6.4)
Bukovsky et al. (29)¶	1979	N/A	24	20	14 (70.0)	1 (5.0)
DeCherney and Kase (22)	1979	1 to 4 y	98	48	19 (39.6)	9 (18.8)
Stromme (30)¶**††‡‡	1973	2 to 20 y	141	54	30 (55.6)	5 (9.3)
Jarvinen et al. (31)	1972	4 to 40 mo	43	43	22 (51.2)	4 (9.3)
Kucera et al. (23)**§§	1969	N/A	135	21	8 (38.1)	3 (14.3)
Timonen and Nieminen (24)‖‖	1967	N/A	1,067	83	41 (49.4)	15 (18.1)
Skulj et al. (32)‖¶¶	1964	1 to 4 y				
Vehaskari (33)‖	1960	N/A				
Ploman and Wicksell (25)	1960	3 to 15	194	31	17 (54.8)	5 (16.1)
Subtotal			4,493	811	498 (61.4)	125 (15.4)
Laparoscopic						
Silva et al. (18)***	1993	N/A	143	60	36 (60.0)	11 (18.3)
Paulson (34)	1992	>1 y	125	48	26 (54.2)	12 (25.0)
Vermesh and Presser (5)§	1992	3 y	30	19	13 (68.4)	1 (5.3)
Lundorff et al. (7)§	1992	1 y	52	42	22 (52.4)	4 (9.5)
Pouly et al. (35)‖‖††	1991	1 to 15 y, >1 y	465	223	149 (66.8)	39 (17.5)
Keckstein et al. (36)	1990	N/A	22	16	7 (43.8)	3 (18.8)
Mecke et al. (37)	1989	1 to 6 y	202	74	42 (56.8)	5 (6.8)
Reich et al. (38)‖	1988	>6 mo				
DeCherney and Diamond (39)	1987	N/A	79	69	36 (52.2)	7 (10.1)
Pouly et al. (15)	1986	1 y	321	118	76 (64.4)	26 (22.0)
DeCherney et al. (40)	1986	>1 y	18	16	8 (50.0)	0 (0.0)
Bruhat et al. (41)	1980	>6 mo	60	18	14 (77.8)	1 (5.6)
Subtotal			1,517	703	429 (61.0)	109 (15.5)
Total			6,010	1,514	927 (61.2)	234 (15.5)

* Includes all types of surgical treatment.
† After that specific treatment of EP.
‡ Values in parentheses are percentages.
§ Prospective, randomized trial.
‖ Study excluded because the specific fertility rate related to salpingectomy or salpingostomy or the number of patients trying to conceive is not explicit.
¶ Small number of cases of fimbrial expression could not be separated out of the reported fertility rates.
** Conservative group included salpingostomy.
†† Conservative group includes cases of fimbrial expression.
‡‡ Conservative group includes cases of ovarian ectopies.
§§ No description of procedures provided in the conservative group.
‖‖ Some women had more than one EP recurrence.
¶¶ Conservative group includes cases of tubo-utero implantations.
*** Prospective cohorts.
††† A large number of pregnancies resulting from IVF after secondary infertility was not included here.

significantly resulted in a lower pregnancy rate and higher recurrent EP. They are ipsilateral periadnexal adhesions, history of infertility, and contralateral tubal status. Silva et al. (18) found prior tubal damage to be associated significantly with decreased pregnancy rate: 79% pregnancy rate in group without prior tubal damage versus 42% in the group with prior tubal damage.

Dubuisson et al. (42) found that 92.9% of all spontaneous pregnancies after surgical treatment of EP occurred in the first 18 months. They recommended IVF to patients with a damaged or absent contralateral tube, especially if there were no spontaneous conceptions in the first 12 to 18 months.

NONSURGICAL MANAGEMENT

Methotrexate

Methotrexate is an antimetabolite that interferes with the synthesis of DNA by inhibiting the action of dihydrofolate reductase in the conversion of dihydrofolic acid to tetrahydrofolic acid. It interrupts the synthesis of the purine nucleotide thymidilate and the amino acids serine and methionine. The safety of methotrexate in women of the reproductive age group with respect to future pregnancies has been proven in studies from the 1970s involving methotrexate as a treatment of gestational trophoblastic

Table 6 Reproductive Performance After Treatment of EP Salpingectomy

Author	Year	Duration of follow-up	Total no. of patients treated*	No. of patients attempting to conceive†	No. of IUPs‡	No. of EPs‡
Ory et al. (17)	1993	3 y	188	50	29 (58.0)	4 (8.0)
Silva et al. (18)§‖	1993	N/A¶	143	26	14 (53.8)	2 (7.7)
Dubuisson et al. (42)‖**	1990	>18 mo	241	125	28 (22.4)	16 (12.8)
Tuomivaara and Kauppila (19)	1988	1 to 11 y; m = 5 y	523	237	169 (71.3)	25 (10.5)
Badawy et al. (20)	1986	N/A	37	7	5 (71.4)	0 (0.0)
Sherman et al. (21)	1982	3 mo. to 11 y	250	104	75 (72.1)	6 (5.8)
Franklin et al. (43)††	1973	2.5 to 8 y	492	208	106 (51.0)	58 (27.9)
Schenker et al. (44)††	1972	6 to 16 y	277	240	75 (31.3)	39 (16.3)
Swolin and Fall (45)‡‡	1972	N/A				
Kucera et al. (23)§§‖‖	1969	N/A	135	53	20 (37.7)	5 (9.4)
Douglas et al. (46)††¶¶	1969	>3 y, m = 8.3 y	230	106	63 (59.4)	8 (7.5)
Timonen and Nieminen (24)	1967	N/A	1,067	558	222 (39.8)	64 (11.5)
Bobrow and Bell (47)††	1962	N/A	905	905	208 (23.0)	29 (3.2)
Abrams and Farell (48)	1961	>2 y	150	70	30 (42.9)	13 (18.6)
Ploman and Wicksell (25)	1960	3 to 15 y	194	161	59 (36.6)	11 (6.8)
Jarvinen and Kinnunen (49)	1957	N/A	439	439	132 (30.1)	42 (9.6)
Bender (50)	1956	N/A	222	222	98 (44.1)	18 (8.1)
Lund (51)	1955	N/A	73	73	32 (43.8)	11 (15.1)
Total			5,566	3,584	1,365 (38.1)	351 (9.8)

* Including all types of surgical treatment.
† After that specific treatment of EP.
‡ Values in parentheses are percentages.
§ Prospective cohorts.
‖ All the studies listed in this table were laparotomy cases except these two, which were laparoscopic.
¶ N/A, not applicable or not available.
** A large number of studies resulting from IVF after secondary infertility was not included here.
†† Radical group includes cases of salpingo-oophorectomy.
‡‡ Study excluded because the specific fertility rate related to salpingectomy or salpingostomy or the number of patients trying to conceive is not explicit.
§§ Conservative group includes salpingostomy.
‖‖ No description of procedures provided in the conservative group.
¶¶ Some women had more than one EP recurrence.

disease. There was no increase in the rate of subsequent spontaneous abortions or the rate of congenital anomalies after its use. Further, there was no increase in second tumors after methotrexate for gestational trophoblastic tumors. The much lower dosage of methotrexate given to treat EP is a further assurance of its safety in subsequent pregnancies.

Table 7 Reproductive Outcome After Conservative Surgery for Ectopic Pregnancy in Women with a Solitary Tube or Occlusion in the Contralateral Tube*

Author	Year	Total no. of cases	No. of IUPs	No. of EPs
Tulandi (53)	1988	16	8 (50.0)	3 (18.8)
Oelsner et al. (27)	1987	26	12 (46.1)	10 (38.5)
Pouly et al. (15)	1986	24	11 (45.8)	7 (29.1)
Valle and Lifchez (54)	1983	11	11 (100.0)	0 (0.0)
DeCherney et al. (55)	1982	15	8 (53.0)	3 (20.0)
Langer et al. (56)	1982	8	5 (62.5)	3 (37.5)
Bruhat et al. (41)	1980	5	3 (60.0)	0 (0.0)
Bukovsky et al. (29)	1979	2	2 (100.0)	0 (0.0)
Henri-Suchet et al. (57)	1979	14	8 (57.0)	2 (15.0)
Wilson (58)	1979	1	1 (100.0)	0 (0.0)
Giana et al. (59)	1978	2	1 (50.0)	0 (0.0)
Stangel et al. (60)	1976	2	2 (100.0)	0 (0.0)
Jarvinen et al. (31)	1972	10	6 (60.0)	3 (30.0)
Mintz (61)	1962	25	8 (32.0)	3 (12.0)
Barclay (62)	1961	2	1 (50.0)	0 (0.0)
Ploman and Wicksell (25)	1960	7	3 (43.0)	2 (28.0)
Vehaskari (33)	1960	5	5 (100.0)	0 (0.0)
Tompkins (63)	1956	1	1 (100.0)	0 (0.0)
Total		176	96 (54.5)	36 (20.5)

* Values in parentheses are percentages.

Systemic Methotrexate

Methotrexate can be given systemically (IV or IM or oral administration) or by local injection under US or laparoscopic guidance. Kooi and Kock (66) reviewed 24 studies on the use of methotrexate in EP and found that only 15 of 284 cases (5%) required further surgery for methotrexate failure. Their review included studies using parenteral and local administration of methotrexate. Slaughter and Grimes (67) reviewed 17 studies on 400 patients treated with parenteral methotrexate and found the success rate to be 92%. Contrary to the multiple-dose schedules that were prevalent in older studies, recent studies used more unified, single-dose methotrexate (1 mg/kg body weight or 50 mg/m^2 body surface area) (Table 8) (68–80). The use of citrovorum rescue has been shown to be unnecessary (81).

The reproductive outcome after methotrexate treatment is depicted in Table 8. It is difficult to compare the results of these studies because the duration of follow-up varies or is <1 year in some cases. In addition, most of the studies did not distinguish

Table 8 Results of Methotrexate Treatment of EP

Author	Year	Dosage	Study design	No. of ectopics treated with study protocol	No. of successful cases	Pregnancy outcome		
						No. of patients who attempted	No. of IVFs	No. of EPs
Local injection under ultrasound guidance								
Fernandez et al.* (68)	1995	1 mg/kg	Prospective	20	19 (95)†	10	6	0
Fernandez et al. (69)	1993	1 mg/kg	Prospective	100	83 (83)	58	30	3
Tulandi et al. (70)	1992	1 mg/kg	Prospective	40	28 (70)	11	2	2
Menard et al. (71)	1990	50 mg	N/A‡	17	13 (76)	N/A	N/A	N/A
Subtotal				177	143 (81)	79	38 (48)	5 (6)
Local injection under laparoscopic guidance								
Shalev et al.§ (72)	1995	50 mg in 2 mL	Prospective	44	27 (61)	27	12	3
O'Shea et al.* (73)	1994	20 mg in 0.8 mL	Prospective	29	26 (90)	N/A	N/A	N/A
Pansky et al. (74)	1993	12.5 to 25 mg in 2 mL	Prospective	77	61 (79)	31	21	4
Mottla et al.* (75)	1992	12.5 to 25 mg in 2 to 7 mL	Prospective	7	3 (43)	N/A	N/A	N/A
Kojima et al. (76)	1990	5 to 25 mg in 10 mL	N/A	9	9 (100)	N/A	N/A	N/A
Kooi and Kock (77)	1990	100 mg in 4 mL Leucovorin by mouth	Prospective	25	24 (96)	14	9	0
Subtotal				191	150 (79)	72	42 (58)	7 (10)
Single systemic dose IM								
Gross et al. (78)	1995	50 mg/m^2	Prospective	17	16 (94)	N/A	N/A	N/A
Glock et al. (79)	1994	50 mg/m^2	Prospective	35	30 (86)	15	3	1
Stovall and Lina (80)	1993	50 mg/m^2	Prospective	120	113 (94)	49	34	5
Subtotal				172	159 (92)	64	37 (58)	6 (9)
Total				540	452 (84)	215	117 (54)	18 (8)

* These results were part of a prospective randomized trial comparing methotrexate and laparoscopic salpingostomy.
† Values in parentheses are percentages.
‡ N/A, not applicable or not available.
§ This study was a trial testing a prospective protocol determining the use of methotrexate versus laparoscopic salpingostomy and was not randomized.

patients who were treated successfully with methotrexate and those who needed further treatment.

Local Methotrexate

The success rate of local injection of methotrexate under US guidance ranged from 70% to 95% in a total of 177 patients treated (68–71). Among 79 patients desiring fertility, the overall IUP rate was 48% and the recurrent EP rate was 6%. The duration to reach undetectable serum β-hCG levels was 26.5 (69) to 35 days (70). Hysterosalpingogram demonstrated ipsilateral tubal patency in 81% (70) to 90% (69) of patients.

Administration of methotrexate into the gestational site under laparoscopic guidance was performed with varying dosages ranging from 5 to 100 mg and the amount of normal saline as diluent ranged from 0.8 to 10 mL. The success rate ranges between 43% and 100%. Of 72 patients who attempted to conceive, the overall intrauterine and recurrent pregnancy rates were 58% and 10%, respectively. Laparoscopic injection of methotrexate still requires surgery, and, if it fails, another surgery may be needed. Therefore, local injection under US is preferable for local treatment.

Local Versus Systemic Methotrexate

Studies on pharmacokinetics of local versus systemic methotrexate showed that the maximum plasma concentration of methotrexate and area-under-the-curve were similar between the local and systemic groups (81, 82). A prospective, randomized clinical trial further confirms that the efficacy of local injection of methotrexate is equivalent to IM injection and produces fewer side effects (81). This study was not included in Table 8 because there were four groups of 12 patients each and each group was treated with a different dose schedule. Although power was lacking due to the small number of subjects, the authors strongly advocated local treatment. This was based on a larger, as yet unpublished study (83).

The success rate of a single IM injection of methotrexate among 172 patients treated was 92% (86% to 94%). This success rate seems higher and more consistent compared with local treatment. All three prospective trials used a single IM dose of 50 mg/m^2 body surface area. Among 64 patients attempting to conceive, 37 patients (58%) had subsequent IUPs whereas 6 patients (9%) had recurrent EPs. The mean time to serum hCG resolution was 23 to 35.5 days (79, 80).

The overall success rate of methotrexate is undoubtedly high and, considering its noninvasiveness, makes it a viable alternative. Reproductive outcome was reported in 8 of 13 studies (Table 8). Among 215 patients who attempted to conceive, there were 117 (54%) IUPs and 18 (8%) recurrent EPs. The follow-up on the reproductive outcome after methotrexate treatment still is limited by small numbers and short duration of follow-up, but it appears that it is only slightly lower or even similar to the reproductive outcome after salpingostomy. It is important to note that methotrexate treatment is given only to a selected group of patients, whereas surgical treatment is a more universal treatment for all patients with EP. The difficulty of methotrexate treatment lies in the lack of consensus on selection criteria. Different recommendations have been made, but there is no agreement on reliable prognostic factors.

Prognostic Factors

In their review of 24 studies, Kooi and Kock (66) concluded that the incidence of tubal rupture is 32% if the initial serum β-hCG > 10,000 mIU/mL (conversion factor to SI unit, 1.00), and 3% if the β-hCG is < 10,000 mIU/mL. Shalev et al. (72) recommended that methotrexate be used only when the serum β-hCG is <2,000 mIU/mL and the size of the ectopic is <2 cm. In their study, 23% patients with serum β-hCG < 2,000 mIU/mL failed methotrexate treatment compared with 71% when the serum β-hCG was >2,000 mIU/mL. Similarly, the failure rate was 24% when the ectopic size was <2 cm and 48% when the size was >2 cm. Fernandez et al. (69) described a scoring system based on six criteria, each of which were graded 1 to 3: gestational age, serum β-hCG level, serum P level, degree of abdominal pain, volume of hemoperitoneum, and tubal diameter on US. A score ≤ 12 was associated with >90% success rate. It still is unclear whether the presence of fetal cardiac activity should be a contraindication. Stovall and Ling (80) included patients with fetal cardiac activity and found that the failure rate was 14.3% when it was present and 4.7% in its absence.

Although there is no clear cutoff, it is accepted that there is a trend toward higher failure rate with higher serum β-hCG levels, larger tubal diameter, severe abdominal pain, and the presence of fetal cardiac activity. By imposing strict criteria, one may improve the success rate, but fewer patients would be eligible for such treatment. The use of receiver-operator curves in a large trial may be able to determine the optimal inclusion criteria that will benefit the maximum number of patients. Serum P is a potentially valuable prognostic factor that deserves more investigation. Data from two studies with a total of 42 patients showed that initial serum P of <10 or 15 ng/mL was useful in identifying methotrexate success (84, 85). However, apart from one study (69), serum P usually is not part of the inclusion or exclusion criteria.

Pain, β-hCG and US Findings After Methotrexate Treatment

Physicians and patients must understand the natural history of the EP after methotrexate treatment so that methotrexate failure will not be overdiagnosed, leading to unnecessary additional treatment. Patients should be advised that there may be increased abdominal pain 6 to 7 days after methotrexate administration (79). The incidence of this phenomenon ranges from 33.3% (79) to 59.2% (80).

In following serial serum β-hCG levels, it is common to see a transient rise within the first few days after treatment. In fact, Stovall and Ling (80) noted that 86% of patients had a transient increase in serum β-hCG between days 1 and 4 after treatment. Thompson et al. (86) reported plateauing or rising serum β-hCG levels up to 17 days after salpingostomy or methotrexate administration. Eventually, 86% of these patients had spontaneous resolution. It is possible that, although methotrexate is arresting mitosis in cytotrophoblasts, the syncytiotrophoblastic mass still may be increasing and producing more hCG (84, 86).

Atri et al. (87) followed 25 patients treated after methotrexate treatment with serial US examinations and found that the tubal EP may increase in size and become more vascular before its resolution. However, this increase in size did not correspond with methotrexate failure. Brown et al. (88) followed 18 patients with serial US examinations and found that there was no correlation between the hCG resolution and the sonographic resolution. They concluded that routine USs are not necessary after methotrexate treatment.

Adverse Effects

The major side effects of methotrexate include impaired liver function, stomatitis, gastritis-enteritis, and bone marrow suppression. The incidence was 21% in patients treated systemically and 2% in those treated locally (66). The high incidence of side effects in earlier studies likely is due to the higher dose of methotrexate or longer duration of treatment. Stovall and Ling (80) reported no significant side effects in 120 patients treated systemically, whereas Glock et al. (79) reported mild side effects in 34% of their 35 patients. Fernandez et al. (69) reported cases of

stomatitis in 3 of 100 patients. Rare side effects, such as reversible alopecia, persistent hematosalpinx, and impairment of tubal mucosa have been reported.

LAPAROSCOPIC SURGERY VERSUS METHOTREXATE

Two prospective randomized trials have been done to compare laparoscopic salpingostomy versus local methotrexate by laparoscopy (73, 75). O'Shea et al. (73) reported a success rate of 87.5% in 24 patients treated by salpingostomy and a success rate of 89.7% in 29 patients treated with local methotrexate under laparoscopic guidance. Another randomized study (75) was discontinued because of poor results in the group treated with methotrexate. In a prospective study using a predesigned protocol (72), a success rate of 92.7% in 55 patients treated by laparoscopic salpingostomy and a significantly lower rate of 61.4% in 44 patients treated by laparoscopic-guided injection of methotrexate were reported. This study was not randomized. As a result, the size of the EP was significantly smaller in the methotrexate group.

Fernandez et al. (68) reported a prospective randomized study comparing laparoscopic salpingostomy and US-guided injection of methotrexate. The hospital stay was significantly shorter in the methotrexate group, but the resolution of serum β-hCG level was much faster in the surgery group. In each group, 19 of 20 patients were treated successfully. Despite the lack of power, these results are promising.

There is no definitive answer on whether laparoscopic surgery or methotrexate should be the first-line treatment. One major difficulty is that a large number of patients is needed to attain adequate statistical power. In any event, methotrexate treatment is an option for a selected group of patients with EP and we recommend IM administration. Because the main advantage of medical treatment is its noninvasiveness, there is little value of administering methotrexate under laparoscopic guidance, when the risks of general anesthesia and trocar insertion still are present. Further, IM methotrexate injection is more practical and less operator dependent than local injection under US guidance.

EXPECTANT MANAGEMENT

Expectant management of EP is not a new concept. In 1955, Lund (51) randomized patients to receive expectant management or surgical treatment. Among 114 patients randomized to be treated expectantly, the success rate was 57%. However, most of the patients who failed expectant management returned with significant symptoms, hemoperitoneum, or rupture. The availability of sensitive β-hCG assays and the ability to detect early EP by transvaginal US have made this approach more attractive.

Ten studies that prospectively examined the efficacy of expectant management were reviewed (89–98) (Table 9). The number of patients in each study varied from 5 (96) to 118 (91) and the reported success rates varied from 46.7% (89) to 100% (96, 97). Overall, 347 patients were treated expectantly, with a success rate of 69.2% (89–98). All patients were hemodynamically stable and had decreasing serum β-hCG levels. In contrast, other variables, such as size and location of EP, the presence of fetal cardiac activity, the presence of symptoms, and the amount of free fluid, were not always specified. In addition, the diagnosis was not always confirmed by US or laparoscopy.

As with methotrexate, there are no reliable and specific prognostic factors in predicting failure of expectant management. A decrease in the size of the EP on day 7 had a sensitivity of 84% and specificity of 100% in predicting spontaneous resolution (99). This prediction would depend on the timing of the diagnosis and therefore has limited applicability. Shalev et al. (89) found that when the serum β-hCG was >2,000 mIU/mL, the failure rate was 93.3% compared with 40% when the serum β-hCG was <2,000 mIU/mL. Trio et al. (90) used the receiver-operator curve and determined that cases with serum β-hCG of <1,000 mIU/mL had a success rate of 88% and was more than four times more likely to be successful. Korhonen et al. (91) reported that the success rates of expectant management for patients with serum β-hCG of <200, <500, and >2,000 mIU/mL were 98%, 73%, and 25%, respectively. It is apparent that there is a decreasing chance of success with higher initial serum β-hCG levels, but there is no agreement on the specific inclusion criteria. Indeed, tubal rupture has been reported in cases of very low and decreasing serum β-hCG levels. Accordingly, methotrexate treatment may be a more appropriate alternative.

COSTS OF TREATMENT MODALITIES

Laparoscopic surgery has replaced laparotomy as the standard of treatment of EP in hemodynamically stable patients. It is as effective as, and significantly less expensive than, laparotomy (8). Furthermore, the hospital stay is shorter and the recovery is faster. For methotrexate to be an acceptable treatment option, its cost also must be competitive. Based on med-

Table 9 A Summary of Studies on the Expectant Management of EP*

Author	Year	Patient selection and protocol	Confirmed by laparoscope	Total no. of patients with EP	No. of patients treated expectantly	No. of successful cases
Shalev et al. (89)	1995	Prospective	All	298	60 (20.1)	28 (46.7)
Trio et al. (90)	1995	Prospective	No.	112	67 (59.8)	49 (73.1)
Korhonen et al. (91)	1994	Prospective	No	493	118 (24.0)	77 (65.0)
Makinen et al. (92)	1990	Prospective	All	102	33 (32.4)	27 (81.8)
Fernandez et al. (93)	1988	Prospective	All	49	14 (28.6)	9 (64.0)
Derricks-Tan et al. (94)	1987	N/A	Not all	N/A	12 (N/A)	11 (89.0)
Garcia et al. (95)	1987	N/A	All	56	13 (23.2)	12 (92.0)
Sauer et al. (96)	1987	Prospective	No	70	5 (7.1)	5 (100.0)
Adoni et al. (97)	1986	Prospective	Not all	21	11 (52.4)	11 (100.0)
Carp et al. (98)	1986	N/A	Not all	N/A	14 (N/A)	11 (79.0)
Total				>1,200	347 (N/A)	240 (69.2)

* Values in parentheses are percentages. N/A, not applicable or not available.

ical records, billing statements, and published data, Creinin et al. (100) compared the direct and indirect costs of the methotrexate treatment and the standard laparotomy treatment. Assuming that 30% of cases are eligible for methotrexate and that the success rate of methotrexate is 95%, the national annual cost savings in the United States is extrapolated to be more than $280 million.

In a retrospective study, Yao et al. (101) examined the direct medical costs of 40 patients treated with methotrexate and 40 patients treated with laparoscopic surgery. Taking into consideration the costs of failure, secondary treatment, and follow-up, the direct cost per patient was found to be significantly lower in the methotrexate group (Canadian $880 ± 160) compared with the laparoscopic surgery group (Canadian $1,840 ± 150). Extrapolation of data showed that, for a methotrexate success rate of 90%, the cost savings would be Canadian $131,055 for every 100 patients eligible for methotrexate.

CONCLUSIONS

Laparoscopic salpingostomy remains the standard treatment of EP in patients who are hemodynamically stable and who wish to preserve their fertility. The reproductive performance after salpingostomy appears to be equivalent or better than salpingectomy, but the recurrent EP rate may be slightly higher.

Expectant management has a poor efficacy and unproven benefit in subsequent reproductive outcome; therefore, its use should be limited to situations in which the EP is suspected but cannot be detected by transvaginal US. Other conditions for use of expectant management occur when surgery and methotrexate carry a higher risk, such as in the presence of heterotopic pregnancy or ovarian hyperstimulation syndrome.

The success rates of systemic, single-dose methotrexate (83% to 96%) are similar to those of local methotrexate administration under laparoscopic guidance (89% to 100%), but the success rate of methotrexate under US guidance seems to be lower (70% to 83%). Overall, the efficacy, IUP rate, and recurrent EP rate after methotrexate treatment are comparable to those after laparoscopic salpingostomy.

Methotrexate seems to be a reasonable treatment modality in cervical EPs as reports of success accumulate in the literature. However, discussion in this area is beyond the scope of this review.

Methotrexate should be considered as a viable alternative to surgical treatment in patients who fulfill strict inclusion criteria, including compliance with follow-up. However, a large, prospective, randomized trial with significant power is needed to study the prognostic factors for methotrexate success. Unified guidelines for methotrexate treatment then can be developed. Until then, we recommend methotrexate treatment of EP only to asymptomatic women with serum β-hCG levels of <2,000 mIU/mL, tubal diameter of <2 cm, and absence of fetal cardiac activity. Most importantly, the patient's understanding about her condition and her compliance are mandatory. The most practical and efficient method of methotrexate administration is IM injection. Those who do not meet the above criteria should be treated surgically and this can be done by laparoscopy.

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Note. Additional references are available from the authors upon request.