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Medical treatment of ectopic pregnancy

Ectopic pregnancy occurs when the conceptus implants outside the uterine cavity. The most common site is the fallopian tube (98.3%), followed by abdominal (1.4%), ovarian (0.15%), and cervical (0.15%) ectopic pregnancy. Considering tubal ectopic pregnancies, 80% occur at the ampulla, 12% at the isthmus, 6% are fimbrial, and 2% are interstitial.

The rate of ectopic pregnancy is constantly increasing, but the morbidity and associated mortality of ectopic pregnancy have substantially decreased due to improved diagnostic methods. With the use of high-resolution transvaginal probes and sensitive immunoassays for human chorionic gonadotropin (hCG), the number of stable ectopic pregnancies diagnosed has significantly increased and consequently treatment modalities have become less radical. The evolution of treatment has progressed from salpingectomy at the time of laparotomy to salpingostomy with conservation of the fallopian tube performed by laparoscopy. More recently, medical management in the form of systemic methotrexate and even expectant management have been adopted in selected cases.

The most important risk factors are: previous ectopic pregnancy, documental tubal disease (pelvic infection, previous tubal surgery, endometriosis), failed sterilization by tubal occlusion, failed intrauterine contraceptive device, diethylstilbesterol exposure *in utero*. Previous pelvic infections e.g. *Chlamydia trachomatis* and infertility are less significant (11).

DIAGNOSTIC INVESTIGATIONS

The classical symptoms of ectopic pregnancy are: amenorrhoea, abdominal pain and vaginal bleeding. Not all ectopic pregnancies are symptomatic. A firm diagnosis of ectopic pregnancy, with the gestational sac or fetal pool positively identified in the adnexal region, is rarely made by sonography alone. However, identifying an empty uterus in conjunction with an adnexal mass that is not of ovarian origin and/or pelvic free fluid is highly predictive (85–95%) of ectopic pregnancy. If a pregnancy cannot be seen using transvaginal sonography, then it is classified as a pregnancy of unknown location, 10% of which are ectopic pregnancies.

In normal pregnancy serum hCG increases by 66% over 48 h and doubles every 2–3.5 days (doubling time) between the fourth and eighth week of gestation. Pathological pregnancies (intrauterine miscarriage or ectopic) often have impaired hCG increments, with doubling time longer than 48 h (around 17% of ectopic pregnancies may have normal hCG doubling times).

The discriminatory human chorionic gonadotrophin (hCG) zone is the minimal hCG titre above which an intrauterine gestation sac can always be visualized by pelvic ultrasound. Transvaginal

sonography reliably detects an intrauterine gestation where the serum hCG titre is greater than or equal to 1,000–1,500 IU/l. Absence of an intrauterine gestation sac with the serum hCG titre above this 1,000–15,000 IU/l discriminatory zone has been shown to be highly predictive of ectopic pregnancy.

Combining empty uterus, serial hCG and discriminatory zone principles, the diagnosis of ectopic pregnancy can be made with a sensitivity of 95–99% and a specificity of 98%.

A single measurement of serum progesterone is an effective screening test in identifying a normally developing pregnancy. A level greater than 25 ng/ml is associated with a viable intrauterine pregnancy and can exclude ectopic pregnancy, whereas a value less than 5 ng/ml is highly suggestive of a non-viable (ectopic or intrauterine) pregnancy (10). Direct visualization of ectopic pregnancy by laparoscopy remains the 'gold standard'. Its main advantage is that diagnosis and effective treatment can be combined at the same time. On the other hand, laparoscopy is an invasive procedure, associated with patient mortality and morbidity. The most significant complications were visceral or vascular injury.

Dilatation and curettage is recommended as a diagnostic method for use in conjunction with low progesterone or β -hCG concentrations and in women in whom transvaginal ultrasound suggests a non-viable intrauterine pregnancy. The absence of chorionic villi is associated with an ectopic pregnancy in 40% of women with an empty uterus on ultrasound (4). A decrease in the β -hCG concentration of 15% or more 8–12 h after curettage is diagnostic of complete abortion. If hCG concentration does not fall, ectopic pregnancy is diagnosed (13).

Treatment options involve: • expectant • medical – usually systematic • surgery – laparotomy or laparoscopy.

EXPECTANT MANAGEMENT

Expectant management of ectopic pregnancy is an option for women with early, unruptured ectopic pregnancies, and is successful in 50–70% of women (1, 5, 11). In one study (5), in women with hCG concentrations of 175 IU/l or less, treatment was successful in 96% of cases, whereas in those with hCG concentration of 175–1500 IU/l, expectant management was effective only in 66%.

We could offer expectant management to stable women with an initial serum hCG less than 1,500–2,000 IU/l, an ectopic pregnancy size of less than 4 cm, without a fetal heart beat and haemoperitoneum less than 50 ml (4). This accounts for only 10% of ectopic pregnancy. However, the risk of tubal rupture and persistent trophoblast remains despite adequately declining serum hCG concentrations, and several cases of tubal rupture have been reported with serum hCGs below 100 IU/l.

Expectant management requires a very close follow-up and is reserved for selected cases. Women suitable for such management should have declining β -hCG concentrations, though the threshold for treatment remains unclear and a decision is to be taken after discussion between the patient and the doctor.

We have to remember that no cutoff value below which expectant management is uniformly safe has been established. Furthermore, rupture despite low and declining serum levels of hCG has been reported, making a close follow-up and patient compliance of paramount importance.

We describe a case of ectopic pregnancy diagnosed ultrasonographically at five weeks' gestation, treated conservatively with expectant management.

A 26-year-old multigravid patient was admitted with vaginal bleeding since the last menstrual period, lasting three weeks. She had had a successful pregnancy one year earlier delivered by Caesarean section. Speculum examination revealed a closed cervix with minimal blood clots at the cervical os. The uterus was anteverted, enlarged and compatible with the menstrual history. Systemic review

was unremarkable except for mild right iliac fossa tenderness. The complete blood count showed a white blood cell count of $7.050/\text{mm}^3$. The hematocrit was 37.1%, and hemoglobin 125 g/L. The β -human chorionic gonadotrophin (β -hCG) concentration was 220.6 IU/L. Other blood chemistry levels were normal. Blood pressure (120/75 mmHg) and pulse (80/min) were stable. An ultrasono-graphic examination performed a day before coming to the hospital using transvaginal probe showed an empty uterine cavity and a hyperechogenic mass separate from the right ovary (Fig. 1). The next examination was two days after and shows close to the right ovary hyperchogenic mass of 2.34×3.58 cm in diameter and small amount of free fluid in the pouch of Douglas. Follow-through TVUS demonstrated decrease in diameter of abnormal mass and in amount of free fluid.



Fig. 1. TVUS image shows a hyperechogenic mass close to the right ovary (2.32×1.25 cm)

After discussing the diagnosis, the patient elected the expectant management followed up with an hCG measurement, blood pressure, pulse and temperature on every day. Quantitative β -hCG level was serially evaluated. The first day of management β -hCG level dropped to 174.5 mIU/L, and it was 200.3 mIU/L on the fourth day; 151.8 mIU/L on the seventh, and 81.5 mIU/L on the ninth day of treatment (Fig. 2). Blood pressure (120/75, 110/70, 120/85, 100/70 mmHg), temperature (35.0 – 36.8°C) and pulse (58–82/min) was stable. The patient was given vitamin B6 with the purpose of suppressed lactation. After 13 days of treatment the patient left the hospital.

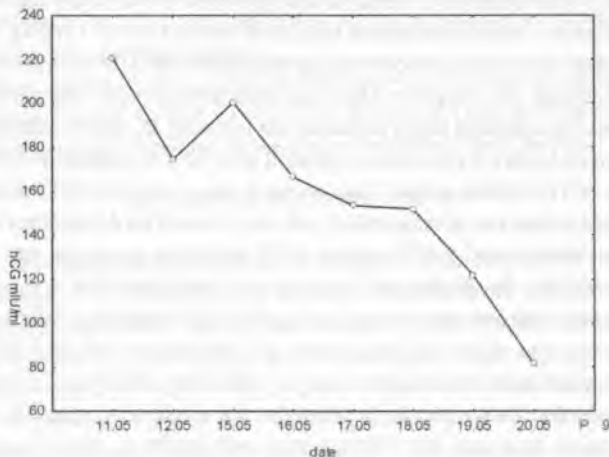


Fig. 2. Follow-up β -human chorionic gonadotrophin (β -hCG) concentrations following expectant management

MEDICAL TREATMENT

Tanaka and associates (14) were the first to recommend the use of methotrexate for an ectopic interstitial pregnancy. Since then, there have been numerous reports describing successful treatment of all varieties of ectopic pregnancy using a number of methotrexate regimens.

Methotrexate is a folinic acid antagonist, which interferes with DNA synthesis by inhibiting the activity of dihydrofolic acid reductase that is essential in the synthesis of the purine nucleotide thymidilate and the amino acids serine and methionine. Actively proliferating trophoblast is highly vulnerable to methotrexate.

In case of clinically stable women, the β -hCG concentration at presentation is the most important determinant of failure of medical treatment (9). Size of adnexal mass did not affect medical outcome.

Criteria for receiving methotrexate based on the ACOG recommendations (15): **Absolute indications** • haemodynamically stable, no active bleeding, no haemoperitoneum • non-laparoscopic diagnosis • patient desires future fertility • general anaesthesia poses a significant risk • patient is able to return for follow-up care • patient has no contraindications to methotrexate. **Relative indications** • unruptured mass < 3.5 cm in size on scan • no fetal cardiac activity • hCG does not exceed predetermined value (6,000–15,000 IU/l).

Before initiating therapy, draw blood to determine baseline laboratory values for renal, hepatic, and bone marrow function, as well as a baseline hCG level. Determine blood type, Rhesus (Rh) factor, and the presence of antibodies. Patients who are Rh negative should receive Rh immune globulin. Women with certain medical conditions (e.g., liver disease with a transaminase level two times higher than normal, renal disease with a creatinine level higher than 1.5 mg/dL (133 μ mol/L), immune compromise with a white blood cell count less than 1,500/mm³ and platelets less than 100,000 \times 10³/mm³, significant pulmonary disease) are not candidates for methotrexate.

Methotrexate can be administered intravenously, intramuscularly or locally (injection direct into the ectopic pregnancy). There is no consensus on the best treatment protocol to be used. The two most commonly used treatment protocols involve either a multidose or single-dose protocol. The multidose protocol involves the administration of intramuscular methotrexate every other day at a dose of 1 mg/kg of body weight alternated with intramuscular leucovorin rescue factor 0.1 mg/kg of body weight the day after methotrexate until the human chorionic gonadotropin (hCG) level drops by at least 15%. Up to 4 doses of methotrexate may be given. The single-dose protocol uses only methotrexate, 50 mg/m² of body surface area for a planned single intramuscular injection. Despite the term single-dose, repeat injections are permitted every 7 days and are needed in > 20% of patients (7). The second dose is administered if the hCG is higher on day 7 than on day 4, also a failure of hCG decrease by 15% from day 4 to day 7 after methotrexate administration indicates the need for further intervention.

A recent meta-analysis of 1,327 patients (260 multidose protocols and 1,067 single-dose protocols) concluded that the single-dose protocol was associated with a significantly increased failure rate (multidose methotrexate therapy was significantly superior to single-dose methotrexate therapy with success rates of 241 of 260 patients (92.7%) versus 940 of 1,067 patients (88.1%; $p = .035$) (2), but in the next analysis, there was no significant difference in failure rates between multidose and single-dose protocols (8). In citing that the single-dose approach is the most widely used medical treatment, they state that 14% of women will require >1 dose of methotrexate and less than 10% of women who are treated with this regimen, will require surgical intervention.

Direct injection delivers very high concentrations of methotrexate to the site of implantation. However, this approach has the substantial disadvantage that laparoscopic or ultrasonographic needle guidance is needed. Rates of successful treatment are lower than with systematic methotrexate.

Serious adverse events – e.g. severe neutropenia and alopecia-associated with short-term use of methotrexate are rare, but less serious side-effects – e.g. nausea, vomiting, gastritis, diarrhoea, abnormal liver function tests, stomatitis, transient pneumonitis, and bone marrow suppression – are more common (3). During methotrexate therapy, transient pelvic pain is common, frequently occurring 3–7 days after the start of therapy, and lasting 4–12 h; it is presumably due to tubal abortion. Perhaps the most difficult part of methotrexate therapy is distinction of the transient abdominal pain of successful therapy from that of a rupturing ectopic pregnancy. Objective criteria help; surgical intervention is necessary only when there is orthostatic hypotension or a decrease in packed-cell volume (11). Treatment effects of methotrexate include also an increase in hCG levels during first 1–3 days of treatment and vaginal bleeding or spotting.

SURGICAL TREATMENT

The decision to manage an ectopic pregnancy surgically will depend on the likelihood of success of non-surgical treatment. Since medical therapy is less likely to succeed, surgery is the preferred approach for ectopic pregnancy when there are signs of cardiac activity and hCG concentrations are higher than 5,000 IU/l (9). Other indications for surgery include an adnexal mass greater than 4 cm in diameter and free fluid in the pelvis on transvaginal ultrasound, although results of recent studies suggest these factors are not always predictors of failure with medical management (12).

Whether conservative surgery is done via laparoscopy or laparotomy, persistent ectopic pregnancy is the most important common complication. Persistent ectopic pregnancy is the persistence of trophoblastic tissue with a rising or plateauing hCG titer after the initial approach. A randomized controlled trial comparing laparoscopic salpingostomy with salpingectomy at laparotomy showed higher rates of persistent trophoblast with salpingostomy (3–20% of cases). Therefore, hCG concentrations should be followed up until they are undetectable. A post-operative day 1 serum hCG decrement of less than 50% of the preoperative value may predict of persistent trophoblast. If the patient develops abdominal pain or persistent bleeding, or becomes haemodynamically unstable, repeated surgery may be required. Those patients who are stable may be able to undergo medical management with methotrexate (e.g. single dose systemic methotrexate 50 mg/m²). Some authors have suggested administration of a prophylactic dose of methotrexate after conservative surgery to reduce the risk of persistent ectopic pregnancy.

Factors increasing the risk of persistent trophoblast are • small ectopic pregnancies, smaller than 2 cm • early gestation <7 weeks • a high level (> 3,000 IU/l) of hCG before treatment • implantation medial to the salpingotomy site • milking of the ectopic pregnancy from the tube.

MEDICAL VERSUS SURGICAL THERAPY

In the multicentre randomized controlled trial that compared variable-dose systemic methotrexate with laparoscopic surgery (6), 14% of the women assigned methotrexate needed surgery because of tubal rupture. Persistent trophoblast occurred less commonly after variable-dose methotrexate (4%) than after salpingotomy (20%). Two of the trials compared single-dose regimens with laparoscopic salpingostomy, and the need for surgery for persistent trophoblast varied from 4% to 15%. There was no difference between the surgical and medical treatment groups in rates of tubal patency or subsequent intrauterine pregnancy. Health-related quality of life was more severely impaired after repeated doses of systemic methotrexate than after laparoscopic salpingostomy, but women who received single-dose methotrexate had much better physical functioning than those who were operated on.

CONCLUSIONS

The heterogeneous nature of ectopic pregnancy in terms of population, patient choice and treatment diversity needs to be respected. The original premise of conservative surgery, medical management and expectant management is the preservation of fertility, especially when the only other treatment option is salpingectomy. Regarding such conservative 'tubal-preserving' treatment against salpingectomy, the balance is not yet clear as to whether an improved subsequent intrauterine pregnancy rate overrides the potentially increased risk of persistent trophoblast and future ectopic pregnancy.

Advantages of medical treatment are its non-invasiveness avoiding anaesthetic and surgical risks, shorter hospital stay and perhaps lower cost. However, the surgical approach can be performed for nearly all patients with ectopic pregnancy, whereas methotrexate treatment can only be given to a selected group.

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SUMMARY

The methods used for the diagnosis and management of ectopic pregnancy have developed over the past 10 years. Because of current availability of early diagnosis of ectopic pregnancy, medical treatment may be an important alternative to surgical therapy. There are many examples in the literature reporting successful conservative management of ectopic pregnancy, especially in tubal form. A case of ectopic pregnancy is presented. It was diagnosed in the fifth week of gestation by ultrasonography, and treated conservatively with expectant management.

Cięża ektopowa – leczenie zachowawcze

Cięża ektopowa stanowi nadal wyzwanie diagnostyczne i terapeutyczne dla ginekologów. Wprowadzenie bardziej czułych testów diagnostycznych i ultrasonografii przezpochwowej zmieniło sposoby postępowania w przypadku ciąży ektopowej. Obecnie często wybiera się postępowanie zachowawcze: wyczekujące lub farmakologiczne. W pracy dokonano przeglądu piśmiennictwa, zwracając uwagę na preferowane przez innych autorów sposoby diagnostyki i leczenia ciąży pozamacicznej. Przedstawiliśmy również przypadek pacjentki z ciążą ektopową leczoną z powodzeniem zachowawczo w naszej klinice.