Controversies and problems in the current management of tubal pregnancy

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The two main conservative treatment alternatives for tubal pregnancy, methotrexate administration and laparoscopic salpingostomy are under constant review. Recently, expectant management of tubal pregnancy has become increasingly popular. In this review, we assess the outcome of conservative management modalities for extrauterine pregnancy and compare the results of treatment with methotrexate and operative laparoscopy. Outcomes of extrauterine pregnancy were obtained from a review compiled from the English literature identified by directed Medline search. Methotrexate and laparoscopic salpingostomies yield good final treatment rates of 85–95% respectively and relatively low rates for further surgical complication (5–10% respectively). Tubal patency, as well as future fertility performance, are quite similar after both techniques. Although they appear to suit the demands of the 21st century, each one has its own benefits and contraindications. With adequate patient selection, expectant management of the tubal pregnancy is a reasonable approach with good results. Although the morbidity rate after tubal pregnancy treatment is decreasing and the main concern is to reduce the decline in fertility potential, the real future challenge remains prevention of the disease, especially among high risk patients, such as those undergoing infertility treatment.

Key words: assisted reproductive techniques/conservative treatment/methotrexate/operative laparoscopy/tubal pregnancy

Introduction

Ectopic pregnancy is a disease acknowledged from antiquity, and the first report appears in the writings of the famous Arabian physician Abulcasis (936–1013) (Albucasio, 1778). It was considered to be fatal, and a maternal death rate of 72–99% was recorded at the end of the 19th century (Thomas, 1880). The first successful salpingectomy was reported by Lawson Tait who described it as the definitive treatment for tubal pregnancy (Tait, 1884, 1888). This radical treatment persisted until 1953 when Stromme (1953) described salpingostomy, permitting removal of an ectopic gestation without sacrificing the Fallopian tube.

The past few decades have witnessed an unprecedented rise in the number of ectopic pregnancies, some of which are associated with assisted reproductive techniques (ART) and ovulation induction. Since early diagnosis of an ectopic/tubal pregnancy before its rupture is generally standard care today, the focus of treatment has concentrated on reducing morbidity and restoring fertility potential.

Very early detection of tubal pregnancy generates its own problems, among which are an increasing number of surgical interventions, many of which in the past may have been resolved spontaneously (Gomel, 1995; Stovall, 1995). Recent advances in medical technology have blurred the distinctions between the two general surgical options of radical versus conservative treatment. Improvements to the original salpingostomy through laparoscopic techniques and the use of various pharmaceutical agents may change future terminology. We may come to regard any form of laparotomy for tubal pregnancy as radical therapy, whereas any laparoscopic or medical treatment will be transformed into a conservative approach.

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The current review will compare the nonradical treatment options for tubal gestation, i.e. expectant management, medical treatment and laparoscopic salpingostomy, by focusing on the various indications, contraindications, as well as intra- and postoperative complications and fertility performance. The creation of an iatrogenic disease among in-vitro fertilization (IVF) patients, its difficult early diagnosis, as well as the therapeutic challenge, are discussed.

**Epidemiology**

Between 1970 and 1987, the number of ectopic pregnancies increased five-fold in the US from 17 800 to 88 000. In this respect, the rate of ectopic pregnancies increased from 4.5 to 16.8 per 1000 pregnancies (Ory, 1992).

The incidence of tubal pregnancy after ART is very high (4.5% after oocyte retrieval/embryo transfer). Gamete intra-Fallopian transfer (GIFT) procedures involving gamete transfer into presumably normal tubes still causes an incidence of 4% of tubal pregnancies of the total pregnancies achieved (Assisted Reproductive Technology in the United States and Canada, 1995).

Many studies identify a history of ectopic pregnancy or tubal pathology as the major risk factor for developing an extrauterine pregnancy among IVF patients (Karande et al., 1992), most probably since the pre-embryo has a tendency to implant in the tubes of these patients. This seems to be true both during natural conception and embryo transfer (Schindler and Duderstadt, 1980).

Another aspect of this ‘iatrogenic problem’ is the heterotropic pregnancy phenomenon. In 1948, it was considered to occur in 1:30 000 pregnancies, which was based on ectopic pregnancy and dizygotic twinning rates prevalent at the time (DeVoe and Pratt, 1948). As reported, both the incidence of ectopic pregnancy and dizygotic twinning have also increased as a consequence of the prevalent use of ovulation induction agents. Recent estimates of heterotropic pregnancies range from 1:100 pregnancies in IVF patients to 1:4000 pregnancies in the general population (Ory, 1992). This phenomenon poses additional diagnostic and treatment challenges, since clinicians must now investigate all patients complaining of symptoms of ectopic pregnancy, even after an intrauterine pregnancy has been diagnosed, and the treatment will be complex, directed towards preserving the intrauterine embryo and eliminating the ectopic one. Furthermore, this probably will create a critical delay from which many of those patients will present with a clinical picture of ruptured tubal pregnancy, a version of an already forgotten disease.

**Diagnosis**

The fundamental contribution that has permitted the change in treatment of this disease is its early detection, based on very sensitive hormonal assays [β-human chorionic gonadotrophin (HCG) and progesterone] (Batzer et al., 1981; Yeko et al., 1987; Hahlin et al., 1991), and the use of high resolution transvaginal ultrasonography (Coleman and Arger, 1988; Fossum et al., 1988) which can detect an intrauterine pregnancy when serum β-HCG concentrations register in the ‘discriminatory zone’ of >1000–2000 IU/l (Torp, 1992).

Vaginal sonography coupled with colour and pulsed Doppler flow imaging technology has been promoted as significantly improving preoperative diagnosis (Emerson et al., 1992; Pellerito et al., 1992). The technique involves identifying an extraterine site of vascular colour, with high velocity and low impedance flow pattern, characteristic of placental shape flow, called ‘ring of fire’ pattern. If this pattern is seen outside the empty uterine cavity, then the diagnosis of tubal gestation is highly likely. Unfortunately, this scanning technique falls short of expectations due to difficulty in distinguishing placental from luteal flow and failure to characterize adnexal masses accurately (Pellerito et al., 1995).

Recently, Gleicher et al. (1992) have suggested hysterosalpingography and selective salpingography for the differential diagnosis of the more delicate condition, such as early missed intrauterine pregnancies (IUP) compared with intratubal pregnancies.

Lower plasma progesterone concentration is a hallmark of tubal gestation after spontaneous cycles. However, the corpus luteum (CL) secretes high amounts of steroid hormones in a tubal pregnancy achieved after IVF. In those patients diagnosed with tubal pregnancy after IVF, Shulman et al. (1994) found plasma progesterone concentrations which were several times higher than the ‘discriminatory levels’ expected for tubal pregnancies in non-stimulated cycles, and were found to be in the range compatible with intrauterine gestations. Perhaps there is a summation effect of multiple CL which develops in controlled ovulation stimulation cycles and by CL rescue after luteal support of HCG injection. The failure of a sonographic scan to detect an extraterine sac is common during the first weeks of gestation among IVF patients due to enlarged, stimulated cystic ovaries. Furthermore, the possibility of multiple intrauterine implantations alters the importance of absolute β-HCG concentrations in IVF.
cases (Yeko et al., 1987). It is important to clarify that ‘early recognition’ of tubal pregnancy should refer to the identification of a tubal pregnancy prior to its rupture, which is consistent only with a short gestational age (Lindblom, 1984). The term is not suitable for a small mass of ectopic site, since there is no correlation between gestational length and serum $\beta$-HCG concentration, nor is there a correlation between HCG concentration and the size of the tubal pregnancy (Barnea et al., 1984; Cartwright et al., 1987).

Therefore, only the time interval from embryo transfer, rather than the absolute $\beta$-HCG value, attains significance for which day an intrauterine gestation can be visualized by transvaginal ultrasonography in an IVF/ART achieved pregnancy. In this manner a tubal pregnancy can be suspected.

A. Expectant management

Spontaneous tubal abortion is a well known phenomenon (Burrows et al., 1980). The efficacy of this was acknowledged in 1955 by Lund, who reported the resolution of tubal pregnancy in 68 of 119 conservatively observed patients. However, massive peritubal adhesions, hydrosalpinx and prolonged hospitalization (>30 days) were among the major complications with his conservatively managed group.

The efficacy of expectant management in highly selected and haemodynamically stable patients has been shown in recent studies. In a survey of 81 cases over a 15 year period, 62 (76%) resolved spontaneously and 19 (24%) required further surgical treatment (Maymon et al., 1992). Follow-up hysterosalpingography in 29 patients from the same review revealed 21% tubal occlusion and 16% reported pregnancies. Similar results were recently reported by Ylostalo et al. (1992).

Among the disadvantages of this approach is the difficulty in predicting the course of the disease. Even declining $\beta$-HCG values are not always reassuring, since tubal rupture has been reported following a rapid decrease in serial $\beta$-HCG concentrations (Gretz and Quagliarello, 1991; Tulandi et al., 1991). The fertilized ovum burrows through the tubal epithelium. This trophoblastic invasion into the myosalpinx ranges from localized superficial penetration by anchoring villi, with maintenance of an otherwise intact muscularis, to complete destruction of areas of the muscularis (Pauerstein et al., 1986). Thus, the tubal wall connected to the conceptus offers only minimal resistance to the trophoblastic invasion which soon penetrates it, opening maternal vessels, causing tubal rupture and uncontrolled maternal haemorrhage (Cunningham, 1993).

Other long term complications can be ‘chronic ectopic’, i.e. formation of dense pelvic adhesions following resorption of the tubal gestation (Cole and Corlett, 1982). After expectant management, serum $\beta$-HCG concentrations have been found to normalize within roughly 22 days (range 5–51 days) (Ylostalo et al., 1992). Chorionic villi are capable of surviving for at least 15 months following cessation of a tubal pregnancy (Gomel and Filmar, 1987).

The advantages of expectant management include minimizing risks and the possibility of promising long-term results, as shown by Shalev et al. (1995), who found no difference in the outcome of those patients who were observed or those who required another treatment modality. Repeat intra- and extraterine pregnancies occurred in 83 and 17% respectively, for patients with expectant management and 85 and 15% respectively for those treated by salpingectomy/salpingostomy.

Patient follow-up and monitoring

When expectant management is chosen, $\beta$-HCG determination and transvaginal sonography should be performed twice during the first 24–48 h interval. If $\beta$-HCG values are still declining, further observation is indicated. During follow-up, repeat serial $\beta$-HCG monitoring and vaginal sonography are recommended until the $\beta$-HCG concentration is undetectable (Ylostalo et al., 1992). Meanwhile, if there is any deterioration in the clinical symptoms or sonographic findings indicating impairment, active management is suggested. Following treatment in cases of infertility problems or if vaginal sonography shows a persisting adnexal mass, ‘second look’ hysterosalpingography or laparoscopy can be performed.

B. Medical treatment

In a previous review (Maymon et al., 1992), we surveyed various chemical agents, such as methotrexate (MTX), prostaglandin, RU 486 (Maymon et al., 1992), and actinomycin D (Altaras et al., 1988), which are administered systemically, and others, such as KCl 20% (Maymon et al., 1992). MTX, prostaglandin, and glucose 50% (Lang et al., 1992) are injected directly into the ectopic mass. With the exception of MTX, which has been extensively used and is the most well documented drug in the literature, we will exclude all the remaining agents from this discussion. The interested reader can obtain additional data on local drug therapy in the above references.

MTX is a folinic acid antagonist which blocks DNA, and to some extent RNA, synthesis. Consequently, tissues undergoing rapid cellular turnover, such as trophoblasts,
are most susceptible to its action (Stovall, 1995). Floridon et al. (1996) found that local administration of MTX compromises the trophoblastic spread, differentiation and invasion. Addition of citrovorum factor, an antidote to MTX, has been shown to increase the safety and effectiveness of high-dose MTX (Goldstein et al., 1976). Side-effects usually correlate with the amount of drug administered, including myelosuppression, hepatitis, gastrointestinal mucositis, pleuritis, alopecia, and dermatitis (Goldstein et al., 1976). Even pneumonitis has been reported following tubal administration of 12.5 mg MTX (Schoenfeld et al., 1992). Nephrotoxicosis can be seen with high-dose regimens and neurotoxicosis may be encountered with intrathecal MTX administration (Stovall, 1995).

MTX treatment for extraterine pregnancy was initially used in cases of abdominal pregnancy, then in cervical pregnancy and, more recently, for persistent tubal pregnancy and tubal gestation. For a more detailed overview, see the review by Maymon et al. (1992). From 30 years of experience, the success rate seems to depend upon the amount of trophoblastic cells, as reflected by serum $\beta$-hCG concentrations (Corsan et al., 1995) and by the presence or absence of embryonic tissue (Darai et al., 1995).

Thus, it seems that the basic inclusion criteria for systemic MTX treatment are: (i) an unruptured tubal pregnancy; (ii) no evidence of active intraabdominal bleeding, with a haemodynamically stable and clinically asymptomatic patient; and (iii) no active renal or hepatic disease with no evidence of blood dyscrasias (Sauer et al., 1988; Prevost et al., 1992; Ransom et al., 1994; Gomel, 1995).

Whether a specific $\beta$-hCG threshold value (Corsan et al., 1995) or a live embryo seen at ultrasonography determines the choice of a surgical option over MTX administration (Darai et al., 1995) is still open to debate. A review of published studies on this topic points toward multifactorial factors which determine the treatment outcome and explains why $\beta$-hCG concentrations alone are not sufficiently predictive. Fernandez et al. (1991) suggested a pretherapeutic score before the decision for medical treatment. This score is based on six criteria graded on a scale from 1 to 3: gestational age, $\beta$-hCG values, plasma progesterone concentrations, abdominal pain, volume of the haemoperitoneum, and diameter of the haematosalpinx as assessed by ultrasound. He found a success rate of >90% for the medical treatment whenever the pretreatment score was $\leq$ 13 (Fernandez et al., 1991, 1993).

It has been reported that one dose of MTX i.m. of 50 mg/m$^2$ of body surface area can terminate a first trimester pregnancy, regardless of gestational age or implantation site (Hausknecht, 1995). The problem is controlling the placental site bleeding induced by the tubal abortion in pregnancies with a live embryo. This is most probably the cause of increased failure rates requiring laparoscopy or laparotomy (Darai et al., 1995).

Systemic MTX was first used for an interstitial ectopic pregnancy by Tanaka et al. (1982). Over successive years, the suggested protocols have recommended i.m. or i.v. administration of 1 mg/kg/day on 4 alternating days, and citrovorum factor at 0.1 mg/kg/day on the intervening days. Recently, a single i.m. injection of 50 mg/m$^2$ of MTX has been proposed (Stovall et al., 1991). This is in agreement with other studies which recommend a single MTX dose of 50 mg/m$^2$ (Corsan et al., 1995; Fernandez et al., 1995). In 1987, Feichtinger and Kemeter were the first to suggest tubal administration of MTX delivered via a transvaginal puncturing technique under ultrasound guidance. Since this report, several other articles have reported using local MTX injection for the treatment of unruptured tubal gestation, assuming that the pregnancy sac was visualized by ultrasound (clinical data on local MTX administration as well as systemic administration are summarized in Table I). In cases where a gestational sac cannot be visualized, selective salpingography for the diagnosis of extraterine pregnancy and further intra-luminal MTX administration was successfully applied by Risquez et al. (1992) and Confino et al. (1994).

We have summarized the data of 23 publications that describe a variety of systemic, combined systemic and local treatments or injection of the agent directly into the affected tube (Table I). Resolution was achieved in 83% of the 459 treated patients, 76 (17%) required laparotomy or surgical laparoscopy, and 32 (7%) experienced systemic MTX side-effects.

**MTX: safety and fertility performance**

The proportion of patent tubes, assessed by HSG following medical treatment, range between 75% and 85% (Stovall et al., 1991; Maymon et al., 1992; Stovall and Ling, 1993; Schaefer et al., 1994; Fujisita et al., 1995). The pregnancy rate following the various treatment protocols is ~60–80%, of which 10–13% are repeat tubal pregnancies (Stovall et al., 1990; Stovall et al., 1991; Stovall and Ling, 1993; Ransom et al., 1994; Job-Spira et al., 1996). Concern about subsequent pregnancy outcome among gestational trophoblastic tumour patients who conceive after
completion of MTX chemotherapy protocols has been voiced in the literature. There have been 449 pregnancies among 671 patients who completed full dose chemotherapy, of whom 3% had either major or minor congenital anomalies, with a first and second trimester spontaneous abortion rate of 15–19% (Rustin et al., 1983; Maymon et al., 1992). We believe that the safety of this regimen should be evaluated further, especially among the first and second generations of such children, principally because some protocols inject MTX in very close proximity to the oocytes.

Systemic side-effects due to parenteral MTX administration (12.43%, see Table I) are diverse and, in all the published cases, reversible. The majority of cases reported mild stomatitis or gastritis, but more severe complaints including transient leukopenia, transient increase in liver enzymes, and reversible alopecia (Trout and Kemmann, 1995) have been reported. We believe that future reports of the incidence of these side-effects will be significantly lower due to the change in the protocols from multiple successive daily MTX administration (0.5–1 mg/kg body weight) to one single dose of 1 mg/kg body weight (Stovall and Ling, 1993; Corsan et al., 1995).

Local MTX treatment is associated with high tissue concentrations of the drug and fewer systemic side-effects than i.m. administration (Fernandez et al., 1994; Table I). The drug’s pharmacokinetics differ according to whether it is injected into the sac or is administered parenterally. Fernandez et al. (1994) reported that the area under the curve for MTX concentration decreased more rapidly after injection into the gestational sac alone than after i.m. injection. This finding may relate to a decrease in bioavailability of MTX that is linked to the presence of trophoblastic cells (Schiff et al., 1992).

Some local inflammatory response and tubal epithelial desquamation have been reported (Ory, 1991; Klinkert et al., 1993). Therefore, while local administration of MTX decreases systemic toxicity, long-term effects upon the endosalpinx have not been adequately assessed (Cannon and Jesionowska, 1991; Fernandez et al., 1994).

**Patient follow-up and monitoring**
Whatever the route of administration, treatment failure after MTX is attributed to the failure of β-HCG to decrease, to tubal rupture, or to severe i.p. bleeding. A viable residual trophoblast may remain in the affected tube, resulting in further proliferation and delayed haemorrhage (Maymon et al., 1992). When single dose (50 mg/m²) i.m. MTX is used, HCG may increase initially beyond the pretreatment values (Peleg et al., 1994; Stovall, 1995), but begins to decline 4–7 days after the initial injection. Failure of β-HCG to decrease by day 7 (4% of the patients) below the values on day 4 indicates the need for one more injection of MTX. Furthermore, an additional injection of MTX is necessary when the β-HCG values do not decrease further on weekly assessment. Therefore, it is mandatory to follow all patients with serial β-HCG assessments until the β-HCG becomes undetectable. This ensures early detection in the event of any trophoblastic cell proliferation. According to Stovall and Ling (1993) and Stovall (1995), the mean time from treatment initiation to the resolution of β-HCG titre is 35.5 ± 11.8 days, which is slightly longer than after laparoscopic salpingostomy. According to other authors, the resolution time of tubal pregnancy is 14–92 days after systemic MTX treatment, and 14–120 days after transvaginal intratubal MTX administration (Tulandi, 1992). The tube may remain distended and a sonographic mass may be detected in the previously treated tube for up to 100 days after serum β-HCG values are undetectable, suggesting that a persistent mass should not be interpreted as treatment failure (Brown et al., 1991). Abdominal pain following MTX treatment has been described (Stovall et al., 1995). It may be secondary to trophoblastic degeneration, with bleeding from the tubal ostia creating peritoneal irritation.

**Table I. Comparison of conservative treatment options for ectopic pregnancy based on a literature survey. Figures in parentheses are percentages**

<table>
<thead>
<tr>
<th>Mode of treatment</th>
<th>No. of patients</th>
<th>Success rate*</th>
<th>Repeated laparoscopy or laparotomy</th>
<th>Drug related complications</th>
<th>Patency on hysterosalpingography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expectant management</td>
<td>81</td>
<td>62 (76.5)</td>
<td>19 (23.5)</td>
<td>–</td>
<td>23/29 (79)</td>
</tr>
<tr>
<td>Local MTX</td>
<td>245</td>
<td>196 (80)</td>
<td>49 (20)</td>
<td>6 (2.44)</td>
<td>67/80 (83.75)</td>
</tr>
<tr>
<td>Systemic MTX</td>
<td>201</td>
<td>178 (88.55)</td>
<td>23 (11.44)</td>
<td>25 (12.43)</td>
<td>80/105 (76.19)</td>
</tr>
<tr>
<td>Cumulative MTX*</td>
<td>459</td>
<td>383 (83.44)</td>
<td>76 (16.56)</td>
<td>32 (6.97)</td>
<td>147/185 (79.45)</td>
</tr>
<tr>
<td>Laparoscopic salpingostomy</td>
<td>1001</td>
<td>930 (92.9)</td>
<td>71 (7.1)</td>
<td>–</td>
<td>145/174 (83.33)</td>
</tr>
</tbody>
</table>

*No further intervention.
**Including 13 patients who received combined treatment from the beginning (local and systemic).

MTX = methotrexate.
A continuous decrease in hormonal values does not necessarily ensure successful treatment. Decreasing β-HCG values may reflect a decline in the mitosing cytotrophoblasts as a direct result of chemotherapy, regardless of whether concurrent events in the tube may include separation of the trophoblast from the tubal wall, intratubal bleeding, a pressure necrosis from an intraluminal clot, or other intratubal mechanical events that may initiate rupture. Thus, although crucial, the measurement of β-HCG until it is undetectable, is not of absolute value in assessing the success of the treatment. A concomitant decrease in the ultrasonographic findings is imperative.

In conclusion, conservative management and close follow-up is recommended until β-HCG is undetectable. Should β-HCG concentrations fail to decrease by day 7 (a poor prognostic sign) after systemic MTX administration, Stovall et al. (1995) recommend additional MTX (50 mg/m^2) treatment.

C. Laparoscopic salpingostomy

This treatment (Bruhat et al., 1980) is another aspect of the conservative treatment, based on the traditional approach, as described by Stromme (1953). Aside from the general contraindications for diagnostic laparoscopic procedures, there are certain specific exclusion criteria related to operative laparoscopy which pertain to the haemodynamically unstable patient, extensive intra-abdominal adhesions or serum β-HCG concentrations >15000 IU/l (Pouly et al., 1986; Maymon et al., 1995). New operative instrumentation and techniques often allow attempts at laparoscopic treatment in cases previously considered to be contraindicated, such as cornual, ovarian, isthmic or even ruptured tubal gestation. More details are available in the review by Maymon et al. (1995). Description of the basic techniques is beyond the scope of this article and interested readers can refer to other reports (Pouly et al., 1986; Murphy, 1987; Semm and O’Neill-Freys, 1989). Generally a three-puncture technique is applied with two suprapubic trocars. For salpingostomy, electrocautery, laser or scissors can be used. A spoon-shaped grasping forceps and suction irrigation unit are required for evacuation.

Table 1 summarizes a survey of 1001 documented patients’ details, which include 6% intraoperative and 6% postoperative complications, comprising haemorrhage, injury to adjacent organs, and infection and a 4% occurrence of persistent ectopic pregnancy. As previously described, following its attachment to the tubal lumen, the trophoblastic mass may penetrate through the various tubal layers making its complete removal difficult and, sometimes, ineffective. Thus, residual trophoblastic cells may continue to proliferate, causing recurrence of signs and symptoms of tubal pregnancy within some 2 weeks of the initial surgery.

Patient follow-up and monitoring

Any conservative surgery should be complemented by weekly β-HCG monitoring to ensure that appropriate clearance has been achieved. The incidence of persistent ectopic pregnancy after laparoscopic salpingostomy approaches ~5% (Pouly et al., 1986; Fernandez et al., 1995). In the event of persistent ectopic pregnancy, the recommended options include further expectant management, MTX, or salpingectomy (Maymon et al., 1995).

Fertility performance

Follow-up of patients treated for tubal pregnancy, regardless of which procedure is performed, shows a pregnancy rate of 66% with 90% intrauterine pregnancy (Job-Spira et al., 1996). While repeat tubal pregnancy rates following both radical and conservative management are quite similar, the intrauterine pregnancy rate seems to be higher following conservative tubal surgery (40 versus 60% respectively) (DeCherney and Kase, 1979; Kadar, 1990). Thus, it is accepted that a conservative approach should be attempted whenever a distal tubal pregnancy is diagnosed, especially when the woman desires to preserve her fertility potential. In cases of laparoscopic salpingostomies, repeated intrauterine pregnancies have been reported with a rate of 48–63%, and a rate of 8–18% for repeated tubal pregnancies (Maymon et al., 1995).

The only two ectopic pregnancy characteristics that show any significant correlation with future fertility are the existence of ipsilateral adhesions and the condition of the contralateral tube (Pouly et al., 1991; Dubuisson et al., 1996). We share the concern that not all the patients with tubal gestations may benefit from the conservative surgical approach because it may predispose them to an unacceptably high risk of subsequent infertility and recurrent ectopic pregnancies. These patients may have a better prognosis from IVF than conservative surgery. Pouly et al. (1991) proposed a therapeutic scoring system for the laparoscopic management of tubal gestations and the future fertility performances. The score is calculated based on previous medical history obtained before the operation and on findings during the laparoscopic assessment of ectopic pregnancy. Only patients with a score of 0–3 are suitable for laparoscopic salpingostomy. For those with higher scores, laparoscopic salpingectomy with or without contralateral sterilization (according to the
severity of the findings) is the best treatment of choice. This attitude is supported also by the findings of Dubuisson et al. (1996). They reported 75% intrauterine pregnancies in patients with ectopic pregnancies and a normal contralateral tube (group 1) treated by laparoscopic salpingectomy, but only 36.6% ($P < 0.001$) in patients with a previous history of tubal surgery and/or those whose contralateral tube was pathological but not obstructed (group 2). As anticipated, the incidence of ectopic pregnancy recurrence was statistically higher in group 2 (18.3%) compared with group 1 (9.6%).

The best option?

Treating an unruptured tubal pregnancy following IVF/ART is a special challenge. An ongoing debate concerning the most suitable options alternates between an approach similar to that of a tubal pregnancy, regardless of aetiology, and a more complex approach that creates a balance between actual status, the necessity for IVF in the future and the severe psychological trauma produced by a repeat tubal gestation, especially if in the same Fallopian tube. Although an injection of MTX into the tubal sac, via transvaginal ultrasound, is very effective and less invasive than laparoscopic salpingostomy, it may be technically difficult and even dangerous due to the enlarged ovaries (Fernandez et al., 1995), even though both provide similar results and outcome (Fernandez et al., 1991, 1995).

Systemic administration of MTX is reliable for unruptured tubal pregnancies, but may engender some follow-up difficulties and cannot prevent recurrence in the same tube (Fernandez et al., 1994). The systemic medical treatment requires a longer resolution period with some question about optimal time to restart ovarian stimulation. Moreover, among older patients, impaired IVF results in irretrievably lost time, therefore this treatment option may be less desirable. Operative laparoscopy is feasible, although enlarged ovaries may be a technical limitation. Here again, patient age is a key factor for option choice. The high recurrence incidence of 12.3% for tubal pregnancy must offset conservative treatment.

Another challenge is the treatment of heterotopic pregnancies. Once a very rare condition, today it is reported in 1% of IVF-achieved pregnancies. It is obvious that neither systemic nor local MTX can be used because of the unpredictable adverse effect on the intrauterine gestation. Furthermore, salpingostomy raises difficulties of follow up. Therefore, laparoscopic salpingectomy seems to be the procedure of choice.

The advantages of medical treatment

These include: (i) laparoscopic incision may be unnecessarily traumatic, as it is sometimes difficult to locate the area of the active viable trophoblast, since many tubal cases are recognized at an early stage; (ii) medical treatment avoids the need for a surgical procedure, with its inherent risks, especially in complicated ectopic cases such as cornual, abdominal or cervical pregnancies (Gomel, 1995), and retained trophoblastic tissue (Maymon et al., 1992) or in cases of extensive intra-abdominal adhesions, massive obesity or other surgical obstacles. Furthermore, MTX has a prominent luteolytic effect which increases its antigestation action (Shulman et al., 1992); (iii) medical treatment eliminates the need for expensive operating facilities and prolonged use of anaesthesia; (iv) according to some authors, this is the cheapest treatment, since the mean direct cost of MTX treatment is ~US$1563 compared with US$6626 for laparoscopic treatment (Stovall, 1995).

Local MTX treatment via either laparoscopy or ultrasonic guidance offers several advantages over parenteral treatment. The most important point is that this approach offers a relatively high trophoblastic concentration while significantly reducing the risk of systemic MTX toxicity. This may reduce both hospitalization and resolution time, and may result in preservation of reproductive potential. Furthermore, direct administration of MTX may be applicable when fetal heart motion is detected in tubal gestations for which parenteral MTX administration is a debatable issue.

The disadvantages of the medical treatment

These are: (i) it is appropriate only for haemodynamically stable patients; (ii) the treatment has some toxic side-effects (15% in our survey). This antifolinic agent is contraindicated for administration during normal pregnancy, which eliminates this option for cases of heterotopic gestations. Also, we feel that the absolute safety of this medication is not completely established; (iii) while follow-up is on an outpatient basis, it can continue for as long as 40–50 days (Stovall, 1995); (iv) in our survey (Maymon et al., 1992), tubal patency following the procedure was 75% (Table I), which may influence those couples who are interested in future fertility; (v) as in expectant management, a number of patients might require surgical intervention, mainly due to tubal rupture (Maymon et al., 1992), and others will complain of abdominal pain, requiring repeat visits and hospital readmission (Gomel, 1995); (vi) systemic MTX therapy is not applicable in cases of advanced tubal gestation.
Transvaginal ultrasound-guided MTX intratubal administration is an option which might bypass some of the limitations of medically treating this disease; however, it is suitable only for those rare cases of definitively sonographically diagnosed extrauterine pregnancies where the patient is completely asymptomatic.

Some of the advantages of MTX treatment represent the disadvantages for laparoscopic salpingotomies (and vice versa). However, the most important advantage of laparoscopy is the complete visualization of the pelvis and genital organs, allowing prompt treatment with a relatively short follow-up period (Gomel, 1995). It is advisable to discuss the choice of therapy with the patient before making decisions. When fertility preservation is not requested by the patient, laparoscopic salpingectomy is the most appropriate option (Lindblom, 1984).

**Summary**

In 1888, Lawson Tait made a revolutionary recommendation for the surgical treatment of ectopic pregnancy. He was convinced that there could not possibly be absolute accuracy for the preoperative detection of ectopic pregnancy, and that injection of poisonous fluids into the ectopic conceptus was ridiculous (Lurie, 1992). Now, some 100 years later, the early diagnosis of ectopic pregnancy is generally standard care. The method of injecting a poisonous fluid (such as MTX) into the ectopic
mass has been introduced once again, thereby providing an efficient and safe alternative to conventional surgery, which has also undergone remarkable changes.

In view of these data, we suggest an algorithmic approach for the patient with proven or suspected tubal gestation (Figure 1). This approach supports the above recommendations and provides a suitable answer to the varying levels of hospital facilities and staff. We recognize two main limitations: (i) when a tubal gestation is visualized during an ultrasonographic scan; and (ii) whenever the diagnosis is presumed only by ‘exclusion’, and the ultrasound scan has failed to identify an intrauterine sac.

Whenever a tubal gestation is detected ultrasonographically, we suggest a local, directed treatment. Based on available medical facilities and the patient’s wishes (see above), we recommend that the first line treatment be laparoscopic salpingostomy or ultrasound-guided local MTX injection. If neither is available or in the event of treatment failure and the patient remains haemodynamically stable, systemic administration of MTX can be an alternative option.

When the diagnosis is only suspected, then a meticulous patient history must be obtained to accurately establish the gestational age (including the date of last menstrual period, date of ovulation and/or conception, the date of β-HCG seroconversion, and the highest β-HCG values and behaviour). If these data rule out a normal intrauterine pregnancy, thus confirming the diagnosis of tubal gestation, we suggest laparoscopic intervention (diagnostic procedure which can be used for definitive treatment if necessary) or systemic MTX administration. For a patient with a history of infertility, laparoscopy seems to be more appropriate, because more precise details about the patient’s pelvic organs and peritoneum can be visualized. This information will be helpful for both immediate and future infertility treatment options. If, however, we lack data to exclude a normal intrauterine pregnancy or, conversely, we have indications for a spontaneous resolution, then expectant management is recommended.

Thus, with the assistance of the modern work-up, early diagnosis and competent treatment of tubal pregnancy has shifted from an art to a science, permitting both preservation of fertility and a reduction in morbidity, a luxury that Dr Tait did not possess.

Further studies are needed to compare different conservative treatment options with regard to their safety, reproductive outcome and economic feasibility.

The history of infertility conveys a poor prognosis for future fertility following treatment of tubal pregnancy, regardless of the procedure used. Of 88 000 American women who annually experience this sad event, 30% will be infertile (Ory, 1991, 1992). Many will have an ectopic pregnancy as a complication of pre-existing infertility or assisted reproduction technique and will continue to exhibit poor fertility outcome. The 21st century gynaecologist should be prepared to prevent the causes related to tubal pregnancy, mainly those of iatrogenic origin concerning ART and ovulation induction. In the event of failure, familiarity with all the early diagnostic and treatment options will enable the clinician to apply the one most suitable for his skills and the patient’s needs.

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References


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