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Original Research

Analysis of Clinical Effect and Influencing Factors for Conservative Treatment in Ectopic Pregnancy

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Abstract

Background: The curative effect of four different kinds of conservative treatment of ectopic pregnancy (EP) and the risk factors affecting the curative effect of conservative treatment of ectopic pregnancy were compared and analyzed. **Methods**: Retrospective analysis of the clinical data of patients with ectopic pregnancy treated conservatively in our hospital during the last 10 years. We compared and analyzed the clinical efficacy of four regimens: the expectant treatment, methotrexate (MTX), and methotrexate combined with mifepristone. Logistic regression was used to analyze the influencing factors of the curative effect for conservative treatment of ectopic pregnancy. **Results**: Initial serum of β human chorionic gonadotrophin (β-hCG) for the four groups of patients demonstrated statistically significant differences in β-hCG level and treatment success rate between groups ($p < 0.05$). When the serum β-hCG level was less than 1000 mIU/mL, the levels in the expected treatment group and mifepristone group were statistically significant ($p = 0.002$). There were no statistically significant differences in the treatment success rates between the four groups ($p = 0.263$). When the serum β-hCG level was $\geq$1000 mIU/mL, the treatment success rate of MTX combined with mifepristone group (9/15, 60%) was significantly higher than that of the other treatment groups (10/34, 29.4%). This difference was statistically significant ($p = 0.045$). When logistic regression analysis was performed, the initial serum β-hCG level (odds ratio (OR) = 0.999, 95% confidence interval (95% CI) 0.999–1) and abdominal pain score (OR = 0.4, 95% CI 0.267–0.6) were independent risk factors affecting the success of conservative treatment of ectopic pregnancy. **Conclusions**: Initial serum β-hCG level and abdominal pain score are the main risk factors affecting the success of conservative treatment of EP. When the serum β-hCG level was less than 1000 mIU/mL, there was no significant difference between the four conservative treatment regimens. When the serum β-hCG level was $\geq$1000 mIU/mL, the cure rate of MTX combined with mifepristone had obvious advantages over other regimens.

Keywords: ectopic pregnancy; conservative treatment; methotrexate; mifepristone

1. Introduction

Ectopic pregnancy (EP) refers to the implantation and development of fertilized eggs in organs or tissues outside the uterine cavity, with an incidence of 2.0%, which can lead to an acute abdomen and internal bleeding [1]. With the development of new medications, the continuous improvement of ultrasonic diagnostic technology, and the clinical application of serum β human chorionic gonadotrophin (β-hCG) ultrasonic threshold [2], the early diagnosis of ectopic pregnancy has been significantly improved. A large proportion of patients with ectopic pregnancy can be conservatively managed [1,3]. The conservative treatment of ectopic pregnancy includes expectant treatment, mifepristone, methotrexate, methotrexate combined with mifepristone and other drugs [4]. There are various conservative treatments for ectopic pregnancy, all with different curative effects. The success rate of methotrexate (MTX) treatment of ectopic pregnancy is 70%–95%, and there are some patients who require to surgical treatment due to the failure of conservative management [5–7]. Therefore, the efficacy of conservative treatment for ectopic pregnancy and the risk factors that affect its success need to be further explored. This study analyzed the clinical data of conservative treatment of ectopic pregnancy in our hospital during the past 10 years, explored the high-risk factors for failure in conservative treatment of ectopic pregnancy, and compared the clinical success rates of the expected treatment group, mifepristone group, methotrexate group, and methotrexate combined with mifepristone group.

2. Materials and Methods

2.1 Case Data

This study used convenience sampling to include a total of 225 patients diagnosed with ectopic pregnancy in

the obstetrics and gynecology department of our hospital from January 2012 to November 2022. According to the treatment plan, the patients were into 4 groups: 41 cases in the expected treatment group, 30 cases in the mifepristone group, 104 cases in the MTX group, and 50 cases in the MTX combined with mifepristone group. Inclusion criteria: (1) elevated serum β-hCG; (2) gynecologic ultrasound: ultrasound did not reveal a gestational sac or cystic echo in the uterine cavity, but demonstrated an abnormal echogenic mass in the adnexal area, which was considered to be an ectopic pregnancy; (3) the patient had no psoriasis or rheumatoid arthritis, no history of drug allergies to methotrexate or mifepristone, no family planning during this pregnancy, no abnormalities in routine blood screening, liver and kidney function, and normal coagulation tests prior to treatment; (4) therapeutic methods: expected treatment group: regular follow-up of serum β-hCG levels and ultrasound every 3 to 7 days. If the serum β-hCG returned to normal and the patient had not received any other treatment, this was considered a therapeutic success. Mifepristone treatment group: Patients received 50 mg of mifepristone twice a day for 5–7 consecutive days with serial measurements of serum β-hCG and ultrasound every 3–7 days. If the serum β-hCG returned to normal and the patient had not received any other treatment, the treatment was considered to be successful. Methotrexate treatment group: methotrexate 0.4 mg/kg/d was administered intramuscularly for 5 days; serial serum measurements of β-hCG and ultrasound every 3 to 7 days. If the serum β-hCG returned to normal and the patient did not receive any other treatment, the regimen was considered successful. The combination of methotrexate and mifepristone treatment group: methotrexate 0.4 mg/kg/d was administered by intramuscular injection for 5 days, and oral mifepristone 50 mg twice a day for 5–7 days; serial levels of serum β-hCG and ultrasound every 3 to 7 days. If the serum β-hCG returned to normal and the patient did not receive any other treatment, the treatment was considered successful. Exclusion criteria: (1) persistent ectopic pregnancy; (2) MTX was used for more than 1 course in the methotrexate or MTX combined with mifepristone groups; (3) the utilization of other drug treatment, such as Chinese patent medicine, traditional Chinese medicine, *etc.*; (4) abnormalities in blood work, liver and kidney function before treatment; (5) or patients with incomplete follow-up data in the medical records.

2.2 Research Methods

2.2.1 Research Tools

2.2.1.1 Case Data Questionnaire. By using Microsoft Office EXCEL 2013 (Microsoft Corporation, Redmond, WA, USA), we designed a self-designed questionnaire for case data, including the patient's age, gender, weight, height, body mass index (BMI), amenorrhea length, pre-treatment abdominal pain score (using the Pain Visual Analog Scale (VAS) score 0–10) vaginal bleeding, initial serum β-hCG level, initial serum progesterone level, maximum diameter of mass in the adnexal area, maximum depth of pelvic effusion, and treatment outcome of each regimen.

2.2.1.2 Treatment Outcome Criteria. The outcomes of this study were divided into success and failure. Success: using one of the four regimens alone, the patient was followed up for a decrease in serum β-hCG value to normal and did not undergo surgery or other treatments. Failure: patients who were transferred to surgery or received other treatment options due to an increase in abdominal pain or intraperitoneal bleeding during or after treatment, or an increase or decrease of $<$15% in serum β-hCG levels on days 4–7 after treatment.

2.2.2 Data Collection Methods

One investigator collected the data according to the self-designed case data questionnaire, and the accuracy of the collected data was checked by another investigator. Abdominal pain score, serum β-hCG level, progesterone level, maximum diameter of adnexal mass, and maximum depth of pelvic effusion were measured within the first 1–2 days for the four conservative treatment groups.

2.2.3 Statistical Methods

SPSS 20.0 (IBM Corp., Armonk, NY, USA) and Microsoft Office EXCEL 2013 were used to analyze the data. The statistical data were expressed by frequency or percentage, and χ^2 test was used for comparison between groups. Continuous data were described by mean $\pm$ standard deviation or M (quartile). One-way analysis of variance was used for comparison between groups, and Student-Newman-Keuls (SNK) or Tamhane method was used for pairwise comparison. Binary logistic regression model was used to analyze the influencing factors of conservative treatment for all ectopic pregnancies, and the area under the receiver operating characteristic (ROC) curve was used to test the predictive effect of the model. $p < 0.05$ was considered statistically significant.

3. Results

3.1 Comparison of General and Clinical Data among the Four Groups

Using one-way analysis of variance, there were no statistically significant differences in age, weight, height, BMI, length of amenorrhea, abdominal pain score, initial progesterone level, maximum diameter of ultrasonic detected mass, and maximum depth of pelvic effusion between the four groups ($p > 0.05$). There were statistically significant differences in the initial serum β-hCG levels among the four groups ($p < 0.05$). Vaginal bleeding occurrence was statistically significant ($p < 0.05$) as was the treatment success rate ($p < 0.05$).

Table 1. Comparison of general and clinical data among the four groups.

	Group				Statistical value	*p* value
	Expectant treatment	Mifepristone	MTX	MTX + Mifepristone		
Cases (n)	41	30	104	50		
Age (y)	30.46 ± 5.85	31.97 ± 6.26	31.31 ± 5.83	30.12 ± 5.79	0.851	0.467
BMI (kg/m^2)	21.94 ± 3.61	22.47 ± 3.32	21.10 ± 2.80	21.50 ± 3.20	1.823	0.144
Amenorrhea length (d)	44.17 ± 7.87	47.17 ± 9.52	46.48 ± 10.16	45.95 ± 9.75	0.737	0.531
Abdominal pain score (F)	0 (0, 2)	0 (0, 2)	1 (0, 2)	0 (0, 2)	1.167	0.323
Initial progesterone level (ng/mL)	2.33 (1.21, 4.57)	3.28 (1.57, 6.14)	4.54 (2.72, 7.92)	4.1 (1.71, 8.10)	1.98	0.119
Maximum diameter of the mass (cm)	2.1 (1.33, 2.9)	2.0 (1.48, 2.9)	2.0 (1.18, 2.73)	1.7 (1.40, 2.40)	0.091	0.965
Maximum depth of pelvic effusion (cm)	0 (0, 1.85)	0 (0, 1.68)	0.8 (0, 1.73)	1.1 (0, 1.60)	1.126	0.339
Initial serum β-hCG level (mIU/mL)	200.45 (105.13, 517.58)	206.50 (81.85, 488.08)	497.15 (278.55, 1971.95)	560 (250.00, 1480.00)	2.773	0.042
Vaginal bleeding rate (%)	92.68	90	83.65	98	7.959	0.047
Treatment success rate (%)	90.24	83.33	67.3	80	10.299	0.016

MTX, methotrexate; BMI, body mass index; β-hCG, β human chorionic gonadotrophin.

Table 2. Comparison of general and clinical data of serum β-hCG level less than 1000 mIU/mL in four groups.

	Group				Statistical value	*p* value
	Expectant treatment	Mifepristone	MTX	MTX + Mifepristone		
Cases (n)	37	28	76	35		
Age (y)	30.51 ± 6.10	32.11 ± 6.47	31.58 ± 6.06	30.43 ± 4.95	0.684	0.563
BMI (kg/m^2)	21.88 ± 3.57	22.64 ± 3.36	21.22 ± 2.97	21.70 ± 3.31	1.443	0.232
Amenorrhea length (d)	44.22 ± 7.77	47.36 ± 9.83	45.95 ± 9.74	44.51 ± 9.75	0.782	0.505
Abdominal pain score (F)	0 (0, 2)	0 (0, 2)	0 (0, 2)	0 (0, 2)	1.029	0.381
Initial progesterone level (ng/mL)	2.33 (1.24, 4.23)	3.27 (1.72, 6.73)	4.38 (2.56, 7.19)	5.17 (1.69, 8.13)	1.801	0.151
Maximum diameter of the pelvic mass (cm)	2.00 (1.40, 3.20)	2.00 (1.63, 3.03)	2.10 (1.20, 2.70)	1.65 (1.35, 2.30)	0.318	0.812
Maximum depth of pelvic effusion (cm)	0 (0, 2)	0 (0, 1.65)	1.10 (0, 1.80)	1.15 (0, 1.65)	1.253	0.292
Initial serum β-hCG level (mIU/mL)	188.80 (102.20, 337.00)	186.05 (80.00, 316.40)	387.60 (214.30, 562.80)	307.50 (123.78, 561.65)	5.343	0.002
Vaginal bleeding rate (%)	94.59	92.86	85.53	94.29	3.613	0.306
Treatment success rate (%)	94.59	82.14	81.58	88.57	3.987	0.263

Table 3. Comparison of general and clinical data of blood β-hCG level greater than or equal to 1000 mIU/mL in four groups.

	Group		Statistical value	p value
	Other treatment groups	MTX + Mifepristone		
Cases (n)	34	15		
Age (y)	30.47 $\pm$ 4.78	29.40 $\pm$ 7.55	0.362	0.55
BMI (kg/m^2)	20.93 $\pm$ 2.55	21.06 $\pm$ 3.68	0.021	0.886
Amenorrhea length (d)	47.24 $\pm$ 10.76	48.00 $\pm$ 11.92	0.049	0.825
Abdominal pain score (F)	2 (0, 1.75)	0 (0, 1.50)	1.479	0.23
Initial progesterone level (ng/mL)	5.44 (2.76, 14.78)	2.60 (1.57, 8.79)	1.534	0.224
Maximum diameter of pelvic mass (cm)	1.9 (1.03, 2.80)	2 (1.20, 1.95)	1.527	0.223
Maximum depth of pelvic effusion (cm)	0 (0, 1.6)	0 (0, 1.4)	0.333	0.567
Initial serum β-hCG level (mIU/mL)	2476.90 (1454.5, 3313.70)	3106.75 (2130.97, 4555.17)	1.484	0.229
Vaginal bleeding rate (%)	76.47	100	4.218	0.04
Treatment success rate (%)	29.4	60	4.036	0.045

The three indicators (initial serum β-hCG level, vaginal bleeding rate, and treatment success rate) that were statistically significant between the groups were compared pairwise respectively. For initial serum β-hCG levels: the serum β-hCG 200.45 mIU/mL (105.13, 517.58) in the expectant treatment group was compared with that in the MTX group 497.15 mIU/mL (278.55, 1971.95) and the serum β-hCG 560 mIU/mL (250.00, 1480.00) in the MTX combined mifepristone group, and the differences were statistically significant (p = 0.004, p = 0.021). There was no significant difference between the other groups ($p > 0.05$). The comparison of the vaginal bleeding rate between MTX group (87/104, 83.65%) and MTX combined mifepristone group (49/50, 98%) demonstrated statistical significance (p = 0.009), while no significant difference was noted among other groups ($p > 0.05$). For the success rate of treatment, there was a significant difference between the expectant treatment (37/41, 90.24%) and MTX group (70/104, 67.31%) (p = 0.005), and there was no significant difference between the other groups ($p > 0.05$) (Table 1).

3.2 Comparison of General and Clinical Data for the Four Groups of Patients with Serum β-hCG Levels Less than 1000 mIU/mL

Among the four groups of patients with serum β-hCG level less than 1000 (37 patients in the expectant treatment group, 28 patients in the mifepristone group, 76 patients in the MTX group, and 35 patients in the MTX combined with mifepristone group), there were no significant differences in age, BMI, length of amenorrhea, abdominal pain score, initial progesterone level, vaginal bleeding rate, maximum diameter of adnexal mass, and maximum depth of pelvic effusion among the four groups ($p > 0.05$). Serum β-hCG levels of four groups of patients before treatment showed statistical significance between the expected treatment group and the mifepristone group (p = 0.002), while the other groups (expected treatment group, MTX group, MTX combined with mifepristone group) showed no significant difference ($p > 0.05$). The success rates of treatment in the four groups were 94.59%, 82.14%, 81.58% and 88.57%, respectively. Pearson Chi-square test showed no significant difference between groups (p = 0.263) (Table 2).

3.3 Comparison of General and Clinical Data for the Four Groups of Patients with Serum β-hCG Levels $\geq$1000 mIU/mL

Among the four groups of patients with serum β-hCG level $\geq$1000 mIU/mL, there were 4 patients in the expectant treatment group, 2 in the mifepristone group, 28 in the MTX group, and 15 in the MTX combined mifepristone group. Due to the small number of patients in the expectant management group, mifepristone group and MTX group, the three groups were combined into one group and renamed as the other treatment group, with a total of 34 patients. The MTX combined with mifepristone group was compared with the other treatment groups, and there were no significant differences in age, BMI, length of amenorrhea, abdominal pain score, serum β-hCG level, progesterone level, maximum diameter of adnexal mass, and maximum depth of pelvic effusion between the two groups ($p > 0.05$). For the comparison of treatment success rate, MTX combined with mifepristone group (9/15, 60%) was significantly higher than other treatment groups (10/34, 29.4%), and the difference was statistically significant (p = 0.045) (Table 3).

3.4 Binary Logistic Regression Model Analysis of the Effect of Conservative Treatment on Ectopic Pregnancy

The clinical data of 225 patients in 4 groups were included in the logistic regression equation to explore the main risk factors affecting the efficacy of conservative treatment of ectopic pregnancy. The risk factors that may be considered to be influential, including age, weight, height, BMI, length of amenorrhea, maximum diameter of adnexal mass, maximum depth of pelvic effusion, serum β-hCG value, serum progesterone level, abdominal pain score and vaginal bleeding, were used as independent variables. Treatment efficacy was used as the dependent variable. The independent variable of vaginal bleeding was assigned as

Table 4. Results of Logistic regression analysis of the efficacy of conservative treatment of ectopic pregnancy.

Risk factors	Partial regression coefficient	Standard error	Wald χ^2 value	p value	OR value	95% CI
Age	0.027	0.048	0.322	0.571	1.027	0.936–1.128
Weight	0.042	0.543	0.006	0.938	1.043	0.360–3.021
Height	0	0.38	0	1	1	0.475–2.106
BMI	−0.061	1.341	0.002	0.964	0.941	0.068–13.026
Amenorrhea length	−0.021	0.026	0.706	0.401	0.979	0.931–1.029
Abdominal pain score	−0.916	0.207	19.646	0	0.4	0.267–0.6
Vaginal bleeding	−0.062	0.753	0.007	0.935	0.94	0.215–4.11
Progesterone	−0.048	0.046	1.079	0.299	0.953	0.871–1.044
Serum β-hCG	−0.001	0	9.835	0.002	0.999	0.999–1
Mass diameter	−0.334	0.28	1.425	0.233	0.716	0.413–1.24
Pelvic effusion	−0.087	0.254	0.118	0.731	0.916	0.557–1.507

OR, odds ratio; 95% CI, 95% confidence interval.

"0" = none, "1" = yes; the efficacy was assigned a value of "0" = failure and "1" = success. Using binary logistic regression for statistical analysis, the results demonstrated that the pre-treatment serum β-hCG level (odds ratio (OR) = 0.999, 95% confidence interval (95% CI) 0.999–1) and abdominal pain score (OR = 0.4, 95% CI 0.267–0.6) were independent risk factors. Serum β-hCG was more valuable in predicting the outcome of conservative treatment for ectopic pregnancy, while other indicators had no significant impact on the treatment outcome (Table 4). The ROC curve was used to test the prediction effect of the model, and the area under the ROC curve was 0.881, 95% CI (0.814, 0.949), indicating a positive prediction effect (Fig. 1).

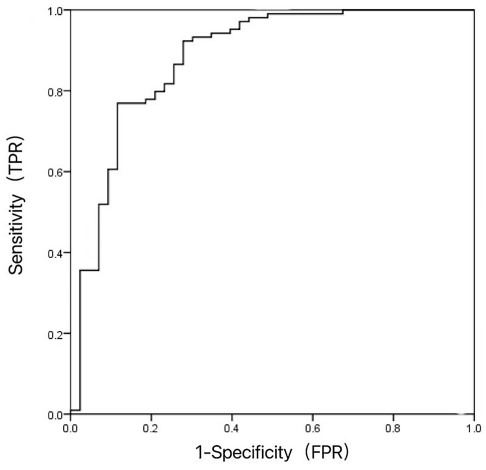

Fig. 1. ROC curve of binary logistic regression model influencing the efficacy of conservative treatment of ectopic pregnancy. ROC, receiver operating characteristic; TPR, true positive rate; FPR, false positive rate.

4. Discussion

Ectopic pregnancy is the implantation and development of the fertilized egg outside the uterine cavity, which is a common gynecologic condition causing an acute abdomen and has the risk of massive intra-abdominal hemorrhage. With the improvement of medical diagnosis and treatment and the enhancement of patients' awareness of treatment, most patients diagnosed with ectopic pregnancy do not have the typical manifestations of acute abdomen. Conservative treatment mainly includes expectant therapy, mifepristone, methotrexate, and methotrexate combined with mifepristone. However, in the process of conservative treatment, some patients will require surgical treatment because of an unsatisfactory decrease in serum β-hCG, increasing abdominal pain, and occurrence of intra-abdominal hemorrhage [8].

Multiple comparisons of the results of this study found that within the serum β-hCG levels of four groups of patients, there are differences in the β-hCG levels. When the expected treatment group serum β-hCG levels were compared with the MTX group and the MTX combined with mifepristone group, the difference was statistically significant ($p < 0.05$). There was no significant difference in comparison between the other groups ($p > 0.05$). Comparison of treatment success rates: the expected treatment group success was significantly higher than the MTX group, and there was no significant difference in comparison between the other groups. This indicates that the serum β-hCG level prior to treatment is the main factor affecting the success of conservative treatment for ectopic pregnancy. Therefore, the level of serum β-hCG at the time of the initial treatment is the most important factor affecting the success of conservative treatment. Based on previous literature reports, Kingsbury's [9] study found that baseline serum β-hCG level was an important factor for predicting the success of conservative treatment of EP ($p < 0.05$). Women with initial serum β-hCG level $<$1500 mIU/mL could receive expectant treatment, and women with serum β-hCG level $<$1000 mIU/mL had a higher success rate. In addition,

Alsammani *et al*. [10] investigated predictors of successful single-dose MTX treatment of EP, and the results demonstrated that initial serum β-hCG concentration was the best predictor of successful MTX treatment. Their conclusions are consistent with the results of this study.

There are many factors affecting the success of conservative treatment of ectopic pregnancy, most being related to the diameter of ectopic pregnancy mass, the trend of serum β-hCG values, abdominal pain symptoms, and the depth of pelvic free effusion. Other important factors include the patient's age, weight, height, length of amenorrhea, and vaginal bleeding [11,12]. In order to explore the main risk factors affecting the efficacy of conservative treatment of ectopic pregnancy, logistic regression analysis was used to show that the initial serum β-hCG level and abdominal pain score were the most important risk factors affecting the success of conservative treatment of ectopic pregnancy. The area under the ROC curve was 0.881, 95% CI (0.814, 0.949). This indicates that the predictive effect is good. It further proves that the serum β-hCG level before treatment was closely related to the success of conservative treatment of ectopic pregnancy.

The degree of abdominal pain is related to the abortion or rupture of the tubal pregnancy, and the level of β-hCG in patients with severe abdominal pain is often higher than that in patients with mild abdominal pain [13], which has a great influence on the choice of the clinical treatment [14,15]. It is necessary to evaluate the severity of abdominal pain before choosing drug conservative treatment or expectant management, and to evaluate the intra-abdominal bleeding by combining ultrasound examination and vaginal posterior fornix puncture. If there is minimal intra-abdominal bleeding and abdominal pain is absent, conservative treatment can be selected. In addition, attention should be paid to the degree of abdominal pain in the treatment process, because the aggravation of abdominal pain usually indicates the possibility of increased abdominal bleeding or rupture of the tubal pregnancy.

The conservative treatment options for ectopic pregnancy mainly include expectant management, mifepristone, methotrexate, and methotrexate combined with mifepristone. Determining the efficacy of these four options and how to choose them in clinical practice remains to be explored. Since serum β-hCG level is the main risk factor affecting the conservative treatment of ectopic pregnancy, the serum β-hCG level was divided into two levels: less than 1000 mIU/mL and greater than or equal to 1000 mIU/mL. Comparison of general and clinical data of serum β-hCG level less than 1000 mIU/mL among the four groups showed statistical significance between the expectant treatment group and the mifepristone group ($p = 0.002$), and no significant difference among the other groups ($p > 0.05$). The success rates of the four groups were 94.59%, 82.14%, 81.5% and 88.57%, respectively. There was no significant difference among the four groups ($p = 0.263$). Comparing the general and clinical data of the four groups of patients with serum β-hCG levels greater than or equal to 1000 mIU/mL, the MTX combined with mifepristone group (9/15, 60%) was significantly higher than the other treatment groups (10/34, 29.4%), and the difference was statistically significant ($p = 0.045$). Therefore, this study suggests that there is no significant difference in the efficacy of these four conservative treatments for patients with serum β-hCG level less than 1000 mIU/mL. For patients with serum β-hCG level greater than or equal to 1000 mIU/mL, the cure rate of MTX combined with mifepristone is significantly superior to the other regimens. Since this study was a retrospective study with a small sample size and was limited to only one hospital, the conclusions of this study need to be supported by further multi-center clinical studies.

5. Conclusions

Initial serum β-hCG level and abdominal pain score are the main risk factors affecting the success rate of conservative management of ectopic pregnancy. When the serum β-hCG level was less than 1000 mIU/mL, there was no significant difference between the four conservative treatment regimens. When the serum β-hCG level $\geq$1000 mIU/mL, the success rate of MTX combined with mifepristone had obvious advantages over the other treatments. However, there are some limitations in this study, and the conclusions need to be supported by more multicenter clinical trials.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

HX and HT designed the research study. QJ and YC performed the research. WS and WL analyzed the data. CS and JC designed the research. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Notification Letter of Ethics Committee of Zigong Fourth People's Hospital (approval number: 2023 No. (005)).

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Conflict of Interest

The authors declare no conflict of interest. Jiming Chen is serving as one of the Guest editors of this journal. We declare that Jiming Chen had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Michael H. Dahan.

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