CONSERVATIVE APPROACH IN THE MANAGEMENT OF ECTOPIC PREGNANCY

KONZERVATVNI PRISTUP U LEČENJU EKTOPIČNE TRUDNOĆE

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Summary

Introduction. Ectopic pregnancy is defined as the implantation of a fertilized ovum outside the uterine cavity and it is one of the leading causes of maternal morbidity and mortality. Localization and risk factors. The most common localization of ectopic pregnancy is within the fallopian tube, while other localizations include abdominal organs, ovaries, scars after previous cesarean sections, and cervix. Risk factors for ectopic pregnancy include previous fallopian tube injuries, infertility including multiple embryo transfers, use of contraceptives, smoking, older age, prior history of ectopic pregnancy, intentional abortions. Diagnostic procedures. Measurement of serum beta-human chorionic gonadotropin levels along with certain ultrasonography signs, i.e. extraterine gestational sac, with a present yolk sac and/or embryo, with or without a cardiac activity, have the highest degree of reliability in making the diagnosis, whereas uncertain signs, such as “blob” and “bagel” signs, also have a high positive predictive value. Therapeutic modalities. Ectopic pregnancy can be treated by surgical, medical or expectant management. Expectant and medical management are reserved for hemodynamically stable patients who are adequately informed and where monitoring and control are possible. Conservative treatment. Before the initiation of treatment with methotrexate, it is necessary to rule out a vital intrauterine pregnancy, and consider the contraindications for methotrexate therapy, based on detailed medical history and laboratory tests. The Clinic of Obstetrics and Gynecology of the Clinical Center of Vojvodina uses a two-dose protocol by which methotrexate is administered intramuscularly and which has proven to be highly successful with few side effects. Surgical treatment modalities. Candidates for emergency laparoscopy or laparotomy are women who are hemodynamically unstable and who should not receive methotrexate. Conclusion. In properly selected patients, the success rate of methotrexate therapy is around 93%.

Key words: Pregnancy, Ectopic; Conservative Treatment; Methotrexate; Fallopian Tubes; Risk Factors; Signs and Symptoms; Clinical Protocols; Diagnosis

Sažetak

Uvod. Ektopična trudnoća podrazumeva implantaciju oplodene jajne čelije izvan materične duplje i predstavlja jedan od vodećih uzroka maternalnog mortaliteta i morbiditeta čija je pojava u stalnom porastu. Lokalizacija i faktori rizika. Najčešća lokalizacija ektopične trudnoće je u jajovodu, dok druge lokalizacije uključuju trbušne organe, jajnine, ožiljke nakon prethodnih carskih rezova i grlić materice. Faktori rizika za vanmateričnu trudnoću uključuju prethodne povrede jajovoda, neplodnost, uključujući višestruke transfere embriona, upotrebu kontraceptivnih sredstava, pušenje, starije godine, istoreiju ektopične trudnoće u prošlosti, namerni pobačaj. Dijagnostičke procedure. Dok određivanje serumske koncentracije beta humanog horionskog gonadotropina u prisustvu sigurnog sonografskog znaka, odnosno gestacijskog meška izvan materice sa prisutnom žumančanom vrećom i/ili embrionom, sa srčanom akcijom ili bez nje, ima najviši stepen pouzdanosti u postavljanju dijagnoze, uočavanje nesigurnih znakova poput „blob” i „bagel” znaka, takođe ima visoku pozitivnu prediktivnu vrednost. Terapijski modaliteti. Ektopična trudnoća može da se leći hirurški, medikamentno i ekspektativno. Ekspektativni i medikamentni tretman su rezervisani za hemodinamički stabilne pacijentkinje koje su adekvatno informisane i sa mogućnošću monitoringa i kontrole. Konzervativna terapija. Da bi se započeo tretman metotreksatom, neophodno je isključiti prisustvo vitalne intrauterine trudnoće, kao i prisustvo kontraindikacija za primenu leka, a na osnovu detaljne anamneze i laboratorijskih pretraga. Na Klinici za ginekologiju i akušerstvo Kliničkog centra Vojvodine koristi se dvodozni protokol kojim se metotreksat aplikuje intramuskularno i koji se pokazao visoko uspešnim uz nizak stepen neželjenih dejstava. Hirurški terapijski modaliteti. Kandidatkinje za hitnu laparoskopiju ili laparotomiju jesu one žene koje su hemodinamički nestabilne i nisu pogodne za upotrebu metotreksata. Zaključak. Kod pravilno odabranih pacijentkinja, stopa uspešnosti terapije metotreksatom je oko 93%.

Ključne reči: ektopična trudnoća; konzervativni tretman; metotreksat; javovodi; faktori rizika; znaci i simptomi; klinički protokoli; dijagnoza

Introduction

Ectopic pregnancy is defined as the implantation of a fertilized ovum outside the uterine cavity and it is one of the leading causes of maternal morbidity and mortality [1]. In addition to extraterine localizations (abdominal cavity, ovaries, fallopian tubes), the term ectopic pregnancy also refers to localization inside the uterus but outside the endometrium, such as the interstitial and cervical pregnancies. It is a common life-threatening emergency, and the incidence of ectopic pregnancy is high in the developing world and

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is steadily rising. The estimated maternal mortality rate in 2009 in the United Kingdom was around 3.4% [2]. The term “pregnancy of unknown location” is used when the biochemical test for pregnancy in the blood is positive, but the gestational sac is not seen on ultrasound [3]. This happens in about 8 – 31% of women, which largely depends on the experience of the physician making the diagnosis. The simultaneous existence of pregnancy inside and outside the uterine cavity is called heterotopic pregnancy and it occurs in about 0.09% of pregnancies, more often after assisted reproduction technologies [4].

Localization and risk factors for ectopic pregnancy

The most common localization of ectopic pregnancy is in the fallopian tubes (about 95%) while other localizations include abdominal organs (1%), ovaries (1 – 3%), scars after previous cesarean section (1 – 3%) and cervix (1%) [5] (Figure 1). In the region of the fallopian tube, the most common place of implantation of ectopic pregnancy is in the ampullary (42%), then in the isthmic part of the fallopian tube (28%), in the interstitial (13%) and about 7% in the infundibular part of the fallopian tubes (Figure 2). Ectopic pregnancies outside the fallopian tubes are often overlooked or late diagnosed and are associated with higher maternal morbidity and mortality [6]. A very rare localization is the rudimentary horn of the uterus, while Litwicka et al. reported that there is an increase in the prevalence of ectopic pregnancies located in cesarean section scars, which is expected given the increase in the incidence of surgical termination of labor [7]. Risk factors for ectopic pregnancy include previous fallopian tube injuries (infections and pelvic inflammatory diseases, previous surgeries, ovarian cystectomy, etc.), infertility and assisted reproduction techniques, including multiple embryo transfers, use of contraceptives, smoking, older age (over 35 years), previous occurrence of ectopic pregnancy, and spontaneous or intentional abortions. About 50% of ectopic pregnancies are without established risk factors. Some authors believe that assisted reproduction techniques could account for as much as 2 – 5% of ectopic pregnancies, and that this risk is higher than the risk of ectopic pregnancy in pre-existing diseases of the fallopian tubes [8, 9].

Symptoms and diagnostic procedures

The diagnosis of ectopic pregnancy includes a detailed medical history, physical examination, beta-human chorionic gonadotropin (beta-hCG) blood test, ultrasound examination and culdoscopies. The most common symptoms of an ectopic pregnancy are absence of menstruation and irregular vaginal bleeding and abdominal pain with a feeling of “discomfort” in the pelvis. All sexually active women of reproductive age who develop acute abdominal pain or uterine bleeding should be tested for pregnancy [10]. For a long time, culdocentesis or transvaginal aspiration of the Douglas pouch was used as the most important diagnostic procedure [11]. Nowadays, diagnostic laparoscopy is considered to be the gold standard in the diagnosis of ectopic pregnancy, but less invasive and equally reliable diagnostic procedures, such as ultrasound, are increasingly used. Hemodynamically unstable women and those with an acute abdomen must be urgently evaluated and treated. In such cases, emergency laparoscopy and laparotomy are used for diagnosis, but also for resolving a ruptured ectopic pregnancy with administration of lost fluid and blood derivatives if needed.

Ultrasonographic signs of ectopic pregnancy are very diverse. It would be ideal to visualize the fetus outside the uterine cavity. However, this happens in about 8 – 26% of cases of all ectopic pregnancies [12]. If this is not possible, it is necessary to identify some other ultrasonographic signs of ectopic preg-
nancy, such as empty uterine cavity, presence of free fluid in Douglas space, appearance of “adnexal tumor mass”, altered appearance of the cervix (so-called “barrel shaped”), and gestational or pseudogestational sac [13]. In the middle of the 6th gestational week of pregnancy, a gestational sac should be seen on the endovaginal ultrasound examination. The pseudogestational sac often represents a diagnostic sonographic problem and should be distinguished from the true gestational sac [14]. It should always be borne in mind that gestational sac in the uterine cavity present on ultrasonography does not exclude simultaneous existence of a tubal pregnancy in heterotopic pregnancies. In the conducted meta-analysis, Richardson et al. reported that in case of impossibility of clear visualization of ectopic pregnancy, other mentioned indicators have low sensitivity and good specificity for the identification of tubal pregnancy [13]. However, Kirk et al. explained that during 5,318 performed ultrasound examinations in women with symptomatic and asymptomatic ectopic pregnancies, the sensitivity of endovaginal ultrasound examination was 98.3% and the specificity 99.9% [15]. A certain sonographic sign of an ectopic pregnancy is gestational sac outside the uterus, with the yolk sac and/or embryo, with or without a recorded cardiac action. In contrast, the uncertain sign of the presence of an ectopic pregnancy in the fallopian tube is the characteristic inhomogeneous mass in the area of the adnexa (the so-called “blob sign”) or the extraterine presence of a bag-like structure (“bag sign”) [16]. Nadim et al. concluded that these signs (“blob sign and bagel sign”), although they are uncertain signs of ectopic pregnancy, have a positive predictive value of over 95%. In the presence of pregnancy in a cesarean scar, the ultrasound examination shows an empty uterine cavity, empty and closed cervical canal, a thin myometrium, or absence of a myometrium between the uterine cavity and the bladder and a gestational sac in the anterior lower segment of the uterus at the site of the previous cesarean scar [17]. Endovaginal sonographic examination has found its significance and place in the diagnosis of the so-called “cervical” pregnancies. Ultrasound criteria include empty uterine cavity, barrel-shaped cervix, gestational sac below the level of the inner cervical ostium, and increased peri-trophoblastic vascularity on the color Doppler [17].

Measurement of the serum beta-hCG levels significantly contributes to making an accurate diagnosis in women with suspected ectopic pregnancy. In 50 – 70% of all cases where the values of beta-hCG are elevated and the gestational sac is not sonographically visible, it should be thought about the possibility of ectopic pregnancy [18]. Of much greater importance is the serial measurement of beta-hCG concentration at 48 hour intervals. If the increase of beta-hCG level is less than 40% or if there is a plateau, it is clear that it is not a normal intrauterine pregnancy. Women with a decrease of serum beta-hCG levels should be monitored until the complete decrease in values, because cases of fallopian tube rupture have been described even at very low beta-hCG values. In women with early pregnancies, who bleed and report abdominal pain, progesterone values below 50 nmol/l suggest a tubal pregnancy. When the levels of progesterone in the blood are below 20 nmol/l, it is certain that the fetus is not alive, regardless of the location of the pregnancy [19].

If a reliable diagnosis cannot be made by ultrasound examination, one of the diagnostic options is the use of diagnostic curettage. The intrauterine pregnancy is confirmed by the presence of chorionic villi, while the presence of decidua or proliferative endometrium is an unreliable sign for the final diagnosis of ectopic pregnancy. The experience of clinicians is also important in diagnosing ectopic pregnancy and application of an optimal therapeutic option. Fernandez et al. have developed the “Fernandez score” which should facilitate an accurate diagnosis. The parameters to be monitored and scored are the level of serum beta-hCG and progesterone, abdominal pain, hematosalpinx diameter (cm) and hemoperitoneum volume (ml). A score of less than 12 indicates that expectant or drug treatment should be used with a single dose of methotrexate (MTX), while a score of 12 or more indicates the need for surgical option [20]. Other scores, such as Elito score and others, have been described in the literature [21].

Therapeutic modalities in the treatment of ectopic pregnancy

Ectopic pregnancy can be treated by surgical, medical or expectant management. Expectant management is reserved for patients who are hemodynamically stable and adequately counseled with the possibility of monitoring and control, and access to emergency surgical treatment if necessary [22]. At levels of beta-hCG < 200 mIU/ml, spontaneous resolution occurs in 88% of cases. In a study published by Van Mello et al., at serum beta-hCG levels < 2000 mIU/ml, success of successive treatment was recorded in 59% of patients [25].

Medical treatment with MTX is an option for hemodynamically stable women who are carefully selected.

Medical treatment of ectopic pregnancy using Methotrexate

The MTX is a cytotoxic drug and a folic acid antagonist. It is not primarily registered for ectopic pregnancy treatment, but due to its considerable effect on actively proliferating trophoblastic tissues, this type of treatment is effective and is a standard therapeutic procedure in adequately selected cases (Figure 3). Side effects of MTX include bone marrow suppression, nausea, vomiting, diarrhea, liver damage, stomatitis, rash, alopecia, and so on. As an antidote for these adverse reactions, Leucovorin is given at a dose of 0.1 mg/kg. Although there are studies on the oral use of MTX in the treatment of ectopic pregnancy, it is still most often administered intramuscularly or locally [23].
Transvaginal ultrasound-guided topical application of MTX in ectopic pregnancy with localization in the fallopian tube is less effective than laparoscopic salpingotomy if fetal cardiac activity is present. It has also been shown to be more effective to inject MTX locally under ultrasound control rather than laparoscopically [24]. The application of MTX in situ is an option in the treatment of uncomplicated cervical, interstitial and pregnancy in a cesarean scar. In case of cervical pregnancy, MTX can be administered systemically or “in situ”, however, patients should be informed in advance about the possible risks of bleeding and other complications [25]. Considering pregnancies in a cesarean scar, preference is given to local application over systemic, especially in case of present fetal cardiac activity. It should be combined with procedures that prevent secondary bleeding [26]. Nevertheless, cases of failed MTX therapy and subsequent surgical excision and reparation of the cesarean scar site have been described [27]. In case of ovarian pregnancy, MTX should not be the first choice therapy. Koch et al. studied a sample of 5,446 women and proved that in case of local application of MTX (cervical, interstitial and pregnancy in a cesarean scar) there is a significantly longer period of decline of beta-hCG levels (29.2 days) than in case of systemic MTX application [28].

In order to start treatment with MTX, vital intrauterine pregnancy should first be ruled out. Then, it is necessary to objectively assess the woman’s condition, as well as to exclude the possibility of elevated serum creatinine, liver transaminases or bone marrow dysfunction, severe anemia, leukopenia, or thrombocytopenia. It is necessary to perform laboratory tests: serum beta-hCG concentration, complete blood count, hemostasis, liver and kidney panel, blood group and Rh factor. Relative contraindications for using MTX include: presence of fetal cardiac action, sac size > 4 cm, transfusion rejection, inability to monitor and control, hematosalpinx, high basal progesterone levels, and beta-hCG levels > 5000 mIU/ml. Some studies have reported failure of MTX treatment in 57 – 62% of cases with beta-hCG levels above 5000 mIU/ml, while Menon et al. reported that at beta-hCG levels > 5000 mIU/ml, treatment failure is 14.3% versus only 3.7% of failure at values less than 5000 mIU/ml [29]. Potter et al. showed that the risk of failure is 5.5 times higher for beta-hCG levels above 5000 mIU/ml [30]. Absolute contraindications include vital intrauterine pregnancy, immunodeficiency, moderate to severe anemia, leukopenia or thrombocytopenia, sensitivity to MTX, active lung disease and ulcer disease, clinically significant liver dysfunction, renal dysfunction, breastfeeding, lactation and rupture. There is also evidence of failure of MTX therapy in women in whom there is a rapid increase of beta-hCG levels, i.e. an increase of more than 50% over a period of 48 hours [32].

If the criteria for the use of MTX are met, the MTX protocol is selected. Three protocols have been published: single-dose, two-dose and the multiple dose protocol [33–35]. Single-dose protocol involves intramuscular administration of MTX 50 mg/m² on day 1. After that, serum beta-hCG levels are measured on days 4 and 7. If the decrease of beta-hCG levels is less than 15% in the period of 4 – 7 days, it is necessary to repeat the dose of MTX (25% of patients). If the decrease of beta-hCG level is > 15%, the patient should be monitored at intervals of 7 days. If there is no significant decrease of beta-hCG levels after 2 doses, a surgical treatment is considered [33].

The two-dose protocol was first introduced in 2007 and it showed higher efficiency rate and fewer side effects. It includes intramuscular administration of 50 mg/m² MTX on days 1 and 4, and measuring beta-hCG levels on days 4 and 7. If the decrease of beta-hCG level is > 15%, the patient is monitored for 7 days, and if the decrease of beta-hCG is less than 15%, the dose should be repeated on day 7, and beta-hCG measurement should be done on day 11. If the decrease of beta-hCG levels is less than 15% from day 7 – 11, the dose of MTX should be repeated on day 11, and beta-hCG measurement should be repeated on day 14. If there is no significant decline even after the 4th dose of MTX, a surgical treatment is considered [36]. This protocol is also used at the Clinic of Obstetrics and Gynecology of the Clinical Center of Vojvodina in Novi Sad.

The third protocol, the so-called fixed multiple dose protocol, consists of intramuscular MTX 1 mg/kg on days 1, 3, 5 and 7 with folic acid 0.1 mg/kg on days 2, 4, 6 and 8 and/or Leucovorin. Beta-hCG levels are measured on days of MTX administration. If there is a drop over 15%, MTX is discontinued and monitoring is performed for 7 days, and if there is no significant drop after the 4th dose, surgical treatment is considered [37].

From the beginning of MTX application in the therapy of ectopic pregnancy until today, numerous researches have been conducted. Kasum et al. proved that the initial levels of beta-hCG and progesterone were inversely proportional to the success of drug treatment in a selected group of patients and that these two parameters are important predictors in the treatment...
Surgical procedures in the treatment of ectopic pregnancy

Candidates for surgical treatment are women who are hemodynamically unstable, who are not recommended to use MTX or in whom the treatment with MTX had no effect, as well as those with a heterotopic pregnancy. In women with tubal pregnancy who are in the reproductive period, salpingotomy is the method of choice. Also, salpingectomy is the method of choice in women who have repeated pregnancies in the fallopian tube, those who have a pregnancy larger than 5 cm, as well as in those who have completed childbearing [42]. If the contralateral fallopian tube is preserved, salpingotomy and/or salpingectomy have the same effect on pregnancy after the intervention. In 2015, Kutlešić et al. described a rare case of abdominal pregnancy, diagnosed at 6 weeks of gestation, located in the vesicouterine pouch, which was successfully treated by laparoscopy [45].

Conclusion

Ectopic pregnancy is the implantation of a fertilized ovum outside the uterine cavity. The most common localization is in the fallopian tube. Depending on whether it occurs in acute or subacute form, it has different symptoms. The use of endovaginal sonography and determination of serum beta-human chorionic gonadotropin levels have the highest degree of reliability in making the diagnosis. Ectopic pregnancy can be treated by surgical, medical or expectant management. Methotrexate, an antineoplastic drug, given topically or systemically, is used in drug treatment. In properly selected patients, the success rate is around 93%. Methotrexate can be administered in three ways: as a single-dose, a two-dose, and a multiple dose protocol, where the two-dose is described as the most effective with the fewest complications and side effects.

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of ectopic pregnancy with MTX [38]. Li Jin Bo et al. explored the possibility of using MTX in the treatment of heterotopic pregnancy. They concluded that MTX cannot be applied in case of heterotopic pregnancy, either locally or systemically, because it has teratogenic effects on the vital intrauterine fetus [39].

A meta-analysis conducted by Alur-Gupta et al. showed that the two-dose MTX administration protocol is superior to the single-dose protocol in terms of treatment outcome, and they recommend it as the first-line treatment in women with high levels of beta-hCG and large tumorous adnexal masses. Also, they proved that the multiple dose protocol does not have a significant reduction in the number of failed MTX treatments, but has a higher incidence of side effects [40]. An important aspect of MTX therapy is the possibility of achieving a healthy pregnancy after treatment. The teratogenicity of MTX has been proven, as well as the retention of its derivatives in tissues. A 2016 study by Lagarce et al. showed that in the group of women treated with MTX, 6.7% of pregnancies ended in miscarriage and that two major malformations were described among children, one of which was the tetralogy of Fallot, which is consistent with previously described cases of MTX exposure during early pregnancy. It is recommended to avoid conception and pregnancy for 3 to 6 months after MTX administration [41].
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