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Economic Evaluation

Cost-Effectiveness Analysis of Different Methods of Treatment of Tubal Ectopic Pregnancy in the South of Iran

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ABSTRACT

Objectives: The aim of the study was to evaluate the cost-effectiveness of different methods of treating tubal ectopic pregnancy in the south of Iran.

Methods: This study was an economic evaluation that analyzed and compared the cost-effectiveness and cost utility of 3 treatment methods, including single-dose methotrexate, double-dose methotrexate, and surgery in patients with tubal ectopic pregnancy. In this study, a decision tree model was used. The outcomes included in the model were the percentage of successful treatment and the average utility score of each treatment method. The study was conducted from the social perspective, and a one-way and probabilistic sensitivity analysis was performed to measure the effects of uncertainty.

Results: The incremental cost-effectiveness ratio of surgery compared with single-dose methotrexate was positive and equal to $5812 purchasing power parity; moreover, the results of one-way analysis showed the highest sensitivity toward the effectiveness of single-dose methotrexate. Scatter plots also revealed that surgery in 82% and 96% of simulations was at the acceptable region compared with a single-dose and double-dose methotrexate, respectively and was below the threshold. It was identified as a more cost-effective strategy. Furthermore, the acceptability curves showed that in 81.4% of simulations, surgery was the most cost-effective treatment for thresholds less than $20 950 purchasing power parity.

Conclusions: On the basis of the results of this study, surgery can be used as the first line of treatment for ectopic pregnancy. In addition, the best drug strategy was single-dose methotrexate because this strategy reduced costs and increased treatment success and quality-adjusted life-years compared with double-dose methotrexate.

Keywords: cost utility, cost-effectiveness, economic evaluation, ectopic pregnancy, methotrexate, surgery.

VALUE HEALTH REG ISSUES. 2022; 28:90–97

Introduction

Because the fifth goal of the Millennium Development Goal is to improve the health of mothers, providing care services for vulnerable groups of the community is of particular importance.[1] Ectopic pregnancy is one of the most important causes of mortality and disabilities in women of reproductive age.[2] According to the Center for Disease Prevention and Control, this problem occurs in about 2% of pregnancies, and this small proportion accounts for about 6% of pregnancy-related deaths.[3] The incidence of this disease in Iran is estimated to be 0.26%.[4] The rate of maternal mortality per thousand live births in the country in 2012 and 2013 was 19.9% and 19.8%, respectively, and ectopic pregnancy was one of the causes of mortality.[1] The incidence of this disease has increased significantly in the last century, but the rate is currently relatively stable. The increase in the past century may be attributed to the rise in using diagnostic technologies, such as high sensitivity ultrasounds, increased prevalence of sexually transmitted diseases, assisted reproductive techniques, and the use of ovarian stimulants.[5] So far, uterine tubes have been the most common site of abnormal implantation, which account for 98% of ectopic pregnancies.[2] Ectopic pregnancy may damage the uterine tube or lead to infertility in the future,[6] and 10% to 12% of secondary infertility occurs as a result of such diseases.[1] Infertility as a biologic, psychologic, and social crisis can threaten the health of infertile couples.[7] The rapid progress in medical equipment has made it possible to detect ectopic pregnancy by measuring the β-human chorionic gonadotrophin (β-hCG) subtypes. The measurement of β-hCG is a precise, noninvasive, and accurate method for diagnosis.[2] Methotrexate, as a safe and effective medication, is suggested to be used at different dosages for treating ectopic pregnancy; it is comparable with surgery, rate of success, and rate of future pregnancy. Laparoscopy or laparotomies are 2 standard methods used for the treatment of an ectopic pregnancy. Nonetheless, the use of these methods depends on the size and location of the ectopic mass and the hemodynamic stability of the patient.

2212-1099/$36.00 - see front matter © 2021 ISPOR–The professional society for health economics and outcomes research. Published by Elsevier Inc.

It is worth noting that laparotomy is not always necessary for the treatment of a patient with a ruptured ectopic pregnancy.[8] In contrast, the use of a surgical approach depends on 2 main factors: first, the previous experience of a surgeon with laparoscopy; second, the availability of laparoscopic equipment.[9] Except for women with a hemodynamically unstable condition, laparoscopy is the preferred surgical method for the treatment of ectopic pregnancy. In this procedure, intramuscular methotrexate is administered when there is a concern about the probability of remnant trophoblastic cells in the tube or the peritoneal cavity. Usually, a single dose of methotrexate is administered for these patients after laparoscopic surgery.[6] It was first used by Tanaka et al[10] in 1982 and has since then been widely accepted as a suitable method for ectopic pregnancy treatment that is comparable in many respects to surgery. Although drug therapy is a good option for many women with ectopic pregnancy without internal bleeding, it is not necessarily the best treatment option for all patients because the result of treatment is not curative in all patients and delays the return of patients to everyday activities.[11] Methotrexate is a potent inhibitor of rapidly proliferating cells such as trophoblastic tissue, with an overall resolution rate of approximately 90% for ectopic tubal pregnancy.[6] Today, modern diagnostic methods can help in the early detection of ectopic pregnancy and treatment approaches have become less invasive.[12] Annually, because of inappropriate treatment selections, many mothers suffer from related complications, such as high mortality rate, infertility, and increased economic cost.[1] Thus, an ectopic pregnancy may lead to infertility, lower chances of future fertility for some people, and stress of the recurrence of the disease; accordingly, it can affect the lives of women of reproductive age.[10] Successful treatment of ectopic pregnancy can increase the quality of life of patients undergoing treatment and decrease their suffering from mental illness and physical problems after the disease.

Given the lack of research in this field in the country, the high cost of treating ectopic pregnancy and the risk of infertility or death in the absence of timely and appropriate treatment, it was decided to conduct this research and use its results to determine the most cost-effective treatment method for patients with ectopic pregnancy. The results can also help managers, policymakers, and specialists make informed decisions about the most appropriate treatment method for the proper use of limited resources.

Methods

This economic evaluation project was conducted to retrospectively study the cost-effectiveness of 3 methods of single-dose methotrexate, double-dose methotrexate, and surgery in 254 women who had non-ruptured tubal ectopic pregnancies from 2015 to 2017. Of the 254 women with ectopic pregnancies, 116 patients received single-dose methotrexate, 68 received double-dose methotrexate, and 70 were surgically treated. The mentioned patients were selected from the patients who were admitted to 2 public governmental hospitals in Shiraz, Iran that provide ectopic pregnancy treatment services. Patients who had stable hemodynamic conditions and were willing to perform the needed follow ups of medical treatment with methotrexate were enrolled. Women who were breastfeeding or were immunocompromised were excluded from the study. In addition, patients with alcoholism, active peptic ulcers, or hematologic, hepatic, renal, or active lung disease were not enrolled in this study. Furthermore, if fetal heartbeats were detected by an ultrasound examination or if the size of the ectopic mass was >5 cm, the patients were considered as candidates for the surgical approach and were not enrolled for methotrexate treatment. If a single methotrexate dose was not effective in decreasing the β-hCG titer to an acceptable value, a second dose was prescribed according to the protocol.[13] If the size of the mass was more extensive or if β-hCG titer was higher, 2 doses of methotrexate were prescribed from the beginning.

Clinical Input

After enrollment, complete blood cell count, β-hCG, serum urea nitrogen, creatinine, and liver function tests were evaluated for all patients, and they were recommended to avoid consumption of folic acid, nonsteroidal anti-inflammatory drugs, acetylsalicylic acid exposure to sunlight, and sexual intercourse.

For the single-dose method, methotrexate 50 mg/m^2 body surface area was given on the first day (day 1) and serum β-hCG values were measured on the fourth and seventh day. In the double-dose protocol, however, methotrexate 50 mg/m^2 body surface area was given on the first and the fourth day. If the β-hCG value declined by 15% from day 4 to day 7, the treatment was considered to be successful and subsequent weekly β-hCG titers in the patient were recorded. If the decline in β-hCG value was less than 15% at day 7, the medical therapy was repeated for another cycle. Medical treatment was considered unsuccessful if the decline in β-hCG was less than 15% after 3 consecutive cycles.[14]

Effectiveness of treatment was measured by collecting data on the percentage of the success rate of each method for treating ectopic pregnancy and the utility of each technique. The probability of success of each treatment method was measured using a predesigned form and reviewing the patients' records and measuring the utility scores through the EQ-5D inventory and interviews with the patients. The weights for this questionnaire have been estimated by Goudarzi et al[15] in Iran.

Common complications of treatment using different doses of methotrexate were classified into 6 different categories: without complications, hematologic complications (including decreased white blood cell, platelet, or hemoglobulin), intricacies of the digestive system (including oral ulcers, nausea, and diarrhea), renal complications (including increased serum urea nitrogen and creatinine and decreased urine output), liver complications (including a rise in liver enzymes or bilirubin), and dermatologic complications (including itching, swelling, or rash). Moreover, the complications of the surgical procedures were classified into 5 categories: without complications, wound infections, anesthesiology complications, blood transfusions, and other complications. After reviewing the files of patients and their interviews, the rate of onset of each complication was determined.

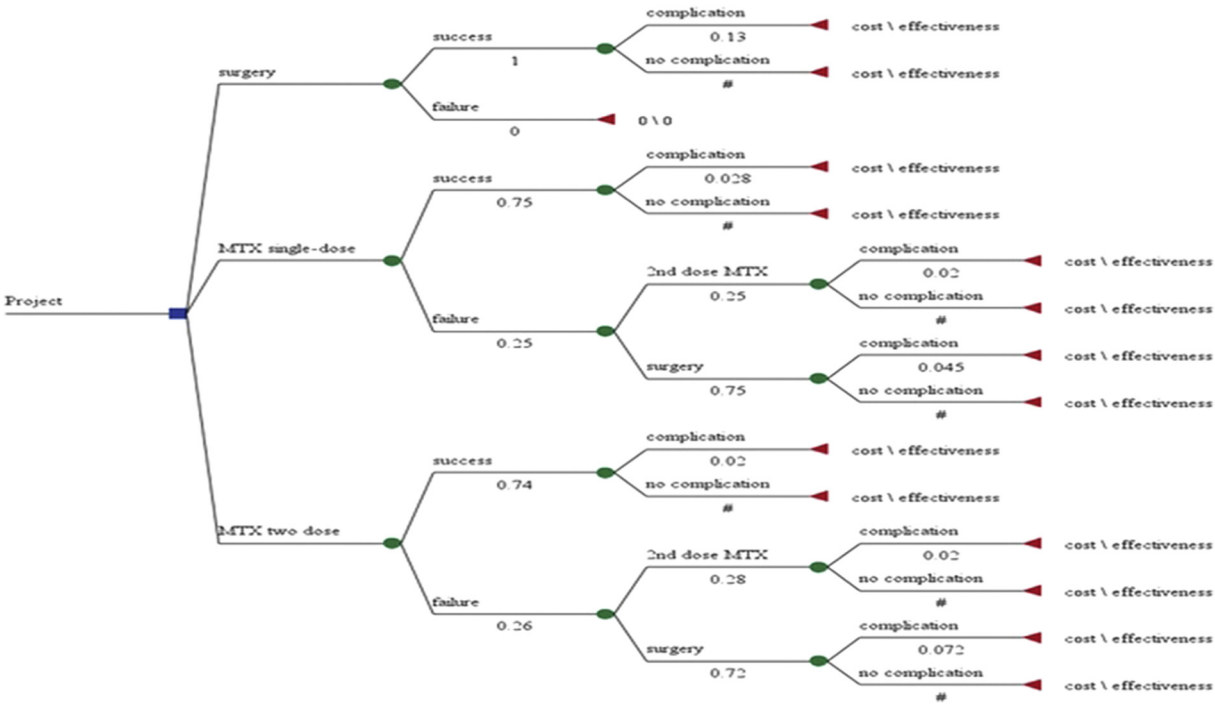
Treatment Cost

Societal perspective was used in the current study, and the data of direct medical costs (DMCs) were extracted from medical records of the patients and self-reports. Direct nonmedical costs (DNMCs) and indirect costs (ICs) were estimated by using the friction cost method[16] and calculated on the basis of the patients' self-reports and data collected through telephone calls. The prices were calculated on the basis of tariffs in 2017 per international dollar (purchasing power parity [PPP]) with an exchange rate of 11 948 rials per dollar.[17]

Model Structure

The decision tree model for single-dose methotrexate, double-dose methotrexate, and surgery is shown in Figure 1. As the diagram shows, using the decision tree model and the TreeAge

Figure 1. Decision tree model for different methods of treating ectopic pregnancy.



MTX indicates methotrexate.

software (TreeAge Software LLC, Williamstown, MA), different treatment methods, their related costs, effectiveness, and complications of the disease were analyzed. This model was used to assess the success of each treatment method, side effects, and utility in each of the 3 groups of patients. For each strategy, the success and failure of the technique and its side effects were investigated, and the related charts were analyzed to select the best treatment strategy.

Cost-Effectiveness Analysis

On the basis of the results of the previous steps, the model was designed in TreeAge software and the extracted data were entered into the model. Then, the costs, effectiveness, cost-effectiveness analysis (CEA), and cost-utility analysis (CUA) for the 3 methods of treatment were assessed, and their incremental cost-effectiveness ratio (ICER) was estimated and compared using the following formula:

$$\mathrm{ICER} = \frac{\mathrm{CostA} - \mathrm{CostB}}{\mathrm{OutcomeA} - \mathrm{OutcomeB}}$$

Sensitivity Analysis

In this study, a 1-way and probabilistic sensitivity analysis was performed to examine the effects of uncertainty of parameters on the outcomes of the model. In a simultaneous multiplex sensitivity analysis, ≥2 parameters were changed. Nonetheless, the more is the number of changing parameters, the more complicated finding a definite result becomes. A multiplex sensitivity analysis, which is called a scenario analysis, assesses the outcomes and effects of different interventions and consequently estimates the impact of various parameters. There was an attempt to modify the critical parameters of the model, including effectiveness and costs for each treatment method. Because of the lack of a specific cost-effectiveness threshold in Iran, the threshold in developing countries for each quality-adjusted life-year (QALY), as recommended by the World Health Organization, was set at 1 and 3 times the gross domestic product (GDP) per capita, which was approximately $20 950 PPP in 2017 for Iran, according to the World Bank report.[18,19]

Results

In this research, 254 women with tubal ectopic pregnancies were enrolled. Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2021.06.004 briefly presents the descriptive data of the patients, including data on the number of patients, mean age, insurance coverage, number of pregnancies, the mean size of the mass, the mean gestational age, history of pelvic surgeries, infertility, abortion, and previous ectopic pregnancies.

Table 1 presents direct and ICs incurred by the 3 groups for the treatment of tubal ectopic pregnancies. The mean DMCs were $1706 for the patients receiving single-dose methotrexate, $2009 for double-dose methotrexate receivers, and $2323 for patients who had undergone surgical intervention. Moreover, the mean DNMCs for the 3 mentioned groups were $431, $684, and $229, respectively, and the mean ICs were $538, $669, and $607, respectively. Accordingly, DMCs accounted for 64%, 60%, and 74%, respectively, of the total costs; DNMCs accounted for 16%, 20%, and 7% of the total costs; and ICs accounted for 20%, 20%, and 19% of the total costs for patients who had received single-dose methotrexate, double-dose methotrexate, and surgical intervention, respectively.

Table 1. The cost components of treatment strategies.

Costs	Costs items	Single-dose methotrexate (PPP$)	Double-dose methotrexate (PPP$)	Surgery (PPP$)
Direct medical costs	Visit	97	119	49
	Patient hospitalization	1030	1226	580
	Laboratory tests	267	263	111
	Radiography	93	132	107
	Medication	28	41	46
	Surgical services	191	228	1430
Direct nonmedical costs	Transportation, accommodation, and meals	431	684	229
Indirect costs	Lost earnings	538	669	607
	Total	2675	3362	3159

Table 2 presents the results of the CEA and CUA. As shown, the expected effectiveness was 0.721, 0.71, and 0.87; and the mean costs for each treatment group were $1984, $3199, and $2850 PPP for treatment via single-dose methotrexate, double-dose methotrexate and surgery, respectively. As shown in Table 2, the results of the CEA showed that double-dose methotrexate incurred higher costs, had a lower level of effectiveness, and was dominated by the other 2 strategies. A comparison of the 2 different methods showed that single-dose methotrexate had a mean weighted cost of $1984 and a treatment success rate of 0.72, whereas surgery had an estimated cost of $2850 and a treatment success rate of 0.87. Thus, the calculated ICER was $5812, indicating that for each percentage of success in treating ectopic pregnancy by surgery, $5812 should be spent. To make a decision, we should compare the ICER with the threshold.[20] Therefore, because the ICER was less than the per capita GDP, the surgical treatment method was considered a more cost-effective option.

As shown, the expected QALYs of treatment via surgery, single-dose methotrexate, and double-dose methotrexate were 0.81, 0.827, and 0.81; and the mean costs for each treatment group were $378, $1968, and $3162 PPP, respectively (Table 2). Moreover, on the basis of the results of CUA, double-dose methotrexate was dominated compared with the other 2 strategies. Comparison of these 2 strategies showed that single-dose methotrexate had a mean weighted cost of $1968 and QALYs of 0.827 (lower cost and higher effectiveness), whereas surgery had an estimated cost of $378 and QALYs of 0.814 (lower cost and less effectiveness). Thus, the calculated ICER was $92 191, indicating that per additional QALY gained in treating ectopic pregnancy by single-dose methotrexate, $92 191 should be spent. Therefore, because the ICER was greater than the per capita GDP, the surgical treatment method was considered a more cost-effective option.

Uncertainty Analysis

As mentioned earlier, the effects of uncertainty were studied using 1-way sensitivity analysis, the value of each variable changed by 20%, and the tornado diagram was plotted. The ICER, as shown in Appendix Figure 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2021.06.004, had the highest level of sensitivity to the effectiveness of single-dose methotrexate, and the lowest level of sensitivity to the cost of single-dose methotrexate.

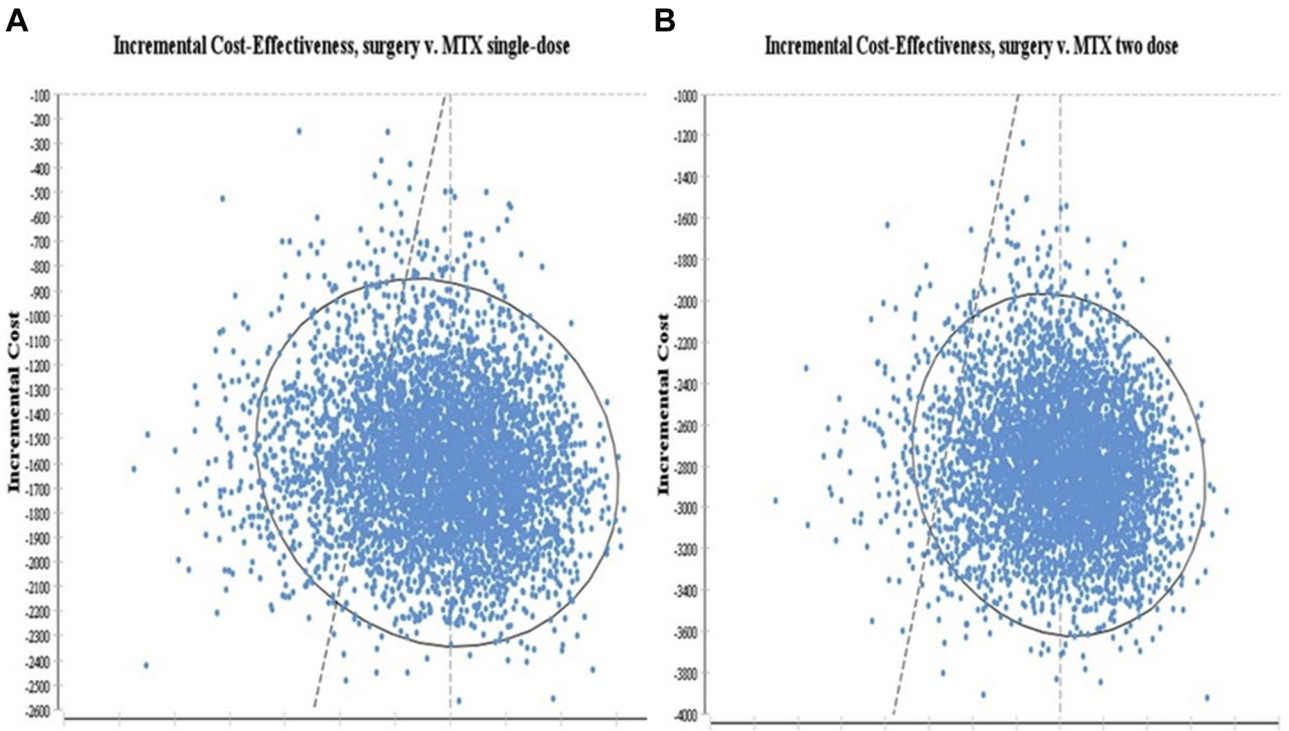
In addition, in the current study, a second-order Monte Carlo simulation was conducted using 5000 trials for PSA. The findings of the uncertainty measurement using cost-effectiveness acceptability curves and incremental cost-effectiveness scatter plot (ICER) distribution curves are presented in Figure 3. In addition, cost-effectiveness scatter plots revealed that general surgery compared with single-dose and double-dose methotrexate in 82% and 96% of simulations, respectively, was at the acceptable region, below the threshold and identified as the more cost-effective

Table 2. Comparing the cost-effectiveness of 3 methods of treating ectopic pregnancy by the decision tree model.

Type of economic evaluation	Strategy	Cost (PPP$)	Effectiveness	Incremental cost	Incremental effectiveness	ICER* (PPP$)
CEA	Single-dose methotrexate	1984	0.721	0	0	0
	Surgery	2850	0.87	866	0.149	5812
	Double-dose methotrexate	3199	0.71	349	−0.16	Abs. dominated
CUA	Surgery	378	0.81	0	0	0
	Single-dose methotrexate	1968	0.827	1590	0.017	92 191
	Double-dose methotrexate	3162	0.81	1194	−0.017	Abs. dominated

CEA indicates cost-effectiveness analysis; CUA, cost-utility analysis; ICER, incremental cost-effectiveness ratio; PPP, purchasing power parity; QALY, quality-adjusted life-year.
*ICER indicates incremental cost per extra success and cost per QALY gained.

Figure 2. Incremental cost-effectiveness of surgery compared with single- and double-dose methotrexate (A and B).



CE indicates cost-effectiveness; MTX, methotrexate.

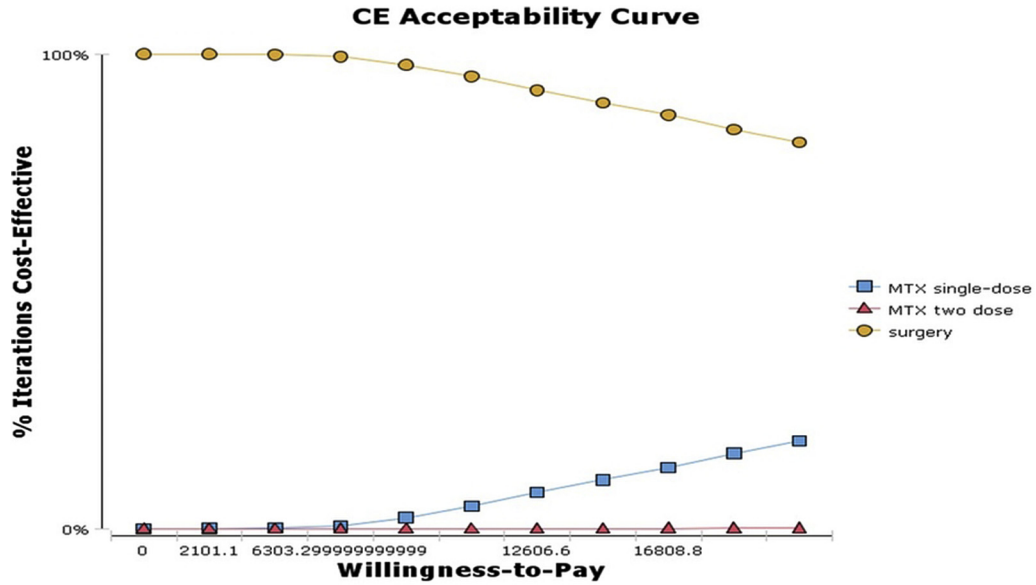
strategy (Fig. 2A,B). The results of the acceptability curves also showed that in 81.4% of simulations, surgery was the most cost-effective treatment for thresholds <$21 011 PPP. The next best drug strategy was single-dose methotrexate, which was the optimal strategy in 18.48% of the simulations (Figure 3).

Discussion

Ectopic pregnancies must be treated well to terminate the pregnancy and to prevent future mortality and infertility.[21] Currently, standard treatments for this disease are medical therapy using methotrexate with different doses and surgery to remove the mass.[22] This study was conducted to determine and compare the cost-effectiveness and cost utility of the 3 methods mentioned previously for the treatment of ectopic pregnancies to propose the best options for the physicians and policymakers to choose the most cost-effective method for terminating the pregnancy and reducing damage to the uterine tubes. On the basis of the findings of the cost components, the mean costs of treatment via single-dose methotrexate, double-dose methotrexate, and surgery were $2675, $3362, and $3159, respectively, per single round of treatment. Therefore, the mean cost of treatment per patient treated with single-dose methotrexate was lower than the mean cost of treatment per patient treated with the other 2 therapies. It seems that the main reasons for the differences in costs are the higher success rate, the lack of the need for secondary treatments, fewer side effects, and lower costs. Given that double-dose methotrexate is prone to higher rates of failure, the direct and ICs are increased, and the patient has to spend more time to treat the illness and recover, which in turn increases the ICs.[23,24] Therefore, the results of this study are consistent with those of the Creinin et al[25] study that compared the costs of treatment via single-dose methotrexate and surgery, and also the Sowter et al[26] study that compared direct and ICs of single-dose methotrexate and laparoscopic surgery. Therefore, as the results show, DMCs, DNMCs, and ICs accounted for 64%, 16%, and 20%, respectively, of the total costs spent by the patients receiving single-dose methotrexate; 60%, 20%, and 20%, respectively, of the total costs spent by the patients receiving double-dose methotrexate; and 74%, 7%, and 19%, respectively, of the total costs spent by the patients undergoing surgery. Thus, DMCs account for the highest cost in all 3 treatment methods. In patients receiving single-dose and double-dose methotrexate, the costs of hospital stay accounted for the highest share of DMCs, whereas for patients who had surgeries, the operation costs accounted for the highest share of DMCs. These findings are in line with the results of the published study performed by Foulk et al.[27] Furthermore, it seems that the higher costs of surgery are because of the high operation expenses, services, and drugs that the patients take after discharge from the hospital.[28] As calculated, the DMCs accounted for a higher percentage of the costs,[29] and although about 99% of the patients undergoing surgical treatment were covered by insurance companies, they incurred high DMCs that may be attributed to the high costs of operation.[30] Therefore, the costs associated with ectopic pregnancy are relatively high.

The results showed that the rate of treatment success was 721% for single-dose methotrexate, 71% for double-dose methotrexate, and 87% for surgery; the findings of this study are in line with results of Hajenius et al[31] study that compared the effectiveness of laparoscopy as a surgical procedure with methotrexate therapy, a study by Chaychian et al[32] that compared single-dose and multi-dose methotrexate, and a study by Mergenthal et al[33] that compared the effectiveness of single-dose and double-dose methotrexate. Nonetheless, our results are not consistent with

Figure 3. Cost-effectiveness acceptability curve through Monte Carlo simulation for patients with ectopic pregnancy under drug therapy.



CE indicates cost-effectiveness; MTX methotrexate.

those of Alyasin et al[34] that compared single-dose and double-dose methotrexate, which found that double-dose methotrexate had a higher success rate than single-dose methotrexate. These different results may be induced by different methods of patient selection. In our study, if the β-hCG titers were higher or the size of the ectopic mass was larger or the first methotrexate dose was not effective, a second dose was given. Therefore, it is logical that these patients would have lower chances to be cured by medical therapy.

Moreover, the results of our study showed that the mean cost of surgery and single-dose methotrexate was $2850 and $1984, respectively, and their treatment success rates were 87% and 721%, respectively. In other words, surgery was more costly and more cost-effective, but because the ICER was below the threshold, this method was identified as a cost-effective option. This finding is not in line with the results of the studies conducted by Alexander et al,[35] Morlock et al,[36] and Yao et al[28]; they compared methotrexate therapy with laparoscopy and concluded that methotrexate was more cost-effective than surgery Nonetheless, Mol et al[37,38] compared methotrexate and laparoscopic surgery and found that a particular type of surgery was more cost-effective than methotrexate.

According to the data obtained from the 3 groups of patients using the EQ-5D questionnaire, the results showed that the patients who received single-dose methotrexate had higher scores in their utility because they underwent less invasive procedures and needed a shorter period of rest after discharge from the hospital. Results of the present study show that the highest utility scores were observed in the single-dose methotrexate group (0.827), followed by the double-dose methotrexate group (0.81) and surgery group (0.81). Moreover, the results of ICER analysis of utility in all 3 groups of patients showed that, among the treatment strategies used in the county, single-dose methotrexate had a higher level of cost and QALYs than the surgery method; but the ICER is greater than the per capita GDP, and thus, the surgical treatment method is considered as a more cost-effective option. So far, to the best of our knowledge, no study has investigated the utility outcome.

The results of the sensitivity analysis showed that the ICER is not sensitive to most of the parameters, which confirms the robustness of the results of the study as the results of 1-way sensitivity analysis revealed that ICER is more sensitive to single-dose methotrexate but less sensitive to other parameters. Although the single-dose effectiveness parameter had the greatest impact on ICER value with a 20% increase in the ICER, increasing the baseline ICER from $5812 PPP to approximately $14 000 PPP; however, the new ICER value is still below the threshold level, and therefore surgery is the superior option.

Besides, scatter plots also demonstrated that surgery in 82% and 96% of simulations was at the acceptable region compared with single-dose and double-dose methotrexate, respectively, and below the threshold. It was identified as a more cost-effective strategy. Furthermore, the acceptability curves showed that in 81.4% of simulations, surgery was the most cost-effective treatment for thresholds <$21 011 PPP.

In the present study, we directly estimated DMCs, DNMCs, ICs, and effectiveness using patient-level data instead of using data from the published literature. This approach is also seen by Bastani and Kiadaliri in the methodology of their study in 2 groups of breast cancer patients receiving adjuvant therapy.[38]

This study also has some limitations. As presented in the data collected on demographic characteristics of patients and their background diseases, none of the files reported a history of pelvic infection; this indicates that women are not paying enough attention to such issues or that they deny it or feel embarrassed about it. Women with ectopic pregnancy are worried about complications such as repeated ectopic pregnancy and subsequent infertility.[39] In addition, the number of patients treated with double-dose methotrexate was lower than those treated via the other 2 methods.

Concerning the generalizability of the results, because methotrexate and surgery in Iran are used for the treatment of ectopic

pregnancies and their prices are the same throughout the country, the results of this study can be generalized to other provinces and the whole country. Nonetheless, to generalize the results of this study to other countries, it is necessary to address different issues, such as epidemiology of the disease, demographic structure, availability of resources, prices, evaluation of outcomes by individuals, thresholds, and the use of various indicators of effectiveness in different studies that may affect the results of the study. Therefore, one must be cautious in generalizing the results to other countries.

Conclusions

Overall, on the basis of the results of this study and considering the ICER and cost-utility ratio, surgery is a superior treatment strategy and can be used as a high-priority method, as compared with single-dose and double-dose methotrexate. In addition, the best drug strategy was single-dose methotrexate. Furthermore, because their use as the first line of treatment reduces the duration and helps to manage costs, as compared with double-dose methotrexate, it is suggested that surgery and/or single-dose methotrexate can be used as the first line of treatment for ectopic pregnancy to reduce the burden of disease and financial burden within the community.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2021.06.004.

Article and Author Information

Accepted for Publication: June 16, 2021

Published Online: November 25, 2021

doi: https://doi.org/10.1016/j.vhri.2021.06.004

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Conflict of Interest Disclosures: The authors reported no conflicts of interest.

Funding/Support: This work was supported by a grant number of 95-01-07-11582 from the deputy chancellor of Shiraz University of Medical Sciences.

Role of the Funder/Sponsor: The funder/sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Availability of Data and Materials: Data sets are available from the corresponding author on reasonable request.

Ethical Consideration: This study was part of a medical thesis supported by Shiraz University of Medical Sciences (project number: 95-01-07-11582). It was approved by the Ethics Committee of Shiraz University of Medical Sciences. Informed consents were obtained from the participants.

Acknowledgment: This manuscript is retrieved from an MSc thesis that was supported and approved by Shiraz University of Medical Sciences, Iran with the ID number of 95-01-07-11582. The authors would like to thank Shiraz University of Medical Sciences, Shiraz, Iran, and also the Center for Development of Clinical Research of Nemazi Hospital and Dr Nasrin Shokrpour for editorial assistance.

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