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MEDICAL APPROACH TO ECTOPIC PREGNANCY

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SUMMARY

The management of ectopic pregnancy has changed dramatically over the years and a conservative approach now predominates. Many women with ectopic pregnancies are now treated with methotrexate instead of surgery. Randomized studies have demonstrated that in selected cases medical treatment with methotrexate is as effective as laparoscopic surgery. However, medical treatment might have a more negative impact of patients health-related quality of life than surgical treatment. In general, medical treatment with methotrexate is less costly than the surgical approach. All patients treated with methotrexate should be followed up closely until hCG is no longer detectable in the serum. The initial serum hCG concentration is the best prognostic indicator of treatment success in women with ectopic pregnancies who are treated according to methotrexate protocol.

Key Words: *Ectopic Pregnancy, Medical Management, Methotrexate.*

ÖZET

EKTOPİK GEBELİKTE MEDİKAL YAKLAŞIM

Günümüzde ektopik gebeliğin tedavisi değişmiş, konservatif yaklaşım ön plana geçmiştir. Ektopik gebeliği olan pek çok kadın cerrahi yerine metotreksat ile tedavi edilmektedir. Randomize çalışmalar uygun vakalarda metotreksat ile tedavinin laparoskopik cerrahi kadar etkili olduğunu göstermektedir. Bununla birlikte medikal ve cerrahi tedavinin yaşam kalitesi üzerine olan etkileri karşılaştırılmalıdır. Genel olarak metotreksat ile medikal tedavi cerrahi yaklaşıma göre daha ekonomiktir. Metotreksat ile tedavi edilen tüm hastalar serumda hCG değerleri negatifleşene kadar yakından takip edilmelidir. Başlangıç serum hCG konsantrasyonu metotreksat protokolüyle tedavi edilen hastalarda tedavi başarısını gösteren en iyi prognostik faktördür.

Anahtar Kelimeler: *Ektopik Gebelik, Medikal Tedavi, Metotreksat*

Ectopic pregnancy is a life-threatening condition. Recent reports affirm that ectopic pregnancy is becoming a medical disease. This evolution is driven first by increasingly reliable nonsurgical diagnosis. Algorithms using combinations of hormone measurements and gynecologic ultrasound facilitate timely diagnosis and eliminate need for surgical visualization. Second, the evolution is driven by lower costs. Third and finally, medical therapy virtually eliminates surgical complications from treatment.1

Epidemiology:

The incidence of ectopic pregnancy is approximately 0.5-1.0% of all pregnancies but

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this rises to about 5% after assisted conception therapies and 20-30% in women with tubal damage after tubal surgery or a past history of ectopic pregnancy. A past history of pelvic infection accounts for about 40% of ectopic pregnancies and it is argued that women with significant tubal damage should be sterilized before they commence IVF. It is therefore important to understand the modern management of ectopic pregnancy in order to minimize any compromise of future fertility.2

Pathogenesis and Risk Factors:

As previously noted, ectopic pregnancy occurs when the blastocyst implants in a location other than the endometrial lining of the uterus. These pregnancies are generally the result of factors that delay or prevent passage of the fertilized egg into the uterine cavity or factors inherent in the embryo that result in premature implantation.3 Over 98% of ectopic pregnancies occur in the fallopian tube itself. Sites for ectopic pregnancy other than the fallopian tube include the cervix (0.1%), ovary (0.5%), and abdominal cavity (0.03%). Of those ectopic pregnancies confined to the fallopian tube, approximately 93% occur in the ampullary portion, 4% in the isthmic portion, and 2.5% in the interstitial or cornual portion of the tube.4

Numerous risk factors for the development of an ectopic pregnancy have been proposed. The more commonly cited risks include prior pelvic inflammatory disease (PID), previous tubal surgery, intrauterine contraceptive device (IUD) use, previous ectopic pregnancy, in vitro fertilization (IVF), progestin-containing contraceptives, smoking, previous abdominal surgery and induced abortion.5,6

Diagnosis:

Patients with normal intrauterine pregnancies can present with the same symptoms encountered in patients with unruptured ectopic pregnancies. The best way to diagnose ectopic pregnancy is to be highly suspicious and sensitive to its possibility, and to utilize the new tools of diagnosis the quantitative measurement of (-hCG and transvaginal ultrasonography.7 Laparoscopy is necessary only when the diagnosis is in doubt, or when laparoscopy is the technique selected for surgical treatment.8

Classically, the most common presenting symptoms seen with an ectopic pregnancy were pain, vaginal bleeding and amenorrhea. Abdominal pain has been reported to occur in 90% to 100% of ectopic pregnancies and frequently begins far in advance of tubal rupture. Other classical symptoms reported in association with ectopic pregnancy were dizziness, pregnancy symptoms, and vaginal passage of tissue.9 The most common classical finding on physical examination is adnexal tenderness. This finding has been reported to occur in 75% to 90% of symptomatic patients.9 Adnexal mass, uterine enlargement, orthostatic changes and fever are other classical findings.

The production of (-hCG by the trophoblast usually starts 6 days after fertilization, and 3-5 days later, traces of (-hCG can be detected in the circulation. In normally growing intrauterine early gestation, the quickly expanding trofoblast is responsible for a rapid increase in the plasma (-hCG level at a doubling rate approximately every 48-72 hours. The dynamics of (-hCG production may vary in ectopic pregnancy.10 It was reported that 49% of women with ectopic pregnancy had decreasing levels of serum (-hCG and in another 44% of women the rice of the (-hCG level was lower than expressed or there was no increase.11 Only 7% of the subjects in their study had a normal increase of the (-hCG level, which was defined as not less than a 66% when tested every 48 hours or not less than a 114% increase every 72 hours. An abnormal pattern of (-hCG secretion in ectopic pregnancy cannot be distinguished from the one observed in a failing intrauterine pregnancy. On rare occasions, an ectopic pregnancy is found in a woman in whom (-hCG cannot be detected in the serum or urine.12 The (-hCG level decreased rapidly after salpingostomy, and on postoperative day 12 it usually decreased to less than 10% of the preoperative value.13 Although an increasing level or a

plateau of (-hCG levels are obvious indicators of persistent ectopic pregnancy, a slowly decreasing (-hCG level poses a more challenging diagnostic issue.

The highest (-hCG level at which an intrauterine pregnancy could not be seen by a 5-MHz transvaginal sonography was 2,600 mIU/ml, and 800mIU/ml was the lowest level at which an intrauterine pregnancy was detected.14 The sonographic signs of a normally developing pregnancy have been correlated with the serum (-hCG levels. Such a correlation is helpful in distinguishing a normal intrauterine pregnancy from an abnormal pregnancy. It should be noted that the (-hCG levels corresponding to the sonographic findings are much higher if transabdominal sonography is used.

A single measurement of the serum progesterone level may be helpful in identifying a normally developing pregnancy. A level exceeding 25 ng/ml is associated with a viable intrauterine pregnancy, whereas values of less than 5 ng/ml are highly suggestive of a nonviable pregnancy. Progesterone levels between 5-25 ng/ml are inconclusive and thus not helpful in making a diagnosis.15

Recently several other endocrine markers have been used to distinguish a normal pregnancy from an abnormally developing ectopic pregnancy. Inhibin levels have been found to be significantly lower in the serum of women diagnosed with ectopic pregnancy when compared with women who had a confirmed single intrauterine pregnancy.16 Recent interest in creatine kinase as a potential marker in the diagnosis of ectopic pregnancy has come from a finding that the tubal muscularis penetration and damage by the expanding trophoblast may increase the presence of creatine kinase in the serum.17 Saha et al evaluated serum creatine kinase levels and found that the levels in women with ectopic pregnancy were higher than in those with intrauterine pregnancy.18 Whether it can be used to distinguish ectopic pregnancy from non-viable intrauterine pregnancy remains to be seen. Others studied fetal fibronectin levels from cervicovaginal swabs19, and serum vascular endothelial growth factor levels.20 They found that the levels in women with ectopic pregnancy were higher than in the other groups.

Laparoscopy is considered as a "gold standard" in the diagnosis of ectopic pregnancy, and at the same time it enables surgical treatment.

Surgery remains the preferred therapy for ruptured ectopic pregnancy. Although operative laparoscopy has significantly decreased complications compared with laparotomy, there remains an irreducible minimum of morbidity, patient discomfort, and expense intrinsic to surgery and anesthesia. Because nonsurgical treatment bypasses these problems, medical approaches now are preferred primary treatment in many centers.21

Methotrexate:

A folic acid antagonist, methotrexate (MTX) inhibits de novo synthesis of purines and pyrimidines, interfering with DNA synthesis and cell division.22

MTX may be given orally, intramuscularly, or by continuous infusion. When large doses of MTX are needed, leucovorin rescue should be used to salvage any normal cells and prevent toxicity to them. When administrating large doses of MTX intravenously, a large volume of alkaline urine output must be maintained to avoid precipitation of the drug in acidic urine. MTX has been shown to be absorbed from the gastrointestinal tract at doses less than 25 mg/m2, whereas larger doses are usually administered intravenously.23

The two most common methods of administering methotrexate to patients with ectopic pregnancy are the single dose method, based on body surface area, employing 50 mg/m2 without the need for leukovorin rescue, and the multidose regimen of 1 mg/kg of MTX, alternating with 0.1 mg/kg of leucovorin rescue for up to four daily doses of each drug.

Use in Ectopic Pregnancy:

Many uncontrolled studies report that systemic intramuscular MTX therapy and laparoscopic salpingostomy have similar outcomes with

respect to success rates, tubal patency, and reproductive outcome.24-26 Other studies demonstrated that MTX can be administered by intratubal injection or intramuscularly with similar result.27

Multi-dose administration: MTX at a dose of 1 mg/kg is administered as the sodium salt intramuscularly, followed by leucovorin in a dose of 0.1 mg/kg as a calcium salt intramuscularly 24 hours later (Table 1). One injection is given daily. This regimen continued until the hCG level decreases by at least 15% on 2 consecutive days.28 Using this multidose regimen, a success rate of 96% with 100 patients was obtained. None of these 96 patients required more than four doses.28

Single-dose administration: It is less expensive, has fewer side effects, requires less intensive patient monitoring, and has greater patient acceptance.29 Success rate is approximately 94%.30 This success rate is similar to that obtained when a multidose protocol was followed. This method carries a higher risk of persistence, requiring more than one course. MTX 50 mg/m2 is administered intramuscularly. A second dose should be administered if the (-hCG is greater on day 7 than on day 4. Seven studies, one cohort and six case control studies, involving 393 patients were evaluated.21 Although overall success of treatment, measured as no surgical intervention, was 87%, 8.0% of patients required more than one course of MTX. Of the patients considered to be treated successfully (either with one or more doses), tubal patency was found in 81% of the 75 women evaluated. Subsequent intrauterine pregnancies were 61% and ectopic pregnancies were 8% in the 64 patients desiring future fertility in the group treated with either one or more doses of MTX, rates comparable with the variable dose regimen.21

The initial serum hCG concentration is the best prognostic indicator of treatment success in women with ectopic pregnancies who are treated according to MTX protocol.31

However, medical treatment with MTX might have a more negative impact on patients' health-related quality of life than surgical treatment. This is partly because of the long resolution time after MTX treatment. New evidence suggests that combining MTX and mifepristone can shorten this resolution time.32,33

MTX by direct injection: Direct injection delivers MTX to the site of implantation at higher concentrations than can be achieved with systemic administration. Less systemic distribution of the drug decreases toxicity. This approach, however, has the substantial disadvantage of requiring laparoscopic or ultrasonographic nee-

Table 1: Multiple dose MTX protocol8

Day1:	Baseline studies, MTX	1.0 mg/kg im.
Day2:	Citrovorum factor	0.1 mg/kg im.
Day3:	MTX	1.0 mg/kg im.
Day4:	Citrovorum factor, hCG titer	0.1 mg/kg im.
Day5:	MTX, hCG titer	1.0 mg/kg im.
Day6:	Citrovorum factor, hCG titer	0.1 mg/kg im.
Day7:	MTX, hCG titer	1.0 mg/kg im.
Day8:	Citrovorum factor, hCG titer	0.1 mg/kg im.
	Complete blood and platelet counts	
	Renal and liver function tests	
Weekly:	hCG titer until negative.	

Table 2: Single dose MTX protocol

Day1:	Baseline studies, MTX	50 mg/m2 im.
Day4:	hCG titer	
Day7:	hCG titer, complete blood and platelet count.	
	Liver and renal function tests.	
Weekly:	hCG titer until negative.	

dle guidance. Between 1989 and 1997 of 660 cases of ectopic pregnancy treated with MTX by direct injection, only 76% were treated successfully, and some patients required more than one injection of MTX.18 Treatment success rates are still unacceptably low for direct injection of MTX. It has not become a standard treatment for ectopic pregnancy.

MTX by tubal cannulation: This instillation of MTX by hysteroscopically directed tubal cannulation has been described. Risquez et al34 reported resolution of 27 of 31 cases by this method, with the remaining 4 ultimately requiring surgery. Although these results are encouraging this approach seems to have no major advantage over other methods.

Indications and contraindications to MTX therapy:

For carefully selected patients, medical management may avoid a surgical procedure with success similar to the outcome of linear salpingostomy. Before one chooses to use single dose or multidose therapy, a definitive diagnosis of ectopic pregnancy must be made, and it must be determined that the patient desires and eligible for medical management. Because the medical management of ectopic pregnancy is relatively new and because there are many published protocols, there is no absolute consensus on the indication for therapy. Medical management should most likely be reserved for hemodynamically stable patients who have been definitively diagnosed with a small unruptured ectopic pregnancy and who will be compliant with rigorous outpatient follow up. MTX should not be administered to patients with a suspected ruptured ectopic pregnancy or to patients who will not be compliant with frequent office visits to check hCG values.35 The resolution of hCG to a negative value averages about 35 days but may take up to 7 weeks.

A modified version of the American College of Obstetricians and Gynecologists criteria for receiving MTX is listed in (Table 3)23 Relative contraindications to medical therapy include parameters that suggest that a woman is at high risk for treatment failure. These parameters include a high initial hCG level, the presence of fetal cardiac activity, or an adnexal mass (the entire mass, not just the gestational sac) of 3.5 cm. The treatment of women with these characteristics is not absolutely contraindicated, but the patient should understand that the success rate is expected to be lower. Approximately 33% to 40% of patients diagnosed with an ectopic pregnancy are eligible to receive medical management.28,35

Contraindications to medical therapy are listed in Table-IV. MTX is contraindicated if there is evidence of immunocompromision, if there is damage to organs that metabolize MTX, or if the patient is effected by a condition that may be screened with a complete blood. count, liver function tests, and serum creatinine. If the woman has a history of pulmonary disease, she should also be screened with chest radiography. Cases of fatal interstitial pneumonitis have occurred in patients with underlying pulmonary disease after MTX administration.

Table 3: Criteria for receiving MTX23

Absolute indications
Hemodynamically stable without active bleeding or signs of hemoperitoneum
Nonlaparoscopic diagnosis
General anesthesia poses a significant risk
Patient can return for follow-up care
Patient has no contraindications to MTX
Relative indications
Unruptured mass (3.5 cm in greatest dimension
No fetal cardiac motion detected
(-hCG level does not exceed a predetermined value (6000-15000 mIU/ml)

Complications of Methotrexate Therapy

A - Side Effects of MTX Therapy:

The most common side effect observed with the single dose MTX protocol is excessive flatulence and bloating caused by intestinal gas formation. This problem is usually self limiting and handled as previously described. Transient mild elevation of liver function values can occur but rarely exceeds twice the upper limits of normal. These values invariably return to normal within 2 weeks. Stomatitis generally only occurs in patients receiving more than one MTX injection. Viscous lidocaine can be used as needed for symptomatic relief in patients with stomatitis. High doses MTX can cause bone marrow suppression, pulmonary fibrosis, alopecia and photosensitivity.36 Life-threatening neutropenia and febrile morbidity were reported after a single dose

Table 4: Contraindications to medical therapy

Absolute contraindications
Breast-feeding
Overt or laboratory evidence of immunodeficiency
Alcoholism, alcoholic liver disease, or other chronic liver disease
Preexisting blood dyscrasia, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia
Known sensitivity to MTX
Active pulmonary disease
Peptic ulcer disease
Hepatic, renal or hematologic dysfunction
Relative contraindications
Gestational sac (3.5 cm
Embryonic cardiac motion

and three doses of intramuscular MTX requiring hospitalization for 1 month and 13 days respectively.37 Two cases of transient pneumonitis were reported from MTX therapy for ectopic pregnancy.38,39

B - Separation Pain:

Approximately 75% of patients will experience an episode of increased abdominal pain during treatment Although the etiology of this pain is unknown, the most logical explanation is that the pain results of hematoma formation.3

C - Hematoma Formation:

Following treatment with MTX, 56% of ectopic masses will increase in size if followed by ultrasound. Most of these patients are asymptomatic. These masses will frequently persist after the disappearance of hCG, with the longest documented time to resolution being 180 days.40

Conclusion:

When ectopic pregnancy is managed in a correct way it will become a medical disease where surgical treatment is necessary only when there is a delay in diagnosis and complication is present.

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