Effectiveness of treatment options for tubal ectopic pregnancy: a systematic review and network meta-analysis

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Short Title: Treatment options for tubal ectopic pregnancy.

Abstract:

Background: Tubal ectopic pregnancy (TEP) is a common gynaecological emergency. Several medical and surgical treatment options exist, but it is not clear which is the safest and most effective treatment.

Objective: To compare the effectiveness of expectant, medical and surgical treatment options for TEP using a systematic review and network meta-analysis.

Search strategy:MEDLINE, EMBASE, and CENTRAL from inception till September 2022.

Selection criteria: Randomised trials that evaluated any treatment option for woman with a TEP.

Data Collection and Analysis: We performed pairwise and network meta-analyses using a random effect model. We assessed the studies' risk of bias, heterogeneity and network inconsistency. We reported primarily on TEP resolution and treatment failure using relative risk(RR) and 95% confidence-intervals(CI).

Main Results: We included 31 randomised trials evaluating nine treatments (n=2938 women). Direct meta-analysis showed no significant benefit for using methotrexate compared to expectant management for TEP resolution.

Network meta-analysis showed similar effect-size for most conservative treatment options compared to expectant management for TEP resolution (glucose intra-sac instillation vs.expectant RR 0.84, 95%CI 0.63-1.12; methotrexate intra-sac instillation vs.expectant RR 0.91, 95%CI 0.75-1.10; multi-dose methotrexate vs.expectant RR 1.00, 95%CI 0.88-1.15; prostaglandin intra-sac instillation vs.expectant RR 0.75, 95%CI 0.53-1.07; salpingotomy vs.expectant RR 0.99, 95%CI 0.84-1.16; single dose methotrexate vs.expectant RR 0.97, 95%CI 0.85-1.10; single dose methotrexate+mifepristone vs.expectant RR 1.09, 95%CI 0.89-1.33).

All treatment options showed a higher risk of failure compared to salpingectomy.

Conclusion: There is insufficient evidence to support the use of any medical treatment option for TEP over expectant management.

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Introduction

Tubal ectopic pregnancy (TEP) is a common gynaecological condition occurring in about 1–2% of all reported pregnancies (1). TEP is the most common type of ectopic pregnancies accounting for 98% of all reported cases (2) leading to significant maternal morbidity and mortality with almost 10% of all pregnancy-related deaths in the USA in 2010–2013 (3).

Surgical removal of the affected fallopian tube is the standard treatment for TEP commonly performed via minimally invasive surgery. A number of conservative treatments have been proposed with the objective of preserving the affected tube and the potential for future fertility including expectant management, systemic pharmacological agents (e.g. methotrexate intramuscular injections), pharmacological agent installation directly into the gestational sac (e.g. transvaginal installation of glucose or prostaglandin), and minimally invasive surgery to excise the ectopic pregnancy while preserving the affected fallopian tube (e.g. salpingotomy or salpingostomy). Advances in transvaginal ultrasonography facilitated the early detection and accurate diagnosis of TEP (4) whereby conservative treatments can be offered to clinically stable women with ultrasonic features of a small gestation sac of TEP, no evidence of embryonic cardiac activity and with relatively low serum ß-hCG levels (5). Recent clinical guidelines supported the option of expectant management of TEP in asymptomatic women with plateauing or reducing ß-hCG levels which can be monitored clinically and biochemically without the need for any active treatment (2). Similarly, performing a salpingotomy or salpingostomy is suggested to preserve the affected tube especially in women with reduced fertility potential (6).

While promising, the use of these conservative treatment options has been associated with a varied success rate (7). The risks of conservative management include systemic illness

following administration of chemotherapeutic agents and the need for emergency surgery in case of TEP rupture (8). With many available treatment options, there is a need to carefully assess their risks and benefits in order to counsel patients appropriately and offer the most suitable treatment option in their individual cases.

Objectives: To perform a comprehensive literature review and evidence synthesis to compare available treatment options for TEP, directly and indirectly, using a systematic review and network meta-analysis approach.

Methods

We conducted this review following a prospectively registered protocol (CRD42020175487) and reported the findings as per established guidelines (9).

Eligibility criteria, information sources, search strategy

We searched the following electronic databases (MEDLINE, EMBASE, and Cochrane CENTRAL) for randomised trials evaluating any treatment option for tubal ectopic pregnancy (from inception till Septembre 2022). We used Mesh headings (*ectopic, tubal, fallopian, pregnancy, pregnant, laparoscopy, laparotomy, salpingectomy, salpingostomy, salpingotomy, methotrexate, glucose instillation, mifepristone, prostaglandin, expectant, wom?n, female*) and combined them using Boolean operators (AND, OR) to conduct our searches and adjusted the strategy for each database (Supplementary Appendix 1). We conducted supplementary searches in Google Scholar and Scopus to identify any missing evidence. No search filters or language limitations were employed, articles in non-English language were obtained and translated if deemed relevant. We manually screened bibliographies of potentially relevant articles and published systematic reviews on the topic to

identify any additional relevant trials. We did not include any unpublished data in the analysis or studies made available online that were not peer-reviewed.

Study selection

We performed the study selection and data extraction processes in duplicate (SS and LDB) which were further checked by a third reviewer (BHA). Inconsistencies and disagreement were resolved by discussion and consensus with a fourth reviewer (DJ). We included all randomised controlled trials that evaluated the effectiveness of any treatment options (expectant, medical, or surgical) in woman diagnosed with a tubal ectopic pregnancy. We included studies with multiple comparison arms, and those evaluating a combination of treatment options (e.g. salpingotomy + methotrexate injection). For the purpose of this review, we considered a salpingostomy and salpingotomy to be equal surgical measures aimed to excise the ectopic pregnancy surgically while preserving the affected Fallopian tube. We excluded studies that included women with non-tubal ectopic pregnancies (e.g. caesarean scar or ovarian ectopic pregnancy), those with quasi or non-randomised design, and those not reporting on any of the outcomes pre-specified in our protocol (e.g studies reporting only future fertility outcomes).

Data extraction

Our main outcome was the resolution of the ectopic pregnancy confirmed biochemically by the gradual decrease in ß-hCG or clinically where no additional treatment was needed at the end of the follow-up period (as defined by the authors) in each study. We also reported on the risk of treatment failure defined as the need for emergency surgery following a primary elective treatment option (e.g. salpingectomy after using methotrexate) and/or the need to convert a primary surgical treatment option to salpingectomy (e.g. performing a salpingectomy after a failed salpingotomy). We reported on the following treatment

complications injury to visceral or pelvic organs, liver or bone marrow damage, haemorrhage, infection, unexpected conversion to open surgery, thrombosis, death, need for blood transfusion and length of hospital stay.

We extracted data on the country of the study, the publication journal, trial settings, population characteristics, the diagnostic criteria for tubal ectopic pregnancy, the duration of treatment, the length of follow-up and the criteria employed for tubal ectopic resolution.

Assessment of risk of bias

Two independent reviewers (SS and LDB) assessed the quality of included studies using the Cochrane risk of bias assessment tool 2 (10). Each study was assessed for the quality of randomisation and sequence generation, allocation to intervention groups, outcome assessment, completeness of outcome data, and selective outcome reporting. Blinding was deemed non-feasible due to the nature of the evaluated interventions and was excluded from the quality assessment. Efforts to standardise the management of women who received sequential treatment doses (e.g. multiple methotrexate injections) were considered to show less risk of bias when evaluating detection and outcome assessment bias. Similarly, trials that employed a quality assurance process to ensure adequate diagnosis of TEP against a defined criteria were deemed to have less risk of performance bias compared to those that did not employ any quality measures or report on protocol violations.

Data synthesis

First, we assessed the network geometry of available evidence comparing all available treatment options for TEP using the network map command in Stata. Where possible, we generated pool effect estimates from direct comparisons of each treatment pair using a random-effect REML model (11). We assessed heterogeneity using I^2 statistics and explored

potentials for risk of publication bias using a funnel plot. We then performed a network meta-analysis within a frequentist framework fitting multivariate meta-analysis models with random effect using the network package in Stata (12,13) exploiting the direct and indirect randomised evidence to determine the relative effects and ranking. We reported using risk ratios (RR) with 95% confidence intervals (CI). For the primary analysis on resolution of TEP, we adopted a pragmatic approach whereby trials evaluating a particular pharmacological agent (e.g. methotrexate) were considered to be equal irrespective of variations in the total dose given, route and format. We calculated the mean rank and the surface under the cumulative ranking curve (SUCRA) for each intervention for all reported outcomes. Treatment options with a SUCRA value close to 100% had the highest cumulative rank (i.e highest likelihood) for achieving the primary outcome (complete resolution of the TEP or treatment failure) (14,15).

We used the design-by-treatment model to check the assumption of consistency in the entire network assuming a common estimate for the heterogeneity variance across the different comparisons in the network for each of the reported outcomes (16). Where relevant, we investigated and detected inconsistency by comparing the direct and indirect evidence within the network using the node-splitting approach (17) assuming a common heterogeneity estimate within each loop (a loop of evidence exists when numerous trials compare a minimum of three treatments e.g A vs B vs C)(18), as well as investigating potential sources of inconsistency within relevant trials. We planned a network meta-regression to explore any detected inconsistency for potential effect modifiers (19). All analyses were done using Stata statistical software, release 14.0 (StataCorp, College Station, TX, 2015) (12,15,20).

Results

Study selection and study characteristics

Our electronic search yielded 444 potentially relevant citations out of which we screened 67 in full and included 38 in our review (Figure 1). Seven (21–27) of the included trials compared variations of the same treatment options either using different routes or different equipments and therefore were not included in the meta-analysis (Supplementary Table 1). All included trials had a two groups parallel design and eight were multi-centre (8/38, 21%). The majority were conducted in European countries (16/38, 42%) and only twelve were conducted in developing countries (12/38, 32%).

Half of the included trials diagnosed TEP on ultrasound (20/38, 52%) while a quarter of studies were non-specific on how TEP was diagnosed (9/38, 23%) and a further quarter did not specify whether TEP was diagnosed on ultrasound at all (9/38, 23%) (Supplementary Table 1). Resolution of TEP was defined biochemically in most trials when ß-hCG fell below 5-15mIU/mL post treatment (Supplementary Table 1).

We identified nine unique treatment options that were included in our network meta-analysis (n=2938) including expectant management (5 RCTs, n=158); single dose methotrexate injection (18 RCTs, n= 850); multiple doses of methotrexate injections (11 RCTs, n=592); single dose methotrexate injection plus mifepristone (2 RCTs, n=138); methotrexate intra-sac instillation (6 RCTs, n=147); glucose intra-sac instillation (3 RCTs, n=35); prostaglandin intra-sac instillation (2 RCTs, n=24); salpingotomy (11 RCTs, n=574); salpingotomy plus methotrexate injection (3 RCTs, n=164); and only one trial that evaluated salpingectomy (1 RCT, n=231) (Supplementary Table 1)(Figure 2).

Risk of bias of included studies

The overall quality of included trials was moderate. Eighteen trials (18/38, 47%) showed high risk of bias for randomisation and twelve (12/38, 31%) for allocation to intervention groups. Sixteen trials showed high risk for outcome assessment (16/38, 43%) and twenty selective reporting bias (20/38, 53%). Only five trials (5/38, 13%) had high loss to follow-up and data incompleteness. Over two-thirds of the included trials were judged to have high risk of performance bias (29/38, 76%) (Supplementary Figure 1, Supplementary Table 2). We assessed the risk of publication bias in included trials visually using a funnel plot (Supplementary Figure 2).

Synthesis of results

TEP resolution and treatment failure

Our direct meta-analysis showed no significant difference in using methotrexate compared to expectant management for TEP resolution (single dose methotrexate vs expectant RR 0.97 95%CI 0.84-1.13; multi-dose methotrexate vs expectant RR 1.33 95%CI 0.53-3.38). Similarly, methotrexate showed a similar effect on TEP resolution compared to salpingotomy (RR 1.03 95%CI 0.67-1.59). Only one trial evaluated the performance of salpingotomy to salpingectomy which showed no difference for TEP resolution (RR 1.43 95%CI 0.51-4.06). Two trials evaluated the use of salpingotomy+methotrexate vs salpingotomy alone which showed higher chance of TEP resolution (RR 1.15 95%CI 1.05-1.25) (Figure 3a). Pairwise, direct meta-analysis did not show significant difference in the risk of failure across all compared treatments (Figure 3a, 3b).

Our network meta-analysis showed similar findings whereby most of the conservative treatment options did not yield a higher chance of TEP resolution compared to expectant management glucose intra-sac instillation vs.expectant RR 0.84, 95%CI 0.63-1.12;

methotrexate intra-sac instillation vs.expectant RR 0.91, 95%CI 0.75-1.10; multi-dose methotrexate vs.expectant RR 1.00, 95%CI 0.88-1.15; prostaglandin intra-sac instillation vs.expectant RR 0.75, 95%CI 0.53-1.07; salpingotomy vs.expectant RR 0.99, 95%CI 0.84-1.16; single dose methotrexate vs.expectant RR 0.97, 95%CI 0.85-1.10; single dose methotrexate+mifepristone vs.expectant RR 1.09, 95%CI 0.89-1.33) (Supplementary Figure 3) .

Salpingotomy+methotrexate outperformed most other conservative treatment options to achieve complete resolution of TEP (salpingotomy+methotrexate vs. glucose intra-sac instillation RR 1.38, 95%CI 1.07-1.80; salpingotomy+methotrexate vs. methotrexate intra-sac instillation RR 1.28, 95%CI 1.11-1.47; salpingotomy+ methotrexate vs. multi-dose MTX RR 1.16, 95%CI 1.02-1.31; salpingotomy+ methotrexate vs. PG intra-sac Instillation RR 1.54, 95%CI 1.11-2.14; salpingotomy+ methotrexate vs. salpingotomy RR 1.18, 95%CI 1.07-1.30; salpingotomy+ methotrexate vs. single dose methotrexate RR 1.20, 95%CI 1.06-1.36) except in comparison to expectant management (RR 1.16, 95%CI 0.99-1.38) and single dose methotrexate+mifepristone (RR 1.06, 95%CI 0.87-1.30) (Supplementary Figure 3). Evidence on effectiveness of salpingotomy+methotrexate was sought from three RCTs (28–30) which showed an overall moderate risk of bias (Supplementary Table 2). Both direct and mixed evidence showed similar effect estimates for TEP resolution . We did not detect significant inconsistency in the network for resolution of TEP (p= 0.52) or treatment failure (p= 0.37).

All treatment options were associated with a higher risk of failure when compared with salpingectomy (salpingectomy vs. expectant RR 0.09, 95%CI 0.03-0.30 salpingectomy vs. glucose intra-sac instillation RR 0.02, 95%CI 0.00-0.11; salpingectomy vs. methotrexate intra-sac instillation RR 0.02, 95%CI 0.00-0.08; salpingectomy vs. multi-dose methotrexate

RR 0.12, 95%CI 0.04-0.38; salpingectomy vs. PG intra-sac instillation RR 0.01, 95%CI 0.00-0.09; salpingotomy vs. salpingectomy 12.46, 95%CI 5.10-30.48; salpingotomy+methotrexate vs. salpingectomy 16.96, 95%CI 1.52-189.90); single dose methotrexate vs. salpingectomy RR 8.59, 95%CI 3.03-24.36); single dose methotrexate+mifepristone vs. salpingectomy RR 6.82, 95%CI 2.17-21.47) (Supplementary Figure 4).

Our ranking assessment was consistent with the detected effect size for each treatment option with salpingotomy+methotrexate ranking first for resolution of TEP (SUCRA 95.4) and seventh for treatment failure (SUCRA 56.0). PG intra-sac -instillation had the highest likelihood for treatment failure (SUCRA 90.4) followed by methotrexate intra-sac instillation (SUCRA 84.6) and glucose intra-sac instillation (SUCRA 84.2) (Figure 4, Supplementary Figure 5). The use of single dose methotrexate and multi-dose methotrexate showed modest ranking for both resolution of TEP and treatment failure with both ranking lower than expectant management (Figure 4, Supplementary Figure 5).

Secondary outcomes

There was limited reporting for other planned secondary outcomes (need for blood transfusion, length of hospital stay, and surgical complications). Only two trials reported on the need for blood transfusion showing no significant difference between evaluated treatments (Supplementary Table 3). Seven trials reported on any surgical complications but evidence synthesis was not possible. Moeller 2009 et al (31) reported a 49% conversion rate from salpingotomy to salpingectomy in their cohort which could indicate the limited surgical expertise in performing this technique. A meta-analysis was not possible to compare the length of hospital stay due to varied reporting across included trials (Supplementary Table 3).

Discussion:

Principal Findings

Our findings provide a comprehensive assessment of all available treatment options for TEP using various expectant, medical, surgical treatment modalities and their combinations. Majority of randomised trials included in our meta-analysis were focused on evaluating conservative measures aimed to preserve the affected fallopian tube with only one trial evaluating the effectiveness of salpingectomy as the standard treatment of TEP. Consequently, performing meta-analyses using direct evidence only would offer an inaccurate assessment of the effectiveness of these conservative treatment options with no appropriate comparison to current clinical practice.

This is particularly relevant as conservative treatment options can only be offered safely to 30-40% of women with low risk TEP in contrast to salpingectomy which is the established standard treatment option offered to the vast majority of affected women.

Methotrexate was the most commonly assessed pharmacological agent administered in various doses, routes, and regimes (single dose, multiple doses, instilled directly into the gestation sac, and combined with surgery). Our analysis of randomised evidence showed no added benefits of using methotrexate compared to expectant management alone as a primary treatment for TEP. The use of salpingotomy with methotrexate seems to offer a good chance of TEP resolution with moderate risk of treatment failure (conversion to salpingectomy), however, direct evidence supporting the effectiveness of this treatment option was limited to three RCTs.

Strengths and limitations

Our evidence synthesis is by far the most comprehensive attempt to identify the optimal management of TEP. We followed standard up-to-date methodology and leveraged both direct and indirect evidence from available trials. We assessed the quality of available trials and the risk of publication bias.

The generalizability of our findings mainly stems from the varied reporting across included trials and the lack of comparison to the current established standard treatment (salpingectomy). We detected a high risk of performance bias in several of the included studies but were unable to adjust for it due to limited reporting. This is particularly applicable to trials which used varied sequential doses of methotrexate. Similarly, we were unable to adjust for several important participant characteristics (e.g. history of previous ectopic pregnancy, gestation sac size, level of ß-hCG) or explore them using meta-regression. Several key characteristics can impact the chances of successful conservative treatments for TEP. Trials evaluating expectant management were most probably highly selective of participants with favourable characteristics of a spontaneously resolving TEP. Adjusting for these factors to establish a dose-response association could only be achieved with individual participant data meta-analysis. We planned to report on several important secondary outcomes (need for blood transfusion, length of hospital stay, and surgical complications) but we were unable to perform this by the lack of consistent reporting across included trials. Time to TEP resolution is an important outcome to consider when counselling patients on available treatment options as medical treatment options require longer follow-ups, more outpatient visits to specialised early pregnancy units, and increased anxiety (32).

Comparison with Existing Literature and implication for clinical practice

Advances in ultrasound technology and the development of diagnostic biochemical algorithms have enabled accurate detection and detailed assessment of women with TEP

which facilitates rapid access to treatment (33)(34). Still, the optimal management of TEP remains controversial with wide variations across available evidence-based clinical practice guidelines(2)(35). Most clinical guidelines recommend rapid surgical management of TEP in haemodynamically unstable women with salpingectomy as the established standard treatment option (via laparoscopy or laparotomy)(2).

Several clinical practice guidelines support the use of methotrexate in various doses, routes and regimes as a viable conservative treatment option to surgery and expectant management (2)(35). This, however, was not reflected in the evidence from available trials as none of the suggested methotrexate regimes seemed to offer an advantage over expectant management. While several observational studies suggested a higher chance for TEP resolution with methotrexate in pregnancies with ß-hCG values between 1500 and 5000 IU/L (36), this evidence was not replicated in our meta-analysis of randomised trials. An IPD meta-analysis might help to identify subgroups where methotrexate might offer clinical value, however, given the overall trend of both direct and indirect evidence, its effectiveness remains debatable.

Several clinical practice guidelines support the use of salpingotomy or salpingostomy in women desiring future fertility with findings of an abnormal contralateral tube at surgery (2)(35). We captured only one trial that directly compared salpingotomy to salpingectomy showing no statistically significant difference in the rates of a subsequent normally sited pregnancy (RR, 1.04; 95% CI, 0.899–1.21) or recurrent TEP (RR, 1.30; 95% CI, 0.72–2.38)(37). Leveraging both direct and indirect evidence, our network meta-analysis supports the value of salpingotomy in offering similar rates of TEP resolution to salpingectomy (RR 0.94, 95%CI 0.83-1.06), however, there was a significantly higher risk of needing additional emergency surgery or conversion to salpingectomy (RR 12.46, 95%CI 5.10-30.48). This

could be attributed to the limited surgical experience in conducting a salpingotomy and achieving adequate haemostasis in the affected tube, especially in centres with no advanced expertise in minimal-access surgery.

Future research need

Robust information regarding the success rate and long-term effects of available treatment options for TEP is essential to appropriately counsel affected women and to aid informed decision making. This is particularly relevant when considering conservative treatment options aiming to preserve the affected fallopian tube bearing in mind the paucity of evidence supporting their effectiveness compared to salpingectomy. In women with no history of tubal factor subfertility, performing salpingectomy does not seem to have a significant negative impact on their future fertility when compared with salpingotomy (37). Observational cohorts reported a slightly better chance of future normally sited pregnancy following expectant or medical management of TEP compared to surgery (38). However, long-term follow-up studies of adequately powered randomised cohort are needed to establish the effect of TEP treatments on future fertility.

We detected high variation in outcomes' reporting with little engagement of lay consumers in the design and reporting in available trials. In view of ongoing efforts to establish core outcome reporting sets for TEP (39) informed by relevant stakeholders and lay consumers, we call on future investigators to comply with standardised reporting to maximise the value of evidence synthesis.

Our assessment of the literature on the management of TEP highlights the need for future trials to evaluate the non-inferiority of any new treatment option to the standard treatment of salpingectomy. Recently the use of Gefitinib (an orally available epidermal growth factor

receptor inhibitor) combined with methotrexate has been suggested to offer faster resolution of ectopic pregnancies in pre-clinical studies (40) although the findings of the GEM3 multi-centre randomised trial suggest no added clinical value of using methotrexate alone (41)(42). In such trial design, the key limitation is the lack of direct comparison to salpingectomy which will limit the adoption of any new treatment in clinical practice even if found to be superior to methotrexate alone.

Our analysis suggests that offering salpingotomy with methotrexate might provide good chance of TEP resolution with lower risk of failure. However, compared to salpingectomy this treatment would require longer follow-up and it might be associated with more side-effects and higher health costs. Our analysis was limited to direct evidence sought from three relatively small trials comparing salpingotomy plus methotrexate to salpingotomy alone (43,44) and methotrexate alone (45). Therefore, larger trials are needed to confirm its clinical and cost-effectiveness as a viable conservative treatment option for TEP before adopting it in clinical practice.

Conclusions

Current evidence does not support the use of pharmacological treatments over expectant management in women having non-surgical management of tubal ectopic pregnancy. Surgical treatment with salpingotomy plus methotrexate could offer an effective alternative conservative treatment option but larger trials are needed before adopting it in clinical practice. Future trials should compare novel treatment options to the standard treatment of salpingectomy to enable better quality evidence synthesis.

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