



### A detailed study of Methotrexate treatment in ectopic pregnancy

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#### ABSTRACT

Methotrexate is a folic acid antagonist, it works by inhibiting the dihydrofolate by interfering with the DNA synthesis. Ectopic pregnancy is a life threatening condition that may cause maternal mortality. The main aim of this review to show the efficacy of systemic methotrexate and shows the importance of methotrexate treatment in management of ectopic pregnancy with surgical treatment and dosage regimen with protocol treatment. The selection criteria of candidates in this review is pregnant women with <5000miu/ml, adrenal mass <4cm, presence of peritoneum <100mland no sign of cardiac activity. Data collections are made from most relevant article between the periods of 1987-2020. Ectopic pregnancy is an emergency condition if not timely diagnosed and most of the cases where identified in first trimester.

**Keywords:** Ectopic Pregnancy; Methotrexate; Treatment; Dose;  $\beta$  hcg.

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#### INTRODUCTION

Ectopic pregnancy is the implantation of fertilized ovum on any tissue outside the uterine cavity [1]. It is acute emergency if not treated in right time. Mainly ectopic pregnancies are occurred in fallopian tube, ovary and cervix [2]. About more than 98% ectopic pregnancies are occurred in fallopian tube [3]. Ectopic pregnancy cause increased rate of mortality and morbidity [4,5]. The common symptoms include internal bleeding, abdominal pain, and amenorrhea [6]. Mainly ectopic pregnancies are occurred due to the obstruction of fallopian tube and pelvic inflammatory disease, in many cases the ectopic pregnancies are misdiagnosed, it is diagnosed by history of pelvic inflammatory disease, physical examination, measurement of  $\beta$ -hcg level with

transvaginal ultrasonography [7]. Pregnancy of unknown location (PUL) is the preferred terminology when the serum hcg is positive, but no signs of intrauterine or extra uterine pregnancy can be detected using transvaginal ultrasonography and the main management of ectopic pregnancy includes surgical management and medical treatment [8]. Ectopic pregnancies are primarily managed by surgical procedure includes laparoscopic management and salpingectomy and now medical treatment are available [9,2,8]. Ectopic pregnancy is very dangerous for pregnant women, if the fertilized egg grows, they will eventually rupture the organ that contains it, and this will cause severe life threatening bleeding inside the body. Women have an ectopic pregnancy may cause a delay or variation in their menstrual periods, Women who experience incomplete abortion have long periods of amenorrhea [6]. Now a days the rate of ectopic pregnancies were increased and its mortality rate was decreased from the use of methotrexate [8].

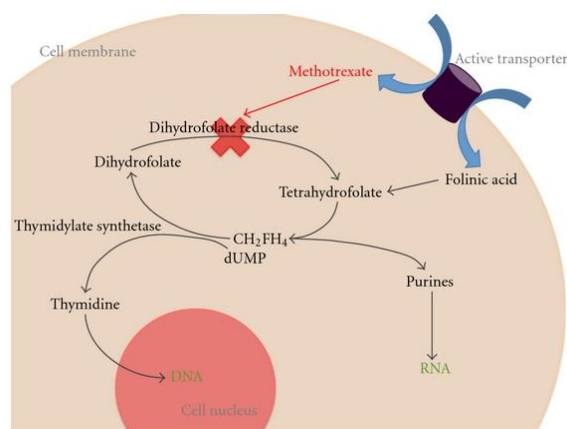
Methotrexate was introduced in 1948 with the history of initial report by Sidney farber and the successful aminopterin, is an anti-folate in the treatment of child leukemia [10]. It is a synthetic folic acid analogue, which inhibit the enzyme dihydrofolate reductase and prevent conversion of dihydrofolate to tetrahydrofolate [11,4]. Methotrexate compete with the folic acid and interfere cell replication. Methotrexate was invented as a second drug of folic acid analogue from the study of folic acid deficient diets were shown to be declined in leukemic cell count and it was first used in ectopic pregnancies

in 1960, also it is an antimetabolite used in 1980 for the treatment of the ectopic pregnancy, by the extension of its use in gestational trophoblastic neoplasia [11,3]. Methotrexate have a structure similar to the folic acid and it is used in leukemia, neoplasia, and lymphomas [11]

Systemic route of administration of methotrexate was highly effective, mainly IM route for the treatment of the ectopic pregnancies [8]. Methotrexate have an immunomodulatory action in autoimmune disease, it may cause teratogenicity while using this on the first trimester of the pregnancy [11]. Methotrexate have a teratogenic effect in ectopic pregnancy during presence of cardiac activity, it have an action in skin related problem and also have function in autoimmune condition. Their treatment is associated with the beta human chorionic gonadotropin [2,8]. They are contraindicated in case of rising beta hcg, they are act in rapidly growing cells [4]. A proper follow up should be considered before using methotrexate because it have some risk factors include renal impairment and hepatic impairment, it is not used in the case of presence of cardiac activity. it shows a relatively contraindicated in pregnancy of unknown location (PUL) [12]. The incidence of ectopic pregnancy is about 1-2% in developed countries [3].

**Methotrexate:** Methotrexate is a folic acid antagonist, which is invented as an anticancer agents, it inhibit rapidly dividing cells includes trophoblastic cells [2]. Primarily it is used for the treatment of acute lymphoblastic leukemia [11]. Methotrexate is a derivative of aminopterin, is an analogue of folic acid also its antimetabolite [13]. It is isolated from spinach leaves and called folic acid [15]. Now a days it is also used for pregnancy related conditions include ectopic pregnancies and trophoblastic leukemia, methotrexate is available in oral and systemic route, methotrexate is used as the first line treatment for the ectopic pregnancies, systemic methotrexate can be given in single-, double-, and multi-dose protocols depending on the clinical findings and beta-human chorionic gonadotropin ( $\beta$ -hcg) values [14]. Methotrexate have a structure similar to the folic acid. Methotrexate is used in ectopic pregnancy in 1980 by the extension of its use in gestational trophoblastic neoplasia [11,3]. The recent study shows methotrexate is safe and effective in unruptured ectopic pregnancies [6,8]. Methotrexate is given with surgical management or it is used as the first line agent in case of unruptured ectopic pregnancies, recent studies shows the result of failure of the use of oral methotrexate compared with systemic use in ectopic pregnancies [3].

**Mechanism of action of methotrexate:** It is a folic acid antagonist. it inhibit the enzyme dihydrofolate reductase by interfering the DNA synthesis, hence conversion of dihydrofolate to trihydrofolate is prevented [9,11].



**Figure 1: Mechanism of methotrexate in ectopic pregnancy**

It is essential for the denovo synthesis of purines nucleotides and thymidilate (essential substrate of the DNA synthesis, repair, and cell proliferation). Tetrahydrofolates have an essential role in synthesis of DNA and RNA precursors such as purines and pyrimidines [11]. Mainly it affect the s phase of the cell cycle and it works rapidly in dividing cells mainly trophoblastic cell, and the methotrexate have nonspecific mechanism of action and shows some side effects [2].

**Indications:** Methotrexate was invented as a folic acid analogue for the treatment of acute lymphoblastic leukemia and is used to treat cancerous and non-cancerous conditions, Folic acid deficient diets were shows to decrease in leukemic cell count and this leads to the development of the folic acid analogue methotrexate as second drug, have an immunomodulatory action in rheumatoid arthritis, psoriasis [11]. Methotrexate is also used as the management for the autoimmune diseases such as rheumatoid arthritis, juvenile dermatomyositis, lupus erythematosus, sarcoidosis, Crohn's disease, some types of severe eczema and a wide range of forms of vasculitis [16,17]. Now a days it is also used for pregnancy related conditions include ectopic pregnancies and trophoblastic leukemia, Methotrexate is used for the treatment of chorioadenoma destruens, gestational choriocarcinoma [11].

It is used for the management of ectopic pregnancies with the combination of other surgical treatment. Methotrexate is used in the treatment of breast cancer, epidermoid cancers of the head and neck and lung cancer, particularly squamous cell and small cell types used alone or in combination with other anticancer agents [18]. It is also used in advanced stage non-Hodgkin's lymphomas, It is used in the treatment of a choriocarcinoma by the application of this drug in women in 1956 [11]. Methotrexate is used a combination treatment with other immunosuppressive drugs, primarily in combination with biologics, In such cases, methotrexate is responsible for inhibition of formation of antibodies

against biologic drugs, thereby increasing their efficacy<sup>[13]</sup>. It is widely used in ophthalmology, mainly in uveitis, scleritis also in advanced diabetic neuropathy<sup>[19]</sup>.

**Contraindication:** Methotrexate is contraindicated in pregnant women with psoriasis, rheumatoid arthritis also it is contraindicated in the case of the nursing mother and in children but this can use in the case of the cancer related condition in pediatrics<sup>[18]</sup>. It should be avoided in increased level of serum creatine and also in liver transaminase contraindicated in the case of psoriasis and in case of rheumatoid arthritis with alcoholism and absolutely contraindicated in the case of the immunosuppressive syndrome with bone marrow hypoplasia, leukopenia, thrombocytopenia and significant anemia, pulmonary disease, renal disease, Active pelvic disease, intrauterine pregnancies, ruptured ectopic pregnancies and hemodynamically unstable patients and relatively contra indicated in the high initial hcg level and also in embryonic cardiac activity is detected by transvaginal ultra sonography, Adrenal mass >4, these contraindications limits the use of methotrexate use in various conditions<sup>[20]</sup>. Methotrexate is contraindicated in the case of the chronic liver disease (methotrexate should be toxic to the hepatocytes) and in immunodeficiency condition<sup>[4]</sup>.

**Side effects:** The side effect of methotrexate is based on the patient conditions. Commonly side effects are no occur in all patients using methotrexate. Serious side effects occurring on the basis of the dosage regimen. Sometimes it may cause serious side effects and its over dose may cause its toxicity in patient receiving methotrexate, high dose intake of it also cause severe life threatening condition. Methotrexate acts in rapidly dividing cells, by this mechanism it may cause the hematological (megaloblastic anemia, thrombocytopenia, pancytopenia, leukopenia), dermatological symptoms (burning sensation, ulceration to the mucosa, urticarial, erythema, photosensitivity, vasculitis) and gastro intestinal symptoms may occur at high or low dose (nausea, vomiting diarrhea, abdominal pain), sometimes it may cause toxic symptoms like neutropenia, nausea vomiting, diarrhea, git inflammation, hypersensitivity reactions occurs<sup>[11,20,21]</sup>. Methotrexate causes teratogenic effects while it's using during first trimester of the pregnancy<sup>[11]</sup>. Hepatotoxicity is the most common cause of the use of the methotrexate also It may cause renal toxicity (acute renal failure, tubular necrosis), neurotoxicity may occur due to the systemic administration of methotrexate (insomnia, cerebral dysfunctions, confusion, seizure, agitation), pulmonary toxicity-most serous one and, may occurring at low dose (pneumonitis, alveolitis, no productive cough, dyspnea, malaise). The side effects may reduce by the use of leucovorin (is similar to the folinic acid)<sup>[21,20]</sup>.

**Dosage and administration:** Methotrexate is administered through oral route as well as systemic route, in ectopic pregnancy methotrexate is treated through Intra muscular route, this route is most widely accepted treatment in ectopic pregnancy also it is used as an alternative to the surgical treatment<sup>[22]</sup>. Methotrexate dosage regimen is available in different form, which is different for each patients based on their condition as well as Modern treatment is safe with the use of systemic methotrexate, differnt dosage regimen is available for the ectopic pregnancy- Single dose (50mg/m<sup>2</sup>), double dose(50mg/m<sup>2</sup>) and multi dose regimen with {1mg/kg and is treated with 0.1mg/kg leucovorin (is a folinic acid, it is an active form and is used only with the multiple dose and not in single use of methotrexate )}<sup>[14,4]</sup>.

**Pharmacokinetics:** Methotrexate is absorbed through intra muscular route or oral route with smaller dose less than 30 mg/m<sup>2</sup> and decreased absorption while receiving dose greater than 80 mg/m<sup>2</sup>, after I.V administration initial volume of distribution is about 0.18L/kg and steady state volume is approximately 0.4-0.8L/kg and metabolized through hepatic intercellular membrane ,it forms polyglutamated form that block enzyme reductase and thymidylate synthase, its oral dose is metabolized by the intestinal bacteria, elimination half-life is from 6-69 hrs and they are eliminated through renal excretion and plasma clearance become saturated at high dose (20g), high dose administration cause the presence of small amount of thyoymethotrexate, its clearance is decreased by the administration of salicylates like organic acid methotrexate is poorly penetrate cell membrane by carrier mediated transport mechanism and it does not penetrate blood - cerebro spinal fluid barrier, the absorption rate of methotrexate is different for different patients, the recent studies shows that intra muscular methotrexate is effective compared to the oral methotrexate<sup>[18,22]</sup>.

**Drug interactions:** Methotrexate having some interactions with certain vaccines, drugs and other product. Some drug cause a serious interactions with mqtthotrexate. some have mild and moderate interactions, certain vaccines and drugs that cause severe interactions with methotrexate are given below<sup>[23,24]</sup>:

- Influenza A virus vaccine, Rubella vaccine, Varicella vaccine, Polio virus vaccines, Measles, mumps, Rotavirus vaccine, Typhoid vaccine, Small pox vaccine and Yellow fever vaccine and Acitretin.
- Some mild interaction with methotrexate includes: Folic acid, Adalimumab, l-methylfolate, Golimumab, Hydrochlorothiazide, Methychlothiazide.
- Other drug includes: Chloramphenicol, Leflunomide.

Azathioprine, Sulfasalazine - cause liver problems  
 Retinoid – Isotretinoin  
 Penicillin, Probencid, phenytoin  
 PPI- Pantoprazole, Omeprazole, Esomeprazole.

### Ectopic pregnancy

Ectopic pregnancy is defined as implantation and subsequent development of the zygote at a site other than normal intrauterine cavity [25]. The most common site of ectopic pregnancy is the fallopian tube other sites include ovary, abdomen and cervix, methotrexate is select as the medical treatment for this condition. Recently methotrexate is usually used in the stable women having unruptured pregnancy. The case of ectopic pregnancy is increased day to day. The existing treatment for the ectopic pregnancy is surgical management and the medical management with systemic methotrexate. while using this medication human chorionic gonadotropin [hcg] should be considered, it is also an important factor before using the methotrexate, the most common complication of ectopic pregnancies include rupture, internal bleeding and this may be the cause of hypovolemic shock., in ectopic pregnancy the most common cause leading to maternal death [6].

### Clinical manifestations

The clinical manifestations of ectopic pregnancies are abnormal bleeding amenorrhea and abdominal pain, pelvic inflammatory disease, and spontaneous abortion, vaginal spotting may see in first trimester of ectopic pregnancies [6]. Less common symptoms include shoulder pain, dizziness, weakness, fainting. other symptoms include urinary symptoms and rectal pressure, women who experienced ectopic pregnancy have may have a variations in their menstrual periods, pain and bleeding in women at first trimester of their pregnancy[8,6]. Hemodynamically unstable patient may experience the syncope and the signs include shock, tachycardia on ruptured ectopic pregnancy [6].

**Causes and risk factors:** A fertilized egg have difficulty to passing through ruptured tube and this will leads to the growing and implant the egg in tube this will leading to ectopic pregnancy, ruptured ectopic pregnancies cause hemorrhage and shock these are the leading cause of maternal mortality in the first trimester, most tubal pregnancies are caused by tubal obstruction or delayed passage of the fertilized ovum [6] other causes include [8]:

- Cigarette smoking
- Tubal damage
- Previous surgery
- Chlamydia trachomatis infection.

Women who experienced ectopic pregnancy have may have a variations in their menstrual periods, pain and bleeding in women at first trimester of their

pregnancy, hemodynamically unstable patient may experience the syncope and the signs include shock, tachycardia on ruptured ectopic pregnancy [6,8]. Other symptoms of ectopic pregnancies are infertility, contraceptive failure and previous ectopic pregnancy [3]. A ruptured ectopic pregnancy should be strongly suspected if a woman has a positive pregnancy test and having syncope and signs of shock including, pallor and collapse, tachycardia, there may be abdominal distension and tenderness may occur, while a bimanual examination may reveal tenderness, cervical excitation and an adnexal mass, great caution is required as this may exacerbate bleeding, in an emergency, where the patient has collapsed and there is high clinical suspicion of tubal rupture [26].

Other Risk factors include: previous surgery, endometriosis, previous ectopic pregnancy, intrauterine device, infertility treatment, mechanical factor infertility, longer stimulation [26,27].

### Diagnosis:

- History and physical examination
- Speculum and binomial examination
- Trans vaginal ultra-sonography
- Measurement of beta hcg

Diagnosis of ectopic pregnancies were difficult. Sometimes there will be a misdiagnosis in this case [8]. Usually it is diagnosed in the first trimester of their pregnancies, personal history and physical examination is the initial diagnosis of ectopic pregnancy. Abdominal pain with spotting occur in 6 to 8 weeks after a last normal menstrual period is symptom of tubal pregnancy [28]. Speculum and bimanual examination have limited role in diagnosis, pregnancy test is positive in ectopic pregnancy, early diagnosis is with algorithms which are based on high resolution transvaginal ultrasound (TVS) and quantitative estimation of serum  $\beta$ hcg measured initially and changes in the levels of  $\beta$ hcg can be used to predict ectopic pregnancy [25]. Ultra sound evaluation is the main used to diagnose the ectopic pregnancy, and these ultrasound result should be combined with the qualitative beta subunit of human chorionic gonadotropin levels [29,3]. Hemodynamically unstable women who experienced syncope and signs of tachycardia and the shock should be a diagnosis of the ruptured ectopic pregnancies, an ectopic pregnancy is diagnosed by the presence of an adnexal mass in absence of intrauterine gestation sac, often visible within the Fallopian tube [26]. Detection of an extrauterine gestational sac containing a yolk sac confirms the ectopic pregnancy [30]. If a patient has a  $\beta$ hcg level with 1,500 mIU/mL or greater and transvaginal ultrasonography does not show an intrauterine gestational sac indicates ectopic pregnancy should be suspected [31]. It is better tool to identify the non-tubal, ectopic pregnancy, also ectopic pregnancy is diagnosed by using serum progesterone level, if it is < 5ng/ml indicates an

abnormal pregnancy and greater than 20ng/ml usually indicates abnormal intrauterine pregnancy<sup>[12]</sup>.



**Figure 2: Transvaginal ultra-sonography of ectopic pregnancy**

### Beta HCG and ectopic pregnancy, methotrexate

The body release HCG during the period of pregnancy, human chorionic gonadotropin is a hormone produced by the syntiotrohoblastic cell of placenta during pregnancy, and smaller amounts are produced from the pituitary gland, colon and liver, the hormone is a glycoprotein having two subunits, one alpha and beta—<sup>[32]</sup>. Beta human chorionic gonadotropin is an important test for the diagnosis of ectopic pregnancy. Its level is different in different patient, some women having ectopic pregnancy with increased initial level of beta subunit of hcg and some have decreased level of human chorionic gonadotropin. Methotrexate is highly beneficial to the patient have a decreased  $\beta$  hcg level but in increased level of beta hcg patient were failure to methotrexate treatment <sup>[3]</sup>. Serum  $\beta$  hcg level should detected with investigation of ultrasonography in the first trimester of pregnancies <sup>[31]</sup>.

- A low hcg level is a sign of an ectopic pregnancy <sup>[32,8]</sup>.
- The level of hcg stop rising and dropping indicates – miscarrying <sup>[8]</sup>

Serum beta hcg is detected urine or blood, also in an emergency situation, it is detected from serum or urine. In serum test the detected level of hcg is lower than 5IU/L and in urine test the detected level of hcg is from 20-50 IU/L IF a serum concentration is lower than 1000 IU/L indicates a risk of an ectopic pregnancy which means risk of ectopic pregnancy is associated with the level of the human chorionic gonadotropin. Ectopic pregnancy is presents with increased or decreased level of the hcg level, thus the measurement is most useful in ectopic pregnancy, and is used for the women who have bleeding and pain in first trimester<sup>[30,26]</sup>.

Ectopic pregnancy is suspected if the transvaginal ultrasonography shows no intra uterine gestational sac when increased level of hcg, if the beta hcg plateau fails to double in 48hr, and the ultrasound

examination was fail to identify an intra-uterine gestational sac <sup>[8]</sup>. Some studies shows the prove of methotrexate treatment reduced the beta hcg level and some shows the methotrexate is effective in hemodynamically stable unruptured ectopic pregnancies <sup>[6,30]</sup>. Ectopic pregnancy have an expectant management with low hcg level <sup>[33]</sup>. In methotrexate management serum beta hcg level should be monitoring closely.it is time consuming and not detect in night and evening <sup>[30]</sup>. Serum progesterone measurement is used as an adjunct to serum hcg measurement <sup>[8,12]</sup>.

### Treatment and management of ectopic pregnancy

The management of ectopic pregnancy include <sup>[5, 26, 6, 8, 31]</sup>:

- Surgical management
- Expectant management
- Medical treatment

In surgical management there exist two different methods:

1. Radical – salpingectomy
2. Conservative-salpingostomy, salpingectomy, segmental resection, milking or fimbria expression.

Medical treatment:

1. Systemic - methotrexate
2. Local- Methotrexate  
Prostaglandin (PGF2a)  
Actinomycin D  
Potassium chloride  
Hyperosmolar glucose  
Mifepristone

In earlier ectopic pregnancies were treated with the surgical treatment, although in several conditions there is an evidence of failure rate of surgical pregnancies are occurred due to its complications, women who experienced ectopic pregnancy treated with surgical pregnancy they have a future infertility problem and have a complication of infections and other complications are occurred<sup>[2]</sup>. In several cases surgical treatment along with methotrexate have successful rate in patients who have an ectopic pregnancy <sup>[8]</sup>. Modern studies prove that the patients with ectopic pregnancies are primarily treated with methotrexate, after that they are further treated with surgically if necessary <sup>[2]</sup>. The main treatment are yet to be known is surgical treatment and medical treatment with systemic methotrexate <sup>[2]</sup>.

Surgical method include salpingectomy but it cause future fertility problem and have a history of complications in some patients who experienced ectopic pregnancies <sup>[2]</sup>. Surgical treatment is done in ruptured condition of ectopic pregnancy, salpingectomy is the surgical removal of fallopian tube, it is recommended if fertility is not desired or presence of uncontrolled bleeding and salpingostomy is the creation of opening into the fallopian tube,

pregnancy issue is removed and tube is flushed [12]. Salpingectomy have a risk of infertility in women carrying ectopic pregnancy. In some case include hemodynamically unstable and heterotopic pregnancies, symptoms (pain), diagnostic laparoscopy, and women who have high hcg level require surgery and laparoscopy is an effective approach and management, Laparoscopy is done in case of extrauterine pregnancy and laparotomy is performed only if the laparoscopy is not possible conditions [34]. Indication of salpingectomy includes tubular distribution ipsilateral recurrence, prior ipsilateral sterilization [1].

Laparoscopy is another method in surgical treatment. Laparoscopy is also known as diagnostic laparoscopy, it is a diagnostic procedure to identify an organ inside the abdomen it requires only small incision compared to another, and it is most widely used surgical treatment, laparoscopy is associated with the risk of bleeding, infection, and having several complications include anesthesia problem, blood clot, rarely cough, abdominal pain, anxiety, anemia, mild bleeding or infection, fever, urinary tract infection, postoperative urinary retention, and ileal paralysis, also occurred, laparotomy is performed only if laparoscopy is not done or possible, they have less blood loss [34]. This will leads to the invention of medical treatment, mainly methotrexate is given as the medical treatment for the ectopic pregnancy. A laparoscopic salpingostomy should be considered if future fertility is desired in patients have tubal pregnancy [26].

### Medical treatment of ectopic pregnancy

Methotrexate is an anticancer drug It also under the classification of DMARDs and also it plays an important role in dermatology, methotrexate is first used for the treatment of ectopic pregnancy in 1982[4]. Criteria for the use of methotrexate includes[1]:

- Hemodynamically stable patient
- $\beta$  hcg 5000mIU/L
- Adrenal mass; 4cm
- No tubular damage

Pretreatment should be done before the usage of methotrexate, it mainly include blood typing, sr.hcg, and lab test (CBC, LFT mainly ALT/AST, creatine, RFT), methotrexate mainly act in rapidly proliferating cells. It is available in oral, injection, and powder methotrexate, mainly systemic route is highly recommended for treatment of ectopic pregnancy, most common protocols include single and multi-dose regimens, single dose is given as 50mg/m<sup>2</sup> and multi dose is given in 1mh/kg based on the ectopic pregnancy protocol of university of Alabama at Birmingham shows 90% of success rate in ectopic pregnancy treated with methotrexate in patients with 5000mIU/mL based on modern protocol methotrexate is exact use in

hemodynamically stable with unruptured mass women with ectopic pregnancy[12]. In majority of the case single dose regimen is used but it shows more failure rate, with use of this and special care to be taken in patients with 5000mIU/mL and presence of cardiac activity, in this case methotrexate is relatively contraindicated, several recent studies are yet to be known methotrexate is safe on comparing with the surgical studies with a proper follow up should be considered before and after the use of methotrexate [4,8,12,].

Treated with systemic methotrexate have success rate compared to oral methotrexate. Failure rate of systemic methotrexate increases with raising  $\beta$  hcg, systemic methotrexate have some benefits and tolerability compared to other form. It is shown to be a good alternative to laparoscopy an important criteria is  $\beta$  hcg for ectopic pregnancy. Most recent studies shows a failure rate in single dose protocol for unruptured ectopic pregnancies [3]. Two dose and multi doses are administered in people with high initial  $\beta$  hcg, methotrexate is absolutely contraindicated in presence of cardiac activity during ectopic conditions [1]. Success rate of methotrexate decreasing by increasing  $\beta$ hcg >5000 shows failure to methotrexate with single dose treatment. A single dose regimen of methotrexate is used to minimize the side effects and low cost, to avoid risk problems [3].

Multi dose or two dose should give only in high  $\beta$  hcg condition but they are relatively contraindicated in many of the case of single dosage regimen of methotrexate have success rate of 65% compare with the surgical treatment of 35% success rate based on the literature review of Oman journal of obstetrics and gynecology, based on this single dose protocol is administered with a 50mg/m<sup>2</sup> methotrexate in day 1 and they performed a serial  $\beta$ hcg on 4<sup>th</sup> and 7<sup>th</sup> day, the  $\beta$  hcg level is declined 15% compared with 4<sup>th</sup> day then after they undergo follow up until undetected hcg level a second dose of 50 mg/m<sup>2</sup> methotrexate is given to the patient with  $\beta$ hcg level on 7th day was same higher than 4th day. This proven that the single dose methotrexate have successful rate in  $\beta$ hcg level become negative [2.]

The single dose protocol should follows the condition include [2, 12]:

- Hemodynamically stable patients
- $\beta$  hcg <5000mIU/mL
- Presence of peritoneum <100ml
- Adrenal mass <4cm
- No sign of cardiac activity.

The selected criteria of candidates are exclude from [2]

- Hemodynamically unstable patients
- $\beta$ hcg >5000mIU/mL
- Peritoneum >100ml
- Adrenal mass >4cm

**Table 1: Shows the protocol of single, double and multi dose regimen of methotrexate for ectopic pregnancy**

Dose	Single dose	Two dose	Multi dose
methotrexate	50mg/m <sup>2</sup>	50mg/m <sup>2</sup> in day1and 4	50mg/m <sup>2</sup> /1mg/kg for alternative days
leucovorin	none	None/0.1mg/kg	0.1mg/kg
frequency	βhcg level on day 4 and 7 <15% repeat weekly until <15%	If >15% of drop from 4 and day 7, continue follow up until <15%	Up to 4 dose in alternate days until βhcg is declined by 15%.
βhcg	Follow up undetected hcg	Follow up undetected hcg	Follow up undetected hcg

Several studies have some different approach and suggestions, most of the systematic review used different trials in protocol of single, two dose or multiple doses shown in (Table 1)<sup>[12]</sup>.

Multi dose risk is compensate with the leucovorin 0.1mg/kg, is a folic acid to counteract the folic acid antagonist side effects and impairment, total success rate is increased with βhcg <5000 mIU/L, proper follow up should be done to identified the treatment effect and side effect, other treatment guidelines include<sup>[12,8]</sup>:

- Advised the patient to avoid NSAIDs and alcohol.
- Avoid the pelvic examination or pelvic intercourse during treatment.
- Weekly follow up of βhcg.

## CONCLUSION

Methotrexate is proven to be most effective and safe for unruptured ectopic pregnancy. Tubular damage cause increased the risk of methotrexate. This review article shows a single dose is beneficial to unruptured, stable patients with low beta hcg level and is effective with minimize the side effects compared to other multi or two dosage regimen. Multiple dosage regimen is proven to be effective in high initial beta hcg level that is >5000mIU/mL. A systematic follow up should be done in case medical treatment with methotrexate. Methotrexate is confirm used in ectopic pregnancy also it is used as an alternative to surgical treatment. Ectopic pregnancy is treated in various dosage regimen based on the hcg level and selection criteria of candidates. Hemodynamically stable women is treated with the systemic methotrexate. Systemic route is mainly intramuscular route is very effective in ectopic pregnancy.

## CONFLICT OF INTEREST

The authors declared no conflict of interest with respect to the authorship, research, or publication of the article.

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