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Systematic review

Outcomes of Medical versus Surgical Management of Ectopic Pregnancy in Emergency Settings: A Systematic Review

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Abstract

Background: Ectopic pregnancy requires early assessment of hemorrhage risk, treatment suitability, and future reproductive priorities. Medical and surgical approaches differ in immediate effectiveness, surveillance requirements, and subsequent fertility

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This review compares outcomes of methotrexate and surgery for tubal ectopic pregnancy, emphasizing applicability to emergency care. **Methods:** This study was conducted according to PRISMA guidelines and we analyzed twelve comparative studies published before June 2026. Randomized trials and comparative cohorts were examined for treatment success, additional intervention, biochemical resolution, complications, subsequent pregnancy, recurrence, and resource use. Results were synthesized narratively because treatment regimens, surgical procedures, eligibility criteria, and outcome definitions differed. **Results:** Seven randomized trials and five observational studies informed the comparison. Individual trials reported methotrexate success of 65%-94.7%, with definitions differing regarding repeat doses. Surgery produced faster biochemical resolution, while additional methotrexate or rescue surgery remained necessary in some medically treated patients. Randomized fertility comparisons identified no statistically significant advantage for either strategy. A large population cohort associated methotrexate with higher subsequent live birth and recurrent ectopic pregnancy, alongside greater healthcare utilization. Treatment selection and baseline severity complicated observational comparisons. **Conclusion:** Methotrexate provides an effective option for selected stable patients with unruptured tubal pregnancy and reliable follow-up. Surgery provides rapid definitive treatment and remains essential for instability or suspected rupture.

Keywords: Ectopic pregnancy; methotrexate; surgical management; emergency care; salpingectomy; salpingostomy; fertility; systematic review.

Introduction

Ectopic pregnancy represents implantation outside the endometrial cavity and creates risks of internal hemorrhage, reproductive loss, and subsequent infertility. Tubal implantation accounts for most presentations, making tubal disease the focus of comparisons between medical and surgical treatment. Clinical decisions balance immediate maternal safety against treatment burden and future reproductive expectations, particularly when several management strategies remain clinically appropriate (1).

Accurate localization is central to treatment selection because pregnancy of unknown location is a temporary diagnostic classification rather than a confirmed ectopic pregnancy. Transvaginal ultrasonography and serial serum human chorionic gonadotropin measurements provide complementary information, with interpretation dependent on symptoms, imaging findings, and pregnancy evolution. Premature treatment based solely on an isolated biochemical result risks intervention in an intrauterine pregnancy, reinforcing the importance of diagnostic certainty before methotrexate administration (2).

Emergency presentations range from mild pain or vaginal bleeding to acute intraperitoneal

hemorrhage and circulatory compromise. This spectrum separates patients requiring immediate operative intervention from stable patients suitable for additional assessment and individualized treatment. Early recognition requires suspicion when symptoms are nonspecific and established risk factors are absent from the clinical history (3). Methotrexate inhibits trophoblastic proliferation, whereas surgery removes the affected pregnancy through salpingectomy or a tube-preserving procedure such as salpingotomy. These approaches differ in the speed of resolution, adverse effects, monitoring requirements, and risk of persistent trophoblast, making initial treatment success an incomplete measure of overall benefit (4).

Professional guidance identifies hemodynamic instability as an indication for prompt surgery rather than medical treatment (5). For stable patients, selection incorporates pregnancy characteristics, pretreatment hormone concentrations, medication contraindications, clinical symptoms, and access to follow-up. Reliable reassessment is especially relevant after emergency discharge because biochemical resolution takes time and deterioration requires rapid access to specialist care. A successful emergency pathway includes appropriate initial treatment and a workable plan for surveillance, symptom escalation, and completion of care (6).

Recent literature emphasizes precise classification, avoidance of unnecessary intervention, and attention to reproductive and psychological outcomes after ectopic pregnancy (7). These support separate assessment of immediate resolution, additional intervention, subsequent intrauterine pregnancy, and recurrent ectopic implantation rather than a single composite outcome. The present review evaluates medical versus surgical outcomes in tubal ectopic pregnancy and interprets their relevance to emergency assessment and subsequent care, recognizing that evidence from stable treatment candidates does not directly represent patients presenting with rupture or shock.

Methods

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review compared medical and surgical management of tubal ectopic pregnancy in emergency departments, acute gynecology services, and hospital early-pregnancy pathways. Eligible publications covered database inception through May 31, 2026.

PubMed, Scopus, and Web of Science Core Collection were searched using controlled vocabulary, where available, and free-text terms. Search concepts combined “ectopic pregnancy” or “tubal pregnancy” with “methotrexate” or “medical management” and “surgery,” “laparoscopy,” “salpingectomy,” “salpingotomy,” or “salpingostomy.” Search syntax was adapted to each database, and reference lists of relevant publications were examined for additional studies. Emergency-setting and outcome restrictions were omitted from the electronic searches to retain potentially relevant hospital studies. Complete search strategies and search dates were documented separately for reproducibility.

Randomized controlled trials and comparative cohort studies were eligible when they reported extractable outcomes for medical and surgical treatment groups. Medical management included systemic methotrexate, with local administration evaluated separately. Surgical management included salpingectomy and tube-preserving procedures. Studies involving expectant management were eligible when medical–surgical comparisons were extractable. Case reports, noncomparative series, reviews, and studies restricted to non-tubal pregnancies were excluded from the primary synthesis (Fig 1).

Two authors independently screened titles and abstracts after duplicate removal. Both authors independently assessed eligible full-text reports against the eligibility criteria and documented reasons for exclusion. Disagreements were resolved through discussion and source re-examination until consensus was reached. Study identification, screening, eligibility assessment, and inclusion were summarized in a PRISMA flow diagram.

Two authors independently extracted study characteristics and outcome data using a standardized form. Extracted variables included study design, setting, sample size, hemodynamic status, pretreatment human chorionic gonadotropin concentrations, treatment regimen, surgical procedure, and follow-up duration. Outcomes included treatment success, additional medication, rescue surgery, rupture, persistent trophoblast, biochemical resolution, adverse events, healthcare utilization, subsequent intrauterine pregnancy, live birth, and recurrent ectopic pregnancy.

Both authors independently assessed randomized trials using RoB 2 and nonrandomized studies using ROBINS-I, resolving disagreements through discussion. Findings were synthesized narratively, separating randomized from observational evidence and distinguishing medical regimens and

surgical techniques. Study-specific definitions and denominators were retained, particularly for initial treatment success and subsequent fertility. Adjusted estimates were prioritized when available, and companion publications were linked to prevent

duplicate participant counting. Quantitative pooling was not undertaken because clinical characteristics, treatment protocols, outcome definitions, and follow-up periods differed substantially across studies.

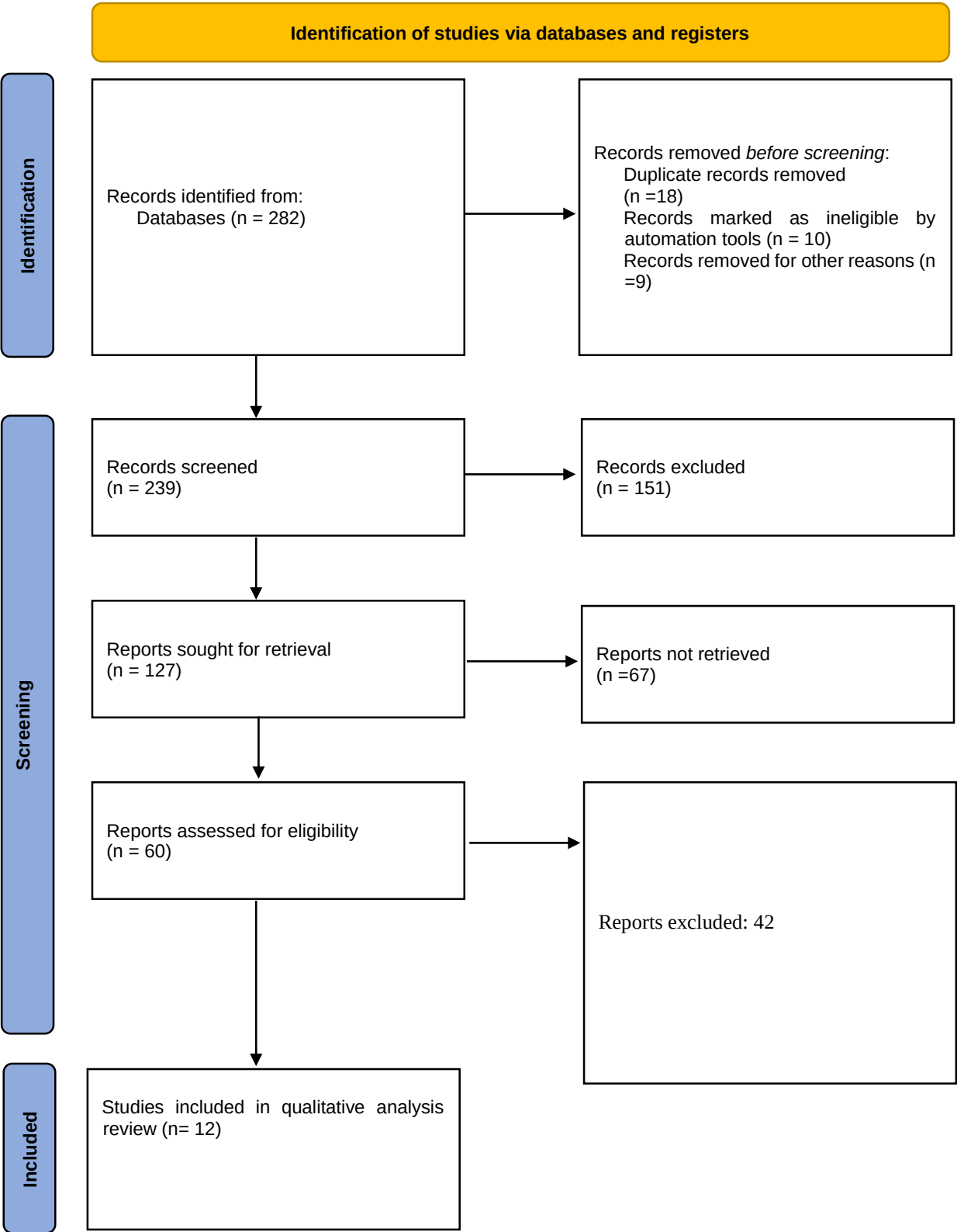


Fig 1: PRISMA flow chart

Results

In an early trial, Zilber et al. randomized 48 women to salpingostomy or laparoscopically administered local methotrexate. Persistent trophoblastic activity occurred in 5% and 14%, respectively. Because medical administration involved laparoscopy, this comparison did not represent fully nonoperative emergency treatment (8). Hajenius et al. randomized 100 stable women with unruptured pregnancy, reporting resolution after one methotrexate course in 42/51 and after salpingostomy alone in 35/49. Seven methotrexate recipients required surgery, including five salpingectomies for rupture, while ten surgical recipients required methotrexate for persistent trophoblast (9). Fernandez et al. reported success in 45/51 medically treated women and 47/49 surgically treated women; hormone normalization took 29 versus 13 days (10). Saraj et al. similarly found faster hormone clearance after surgery, with resolution times of 20.2 versus 27.2 days after methotrexate (11). Different hormone thresholds across trials further limited direct comparisons of the reported intervals between treatment and completed biochemical resolution (9-11) (Table 1).

In Sowter et al., initial treatment required no further intervention in 22/34 methotrexate recipients versus 26/28 surgical recipients, a significant difference favoring surgery. Nine medically allocated women received additional methotrexate and five underwent laparoscopy during follow-up, demonstrating the distinction between single-dose success and eventual avoidance of surgery (12). Krag Moeller et al. reported success rates of 74% with methotrexate and 87% with surgery among 106 women, without a statistically significant difference. Subsequent spontaneous intrauterine pregnancy occurred in 73% versus 62%, respectively, also without statistical significance (13) (Table 2).

In the population-based study by de Bennetot et al., involving 1,064 women, two-year cumulative intrauterine pregnancy rates were 76% after medical treatment, 76% after salpingostomy, and 67% after salpingectomy. Age, infertility history, and tubal disease influenced reproductive prognosis, complicating interpretation of treatment-associated differences (14). In the DEMETER trial's directly relevant 207-woman arm, two-year intrauterine pregnancy rates were 67% after methotrexate and 71% after conservative surgery with postoperative methotrexate, with no statistically significant difference (15).

Baggio et al. evaluated 173 women attempting conception and reported cumulative intrauterine clinical pregnancy incidences of 55.3% after methotrexate and 39.5% after surgery; the medical-surgical pairwise comparison was not statistically significant (16). Asgari et al., studying 194 women over 18 months, likewise identified no significant fertility differences among methotrexate, salpingostomy, and salpingectomy groups (17). Scarpelli et al. reported methotrexate resolution in 26/36 patients and rescue surgery in ten; fertility follow-up covered only 50/107 patients (18).

Rosen et al. identified 17,090 pregnancies, with subsequent live birth in 51.6% after medical versus 45.1% after surgical treatment, adjusted odds ratio 1.30 (95% confidence interval 1.22-1.38). Recurrence was 7.4% versus 6.4%, adjusted odds ratio 1.17 (1.04-1.32), alongside greater healthcare utilization after methotrexate. The review's interpretation is that these associations do not establish causal fertility superiority, given nonrandom treatment allocation and residual confounding (19). Across the twelve studies, seven randomized comparisons and five observational cohorts supplied different outcome-specific denominators, rather than one interchangeable population for assessing resolution and subsequent fertility (8-19). Local injection, postoperative methotrexate, and systemic outpatient treatment

represented distinct therapeutic strategies within this evidence set.

Table 1. Characteristics of the included studies.

Study	Design and sample	Treatment comparison	Main interpretive issue
Zilber, 1996	RCT; 48	Local MTX versus salpingostomy	MTX delivery required laparoscopy (8)
Hajenius, 1997	RCT; 100	Multidose systemic MTX versus salpingostomy	Diagnostic laparoscopy preceded both treatments (9)
Fernandez, 1998	RCT; 100	Local/systemic MTX versus salpingotomy	Medical administration involved different routes (10)
Saraj, 1998	RCT; 75 randomized	Systemic MTX versus salpingostomy	Success allowed repeat MTX administration (11)
Sowter, 2001	RCT; 62	Single-dose protocol versus laparoscopy	Additional treatment counted against initial success (12)
Krag Moeller, 2009	RCT; 106 confirmed EP	Systemic MTX versus salpingotomy	Recruitment below planned sample size (13)
de Bennetot, 2012	Population cohort; 1,064	Medical treatment versus conservative/radical surgery	Fertility influenced by pretreatment characteristics (14)
Fernandez, 2013	DEMETER RCT; relevant arm 207	MTX alone versus conservative surgery plus MTX	Surgical comparison included postoperative medication (15)
Baggio, 2021	Retrospective cohort; 173	MTX, surgery, or expectation	Fertility groups classified by definitive treatment (16)
Asgari, 2021	Retrospective cohort; 194	MTX, salpingostomy, or salpingectomy	Treatment selected according to clinical status (17)
Scarpelli, 2025	Retrospective cohort; 107	MTX versus primary salpingectomy	Fertility follow-up available for 50 patients (18)
Rosen, 2025	Population cohort; 17,090	Medical, surgical, or combined treatment	Administrative-data comparisons retain residual confounding (19)

Table 2. Treatment and reproductive outcomes reported by the comparative studies.

Study	Medical outcome	Surgical outcome	Interpretation
Zilber	Persistent trophoblast: 14%	Persistent trophoblast: 5%	Difference not statistically significant (8)
Hajenius	One-course success: 42/51; surgery required: 7/51	Salpingostomy-alone success: 35/49	Additional treatment occurred in both groups (9)
Fernandez, 1998	Success: 45/51; hCG normalization: 29 days	Success: 47/49; normalization: 13 days	Biochemical resolution favored surgery (10)
Saraj	Success: 36/38; hCG resolution: 27.2 days	Success: 33/36; resolution: 20.2 days	Reported outcome denominators retained (11)
Sowter	No further treatment: 22/34	No further treatment: 26/28	Initial success favored surgery (12)
Krag Moeller	Success: 74%; subsequent spontaneous IUP: 73%	Success: 87%; subsequent spontaneous IUP: 62%	Differences not statistically significant (13)
de Bennetot	Two-year IUP: 76%	Salpingostomy: 76%; salpingectomy: 67%	Nonrandomized fertility comparison (14)
DEMETER	Two-year IUP: 67%	Two-year IUP: 71%	HR 0.85, 95% CI 0.59-1.22 (15)
Baggio	Subsequent clinical IUP: 55.3%	Subsequent clinical IUP: 39.5%	Pairwise difference not statistically significant (16)

Study	Medical outcome	Surgical outcome	Interpretation
Asgari	MTX group: 64 women	Salpingostomy: 52; salpingectomy: 78	No significant fertility difference at 18 months (17)
Scarpelli	Live birth: 9/17 with follow-up	Live birth: 25/33 with follow-up	Limited follow-up; p=0.12 (18)
Rosen	Live birth: 51.6%; recurrent EP: 7.4%	Live birth: 45.1%; recurrent EP: 6.4%	Adjusted associations favored medical treatment for live birth and surgery for recurrence (19)

Discussion

The central finding is that immediate treatment success and longer-term reproductive outcomes answer different clinical questions, with the apparent balance changing according to the endpoint used. The historical Cochrane review found lower success after one methotrexate dose than after salpingostomy, while allowing additional doses reduced the difference between treatment strategies (20). Mol et al. similarly emphasized regimen-specific effectiveness, costs, and reproductive outcomes, supporting interpretation of methotrexate as a monitored treatment pathway requiring sustained access to clinical care (21).

Surgical technique substantially affects the comparator and limits conclusions drawn from treating all operations as equivalent. In the ESEP trial, women with a healthy opposite tube had ongoing natural pregnancy rates of 60.7% after salpingotomy and 56.2% after salpingectomy, without a significant difference. Persistent trophoblast occurred more frequently after salpingotomy, indicating that tubal preservation does not automatically translate into better fertility or complete treatment at the initial operation (22).

Pretreatment disease characteristics also explain variation in medical success and create confounding when observational groups differ in clinical severity (16,18). Lipscomb et al. identified pretreatment human chorionic gonadotropin concentration as the principal independent predictor of methotrexate failure in a 350-woman series (23). This finding supports careful selection and

transparent counseling about repeat dosing and rescue intervention, while avoiding interpretation of a single hormone threshold as a complete assessment of safety (5,23).

Follow-up burden is particularly relevant to emergency services because discharge does not mark the end of treatment (6,24). Davenport et al. reported a median resolution interval of 22 days among methotrexate recipients avoiding surgery, with longer intervals at higher baseline hormone concentrations (24). Serial testing, transport, time away from work, access to urgent reassessment, and patient preferences therefore form part of the practical treatment comparison (6,24).

Economic findings also depend on baseline risk and the organization of care rather than medication price alone (21,25). In the companion economic analysis of Sowter's trial, direct costs favored methotrexate, while the indirect-cost advantage disappeared above pretreatment hormone concentrations of 1,500 IU/L. These historical estimates support including surveillance and additional intervention in contemporary evaluations, without transferring their monetary values directly to other health systems (25).

Randomized fertility findings deserve greater causal weight than unadjusted differences from cohorts, although several trials were small and imprecise, with clinically relevant uncertainty remaining (13,15-19). The large Ontario association between methotrexate and live birth is clinically relevant, alongside its higher recurrence and healthcare-use findings, rather than proof that medication

improves fertility (19). Several studies used biochemical success, whereas others emphasized subsequent pregnancy among women with a continuing desire to conceive, producing denominators that address different populations. Failure to separate these outcomes risks overstating either the immediate benefits of surgery or the reproductive benefits attributed to medical treatment, especially when fertility follow-up excludes patients who did not attempt conception (14,16-19). Emergency applicability is limited by selection of stable trial participants, variable reporting of rupture and transfusion, and mixed hospital settings; accordingly, these findings support individualized management after stabilization, with immediate surgery for instability or suspected rupture.

Conclusion

Methotrexate and surgery provide effective treatment for selected women with tubal ectopic pregnancy, with different burdens of intervention and follow-up. Surgery achieves faster resolution, while medical treatment avoids an operation in many stable patients and carries a continuing risk of additional treatment. Randomized evidence does not establish consistent fertility superiority for either strategy. Observational fertility differences require interpretation alongside baseline disease severity and treatment selection. Emergency decisions require clinical assessment of hemodynamic status, diagnostic certainty, symptoms, pregnancy characteristics, treatment contraindications, and access to surveillance.

Abbreviations

Abbreviation Definition

CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
EP	Ectopic pregnancy
hCG	Human chorionic gonadotropin
HR	Hazard ratio
IUP	Intrauterine pregnancy

Abbreviation Definition

MTX	Methotrexate
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
RoB 2	Risk of Bias 2 tool
ROBINS-I	Risk Of Bias In Non-randomized Studies of Interventions

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