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THE EFFECTIVENESS OF CYTOPROTECTION IN THE TREATMENT OF STABLE ANGINA IN PATIENTS WITH ARTERIAL HYPERTENSION AND HYPERURICEMIA, TAKING INTO ACCOUNT THE PECULIARITIES OF THE COURSE OF CORONARY ARTERY DISEASE IN WARTIME

Viktoriiia Iablonska, Leonid Kholopov, Olena Khyzhnyak, Viktoriia Batashova-Halinska

The aim *of the study is to establish the effectiveness of treatment of severe angina pectoris in patients with hyperuricemia, taking into consideration the peculiarities of the course of coronary artery disease (CAD) in wartime, using ranolazine – a selective inhibitor of the late sodium flow in combined pharmacotherapy.*

Materials and methods. *We studied the anti-anginal effect of ranolazine in 14 patients with CAD, stable angina pectoris III-IV functional class (FC), hyperuricemia and arterial hypertension (AH) during 6 months of the 2022 year. The effectiveness of the study drug on the clinical course of angina pectoris was assessed by questionnaire and clinical examination after three months of treatment.*

The results. *At the end of the second week of ranolazine use, angina attacks at rest, which were registered before the start of the observation, stopped in all patients with angina pectoris III FC and 50 % with angina pectoris IV FC. In 78.6 %, the number of angina attacks and the use of nitrates decreased by more than 2 times; 21.4 % no longer had angina attacks.*

At the end of the first month, anginal attacks were not observed in all patients with angina pectoris III FC and 50 % with angina pectoris FC IV. In 2 patients with angina pectoris IV FC (50 %), anginal attacks continued to be registered during physical exertion and emotional stress, but no more than once a week. At the same time, there were no angina attacks at rest. The same results were obtained during the survey of patients at the end of three months of observation.

Conclusions. *Ranolazine is an effective component of anti-anginal therapy, significantly affecting the patient's quality of life. Therefore, we can recommend ranolazine for patients with hyperuricemia in angina attacks that persist with insufficient effectiveness of zasic therapy with first-line drugs, especially during military conflicts*

Keywords: *cytoprotection, stable angina pectoris, hyperuricemia, coronary artery disease, wartime, arterial hypertension*

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1. Introduction

In wartime, significantly less weight is given to medical care to patients with chronic diseases than injuries, acute conditions, and infectious diseases. Meanwhile, prolonged stress, limited access of patients to timely outpatient medical care, lack of access to inpatient treatment, and restrictions on the purchase of medications lead to the decompensation of many chronic diseases, in particular, negatively affecting the course of coronary artery disease (CAD). According to meta-analyses of studies, anxiety in long-term follow-up is associated with an increased risk of CAD by 26–41 % and cardiovascular diseases by 52 % [1, 2].

In addition, anxiety can increase the risk of myocardial infarction and other acute cardiovascular complications in patients with stable CAD by 74–109 % [3, 4].

During military conflicts, patients with CAD need therapy aimed at reducing the risk of complications and reducing the frequency and intensity of angina attacks, increasing tolerance to physical activity, and psycho-emotional stress factors. This goal cannot always be achieved, despite the use of pharmacological and interventional methods of treatment of angina pectoris.

It is known that the frequency of exposure to stressful stimuli causes a prolonged increase in the activity of the sympathetic nervous system and can cause hyperinsulinemia with its known negative consequences (increased heart rate (HR), delayed renal excretion of sodium and water, impaired cellular transport of electrolytes, metabolic syndrome, etc.)

Recently, much evidence has been published that the level of uric acid in the elderly is a biomarker of poor CAD prognosis. With an increase in serum uric acid

level by each 1 mg/dL (approximately 60 μmol/L), the risk of coronary artery calcification increases by 31 % and cardiovascular mortality by 9 % [5].

One of the possible ways to reduce the frequency of symptoms and improve cardiovascular prognosis in such patients is the administration of metabolic therapy, in particular ranolazine.

Ranolazine, by selectively inhibiting the late sodium current, prevents cardiomyocyte overload with sodium ions, thereby blocking the accumulation of calcium ions in the cells [6–9]; this is one of the main mechanisms of its anti-ischemic action. In addition, ranolazine reduces the severity of ischemic and post-ischemic left ventricular diastolic dysfunction by reducing intracellular calcium overload, which is a secondary effect of inhibition of late sodium flow [10, 11].

Taking into account these data, the use of ranolazine as a second-line drug for the treatment of stable angina pectoris opens up new possibilities for anti-anginal therapy, especially in patients with hyperuricemia.

The aim of the study. To establish the effectiveness of treatment of severe angina pectoris in patients with arterial hypertension (AH) and hyperuricemia, taking into consideration the peculiarities of the course of CAD in wartime, using ranolazine – a selective inhibitor of the late sodium flow in combined pharmacotherapy.

2. Materials and methods

We conducted the open, prospective study of 14 patients with CAD, stable angina pectoris III–IV functional class (FC) at the Center of Reconstructive and Restorative Medicine (University Clinic) of the Odesa National Medical University for 6 months in 2022.

Ethics clearance was given by the Ethics Committee of the Center of Reconstructive and Restorative Medicine (University Clinic) of the Odesa National Medical University, protocol number 224, from Feb 25 2022. Informed consent was taken from all the participants of the study.

The study included patients with stable angina pectoris III–IV FC [12]. All patients received basic, prognosis-modifying therapy (statins, antiplatelet drugs, renin-angiotensin system inhibitors, β-blockers). In order to enhance the anti-anginal effect, ranolazine (Ranexa) was prescribed at a dose of 500 mg 2 times a day in the morning and the evening, regardless of meals. The dose of the drug in 2 patients was increased after 2 weeks from the start of treatment to 1000 mg 2 times a day due to insufficient clinical effect, but with good tolerability. When choosing a drug that eliminates ischemia at the cardiomyocyte level, the presence of hyperuricemia in all patients included in the study was considered. All patients in the study suffered from AH, but at the time of inclusion, they reached the target parameters of blood pressure and heart rate.

Along with CAD and AH, 10 (71.4 %) patients were diagnosed with type 2 diabetes mellitus (T2DM). All patients gave informed consent to participate in the study and had high compliance with basic therapy. Patients with acute coronary syndrome, acute cerebrovascular accident, decompensated heart failure, severe decompensation of T2DM, active cancer, with intolerance to any of the drugs of basic therapy, ranolazine, were not included. The effectiveness of the study drug on the clinical course of angina pectoris was assessed by questionnaire and clinical examination after three months of treatment. Also, in order to rule out adverse events, correct dosages, and make an interim assessment, additional visits were made at the end of the second week, as well as the first month of observation. Therefore, the comparison group was not formed.

The received data was processed using the Microsoft Office Excel 2016 application package. To compare data, non-parametric criteria were used: the significance of differences was assessed using the Mann-Whitney test (U-test). In addition, the Pearson test (χ^2) was used to compare the qualitative characteristics. Differences were considered significant at $p<0.05$.

3. Results

Among the examined patients, 8 (57.1 %) were men, and 6 (42.9 %) were women. Distribution of the total population of patients by age: 60-69 years – 5 (35.7 %), 70–79 years – 6 (42.9 %), 80-89 years – 3 (21.4 %).

Table 1 shows the characteristics of angina attacks in the studied patients at the onset and after 3 months of observation.

Table 1

Characteristics of angina attacks in the studied patients

Indicator	Day 0			Month 3		
	FCIII	FCIV	All	FCIII	FCIV	All
Total number of angina attacks per week	13.5±8.6	21.4±9.2	15.6±9.1	0 *	7.9±4.8 *	2.3±1.0 *
Angina attacks at rest, number per week	6.5±4.2	10.7±6.3	7.7±5.7	0 *	0 *	0 *
Duration of attacks, min	5.7±3.3	11.3±5.6	7.3±3.6	0 *	4.2±2.5 *	1.2±0.6 *
Nitrate intake, number of doses per week	21.7±11.9	36.3±15.7	25.2±12.4	0 *	11.4±7.2 *	3.0±1.2 *

Note: p<0,05 when compared with the corresponding indicator on day 0

Most patients (10 – 71.4 %) observed in the study suffered from angina pectoris III FC; angina pectoris IV FC was present in 4 (28.6 %) patients. At the same time, 11 (78.6 %) of patients experienced angina attacks daily, 8 (57.1 %) had angina at rest.

At the end of the second week of ranolazine use in all patients, both with angina pectoris III FC and IV FC, there were positive dynamics in the form of clinical improvement in the course of angina pectoris, a decrease in the duration and intensity of anginal attacks.

In addition, by the end of the second week of observation, angina attacks at rest, which were registered before the start of the observation, stopped in all patients with angina pectoris III FC (χ^2=20.0, p<0,001) and in 2 (50 %) of patients with angina pectoris IV FC (χ^2=2.67, p=0.103). In 11 (78.6 %) of patients, the number of angina attacks and the use of nitrates decreased by more than 2 times. At the end of the second week of observation, 3 (21.4 %) patients no longer had angina attacks (χ^2=3.36, p=0.67).

At the end of the first month, anginal attacks were not observed in all patients with angina pectoris III FC (χ^2=20.0, p<0,001) and in 2 (50 %) of patients with angina pectoris FC IV (χ^2=2.67, p=0.103). In 2 patients with angina pectoris IV FC (50 %), anginal attacks continued to be registered during physical exertion and emotional stress, but no more than once a week. At the same time, there were no angina attacks at rest. The same results were obtained during the survey of patients at the end of three months of observation (χ^2=21.0, p<0,001).

4. Discussion

Metabolic Processes in the Normal and Failing Heart these processes are the subject of many modern studies. Offers various options for therapy aimed at improving the metabolism of the myocardium and other components of the cardiovascular system. In particular, it is proposed to use some drugs such as trimetazidine, perhexiline, meldonium, ranolazine etc. [13, 14].

Ranolazine demonstrated that people with stable angina who received ranolazine as add-on therapy had fewer angina episodes but an increased risk of presenting non-serious adverse events compared to those given a placebo [15].

Results similar to our study were demonstrated in a big observational study in Austria – the ARETHA AT study of 292 patients with stable angina pectoris. Symptoms were improved, as illustrated by the reduced number of angina attacks, reduced rate of nitrate use, reduced CCS scores and improved quality of life [16]. Moreover, some articles report the antiarrhythmic activity of ranolazine [6, 17].

The limitations of our study are the relatively short follow-up period, given that chronic diseases are the subject of the study, as well as the small number of observations. Subsequently, increasing the number of patients and evaluating them over a longer period will be necessary.

The results of our study can be used in treating patients with CAD, AH and hyperuricemia who are exposed to chronic psychological stress, particularly during military operations or due to other stress factors.

Prospects for further research. We plan to conduct an expanded study with a larger number of patients and additional analysis of different age groups.

5. Conclusions

1. In wartime, long-term stress, depression, and anxiety increase the risk of an adverse course of CAD, which requires mandatory adherence to the tactics of the patient's optimal combined therapy using cytoprotection. An effective component of anti-anginal therapy, which pathogenetically reduces the manifestations of ischemia at the cardiomyocyte level in the treatment of stable angina in patients with hyperuricemia, is the administration of a selective late sodium flow inhibitor – ranolazine, which significantly decreases the total number of angina attacks per week (from 15.6±9.1 to 2.3±1.0, p<0.05), the total number of angina attacks at rest per week (from 6.5±4.2 to 0, p<0.05), mean duration of attacks (from 5.7±3.3 min to 0 min, p<0.05) and a number of nitrate doses intake per week (from 21.7±11.9 min to 0 min, p<0.05).

2. The presented observation demonstrates the positive contribution of ranolazine in the treatment of CAD with a significant decrease in the number of angina attacks in patients of III-IV FC of angina pectoris 3–4 functional class (χ^2=21.0, p<0,001), which allows recommending its use in patients with hyperuricemia in angina attacks that persist with insufficient effectiveness of basic therapy with first-line drugs, especially during military conflicts.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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HIGH HCG LEVELS AS A CUT-OFF TO GUIDE MEDICAL MANAGEMENT OF ECTOPIC PREGNANCY: OUR EXPERIENCE

K. S. S. Madhavi, K. Avani Reddy

Methotrexate is traditionally administered using a multi-dose regimen, but a single-dose regimen was developed for patient compliance and reduced adverse effects.

The aim: *To study the success of methotrexate in our hospital considering a higher cut-off level for β-hCG.*

Materials and methods: *A hospital-based retrospective observational study was done on 40 hemodynamically stable patients diagnosed with ectopic pregnancy from July 2017 to November 2018 at Osmania General Hospital Hyderabad. Hospital-based retrospective observational study done in 40 hemodynamically stable patients diagnosed with ectopic pregnancy for 2 years. Patients diagnosed with ectopic pregnancy by transvaginal scan and who are hemodynamically stable. The selection was made as patients diagnosed with ectopic pregnancy were admitted to the hospital. Initial serum β-hCG levels were measured treated with MTX + Leucovorin (i.m) and serial measurements of serum β-hCG levels every 48 hrs were taken. The qualitative data were presented in numbers and percentages, and the quantitative data were presented in the form of mean and standard deviation.*

Results: *32 patients were treated with methotrexate, and 8 cases with surgically treated. 12 patients have taken one dose for successful treatment. 80 % of cases are successful with methotrexate treatment. The treatment success rate, on average, is 92 % when initial S-β-hCG levels <5000IU/L and 68 % when initial S-β-hCG levels > 5000 IU/L. The overall success rate is 80 % (32 out of 40).*

Conclusion: *Though the success rate is much lower with initial values >5000 (79 %) when compared to values <5000 (100 %), considering the major advantage of medical management, which is preserving the fallopian tube and thus fertility, a trial of medical management can be considered in carefully selected patients when values are >5000 with preparedness to meet any emergency*

Keywords: *Ectopic pregnancy, Human chorionic gonadotropin (hCG), methotrexate, hemodynamically stable*

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1. Introduction

Ectopic pregnancy is a significant cause of morbidity and mortality in the first trimester of pregnancy. There are >100,000 cases reported/per year in India, but the actual number is much greater because only cases managed surgically are reported. In the past, most patients with ectopic pregnancy presented with acute symptoms and intra-abdominal haemorrhage, which meant resorting to immediate surgery, but the scenario has been much different in recent times [1]. Advances in laboratory and imaging technologies in the last few decades allow an early diagnosis of ectopic pregnancy, even before the patient develops any symptoms. Consequently, in many such patients, surgery is not always necessary. The greatest advance in the management of ectopic pregnancy has been the development of medical management, which became available in the mid-1980s [2]. Therefore, medical management is a feasible option and a priority over surgery in properly selected cases. Earlier studies show that success with methotrexate is predicted by initial S-β-hCG values. However, there is no consensus about the upper limit of S-β-hCG levels that can predict a successful treatment [3]. To study the success of methotrexate in our hospital considering a higher cut-off level for β-hCG.

2. Materials and methods

A hospital-based retrospective observational study was done on 40 hemodynamically stable patients diagnosed with ectopic pregnancy from July 2017 to November 2018 at Osmania General Hospital Hyderabad.

Inclusion criteria: patients diagnosed with ectopic pregnancy by transvaginal scan and hemodynamically stable.

Exclusion criteria: Hemodynamically unstable patients, Ruptured ectopic pregnancy, Fetal cardiac activity on TVS and Gestational sac size more than 4 cm.

Ethical approval and informed was obtained.(ECR/180/OMC/AP/2016/07/45 dated on 15/12 2016)

The selection was made as patients diagnosed with ectopic pregnancy were admitted to the hospital. Initial serum β-hCG levels were measured treated with MTX + Leucovorin (i.m) and serial measurements of serum β-hCG levels every 48 hrs were taken.

MTX is given in a dosage of 1 mg/kg IM on day 1,3,5,7, and leucoverin is given in a dosage of 0.1 mg/kg on day 2,4,6,8. If a decrease in S-β-hCG of >15 % compared to the previous value was observed, then injections were stopped, and HCG was measured weekly until it was <10 IU/L.

Raw data were entered into a Microsoft Excel spreadsheet. Appropriate statistical tests were done using SPSS 17A and openepi.com to compare qualitative data and quantitative data. The qualitative data were presented in numbers and percentages, and the quantitative data were presented in the form of mean and standard deviation.

3. Results

Most of the patients are in the 30–35 years age group, followed by 20–25 years, and the most common gravida is G1 (Table 1).

Table 1

Demographic details in the present study

Age in years	Number of patients	Percentages
<20 yrs	12	30
20–25 yrs	8	20
25–30 yrs	4	10
30–35 yrs	16	40
Gravida		
G1	22	55
G2	10	25
G3	6	15
G4	2	5

32 patients were treated with methotrexate, and 8 cases with surgically treated (Fig. 1).

12 patients have taken one dose for successful treatment (Table 2).

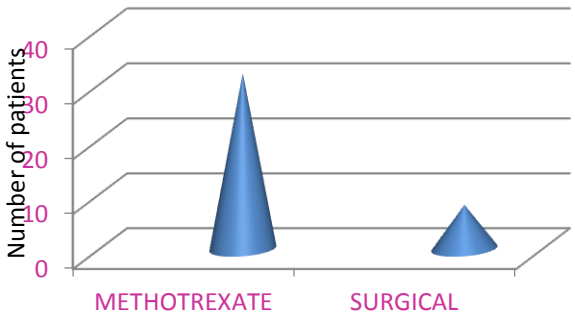

Fig. 1. Treatment given to patients with ectopic pregnancy

Table 2

Number of doses and successful methotrexate treatment

Methotrexate dose	Number of patients	Percentages
1 dose	12	30
2 doses	7	17.5
3 doses	10	25
4 doses	3	7.5
Surgical treatment		
Rising HCG	6	15
Ruptured	2	5

80 % of cases are successful with methotrexate treatment (Table 3).

Table 3

Methotrexate success rate vs initial HCG values

HCG value	Initial before treatment	After treatment with methotrexate	Success Rate
<5000 IU/L	11	11	100 % (11 out of 11)
5000–10000IU/L	24	19	79 % (19 out of 24)
>10000IU/L	5	2	40 % (2 out of 5)
Overall	40	32	80 % (32 out of 40)

The present study's overall success rate is 80 % (32 out of 40) (Fig. 2).

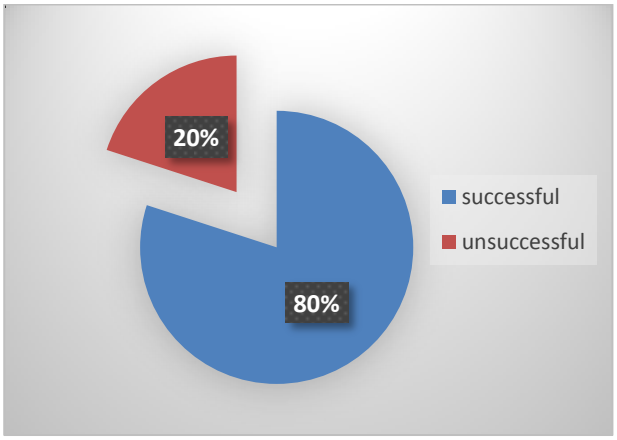

Fig. 2. Success rate with methotrexate treatment

4. Discussion

Ectopic pregnancies are obstetric emergencies that require immediate diagnosis and appropriate treatment. The decision has to be made between following expectant, medical, or surgical management. In this patient, after taking the beta-HCG levels, pelvic ultrasound findings, and clinical presentation into account, we opted to start medical management with methotrexate. According to the American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin 191, patients who are candidates for medical therapy should be hemodynamically stable, have an unruptured mass, and have no absolute contraindications to methotrexate [4]. According to the American Academy of Family Physicians (AAFP), expectant management can be considered when the patient is hemodynamically stable, the beta-HCG level is less than 1500 mIU/mL and fails to double in 48 hours, and the patient is reliable for follow-up. If not, medical management with methotrexate can be considered [5].

The trend between the initial β-hCG values and treatment outcome seems to cohere with earlier studies. In our study, the overall success rate with methotrexate treatment was 80 % (32 out of 40) which is lower compared to the study made by Lipscomb [6] in 2005, which is 90 % (578 out of 643). However, the small study population in this study makes the results uncertain. Relative contraindications for using methotrexate do not serve as absolute cut-offs but rather as indicators of potentially reduced effectiveness; one such contraindication is a high

initial hCG level. Systematic review evidence shows a failure rate of 14.3 % or higher with methotrexate when pretreatment hCG levels are >5,000 mIU/mL compared with a 3.7 % failure rate for hCG levels <5,000 mIU/ml. Studies often have excluded patients from methotrexate treatment when hCG levels are greater than 5,000 mIU/mL based on expert opinion that these levels are a relative contraindication to medical management.

According to a study by Tenore JL, when the pretreatment beta-HCG levels are less than 5,000 mIU/ml, the failure rate is only 3.7 % compared to a failure rate of 14.3 % when the pretreatment beta-HCG levels are more than 5,000 mIU/mL [7]. Similarly, a study done by Corsan et al. found that there is a higher risk of treatment failure only when the beta-HCG levels are greater than 1,500 mIU/mL [8]. This patient had a pretreatment beta-HCG level of 454.1 mIU/mL. Unfortunately, after the second dose, the patient showed clinical features suggestive of a ruptured ectopic and was promptly taken for surgical evacuation. This raises the important question of when to avoid medical management and proceed to surgical management despite low and declining beta-HCG levels.

In a study done by Saxon et al. of 716 patients admitted with ectopic pregnancy, 29 % of those with a beta-HCG level of less than 100 mIU/mL were found to have tubal rupture during laparoscopy [9]. From this, we can conclude that the risk of tubal rupture varies across a wide range of beta-HCG levels and is, therefore, not always a reliable indicator of deferring surgical management for medical management.

Seema Menon et al. [10] included 503 women and reported successes in using single-dose methotrexate stratified by initial hCG concentration. Failure rates increase with increasing hCG levels. A substantial and statistically significant increase in failure rates is seen when comparing patients with initial hCG levels of >5,000 mIU/mL with those with initial levels of <5,000 mIU/mL (odds ratio: 5.45; 95 % confidence interval: 3.04, 9.78). The failure rate for women with an initial concentration between 5,000 and 9,999 mIU/mL was significantly higher than that for those with initial levels between 2,000 and 4,999 mIU/mL (odds ratio: 3.76; 95 % confidence interval: 1.16, 12.33). They support a substantial increase in failure of medical management with single-dose methotrexate when the initial hCG is above 5,000 mIU/mL. Methotrexate can be used cautiously in patients with ectopic pregnancy who present with hCG levels above this level.

Ewa Nowak-Markwitz et al. [11] showed a success rate of 78 % (53 of 64 women). The medians of pretreatment beta-hCG levels in the groups treated successfully and unsuccessfully (943 vs 3085 mIU/mL) and after the first dose of MTX (564 vs 4049 mIU/mL) were statistically significantly different. The decrease in beta-hCG level after one MTX dose differed statistically significantly only in successfully treated women. The receiver operating characteristic (ROC) curve cut-off value in the success group indicated an initial beta-hCG level of 1790 and 1218 mIU/mL after one MTX cycle. The median of beta-hCG titer was not statistically different in patients requiring one or more treatment cycles. Concluded that beta-hCG level of >1790 mIU/mL, the MTX treatment of ectopic pregnancy is at risk of failure. So initial beta-hCG titer is not a predictor of the number of MTX cycles that can guarantee a successful outcome.

Though the success rate is much lower with initial values >5000 (79 %) when compared to values <5000 (100 %), considering the major advantage of medical management, which is preserving the fallopian tube and thus fertility, a trial of medical management can be considered in carefully selected patients when values are >5000 with preparedness to meet any emergency.

Study limitations. The retrospective nature of the study was a prominent limitation during the data collection phase due to the frequent absence of data on potential confounding factors. Additionally, this type of study can be prone to recall or misclassification bias. The small sample size is another limitation of this study, as it may make it difficult to determine the accuracy of the study findings.

Prospects for further research. Some studies have even suggested that methotrexate doses used to treat ectopic pregnancy may worsen ovarian function in the short term, while others do not show an effect. These studies are limited, and further studies are needed to evaluate the effect of low-dose methotrexate on ovarian reserve.

5. Conclusion

Ectopic pregnancy is a common and serious problem, with a significant morbidity rate and the potential for maternal death. Many patients have no documented risk factors or physical indications of ectopic pregnancy. Ultrasonography (either formal or ED-based) is the initial investigation that should be done in an ED patient with 1st-trimester bleeding or pain; indeterminate results may be clarified by measurement (single or serial) of the serum β-hCG and progesterone concentrations. Expert consultation with radiologists and gynaecologists is recommended whenever ectopic pregnancy is suspected.

The clinical presentation, serum β-hCG levels and transvaginal ultrasound findings dictate management. Methotrexate can be given to women who are hemodynamically stable and compliant and have an initial serum β-hCG concentration of less than 5000 IU/L and no ultrasound evidence of fetal cardiac activity. Patients who do not meet these criteria should be treated surgically. The treatment success rate, on average, is 92 % when initial S-β-hCG levels <5000IU/L and 68 % when initial S-β-hCG levels > 5000 IU/L. Though the success rate is much lower with initial values >5000 (79 %) when compared to values <5000 (100 %), considering the major advantage of medical management, which is preserving the fallopian tube and thus fertility, a trial of medical management can be considered in carefully selected patients when values are >5000 with preparedness to meet any emergency.

Conflict of interest

The authors declare that they have no conflict of interest concerning this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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