

Brief description of patient problem/setting (summarize the case very briefly)

20 year old female – presents to the emergency room with sudden syncope, lower right abdominal pain, and amenorrhea. After taking an H&P and conducting multiple tests, she is diagnosed with having an ectopic pregnancy. It also seems that she is the perfect candidate for medical management rather than undergoing surgery. Methotrexate is the recommended drug.

Search Question: In patients with ectopic pregnancies, how is the success rate between the single dose methotrexate compared to the multi dose?

Question Type: What kind of question is this? (boxes now checkable in Word)

- | | | |
|-------------------------------------|---|------------------------------------|
| <input type="checkbox"/> Prevalence | <input type="checkbox"/> Screening | <input type="checkbox"/> Diagnosis |
| <input type="checkbox"/> Prognosis | <input checked="" type="checkbox"/> Treatment | <input type="checkbox"/> Harms |

Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)?

Please explain your choices.

Along with meta-analyses and systemic reviews, I would consider studies that involved Randomized Controlled Trials [RCT] along with Cohort Studies. RCTs would be the better and more preferred study I am looking for since it is often used to test treatments. In addition, both the RCTs and Cohort studies are prospective studies that follow individuals over time where data is collected as circumstances change. This will be perfect considering I want to know whether one form of treatment could potentially result in different success rates compared to another. RCTs and Cohort studies are studies I will be looking out for.

PICO search terms:

P	I	C	O
Young female patients	Methotrexate	Single dose vs	Improved success rates
Diagnosed with ectopic pregnancy		Multi dose	

Search tools and strategy used:

PubMed

“Ectopic pregnancies” → 24,838

+”Methotrexate” → 1476

+”Single dose multi dose” → 216

+ 5 years → 126

Google Scholar

“Ectopic pregnancies” → 260,000

+”Methotrexate” → 19,900

+”Single dose multi dose” → 14,500

+ 5 years → 4,950

Results found:

Article 1

Citation

Alur-Gupta S, Cooney LG, Senapati S, Sammel MD, Barnhart KT. Two-dose versus single-dose methotrexate for treatment of ectopic pregnancy: a meta-analysis. *Am J Obstet Gynecol*. 2019;221(2):95-108.e2. doi:10.1016/j.ajog.2019.01.002

<https://sci-hub.se/10.1016/j.ajog.2019.01.002>

Article Type

Meta analysis

Abstract

Objective:

To compare the treatment success and failure rates, as well as side effects and surgery rates between methotrexate protocols.

Data Sources:

PubMed, Embase and the Cochrane library searched up till July 2018.

Study eligibility criteria:

RCTs that compared women with ectopic pregnancies receiving the single dose, two dose or multi-dose methotrexate protocols.

Study appraisal and synthesis methods:

Odds of treatment success, treatment failure, side effects and surgery for tubal rupture as well as length of follow-up until treatment success compared using random and fixed effects meta-analysis. Sensitivity analyses compared treatment success in high hCG and large adnexal mass groups, as defined by individual studies. Cochrane's collaboration tool used to assess risk of bias.

Results:

The two dose protocol was associated with higher treatment success compared to single dose protocol (OR: 1.84, 95% CI: 1.13, 3.00). The two dose protocol was more successful in women with high hCG (OR: 3.23, 95% CI: 1.53, 6.84) and in women with a large adnexal mass (OR: 2.93 95% CI: 1.23, 6.9). The odds of surgery for tubal rupture were lower in the two dose protocol (OR: 0.65, 95%CI: 0.26, 1.63), but not statistically significant. The length of follow up was 7.9 days shorter for the two dose protocol (95% CI: -12.2, -3.5). Odds of side effects were higher in the two dose protocol (OR: 1.53, 95% CI: 1.01, 2.30).

Compared to the single dose protocol the multi-dose protocol is associated with a nonsignificant reduction in treatment failure (OR: 0.56, 95% CI: 0.28, 1.13) and a higher chance of side effects (OR: 2.10, 95% CI: 1.24, 3.54). Odds of surgery for tubal rupture (OR: 1.62, 95% CI: 0.41, 6.49) and time to follow-up (-1.3, 95% CI: -5.4, 2.7) were similar.

Conclusion:

The two dose methotrexate protocol is superior to the single dose protocol for the treatment of ectopic pregnancy in terms of treatment success and time to success. Importantly, these findings hold true in patients thought to be at a lower likelihood of responding to medical management, such as those with higher hCGs and large adnexal mass.

Key Points

- Compared RCTs done using single dose vs. two-dose/multi-dose protocol
- Two dose protocol superior to single dose protocol in regards to treatment success rates
- Higher success rates with multi-dose protocol were seen in patients who are not as likely to respond to medical management [those patients with high bHCG levels and large adnexal masses]

Reason for choosing:

I really liked how this article was quite recent and published in 2019. I also chose this article since it was a meta-analysis and these type of article sit at the top of the EBM pyramid. The article directly answers my PICO question very clearly based on its analysis and the results were very interesting to read about since I myself did not really think there would be a difference but perhaps there actually is!

Article 2

Citation

Yang, C., Cai, J., Geng, Y., & Gao, Y. (2017). *Multiple-dose and double-dose versus single-dose administration of methotrexate for the treatment of ectopic pregnancy: a systematic review and meta-analysis*. *Reproductive BioMedicine Online*, 34(4), 383–391. doi:10.1016/j.rbmo.2017.01.004

<https://sci-hub.se/https://doi.org/10.1016/j.rbmo.2017.01.004>

Article Type

Systematic review and meta-analysis

Abstract

In this systematic review and meta-analysis, the effectiveness and safety among different dosage of methotrexate protocols for the treatment of unruptured tubal ectopic pregnancy was evaluated. Six studies of randomized controlled trials were identified through searches conducted on PubMed, Embase and Cochrane Library between January 1974 and March 2016. The overall success rate of multiple-dose protocol was similar to the single-dose protocol (RR 1.07, 95% CI 0.99 to 1.17, I² = 0%).

The difference between double-dose and single-dose groups was not significant (RR 1.09, 95% CI 0.98 and 1.20, I² = 0%). The incidence of side-effects of double-dose regimen was similar with single-dose regimen. Side-effects, however, are more common in multiple-dose regimen (RR 1.64, 95% CI 1.15 to 2.34, P = 0.006, I² = 0%). This meta-analysis indicated that the incidence of side-effects of multiple dose protocol was significantly higher than single-dose protocol, and the success rates between them were similar. The double-dose regimen was an efficient and safe alternative to the single-dose protocol. Further high-quality researches are needed to confirm our findings and to develop the optimal protocol.

Key Points

- Compared RCTs done using single dose vs. two-dose/multi-dose protocol
- Overall success rates between the two protocols were very similar and the difference in success rates between the two groups was not significant.
- Incidence of side effects were significantly higher in the multi dose protocol however it was deemed as an efficient and safe alternative to the single dose protocol.

Reason for choosing:

Article was published in 2017 which is relatively recent and I like that. I also like that this article was a meta-analysis/systematic review of RCTs. Nothing beats this type of evidence based medicine. I like how this article specifically focused on my PICO question directly. Contrary to an article that is more recent, this article states that there is no difference between the two protocols in regards to success rates. It is always interesting seeing a different result based on two same types of articles.

Article 3

Citation

Yuk, J.-S., Lee, J. H., Park, W. I., Ahn, H. S., & Kim, H. J. (2018). *Systematic review and meta-analysis of single-dose and non-single-dose methotrexate protocols in the treatment of ectopic pregnancy*. *International Journal of Gynecology & Obstetrics*, 141(3), 295–303. doi:10.1002/ijgo.12473

<https://sci-hub.se/10.1002/ijgo.12473>

Article Type

Systematic review and meta-analysis

Abstract

Background: It remains unclear which methotrexate protocol for the treatment of ectopic pregnancy has a higher success rate or a higher adverse effect rate. **Objective:** To compare the treatment success rates and adverse effect rates of single-dose and non-single-dose (two-dose and multi-dose) methotrexate protocols in the treatment of ectopic pregnancy. **Search strategy:** Various databases including Medline, Embase, and the Cochrane Central Register of Controlled Trials were

searched on July 1, 2017, using search terms including “methotrexate” and “pregnancy.” **Selection criteria:** Randomized controlled trials comparing different methotrexate protocols for the treatment of ectopic pregnancy were included. **Data collection and analysis:** Relative risks (RRs) and 95% confidence intervals (CIs) were calculated to compare treatment success rates and adverse effect rates. **Main results:** The single-dose and non-single-dose protocols had similar success rates (RR 1.00, 95% CI 0.96–1.04; 11 trials, 1121 patients, I² =18%). The non-single-dose protocols had a higher adverse effect rate than did the single-dose protocol (RR 0.73, 95% CI 0.59– 0.91; nine trials, 934 patients, I² =0%). **Conclusions:** The single-dose methotrexate protocol was the optimal protocol for the medical treatment of ectopic pregnancy

Key Points

- Compared RCTs done using single dose vs. two-dose/multi-dose protocol
- Single dose and multi-dose protocol had similar success rates
- Multi-dose protocol had higher adverse effects rate compared to single dose
- Overall single dose was optimal protocol for treatment of ectopic pregnancy

Reason for choosing:

This article is relatively recent being published within the last 5 years [2018]. This article was a systematic review/meta-analysis which is the best kind of article in regards to EBM there is. Like the other articles mentioned above this article directly answers my PICO question. It was interesting yet again to see a difference in conclusion comparing all 3 articles. There is not a clear cut answer so I liked to include this article to demonstrate the different conclusions I had come across.

What is the clinical “bottom line” derived from these articles in answer to your question?

Based on the evidence demonstrated in the articles I had chosen, the bottom line derived from all of them is that single dose methotrexate protocol may be slightly more optimal in regards to treating ectopic pregnancies, but not in regards to success rates! The single dose protocol and multi-dose protocol yielded very similar success rates, however, the multi-dose protocol was seen to have higher incidences of adverse effects. As a clinician, I would want to limit my patient’s exposure to possible adverse effects/reactions yet still achieve the same treatment result and in this case, this can be done with the single-dose protocol.

I feel that it is important to mention that in certain special cases, where a patient is less likely to respond to a single-dose protocol [i.e. high bHCG or very large adnexal mass], then the multi-dose protocol would yield a higher success rate in that regard. Otherwise, there is not much difference in success rates between the single-dose protocol and the multi-dose protocol of administering methotrexate when treating patients with ectopic pregnancies.