Ectopic pregnancies after infertility treatment: modern diagnosis and therapeutic strategy.

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Ectopic pregnancy (EP) is a major event in a woman’s reproductive life. It complicates infertility treatment and must be recognized early to simplify the treatment strategy, which must always be directed towards optimizing subsequent fertility. Epidemiological findings indicate that tubal history and smoking are the principal risk factors of those EP that are considered reproductive (rather than contraceptive) failures. Adding together the attributable risks for EP allows the construction of a risk scale to determine its probability for any given patient. This risk calculation makes it easier to establish a diagnostic strategy that uses abdominal and transvaginal ultrasound and hCG assays. Progesterone assays are useful only for determining the activity of the pregnancy but do not help to identify its site. Conservative treatment is to be preferred unless the EP occurs on a known hydrosalpinx. All the treatment trials and the Cochrane database meta-analysis show that medical treatment with methotrexate, preferably multidose, is equivalent in efficacy to conservative treatment with laparoscopy in the populations studied. Heterotopic pregnancies, which occur most often after assisted reproduction technology (1–3%), should preferably be treated by salpingectomy except in interstitial sites. There is no consensus that IVF is indicated after EP. The patient’s age is probably the determining factor: fertility treatment should not be delayed to an age where the results would be altered, especially with the risk of a recurrent EP.

Key words: assisted reproduction technology/ectopic pregnancy/fertility/laparoscopy/medical treatment

Introduction

Ectopic pregnancy (EP) is a key event in reproduction. A first EP leads the couple into the universe of tubal factor infertility. Occurring during infertility treatment, it marks a reproductive failure, which must always be surmounted psychologically before further treatment. Regardless of the treatment strategy, a successful outcome requires a subsequent ongoing intrauterine pregnancy, the ultimate goal of fertility treatment. Nonetheless EP resulting from fertility treatment is a specific entity, and better knowledge of it should help to improve diagnosis and prognosis, simplify treatment, and optimize subsequent fertility.

Methods of the review

To evaluate the current literature regarding the assessment of ectopic pregnancy after infertility treatment, a literature search was carried out with Medline and manual search of bibliographies of selected publications. The period for the search was from 1985 to 2004. Key words used included: ‘ectopic pregnancy’, ‘epidemiology’, ‘incidence’, ‘risk factor’, ‘transvaginal sonography’, ‘ART’, ‘IVF’, ‘diagnosis’, ‘methotrexate’, ‘laparoscopy’ and ‘conservative treatment’.

We will use here the classification of the strength of evidence developed by the Canadian task force on the periodic health examination (Table I) to describe the strength of the studies performed and therefore the weight they deserve in scientific reasoning (SE = strength of evidence).

Epidemiology

The epidemiology of EP must distinguish those occurring in women not using contraceptives (reproductive failure) from those in women using contraceptives (contraceptive failure). Only the former interest us here, and unless otherwise specified, EP in this review refers to these alone. Except perhaps in the management and immediate efficacy of treatment, these two types of EP differ in almost every respect: incidence (Coste et al., 2000a), site (Bouyer et al., 2002), risk factors (Chow et al., 1987; Bouyer et al., 2000), and subsequent fertility (Mükinen et al., 1989; Pouly et al., 1991a,b,c; Bernoux et al., 2000).
Table I. The strength of the scientific evidence (SE) is classified according to the Canadian Task Force on the periodic health examination:

<table>
<thead>
<tr>
<th>SE</th>
<th>Evidence obtained from...</th>
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<tr>
<td>SE1</td>
<td>Evidence obtained from at least an appropriately conducted randomized clinical trial</td>
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<tr>
<td>SE2</td>
<td>Evidence obtained from a well-conducted but not randomized clinical trials</td>
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<tr>
<td>SE3</td>
<td>Evidence obtained from well-conducted cohort or case–control studies, preferably in more than one centre or by more than one research group</td>
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<tr>
<td>SE4</td>
<td>Evidence from chronological series with or without an intervention</td>
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<tr>
<td>SE5</td>
<td>Evidence based on the opinions of recognized experts, based on clinical experience, descriptive study or expert advisory committee reports</td>
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Previous infertility and assisted reproductive technologies

Women with a history of infertility (defined as failure to conceive after, depending on the author, 1 or 2 years of unprotected intercourse) have a higher risk of EP than other women. Interpretation of this result presents two types of problems. First, it is difficult to separate the effects of fertility treatment, especially ovulation induction, from those of infertility itself (Yang et al, 1987). Second, the associations between infertility and EP are complex, for EP is simultaneously a cause (Ory et al., 1993; Joh-Spira et al., 1996a; Bernoux et al., 2000) and a consequence of infertility. We can therefore presume that there are factors common to infertility and to EP risk and that identifying them would help us to understand the aetiology of each.

Increased risk of EP has been repeatedly noted among women whose pregnancies result from ovulation induction, especially with clomiphene citrate. In the USA in 1999, EP accounted for 2.2% of the clinical pregnancies from all IVF, regardless of the assisted reproduction technology technique, and 1.9% of those from ICSI (Anonymous, 2002); that year in France the rates were 3.4% for IVF and 1.9% for ICSI.

Table II summarizes the principal risk factors for the EP that are reproductive rather than contraceptive failures. The odds ratios indicated are orders of magnitude, based on results from the various studies cited above. They were calculated relative to a reference group of pregnant women with successful outcomes. The results may be slightly different when the control group comprises non-pregnant women (Ankum et al., 1996).

Knowledge of these risk factors made possible the design of an EP risk scale (Coste et al., 1997, 1998). It gives the absolute risk (that is, the probability) of EP for a pregnant woman without contraceptives coming in for a consultation; Figure 1 shows how the risk is calculated.

In addition to the odds ratios, which measure the role of each risk factor at the individual level, it is useful to calculate the attributable risk for each factor, that is, to quantify its statistical weight at the population level. For example, an attributable risk of 20% means that one-fifth of the cases of a given disease are due to that factor. Interpretation must nonetheless remain cautious because the preceding sentence is accurate only if the factor has a causal role in the onset of the disease, and that is rarely certain. Moreover, attributable risks may not be added together, because one case of a disease (EP here) may be due simultaneously to several factors. Table II reports the attributable risk values for the risk factors of EP. Because they come from only one survey (Bouyer et al., 2003), confirmation is necessary. Beyond the very similar weights of infectious factors and smoking, noted below, they indicate that roughly a quarter of EP have no known cause. This has provoked research into other risk factors. Some, such as chromosomal anomalies, have finally been abandoned (Goddijn et al., 1996a). Other factors, including hormone factors, are currently under study (Fernandez et al., 1996a).

The two principal risk factors for EP as reproductive rather than contraceptive failure are a history of genital infection or tubal surgery and smoking. Quantitatively, their role in the risk of EP is similar: each explains approximately one-third of EP. They have a causal role in EP risk (SE 3, practically SE 1). The other risk factors are the woman’s age and her history of spontaneous or elective abortion, or intrauterine device (IUD) contraception, or infertility (SE 3, except elective abortions, SE 4). These risk factors together explained 76% of EP (SE 3, but only one study).

Diagnosis

The epidemiological data allow us to determine the population at risk of EP and therefore to diagnose it earlier, even in patients with minimal symptoms.

Ultrasound

Abdominal (pelvic) ultrasound is an essential element in EP diagnostic algorithms. Its diagnostic sensitivity is nonetheless low because the examination is operator dependent and because clinical presentation is so variable, with asymptomatic and little-known forms.
Recognizing the signs of EP requires analysing the decidua and adnexa and identifying the corpus luteum and often, in the context of infertility treatment, several corpora lutea. Identification of a haematosalpinx is pathognomic of EP (80% of cases). Infertility and its treatment modify the relevant data about the site and clinical forms of EP. Thus, while heterotopic pregnancy is very rare in cases of spontaneous fertilization, the combination of EP + intrauterine pregnancy in IVF pregnancies ranges from 1 to 3% in different studies (Goldman et al., 1992; Li et al., 1992). Accordingly, systematic and attentive examination of the adnexa with transvaginal ultrasound is required, even if the development of one or more conceptus is seen in the uterine cavity.

Depending on the number of embryos transferred, a wide variety of possible forms of ectopic and heterotopic pregnancies have been described: bilateral tubal ectopic (Abusheikha et al., 2000), interstitial (Atri et al., 1996) or ovarian heterotopic (Bonatz et al., 1994), and bilateral interstitial sextuplet ectopic after bilateral salpingectomy (Adoni et al., 1986). A consensus therefore recommends early (6–8 weeks) and systematic ultrasound examinations by specialists (Johnson et al., 1998; Strandell et al., 1999; Vourtsi et al., 1999). Systematic examination is needed because pelvic pain is common in assisted reproduction technology, and specialists are required because visualization of the ectopic conceptus is more difficult, and the normal ultrasound indices disappear:

- stimulated ovaries are much larger, hurt as the probe passes, and can mask the ectopic implantation (Atri et al., 2001),
- peritoneal effusion is frequent and sometimes abundant, especially in the case of hyperstimulation, but is generally anechoic,
- the adnexa are commonly pathologic in assisted reproduction technology (hydrosalpinx, endometriosis etc.), and it is more difficult to identify a haematosalpinx or ectopic sac in this pelvic context.

The rapidity and the sensitivity of the diagnosis of EP are improved by using transvaginal sonography and two-thirds of EP can be identified prior to rupture (SE 4). In the context of IVF, the diagnosis of EP can be excluded by the presence of an embryo or yolk sac in an intrauterine gestational sac (SE4), but a careful observation of adnexas is necessary since 1–3% of these pregnancies are heterotopic.

**hCG**

Interpretation of hCG levels is very different for pregnancies after assisted reproduction technology than for spontaneous pregnancies. Knowledge of the date of fertilization is more precise, but the risk of multiple pregnancy is higher. Moreover, the assisted reproduction technologies themselves or the cause of the sterility or both may affect the course of the hCG concentration.

Most studies of hCG have been conducted among IVF patients. A single plasma hCG assay, even very early, 11–12 days after embryo transfer, can accurately differentiate viable and non-viable pregnancies. Nonetheless, the threshold values vary between studies, depending especially on the exact day of the assay in relation to the date of embryo transfer or ovulation (Heiner et al., 1992; Schmidt et al., 1994; Fristrom et al., 1995; Qasim et al., 1996; Bjercke et al., 1999; Poikkeus et al., 2002).

To improve the assay’s diagnostic value, Chen et al. (1997) have proposed doing two assays, 15 (D15) and 22 (D22) days after embryo transfer. Their study was conducted over 198 treatment cycles. They found that a single plasma hCG assay ≥150 mUI/ml on D15 indicates a normally developing pregnancy with a positive predictive value (PPV) of 89% but a negative predictive value (NPV) of only 51%. When this assay is <150 mUI/ml on D15 but the ratio of hCG on D22 to hCG on D15 (hCGD22:hCGD15 ratio) ≥15, the PPV, that is, the likelihood of a normally developing pregnancy, remained 90%. If hCG on D15 is <150 mUI/ml and the hCGD22:hCGD15 ratio
In the literature, serum progesterone measurements for assessing viability are more often considered together with the evaluation of other biomarkers such as plasma hCG and/or serum estradiol. In a prospective series of 220 patients pregnant after IVF, Yamashita et al. (1989) assessed plasma hCG, estradiol, and progesterone levels 2, 3, and 4 weeks after oocyte retrieval. Each patient received a score based on the level of each hormone assayed: 0 when all three hormones were below the 25th percentile compared with the mean concentration for ongoing pregnancies; 1 or 2 points when one or two hormones were above the 25th percentile; and 3 points when all three were above this threshold value. At 2 weeks after oocyte retrieval, a score of 0 or 1 predicted EP with a sensitivity of 100%, a specificity of 71.8%, a PPV of 17.9%, and a NPV of 100%. Plasma progesterone and estradiol assays after IVF were examined in two other reports, one a prospective study of 282 pregnancies (Bustillo et al., 1993) and the other a retrospective comparison of 135 EP matched with 135 deliveries (Marcus et al., 1995). Both studies observed that these hormones had lower values in EP but were unable to define the discriminant threshold, because of the wide variations observed. The time between the assay and the embryo transfer may be a key factor. Shulman et al. (1994) measured plasma estradiol and progesterone at three different points after embryo transfer (D3, D8, and D10) in 86 post-IVF pregnancies, including 13 EP, and found them to be significantly lower in the EP group only on D10. The authors propose an explanation related to the delay in implantation in EP, due in turn to a delay in trophoblastic activity. On D3 and D8, granulosa cell activity is supported by exogenous hCG (while support for the luteal phase comes from an i.m. injection of 5000 IU of hCG on D3 after oocyte retrieval), which masks the lack of vitality of a pregnancy. On D10 after embryo transfer, however, when the external luteal support is exhausted, trophoblastic expression is visible but is less good in the case of delayed implantation.

Accordingly, in spontaneous conceptions, the serum progesterone assay is discriminant in the diagnosis of viability in very early pregnancy, with a sensitivity of 95% and a specificity of 40% at a threshold value of 20 ng/ml (Mol et al., 1998). It is not effective used alone for a differential diagnosis of ectopic pregnancy or miscarriage (SE 3). Although serum progesterone levels tend to be lower in EP after assisted reproduction technology, the wide variations make it difficult to define any threshold value. The time of the assay relative to the embryo transfer seems to be a major factor in pinpointing the window between exclusively ovarian steroidogenesis and the onset of its synthesis by the trophoblast.

Molecular biology in EP diagnosis

Some teams have looked to molecular biology for ideas to improve EP diagnosis (Abusheikha et al., 2000). It appears to be possible to use some protein profiles from a maternal blood sample to differentiate an intrauterine from an ectopic pregnancy. This method, if confirmed, would revolutionize EP diagnosis and management, by making them earlier, avoiding unnecessary laparoscopy, and allowing medical treatment of asymptomatic EP at the very beginning of the pregnancy.
Diagnostic strategies

To analyse a diagnostic strategy, we must first identify its objectives, for our conclusions may vary according to whether it seeks to diagnose EP or reduce the incidence of tubal rupture. The probability of EP differs according to whether the patient has symptoms and according to her clinical history (previous EP, sterility treatment, etc.). We will differentiate two principal frameworks: screening for EP in patients at risk and diagnosing EP in cases of clinical suspicion.

Screening for EP in at-risk patients

The benefits of screening depend on the prevalence of EP in the population studied. A Finnish study of 225 asymptomatic patients analysed the combination of transvaginal ultrasound and hCG for diagnosing EP in a population with an EP prevalence of 24%. The sensitivity of the diagnostic combination was 84% with a false-positive rate of 1.2% (Cacciatore et al., 1994). A prospective study of 143 patients at risk of EP with no symptoms analysed the diagnostic pertinence of a transvaginal ultrasound, followed if necessary by a βhCG assay (Mol et al., 1997). After the pregnancy was diagnosed with a urine test, transvaginal ultrasound attempted to locate the pregnancy site; failure was followed by a plasma βhCG assay. Above 1500 IU/l, EP was diagnosed and laparoscopy performed. Below this βhCG threshold, ultrasound and assay were repeated 2 days later. In this population, which had an EP prevalence of 5.6%, this strategy has a satisfactory discriminant capacity, with a sensitivity of 88% and a specificity of 100%.

Nonetheless, complete evaluation of such a screening programme must also take into account the potential benefits of earlier diagnosis (fewer complications and less aggressive treatment), as well as the costs (monetary and otherwise) related to the ensuing false-positives and their consequences: laparoscopy or medical treatment for patients without EP. To attempt to respond to these questions, Mol et al. (2002) constructed a mathematical model to compare the two diagnostic strategies:

- rapid consultation as soon as the patient thinks she is pregnant, because she has risk factors for EP and a history of infertility (screening).
- rapid consultation as soon as evocative clinical symptoms appear, such as pelvic pain and/or vaginal bleeding (expectant).

The screening arm analysed two diagnostic protocols. The first screening program, used ultrasound and, in case the result of ultrasound was uninformative, serum hCG measurement.

In the second program, single serum progesterone measurement was performed before ultrasound. Again, if the possibility of EP was < 1%, the diagnosis was rejected and no further testing was performed. If the probability of EP after serum progesterone measurement was ≥ 1% further testing with ultrasound, and if necessary, serum hCG or repeat diagnosis was also applied to the patients with symptoms for whom EP was clinically suspected.

With an EP prevalence of ~6%, screening resulted in a lower than expected rate of ruptured EP. This rate decreased from 2.1 to 0.61% in the strategy without a serum progesterone assay. Results were not better with the serum progesterone assay: the ruptured EP rate was 1.2%. But this reduction came at the price of a high false-positive rate, which increased costs. Overall, screening would thus cost €933 per avoided tubal rupture. These authors conclude that the only justification for such a screening is psychological, to reassure a patient who knows she is at risk by performing a pelvic ultrasound: it cannot produce an early EP diagnosis and will not show anything abnormal!

Overall, the efficacy of screening in an at-risk population is closely linked to the prevalence of EP in that population. Accordingly, in a population that has received infertility treatment, combining transvaginal ultrasound and hCG may reduce the number of patients with ruptured EP but at the price of substantial additional costs.

EP diagnosis in the case of clinical suspicion

As we saw above, numerous diagnostic tools are proposed for EP diagnosis, often to be repeated at variable intervals. No consensus exists for these diverse strategies. The results are very different to compare, because, as we pointed out above, the population prevalence influences the usefulness of the examinations.

Gracia and Barnhart (2001) mathematically modelled six algorithms often proposed for patients with positive pregnancy tests and EP symptoms but who are clinically stable:

- Strategy 1: Ultrasound, then quantitative hCG: if transvaginal ultrasound is not informative, quantitative hCG follows. Above the discriminant level of 1500 IU/l, endometrial curettage is performed. If it shows no chorionic villi, laparoscopy follows for suspected EP. If chorionic villi are observed, the patient is monitored. If the hCG level is < 1500 IU/l, it is monitored until it reaches this point, when ultrasound is performed; if uninformative, it leads to curettage, as above.
- Strategy 2: Quantitative hCG, then ultrasound: if the hCG level is > 1500 IU/l, transvaginal ultrasound is proposed. If it is inconclusive, curettage is performed and the absence of chorionic villi leads to laparoscopy for suspected EP. If the hCG level is < 1500 IU/l, the test is repeated and strategy 1 followed.
- Strategy 3: Serum progesterone, then ultrasound and quantitative hCG:
  - if serum progesterone > 25 ng/ml: normal antenatal surveillance
  - if serum progesterone < 5 ng/ml: curettage; if no chorionic villi observed, laparoscopy
  - between 5 and 25 ng/ml: ultrasound and quantitative hCG, according to strategy 1.
- Strategy 4: Serum progesterone, then quantitative hCG and ultrasound:
  - if serum progesterone > 25 ng/ml: normal antenatal surveillance
  - if serum progesterone < 5 ng/ml: curettage; if no chorionic villi observed, laparoscopy
  - between 5 and 25 ng/ml: quantitative hCG and ultrasound according to strategy 2.
- Strategy 5: Transvaginal ultrasound alone; if inconclusive, hospitalization for surveillance with retesting in 24 h.
- Strategy 6: Clinical surveillance alone.

In the population consulting in this emergency department, the prevalence of EP was 9.4%. The analysis calculated for each strategy the number of undiagnosed EP, the number of wrongly terminated intrauterine pregnancies, and mean time to diagnosis.
Strategies 1 and 2 have the best diagnostic relevance but require the most time to diagnosis. The contribution of serum progesterone measurements to the strategy (strategies 3 and 4) results in fewer wrongly terminated intrauterine pregnancies but misses 2.4% of the EP. Recourse to ultrasound alone also increased the rate of curettage of intrauterine pregnancies. Clinical surveillance alone needs no comment. A prospective study of 1994 patients from an emergency department confirmed the poor sensitivity of clinical examination for early diagnosis of unruptured EP (Stovall et al., 1990).

Gracia and Barnhart (2001) did not discuss the number of tubal ruptures avoided with each of these strategies. A prospective study found that that adding a serum progesterone assay to the quantitative hCG evaluation reduced the mean time to diagnosis to <24 h and significantly reduced the percentage of ruptured EP (Stovall et al., 1989). Another team confirmed this result in a prospective study of 122 patients: a strict algorithm that combines quantitative hCG (threshold value 1200 IU/l, according to the third international standard), transvaginal ultrasound, serum progesterone (threshold value 5 ng/ml) and curettage results in a time to diagnosis significantly shorter and a percentage of tubal rupture significantly lower than found with an individual approach according to history, clinical findings and hCG (Mertz and Yalcinkaya, 2001). Nonetheless, the cost-efficiency ratio of this approach must still be analysed.

Is a decision algorithm necessary?
Numerous EP decision algorithms have been described and compared (Gracia and Barnhart, 2001). The best-known are based on an hCG–ultrasound combination, sometimes in a surprising chronological order (hCG after ultrasound) but, depending on the organization of the initial consultation, often combining clinical data (Mol et al., 1999b) or other bio markers.

The aim of these algorithms is to homogenize the diagnostic strategy, to make it more effective (more sensitive and more specific) and less operator dependent. The principal algorithms correctly govern the initial situation of suspected EP: confirmation of pregnancy, assessment of hCG assays, absence of identifiable intrauterine pregnancy despite hCG level above a given threshold level. In the next stage of the algorithm, ultrasound is the key: it provides information judged essential but which is in practice fairly gross (positive EP diagnosis versus no adnexal abnormalities), leading either to treatment or to an aggressive diagnostic strategy (dilation and curettage, diagnostic laparoscopy, etc.). The second stage of this algorithm appears to us outdated and inappropriate, especially for women undergoing infertility treatment, because its dichotomous character misunderstands the complexity of the imagery and the multiple variables that, in our experience, lead to reliable diagnosis of EP, sometimes immediate but very often somewhat slower, i.e. more unexpectedly. It leads to a needlessly early and aggressive, often harmful, diagnostic strategy, which no longer corresponds to our practice: to diagnostic laparoscopy that shows nothing and to dilatation and curettage, which has low sensitivity and sometimes terminates intrauterine pregnancies. Because the mean sensitivity of a finding of intrauterine chorionic villi with dilatation and curettage is 70% (Hock et al., 1997; Lipscomb et al., 1998), its absence does not justify an EP diagnosis, even though it is included in the so-called ‘reference’ algorithms. The ultrasound stage of EP diagnosis deserves a multiparametric description incompatible with the algorithm concept.

Treatment
Earlier diagnosis of EP enables the successive development of laparoscopic and then medical treatment. Numerous prospective randomized studies have compared these two methods and concluded that medical treatment is a valid alternative to conservative surgical treatment and sometimes even the treatment of choice in the populations included in these trials, regardless of the history of infertility (Fernandez et al., 1995, 1996b; Hajeniuss et al., 1997; Nieuwkerk et al., 1998a,b; Saraj et al., 1998; Dias Pereira et al., 1999; Molet et al., 1999; Sowter et al., 2001a,b). Nonetheless the success rates reported in the literature vary from 65 to 95% for medical treatment and from 72 to 95% for conservative surgical treatment (Fernandez et al., 1995, 1996b; Maymon and Shulman, 1996; Hajeniuss et al., 1997; Fernandez et al., 1998; Nieuwkerk et al., 1998a,b; Saraj et al., 1998; Dias Pereira et al., 1999; Mol et al., 1999; Sowter et al., 2001a,b). This great variation is explained principally by the heterogeneity of the patient inclusion criteria and of the definition of treatment failure. A method with a success rate of <80% is difficult to apply in practice. It is therefore essential to know to which patients we can offer medical treatment with a sufficiently low risk of failure, that is, avoid surgery and a long, tedious follow-up including several ultrasounds and numerous consultations.

According to the French National College of Gynaecologists and Obstetricians (Obstetricians CNGOF, 2003), medical treatment is recommended with patient consent if all the following criteria appear: hCG level <1000 IU/l, non-symptomatic EP, non-visualized EP by transvaginal ultrasonography (SE5). Medical treatment is stay indicated if hCG level is <5000 IU/l (<10 000 for other) and if the adnexal mass is <4 cm (SE5). The following factors do not instigate the surgical choice: contra-indication to general anaesthesia, multi-operated, previous pelvic surgery, morbid obesity (SE5). Surgical therapy is recommended in the following cases: unstable homodynamic, hCG level >10 000, adnexal mass >4 cm, contra-indication to medical therapy, impossible outpatient follow-up (SE5).

Eleven randomized trials (Fernandez et al., 1995, 1996b, 1998; Hajeniuss et al., 1997; Nieuwkerk et al., 1998a,b; Saraj et al., 1998; Dias Pereira et al., 1999; Mol et al., 1999; Sowter et al., 2001a,b) and one meta-analysis (Hajeniuss et al., 2002) have compared purely medical treatment with methotrexate to surgical treatment. The surgical treatment in all these trials was conservative treatment by laparoscopy.

Several protocols of medical treatment were compared with surgical treatment:

- ’Multiple-dose’ protocol (Hajeniuss et al., 1997; Nieuwkerk et al., 1998a,b; Dias Pereira et al., 1999; Mol et al., 1999a) = four i.m. injections of methotrexate at 1 mg/kg (on D0, D2, D4, D6) alternated with four doses of 0.1 mg/kg of folic acid, orally (on D1, D3, D5, D7), as Tanaka (1982) initially proposed.
- ’Single-dose’ protocol = one i.m. injection of 1 mg/kg (Fernandez et al., 1998; Saraj et al., 1998; Hajeniuss et al., 2002) or 50 mg/m² (Sowter et al., 2001a, 2001b) of methotrexate.
Diagnosis and treatment of ectopic pregnancy

Should the laparoscopic treatment be conservative or radical?

This question is essential for the patients who wish to preserve their fertility after their EP. Reviewing the literature on fertility after laparoscopic treatment of EP, we draw the following conclusions:

- Contrary to conventional wisdom, the chances of a subsequent intrauterine pregnancy are similar for all EP patients, regardless of whether their treatment was conservative or radical.

- The risk of recurrence, although significantly lower when laparoscopic treatment is radical, remains high—on average 10%—after salpingectomy. That is, salpingectomy does not eliminate the risk of EP recurrence. This observation has been confirmed by the results of two recent studies that report EP recurrence rates of 11% (Fernandez et al., 1998) and 15% (Dubuisson et al., 1996) after laparoscopic salpingectomy.

After conservative laparoscopic treatment, the characteristics of the EP (size, extent of haemoperitoneum, site) do not have a statistically significant effect on future fertility (Pouly et al., 1991). These observations have important clinical implications:

- Size must not be considered as a limiting factor for conservative laparoscopic treatment. Although this treatment initially was recommended for patients with EP small in size, conservative treatment of an EP > 3 cm in diameter is perfectly possible without affecting fertility (Pouly et al., 1991).

- The success rate was 85.3%.

- The salpingectomy rate is another important aspect of failure. This rate is less than 10% for each method. In the trials reporting this result, it varies from 0 to 9.6% after medical treatment (Hajenius et al., 1997; Fernandez et al., 1998; Saraj et al., 1998) and from 0 to 8% after laparoscopic treatment (Hajenius et al., 1997a; Fernandez et al., 1998; Saraj et al., 1998; Mol et al., 1999a). No detailed data are available on this point.

- The meta-analysis (Hajenius et al., 2002) reviewed the results from the ‘multiple dose’ protocol (four injections i.m.), without pooling them. It found no significant difference in efficacy between medical and surgical treatment. However, this meta-analysis was possible only for the four trials of the single dose protocol (one injection i.m.); it concluded that this treatment protocol was less effective [RR = 0.83 (0.71–0.97)] than surgery but noted that the additional injections were effective.

Accordingly in selected cases medical treatment by multidose methotrexate appears to be an effective alternative to surgical treatment. Side-effects after a single dose of methotrexate are less important than the protocol of multidoses (SE2) (Barnhart et al., 2003), and, to decrease these side-effects more frequently occurring in the protocol multidose, we could reduce the number of supplementary injections in the case of an insufficient decline of hCG level (Korhonen et al., 1994).

A large randomized multicentre study (Rozenberg et al., 2003) examined the addition of mifepristone to methotrexate: it randomized 212 patients, 113 in the methotrexate + mifepristone group and 99 in the placebo group. Success did not differ significantly between the two groups [79.6% (90/113) versus 74.2% (72/99)]. Only the initial hCG level was predictive of success. When the progesterone level was > 10 nmol/l, the efficacy of the methotrexate + mifepristone treatment was significantly better than that of methotrexate + placebo (15/18 versus 5/13). These results should be confirmed, in view of the small study size. Mifepristone might therefore be reserved for so-called ‘active’ EP, with high progesterone levels.

- The methodological heterogeneity of these trials must be stressed. First, the methods of diagnosis vary. Some presume ultrasound visualization of the EP (Fernandez et al., 1995, 1996, 1998); others are based on a decision algorithm in which ultrasound visualization of the EP is not mandatory (Sowter et al., 1998; Sowter et al., 2001a,b), with curettage sometimes to look for chorionic villi (Saraj et al., 1998a); and still others assume laparoscopic confirmation (Hajenius et al., 1997; Nieuwkerk et al., 1998a,b; Dias Pereira et al., 1999; Mol et al., 1999a,b). The populations also vary, with, for example, mean pretreatment hCG levels ranging from 775 (Sowter et al., 2001a,b) to 4900 mUI/ml (Fernandez et al., 1995). Finally the criteria defining failure and success of the treatment vary between studies (Table I):

- failure = recourse to any second treatment, medical or surgical (this includes reinjections in the methotrexate group failures) (Fernandez et al., 1995, 1996b, 1998; Hajenius et al., 1997; Sowter et al., 2001)

- failure = recourse to the other study treatment, that is, surgery in the case of methotrexate treatment and methotrexate in the case of surgery (this does not include reinjections in the failures of the methotrexate group) (Saraj et al., 1998).

Only one of these randomized trials—that of Sowter et al. (2001b)—found any significant difference between the efficacy of medical and of surgical treatment. Nonetheless, the interpretation of each trial’s results must take into account the definition of failure used. In several of the trials (Fernandez et al., 1995, 1996b) which defined failure as recourse to any second treatment, the second treatment turned out to be the other treatment option: laparoscopy for the methotrexate group and methotrexate for the laparoscopy group. These results are thus comparable to those of Saraj et al. (1998), who defined failure as recourse to the other treatment option.

Yet another interpretation is thus needed to explain the only trial (Sowter et al., 2001b) that found a significant difference between methotrexate and surgery. In that study, the success rate of the methotrexate treatment (1 dose i.m. of 50 mg/m²) was 65% and that of surgery 93%. Including salpingectomy in the surgical group yielded by definition a 99% success rate. Including the patients treated successfully by a second injection of methotrexate brings the success rate of the medical method in this trial to 79.4%. If we include the patients cured without recourse to surgery, regardless of the number of methotrexate injections (maximum of four in this trial), the success rate was 85.3%.

- ‘In situ’ protocol (Fernandez et al., 1995, 1996, 1998) = one injection in situ (or i.m. if impossible) of 1 mg/kg of methotrexate.

The risk of recurrence, although significantly lower when laparoscopic treatment is radical, remains high—on average 10%—after salpingectomy. That is, salpingectomy does not eliminate the risk of EP recurrence. This observation has been confirmed by the results of two recent studies that report EP recurrence rates of 11% (Fernandez et al., 1998) and 15% (Dubuisson et al., 1996) after laparoscopic salpingectomy.

After conservative laparoscopic treatment, the characteristics of the EP (size, extent of haemoperitoneum, site) do not have a statistically significant effect on future fertility (Pouly et al., 1991). These observations have important clinical implications:

- Size must not be considered as a limiting factor for conservative laparoscopic treatment. Although this treatment initially was recommended for patients with EP small in size, conservative treatment of an EP > 3 cm in diameter is perfectly possible without affecting fertility (Pouly et al., 1991).
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- Conservative laparoscopic treatment can be offered regardless of the tubal site of the EP, including isthmic sites (Chapron et al., 1992b).
- Tubal rupture should no longer be considered as a strict indication for salpingectomy. If the tubal damage is not too great and the rupture is linear and limited, the rupture site can be used to evacuate the trophoblast and save the tube (Pouly et al., 1991; Dubuisson et al., 1996; Job-Spira et al., 1999).

Prognosis for fertility is significantly correlated with the patient’s history and age, regardless of the type of surgical treatment. Indirect proof of the major prognostic role of tubal history comes from findings of excellent fertility in patients with an EP during IUD use (Pouly et al., 1991).

The patient’s tubal history affects fertility in several ways (Pouly et al., 1991):
- it significantly reduces crude fertility, reducing the likelihood of an intrauterine pregnancy and increasing the risk of recurrence
- it significantly reduces the cumulative intrauterine pregnancy rate
- it delays the onset of intrauterine pregnancies
- a woman’s fertility worsens as she experiences more tubal events
- it promotes ipsilateral recurrence (Chapron et al., 1992a).

Nonetheless, neither history nor intraoperative observation of tubal injuries should modify treatment strategy unless the EP occurs in a known hydrosalpinx after IVF; in this case, salpingectomy is standard practice and the medical strategy is probably undesirable. As Strandell et al. (2001) show, IVF results are best in patients who have had a laparoscopic salpingectomy before IVF in the case of a hydrosalpinx visible on ultrasound. Practising a salpingectomy for the index EP should therefore improve subsequent IVF results.

These findings about surgical treatment of ectopic pregnancy point to the following conclusions:
- The reference surgical treatment, except for rare contraindications, is conservative laparoscopic treatment. Physicians must therefore receive adequate training in laparoscopic techniques. Indeed, laparoscopic skill of the surgeon is important considering the indication of conservative surgery on ruptured or large EP (SE 5).
- Careful cleaning of the abdomen and pelvis is an integral part of laparoscopic treatment, to prevent the risk of postoperative adhesions and trophoblastic implants (SE 5).
- Strict monitoring of hCG decline until it is totally undetectable is essential after conservative laparoscopic treatment (the benefit of an injection of methotrexate associated is not proven) (SE 3).
- The patient’s history is the essential prognostic factor for future fertility.

**Treatment of particular forms of EP**

The context of infertility does not modify the treatment of heterotopic pregnancy except insofar as laparoscopic treatment is practically systematic and salpingectomies are performed most often because persistent intratubal trophoblast implants cannot be diagnosed after conservative treatment while an intrauterine pregnancy is developing. Nonetheless, in heterotopic pregnancies that include an interstitial pregnancy, the intrauterine pregnancy is best protected by ultrasound or laparoscopy-controlled puncture with aspiration and then injection of either potassium chloride or methotrexate (Fernandez et al., 1993).

**Decision in assisted reproduction technology management after an index EP**

Assisted reproduction technology management should be guided not by the EP history but by everything that accompanied it. The decision will be arbitrary in any case because there are no studies of assisted reproduction technology indications after EP that complicated infertility treatment. One of the questions is whether assisted reproduction technology might help to prevent or lessen EP recurrences. Pouly et al. (1991) established a treatment score (Table III and Figure 2), which may still be helpful in reaching a decision about type of surgical treatment. This therapeutic management must be guided by comparing the risks of EP recurrence with the probability of a spontaneous intrauterine pregnancy. In view of the reports about the results of medical treatment compared with conservative surgical treatment, we can extrapolate this therapeutic approach.

Age and history of infertility and of tubal disease have been found to be risk factors for the absence of an ongoing

<table>
<thead>
<tr>
<th>Data</th>
<th>Score</th>
<th>Statistical weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past EP</td>
<td>2</td>
<td>0.434</td>
</tr>
<tr>
<td>For each additional EP</td>
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<td>0.261</td>
</tr>
<tr>
<td>Laparoscopy for adhesions</td>
<td>1</td>
<td>0.258</td>
</tr>
<tr>
<td>History of tubal surgery</td>
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<td>0.351</td>
</tr>
<tr>
<td>Single tube</td>
<td>2</td>
<td>0.472</td>
</tr>
<tr>
<td>Salpingitis history</td>
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<td>0.242</td>
</tr>
<tr>
<td>Ipsilateral adhesions</td>
<td>1</td>
<td>0.207</td>
</tr>
<tr>
<td>Bilateral adhesions</td>
<td>1</td>
<td>0.198</td>
</tr>
</tbody>
</table>

Score 0–3: treatment by conservative laparoscopy; score 4: salpingectomy by laparoscopy; score ≥5: contralateral salpingectomy and sterilization. EP = ectopic pregnancy.

**Figure 2.** Probability of IUP and risk of EP according to the score. (calculated and observed data). Regression lines for the IUP: $y = -12.917x + 83.433$ ($R^2 = 0.931$). Regression lines for the EP: $y = 3.367x + 8.992$ ($R^2 = 0.687$). (Pouly et al., 1991)
intrauterine pregnancy after an EP. These findings come from Ego et al. (2001), who examined the Lille metropolitan area EP registry and identified 345 patients who wanted another pregnancy (SE2). Because fertility diminishes with age and exponentially after the age of 38 years, it is preferable not to lose time or take the risk that pregnancy will not occur or that an EP will recur. EP may express the cause of infertility, and the patient may then be considered to present tubal factor sterility in the first place. There is nonetheless no prospective or exhaustive study of subsequent fertility that considers the treatment used for the index EP. It would thus be necessary to show in an equivalent population that assisted reproduction technology would lead more rapidly and with a lower risk of EP recurrence to intrauterine pregnancy, even though the ongoing pregnancy rates for IVF are highly variable, ranging from 20 to 40%.

Numerous prospective studies must still be conducted to assess the best treatment to offer a woman to preserve her fertility and reduce her risks for recurrent EP. Assisted reproduction technology management in this situation is currently simply a question of habit. Fertility after EP cannot be considered without taking into account the risk of recurrence, which must be considered as part of assisted reproduction technology management.

Conclusion

Epidemiological results enable us to define the expected risk of EP after infertility treatment and have helped us to develop early diagnostic strategies to improve the selection of patients for initial medical or surgical treatment. The efficacy of multidose medical treatment is now recognized when proposed early for inactive EP, and it may make it possible to attenuate the aggressiveness of the treatment and improve its psychological management. In the future, the development of proteomics may make it possible to analyse the hCG spectrum to learn earlier whether the pregnancy will be intrauterine or ectopic; in this case, medical treatment will certainly be still more effective.

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References


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