A Pragmatic and Evidence-Based Management of Ectopic Pregnancy

Galia Oron, MD, and Togas Tulandi, MD, MHCM*

From the Department of Obstetrics and Gynecology, McGill University, Montreal, Quebec, Canada (both authors).

ABSTRACT

The incidence of ectopic pregnancy is approximately 2% of all pregnancies, and it remains the leading cause of death in early pregnancy. Over 95% of ectopic pregnancies are tubal pregnancies, and the remainders are nontubal pregnancies. The highest risk factor for ectopic pregnancy is a previous tubal pregnancy followed by previous tubal surgery, tubal sterilization, tubal pathology, and current intrauterine device use. The apparent increase in the incidence of nontubal ectopic pregnancy including heterotopic pregnancy may be attributed to the increasing number of pregnancies because of in vitro fertilization treatment. In most cases, an ectopic pregnancy can be treated medically with a single dose of methotrexate. Surgical treatment is still needed in women who are hemodynamically unstable and in those who do not fulfill the criteria for methotrexate treatment. Usually surgical treatment can be performed by laparoscopy and in some cases by hysteroscopy. Laparotomy is rarely needed even in women with intraperitoneal bleeding. Journal of Minimally Invasive Gynecology (2013) 20, 446–454 © 2013 AAGL. All rights reserved.

Keywords: Cervical pregnancy; Cesarean scar pregnancy; Ectopic pregnancy; Interstitial pregnancy; Laparoscopy; Methotrexate

DISCUSS

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The implantation and development of a fertilized ovum outside the uterine cavity is defined as an extrauterine or ectopic pregnancy. The incidence of ectopic pregnancy is approximately 2% of all pregnancies. It remains the leading cause of death during the early trimester of pregnancy, accounting for 4% to 6% of all pregnancy-related deaths [1–5].

Over 95% of ectopic pregnancies are in the fallopian tube (tubal pregnancy) and usually in the ampullary part of the tube. Other types of tubal pregnancy are isthmic, infundibular, and interstitial. Nontubal ectopic pregnancies include ovarian, abdominal, and cervical pregnancy and cesarean scar pregnancy. Occasionally, pregnancy is located in both intrauterine and extrauterine sites (i.e., heterotopic pregnancy).

The authors declare that they have no conflict of interest.

Corresponding author: Togas Tulandi, MD, MHCM, Department of Obstetrics and Gynecology, McGill University, Montreal, QC, Canada H3A 1A1.

E-mail: togas.tulandi@mcgill.ca

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Incidence, Epidemiology, and Risk Factors

There has been a 6-fold increase in the number of ectopic pregnancies diagnosed between the early 70s and the mid-90s in the United States [3]. Because most ectopic pregnancies can be treated without surgery in an outpatient setting, the exact incidence of ectopic pregnancy is difficult to estimate. National Hospital Discharge Survey and outpatient National Hospital Ambulatory Medical Care Survey data estimated the incidence of ectopic pregnancies to be 19.7 per 1000 pregnancies for 1990 to 1992 [6].

Risk Factors

Risk factors for ectopic pregnancy can be divided into high, moderate, and low risk factors [7–10] (Table 1). High risk factors appear to be related to conditions that impair embryo migration into the uterine cavity. The highest risk factor for ectopic pregnancy is a previous tubal pregnancy followed by previous tubal surgery, tubal sterilization, tubal pathology, and current intrauterine device (IUD) use. Although (diethylstilbestrol) DES exposure was considered
Table 1

<table>
<thead>
<tr>
<th>Degree of risk</th>
<th>Risk factors</th>
<th>Odds ratio</th>
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<tr>
<td>High</td>
<td>Previous ectopic pregnancy</td>
<td>9.3–47</td>
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<tr>
<td></td>
<td>Previous tubal surgery</td>
<td>6.0–11.5</td>
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<td></td>
<td>Tubal ligation</td>
<td>3.0–139</td>
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<td></td>
<td>Tubal pathology</td>
<td>3.5–25</td>
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<tr>
<td></td>
<td>In utero DES exposure</td>
<td>2.4–13</td>
</tr>
<tr>
<td></td>
<td>Current IUD use</td>
<td>1.1–45</td>
</tr>
<tr>
<td>Moderate</td>
<td>Infertility</td>
<td>1.1–28</td>
</tr>
<tr>
<td></td>
<td>Previous cervicitis (gonorrhea, chlamydia)</td>
<td>2.8–3.7</td>
</tr>
<tr>
<td></td>
<td>History of pelvic inflammatory disease</td>
<td>2.1–3.0</td>
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<tr>
<td></td>
<td>Multiple sexual partners</td>
<td>1.4–4.8</td>
</tr>
<tr>
<td></td>
<td>Smoking</td>
<td>2.3–3.9</td>
</tr>
<tr>
<td>Low</td>
<td>Previous pelvic/abdominal surgery</td>
<td>0.93–3.8</td>
</tr>
<tr>
<td></td>
<td>Vaginal douching</td>
<td>1.1–3.1</td>
</tr>
<tr>
<td></td>
<td>Early age of intercourse (&lt;18 years)</td>
<td>1.1–2.5</td>
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</table>


In a review, Yao and Tulandi [11] found that the rates of recurrent ectopic pregnancy after single-dose methotrexate (MTX), salpingectomy, and linear salpingostomy were 8%, 9.8%, and 15.4%, respectively. After 2 previous ectopic pregnancies, the rate of a third ectopic pregnancy is about 30% [9]. In view of IUD use, the risk of ectopic pregnancy among users of a norgestrel-containing IUD is lower than users of a norgestrel-containing IUD. Moderate risk factors for ectopic pregnancy include infertility, a history of a previous sexually transmitted disease, a previous pelvic inflammatory disease, multiple sexual partners, and smoking. Low risk factors are previous pelvic or abdominal surgery, vaginal douching, and early age of intercourse.

Infertility and its treatment including assisted reproductive technology have been associated with an increased risk for ectopic pregnancy and heterotopic pregnancy. However, the data from registries showed that in vitro fertilization (IVF) is associated with an incidence of ectopic pregnancy of 1% to 2%, which is similar to that in the general population [14,15]. However, IVF is associated with a higher incidence of heterotopic pregnancy. If the estimated incidence of heterotopic pregnancy in the general population is 1:30 000, its incidence among women who conceived after IVF treatment is up to 1:100 pregnancies.

Clinical Picture and Diagnosis

Besides the usual signs and symptoms of pregnancy, women with ectopic pregnancies usually present with abdominal pain, vaginal bleeding, and amenorrhea of 6 to 8 weeks. Ectopic pregnancy should be suspected in all women of reproductive age with these symptoms, especially in those with risk factors. This will lead to an early diagnosis and will allow medical treatment. However, an ectopic pregnancy could still be missed [16]. The estimated rate of missed ectopic pregnancies at the initial presentation was 12% [17]. In case series of women with an ectopic pregnancy who attended the emergency department, 45% of them were discharged with the wrong diagnosis [18].

Physical examination in women with early ectopic pregnancy is not specific. However, cervical motion or adnexal tenderness, slight uterine enlargement, or adnexal mass could be encountered. Hypotension, tachycardia, rebound guarding and tenderness, and low-grade fever are signs of tubal rupture and hemoperitoneum.

Transvaginal Ultrasound

Transvaginal ultrasound (TVUS) is the most useful diagnostic test to locate the gestation either intra- or extraterine. An intrauterine gestational sac could be detected with TVUS at serum human chorionic gonadotropin (hCG) levels of 1500 to 2000 IU/L; this level is called the discriminatory threshold of hCG [19,20]. It corresponds to 4.5 weeks of gestation. A yolk sac is usually observed at 5 weeks of gestation and a fetal pole at 5.5 weeks of gestation. One should always rule out the presence of heterotopic pregnancy especially in women who conceive after treatment for infertility.

In diagnosing an ectopic pregnancy, TVUS has a sensitivity of 87% to 99% and a specificity of 94% to 99% [21]. In some women with an ectopic pregnancy, a “pseudosac” could be observed on TVUS. It is a blood collection within the uterine cavity surrounded by thick endometrium mimicking a gestational sac. Knowing the level of serum hCG will help to distinguish between the 2 conditions.

Serum hCG Level

In normal intrauterine pregnancy, the serum hCG level doubles every 2 days until about 40 days of gestation. In most ectopic and nonviable intrauterine pregnancies, the increase in the hCG level is much slower. A decreased or plateauing hCG level is most likely associated with a failed pregnancy. Because of interassay and intraassay variability and the possibility of laboratory errors, a decision should not be made based on 1 hCG level only.

In the absence of definitive ultrasound findings and a serum β-hCG level of less than 1500 IU/L, a repeat hCG measurement every 3 days should be performed. If the hCG level does not double over 72 hours, then the pregnancy is abnormal (i.e., an ectopic gestation or failed intrauterine pregnancy). Figure 1 shows an algorithm of diagnosing an ectopic pregnancy.
Serum Progesterone

The serum progesterone level is higher in viable intrauterine pregnancies than in ectopic and nonviable intrauterine pregnancies. However, this test is not very helpful because one cannot distinguish ectopic pregnancies from failed intrauterine pregnancies [22].

Curettage

A few authors advocated uterine curettage to distinguish an ectopic pregnancy from a nonviable intrauterine pregnancy [23,24,25]. A finding of trophoblastic tissue certainly establishes the presence of an intrauterine pregnancy, and this approach could detect 30% of nonviable intrauterine pregnancies. However, it is limited by the possibility of disrupting a viable intrauterine pregnancy. In addition, false-negatives can occur. In a study of elective termination of pregnancy, 20% of curettage specimens were devoid of trophoblastic tissue [26].

It is more practical and less invasive to continue observation or administer 1 dose of MTX than to perform curettage [10,27,28]. The side effects of 1 dose of MTX are negligible, and curettage might be associated with intrauterine adhesion formation [29].

Management Options

Ideally, most ectopic pregnancies should be treated medically, and surgical management is reserved for those who...
not fulfill or who have failed medical treatment (Fig. 1). In a limited number of conditions, patients can be managed expectantly.

**Expectant Management**

Small case series have shown a 47% to 73% spontaneous resolution of ectopic pregnancies [30–37]. However, the inclusion criteria and management protocols varied widely. In a randomized multicenter trial, van Mello et al [38] studied 73 patients with a visible ectopic pregnancy with a serum hCG level of <1500 IU/L or a pregnancy of unknown location and a plateauing serum hCG level of <2000 IU/L. They found that systemic MTX treatment did not have a larger treatment effect than expectant management. Yet, almost 80% of their patients had no conclusive evidence of an ectopic pregnancy (i.e., a pregnancy of unknown location). Furthermore, the power of their study was too small to evaluate predictors of treatment failure [38].

In agreement with the recommendation by the American College of Obstetricians and Gynecologists, expectant management is used in limited clinical situations when ectopic pregnancy is suspected but TVUS does not show a gestational sac or an extrauterine mass suspicious for an ectopic pregnancy and the β-hCG concentration is low (≤200 mIU/mL) and declining [39]. However, a low and declining serum hCG level can still be followed by tubal rupture [40].

**Medical Treatment**

Early diagnosis allows medical treatment in the majority of cases of ectopic pregnancy. The main medical treatment is intramuscular MTX. MTX is a folic acid antagonist that binds to the catalytic site of dihydrofolate reductase, interrupting the synthesis of purine and pyrimidine nucleotides and the amino acids serine and methionine. Accordingly, it inhibits DNA synthesis and repair and cell replication [41]. Compared with the treatment for malignant conditions, the dose of MTX for the treatment of an ectopic pregnancy is low (50 mg/m² of body surface intramuscularly or about 1 mg/kg body weight). The overall success rate for medical therapy is 88.1% [42]. A second dose of MTX is sometimes needed.

**Criteria of MTX Treatment**

The best candidates for MTX treatment are women who are hemodynamically stable, have compliance for follow-up, have a hCG concentration of ≤5000 mIU/mL, and have no fetal cardiac activity [10]. The most important predictor associated with treatment failure is a high hCG concentration.

In a review of 503 women with tubal pregnancy treated with a single dose of MTX, the failure rate in women with an initial hCG concentration over 5000 mIU/mL was higher than in those with a lower hCG concentration (odds ratio = 5.5; 95% confidence interval, 3.0–9.8) [43]. An ectopic mass size less than 3 to 4 cm is also commonly used as a patient selection criterion; however, this has not been confirmed as a predictor of successful treatment [10].

**Contraindications**

Contraindications to MTX treatment include breastfeeding; immunodeficiency; alcoholism; chronic liver disease; preexisting blood dyscrasia; known sensitivity to MTX; active pulmonary disease; peptic ulcer disease; and hepatic, renal, or hematologic dysfunction. MTX-associated death has been reported in women with renal failure [44,45].

**Side Effects**

Side effects of a single dose of MTX are mild and self-limited. The most common side effects are conjunctivitis or aphthous stomatitis. Other side effects are gastrointestinal symptoms (i.e., nausea, vomiting, and diarrhea) and rarely pneumonitis, dermatitis, bone marrow suppression, elevated liver enzymes, or alopecia.

**Teratogenicity**

It is important to rule out the presence of a viable intrauterine pregnancy before administering MTX. It is an anti-neoplastic drug that can be associated with the risk of neural tube defects, cardiovascular defects, oral clefts, and urinary tract defects [46].

**Pre- and Post-treatment Monitoring**

Before MTX administration, one should be certain about the diagnosis of ectopic pregnancy. If it is doubtful, serum hCG determination and TVUS examination should be repeated. Visualization of an extraterine pregnancy on ultrasound is insufficient; the uterine cavity has to be evaluated for the possibility of a coexisting intrauterine pregnancy (i.e., a heterotopic pregnancy). In addition, blood sampling for a complete blood count, renal and liver function tests, and blood group should be taken. If the patient is Rh(D)-negative, Rh(D) immune globulin should be administered. Folic acid intake interferes with MTX efficacy and should be avoided.

After MTX injection, the patient should be followed until the serum hCG level is undetectable. Approximately 15% to 20% of patients need a second dose of MTX, and less than 1% need over 2 doses [42].

There are 2 different follow-up protocols. In 1 protocol [47], if the decrease in serum hCG between days 4 and 7 (day 1 is the day of MTX injection) is less than 15%; a second dose of MTX, 50 mg/m² intramuscularly, is administered. It has to be noted that hCG levels might increase in the first several days after therapy because of continued hCG production by syncytiotrophoblast despite the cessation of production by cytotrophoblasts. In another protocol, blood sampling for the hCG level is taken on day 7, and a second dose of MTX is administered if the serum hCG concentration on day 7 has not declined by at least 25% from the
day 1 level [10]. This protocol eliminates a patient visit on day 4 of treatment.

**Multidose MTX**

Single-dose MTX treatment is effective and practical. Three randomized trials show that the effectiveness of a single dose of MTX is comparable with that of multidose treatment [48–50] (Table 2). Multidose MTX treatment might be needed in cases of nontubal pregnancies including interstitial or cervical pregnancies [51]. Methotrexate, 1 mg/kg body weight, is administered intramuscularly on days 1, 3, 5, and 7 and 0.1 mg/kg folic acid (leucovorin) on days 2, 4, 6, and 8. If the serum hCG concentration plateaus or increases in 2 consecutive measurements, a second course may be administered 7 days after the initial dose.

**Surgical Treatment**

Although most tubal ectopic pregnancies can be treated medically, surgery is still needed in some cases of ectopic pregnancy. In general, the procedure should and can be performed by laparoscopy. The indications for surgery include hemodynamic instability, impending or ongoing rupture of an ectopic mass, contraindications to MTX, a coexisting intrauterine pregnancy, inability or unwillingness to comply with post-treatment follow-up, lack of timely access to a medical institution for the management of tubal rupture, desire for permanent contraception, and failed medical therapy [10,52–54]. The success rate (no requirement for further treatment) of medical and conservative surgical treatment of ectopic pregnancies is comparable (Table 3) [55–59]. Table 4 shows the surgical treatment of different types of ectopic pregnancy. In general, laparotomy is rarely needed.

**Laparoscopy in the Presence of Hemoperitoneum**

Excessive bleeding in a relatively short time leads to orthostatic changes in blood pressure and heart rate or shock. However, bleeding in ruptured ectopic pregnancy is slow and gradual. This is despite a hemoperitoneum of 1000 to 1500 mL [60]. As a result, treatment can be performed by using the laparoscopic approach (Fig. 2).

The most important determinant is the surgeon’s laparoscopic skill. He/she should be able to enter the peritoneal cavity and secure hemostasis by laparoscopy as quickly as by laparotomy, if not more quickly [61,62]. Laparotomy is a better option if the procedure is complicated such as in patients with a history of multiple laparotomies or the presence of severe pelvic adhesions and when the surgeon

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**Table 2**

Randomized trials of single-dose or multidose MTX for ectopic pregnancy (evidence I)

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alleyassin et al, 2006 [48]</td>
<td>108</td>
<td>Comparable success rate between single dose (88.9%) and multidose MTX (92.6%; odds ratio = 0.64; 95% confidence interval, 0.17–2.4)</td>
</tr>
<tr>
<td>Guvendag et al, 2010 [49]</td>
<td>120</td>
<td>Comparable success rate between single dose (80.6%) and multidose MTX (89.7%; odds ratio = 0.90; 95% confidence interval, 0.77–1.05)</td>
</tr>
<tr>
<td>Hamed et al, 2012 [50]</td>
<td>157</td>
<td>Comparable success rate between 2-dose (88.6%) and single-dose MTX (82.0%)</td>
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</tbody>
</table>

**Table 3**

Randomized trials of conservative surgery versus MTX treatment for ectopic pregnancy (evidence I)

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hajenius et al, 1997 [55]</td>
<td>100</td>
<td>Comparable rate of tubal preservation in MTX group (90%) and in the salpingostomy group (92%; odds ratio = 0.98; 95% confidence interval, 0.87–1.1)</td>
</tr>
<tr>
<td>Fernandez et al, 1998 [56]</td>
<td>100</td>
<td>Comparable success rate between the MTX group (88.2%) and conservative surgery (95.9%)</td>
</tr>
<tr>
<td>Nieuwkerk et al, 1998 [57]</td>
<td>100</td>
<td>Lower quality of life after MTX therapy than after surgery</td>
</tr>
<tr>
<td>Saraj et al, 1998 [58]</td>
<td>75</td>
<td>Comparable success rates after MTX (94.7%) and after salpingostomy (91.4%)</td>
</tr>
<tr>
<td>Sowter et al, 2001 [59]</td>
<td>62</td>
<td>Persistent ectopic pregnancy in 15.6% of patients in the MTX group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Success rate in the surgery group (93%) was higher than in the MTX group (65%; 95% confidence interval, 10%–47%; ( p &lt; .01 )).</td>
</tr>
</tbody>
</table>
is not comfortable with the laparoscopic approach. In any event, a patient who is hemodynamically unstable has to be stabilized first. Blood transfusion might be needed.

The use of an intrauterine manipulator allows the quick identification of the bleeding site by lifting the uterus away from the pool of blood in the abdominal cavity (Fig. 2). Certainly, one should first rule out the presence of a coexisting viable intrauterine pregnancy. The laparoscope should be inserted gradually without touching the blood in the peritoneal cavity. The tip of the scope will remain clean, allowing visualization of the pelvic organs readily. Hemostasis could be performed immediately, and in general it consists of salpingectomy. The blood in the abdominal cavity can then be evacuated.

Salpingostomy or Salpingectomy

In women who have completed their family or in those with recurrent ectopic pregnancies, severe tubal damage, or hemodynamic instability, salpingectomy is the appropriate surgical treatment. Otherwise, linear salpingostomy can be performed.

In a review by Hajenius et al [55], they concluded that the reproductive outcome after salpingostomy or salpingectomy is comparable. However, salpingostomy might be associated with a 4% to 15% risk of persistent ectopic pregnancy and a 15% incidence of recurrent ectopic pregnancy. In cases in which there is a possibility of leaving trophoblastic tissue inside the Fallopian tube or in the abdominal cavity, 1 dose of MTX can be administered in the immediate postoperative period [63,64]. A serum level of hCG 7 days after surgery of less than 5% of the preoperative value indicates complete resolution of the ectopic pregnancy. If one encounters a tubal abortion, the gestational product can be evacuated using laparoscopic suction or by gentle removal using laparoscopic forceps.

Nontubal Ectopic Pregnancy

Most ectopic pregnancies are located inside the Fallopian tubes with a small percentage in the interstitial part of the tube, endocervix, intraabdominal, or the cesarean scar. Similar to that of tubal pregnancy, medical treatment should be attempted first in hemodynamically stable patients. To date, there have been no criteria for MTX treatment for these types of ectopic pregnancy. Because of the potential major complications of these pregnancies, multidose MTX treatment is preferable.

Interstitial Pregnancy

In women with an interstitial pregnancy (or a cornual pregnancy) who require surgery, laparoscopic cornual resection or cornuostomy (salpingostomy) can be performed [65]. Similar to closure of the myomectomy incision, the myometrium should be sutured thoroughly. Hysteroscopic removal of cornual pregnancy has also been described, but its efficacy is unclear.

Cervical Pregnancy

In cervical pregnancy, the gestation is located in the endocervix below the level of the internal cervical os. Risk factors

<table>
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<th>Table 4</th>
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<tr>
<td>Ectopic pregnancy</td>
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<tr>
<td>Tubal pregnancy</td>
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<tr>
<td>Interstitial pregnancy</td>
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<tr>
<td>Ovarian pregnancy</td>
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<td>Cervical pregnancy</td>
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<tr>
<td>Abdominal pregnancy</td>
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<tr>
<td>Cesarean scar pregnancy</td>
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* Laparotomy is almost never required.
for cervical pregnancies include prior uterine curettage, intrauterine adhesions, uterine myoma, the presence of an IUD, and a uterine anomaly [66,67]. The differential diagnosis includes an incomplete abortion, placenta previa, or trophoblastic disease. The sonographic diagnosis of cervical pregnancy includes cervical enlargement, uterine enlargement, diffuse amorphous intrauterine echoes, and the absence of an intrauterine pregnancy [68,69]. The cervical canal is dilated and barrel shaped [69].

Because of the rich vascularity of cervical pregnancy, surgery might be associated with severe hemorrhage that might necessitate a hysterectomy. Preoperative preparation should include the insertion of an angiographic catheter into the uterine arteries, and arterial embolization could be performed in the case of severe hemorrhage. Surgical attempts to reduce the bleeding include the application of cervical cerclage, balloon tamponade of the cervical canal, or ligation of the descending branch of the uterine vessels vaginally.

Ovarian Pregnancy

The clinical findings of a positive pregnancy test, abdominal pain, and vaginal bleeding with the presence of a sonographic cystic mass within or adjacent to an ovary is suggestive of an ovarian pregnancy. The differential diagnosis is a corpus luteum. Indeed, the preoperative diagnosis is correct in less than 30% of cases only. Surgical treatment consists of simple evacuation of the gestational products or ovarian wedge resection. Oophorectomy is rarely needed.

Abdominal Pregnancy

Abdominal pregnancy is rare, and early diagnosis is difficult. The gestation can be found anywhere in the peritoneal cavity, but the most common site is the posterior cul de sac. Findings of early abdominal pregnancy should be followed by medical or surgical treatment. Discussion about advanced abdominal pregnancy is out of the scope of this review.

Cesarean Scar Pregnancy

With the increasing number of cesarean deliveries, more pregnancies on the defective cesarean scar are reported. The gestation is completely surrounded by myometrium and fibrous tissue of the scar and separated from the endometrial cavity. It appears as a ballooning in the anterior low uterine wall. It could rupture, leading to intraperitoneal bleeding. Treatment consists of medical treatment with MTX or excision of the uterine scar containing the ectopic pregnancy [10].

Conclusions

Ectopic pregnancy is still the leading cause of death in the first trimester of pregnancy. A high index of suspicion is required for an early diagnosis because signs and symptoms are not specific. Expectant management is suitable in a limited number of cases. Most ectopic pregnancies can be treated medically with a single dose of MTX, and surgical management is reserved for those who do not fulfill the criteria of MTX treatment or who have failed medical treatment. It is crucial to rule out the presence of a viable intrauterine pregnancy before administering MTX. Most surgical treatment can be performed by laparoscopy and in some cases by hysteroscopy. Laparotomy is rarely needed even in women with intraperitoneal bleeding.

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