Extra-uterine pregnancy following assisted conception treatment

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Ectopic pregnancy may be the only life-threatening disease in which prevalence has increased as mortality has declined. The most prominent theory to explain this phenomenon involves increased sensitivity of serum β-human chorionic gonadotrophin (HCG) immunoassay and improved quality of transvaginal ultrasound, combined with a heightened awareness and increased suspicion of the condition among clinicians which has allowed early detection of ectopic pregnancy. Laparotomy, once the standard treatment of ectopic pregnancy, has been replaced almost entirely by operative laparoscopy. This is associated with a shorter hospital stay, fewer post-operative analgesic requirements, reduced costs and lower risk of adhesion formation. Laparotomy, however, remains necessary in cases with haemodynamic instability and with exceptional locations, e.g. cervical, abdominal and interstitial implantation. In selected cases, non-surgical management has also obtained high success rates. Among medical therapies, the most common is systemic or local administration of methotrexate. The other option is expectant management involving follow-up using serial serum HCG measurements and ultrasound scans. Thus, life-threatening ectopic pregnancy is now evolving into a medical disease, with the possibility of lower-cost treatment, faster recovery and higher subsequent fertility. In this review we assess the risk of extra-uterine implantation after assisted conception treatment, the accuracy of various diagnostic tools and focus on the efficacy, safety and the fertility outcomes of surgical and non-surgical management of ectopic pregnancy.

Key words: assisted conception/diagnosis/ectopic/management

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Introduction

Ectopic pregnancy refers to the implantation of the blastocyst in any tissue outside the uterine cavity. The majority of ectopic pregnancies implant in the ampullary region of the Fallopian tube, followed by the isthmus, the fimbriae, and the cornual portion; these constitute >95% of all ectopic pregnancies.

Abulcasis (AD 936) was the first to report an ectopic pregnancy, while Duverney in 1708 was the first to describe an heterotopic pregnancy, the combination of intrauterine and extrauterine pregnancy. There is no doubt that the diagnosis and management of ectopic pregnancies underwent another revolution a century later, when Lawson Tait successfully performed a laparotomy to ligate the broad ligament and remove a ruptured Fallopian tube in 1883 (Tait, 1884; Mascarerhas et al., 1997). The first pregnancy reported after in-vitro fertilization (IVF) and embryo transfer was in fact ectopic (Steptoe and Edwards, 1976), and ever since there have been numerous reports of both ectopic and heterotopic pregnancies occurring after IVF. Improved technology has
resulted in an increased likelihood of ectopic pregnancy being unruptured at the time of diagnosis, thus making less-invasive treatment options possible (Ling and Stovall, 1994).

Although the maternal mortality from ectopic pregnancies declined five-fold in the UK between 1975 and 1993 (Department of Health, 1996), ectopic pregnancy is still the leading cause of maternal deaths in the first trimester, accounting for 12 out of the 134 direct maternal deaths (8.9%) in the last triennial report (Department of Health, 1998). In contrast, there were only eight deaths directly attributed to ectopic pregnancy out of the 323 maternal deaths reported in the previous triennium (2.4%). This last report re-emphasized the importance of early diagnosis and the need for increased awareness of the possibility of an extra-uterine pregnancy in any woman of reproductive age.

Incidence

The true incidence of ectopic pregnancy is difficult to determine, but is in the range 0.25–1.0% of all pregnancies (Stabile and Grudzinskas, 1994). In addition, ectopic pregnancies are reported to complicate 2–11% of all pregnancies (Stabile and Grudzinskas, 1994). In addition, ectopic pregnancy, but is in the range 0.25–1.0% of all pregnancies is reported thus far (Tucker, 1996).

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Data on risk factors associated with ectopic pregnancies after IVF/embryo transfer are conflicting. Yovich et al. (1985) reported a higher incidence of ectopic pregnancy when the embryos were replaced higher than mid-cavity. Martinez and Trounson (1986) could not identify any risk factor, while Cohen et al. (1986) identified two factors: the therapeutic use of clomiphene citrate (CC) and the number of patent Fallopian tubes at the time of embryo transfer. Other authors (Dubuisson et al., 1991; Karande et al., 1991) demonstrated that a previous history of an ectopic pregnancy and/or pre-existing tubal pathology was associated with a subsequent increased risk of an ectopic implantation. Verhulst et al. (1993) identified tubal damage and the use of CC combined with human menopausal gonadotrophins (HMG) as risk factors. Marcus and Brinsden (1995) found that a history of PID was the main risk factor, with no statistical evidence of an association between ectopic pregnancy and a past history of abortion, termination of pregnancy, stillbirth, neonatal death, or tubal surgery. They also found no association between the type of ovarian stimulation protocol or the oestradiol, luteinizing hormone (LH) and progesterone concentrations at the time of ovulation induction and ectopic pregnancies. The role of CC in the incidence of ectopic pregnancies is controversial. With some authors suggesting an increased rate of ectopic (Marchbanks et al., 1985) and heterotopic (Bello et al., 1990) conceptions subsequent to CC, while others (Dickey and Holtkamp, 1996) found no association between the type of ovarian stimulation protocol or the oestradiol, luteinizing hormone (LH) and progesterone concentrations at the time of ovulation induction and ectopic pregnancies. The role of CC in the incidence of ectopic pregnancies is controversial. With some authors suggesting an increased rate of ectopic (Marchbanks et al., 1985) and heterotopic (Bello et al., 1990) conceptions subsequent to CC, while others (Dickey and Holtkamp, 1996) found no associated risk between CC and ectopic pregnancy.

An ectopic rate of 4.0% of all pregnancies or 1.5% of transfers has been quoted by the Society for Assisted Reproductive Technology and the American Society for Reproductive Medicine in their analysis of 1472 clinical pregnancies subsequent to 4202 gamete intra-Fallopian transfer (GIFT) retrieval cycles initiated in the USA in 1993 (Society for Assisted Reproductive Technology/American Society for Reproductive Medicine, 1995). A similar rate of ectopic pregnancies following GIFT has been reported in the subsequent report (Society for Assisted Reproductive Technology/American Society for Reproductive Medicine, 1998) and this is comparable with that reported previously (Formigli et al., 1990).

Risk factors

Risk factors are present in 25–50% of patients with an ectopic pregnancy (Ling and Stovall, 1994). They include a history of pelvic inflammatory disease (PID), tubal surgery, previous ectopic pregnancies, a progesterone intrauterine device and exposure to diethylstilboestrol in utero (Ling and Stovall, 1994; Speroff et al., 1994; Ankum et al., 1996). The most convincing evidence that PID is the major cause of ectopic pregnancies comes from reports documenting a seven-fold increase in the ectopic pregnancies rate in women with laparoscopically-proven salpingitis (Westrom, 1975; Westrom et al., 1981).

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Aetiology of ectopic pregnancy

The aetiology of ectopic pregnancy subsequent to assisted conception treatment is multi-factorial, with destruction of the anatomy of the tube as the main factor. It has been proposed that a damaged tube may be unable to propel an embryo that has migrated into the tube back into the uterine cavity, whereas a normal functioning tube may be able to do so (Berman et al., 1986). Reverse migration of the embryos may also be associated with a high concentration of oestriadiol or an altered oestrogen/progesterone ratio (James, 1996). Other factors include the ovarian stimulation protocol (Benger and Taymor, 1972) and the number of embryos transferred (Dicken et al., 1989). The technique of embryo transfer may be to blame for extraterine implantation by forcing the embryos through the tubal ostia by hydrostatic pressure. This may be due to a large volume of transfer medium or use of excessive force during the embryo transfer (Berman et al., 1986; Dor et al., 1991). Placing the transfer catheter beyond the mid-cavity or into the tube itself (Yovich et al., 1985), or to retrograde migration of the embryos into the tube (Job-Spira et al., 1996) have also been blamed for the increased incidence of ectopic pregnancy subsequent to IVF treatment. Nonetheless, Dor et al. (1991) evaluated the use of ultrasound in embryo transfer and concluded that ultrasound-guided embryo transfer does not prevent ectopic pregnancy after IVF. Job-Spira et al. (1996) argued that chromosomal anomalies in the fertilized oocyte might play a role in the etiology of ectopic implantation. It is also possible that an ectopic pregnancy could result from spontaneously fertilized unrecovered oocytes if coitus occurred near the time of oocyte recovery. This possibility cannot be excluded, particularly if the number of oocytes retrieved is less than the number of follicles aspirated.

Pathology of ectopic pregnancy

Any difference between implantation in the uterus and that in the tube can be easily explained by the anatomy of the two organs. As the trophoblast invades the muscle layer of the Fallopian tube, the connective tissue cells of the tubal wall become swollen and resemble decidual cells, but this provides no resistance to the invading trophoblast. Some of the vessels that the trophoblast meets are large, and when these are invaded, the pressure of the blood stream is often sufficient to destroy the embryonic cell mass.

Early placental development in the tube is very similar to that seen at normal sites, although it is often immature and many villi demonstrate loss of vascularity with central hyalinization, characteristic of collapse of the fetal circulation. Subsequently, there is failure of the tubal trophoblast to differentiate into chorioclaeve and chorion frondosum. The degree of decidual reaction around the tubal implantation site is usually minimal. The decidua usually forms in the uterus and not in the tube. As a result of trophoblastic activity, the human blastocyst can implant at any site at the appropriate stage of development. The role of the maternal decidua in this process is a passive one.

Three mechanisms have been proposed to explain ovarian implantation (Marcus and Brinsden, 1993): (i) one theory suggests that fertilization occurs normally and implantation on the ovary follows reflux of the conceptus from the tube (Crimes et al., 1983); (ii) the second theory suggests that various disturbances in ovum release are responsible for ovarian implantation (Tan and Yeo, 1968); and finally (iii) the application of intrauterine insemination could push some spermatozoa all the way to the ovarian surface and lead to ovarian implantation (Bontis et al., 1997).

Clinical features of ectopic pregnancy

Ectopic pregnancy is a great masquerader, since only half of patients with ectopic pregnancies are correctly diagnosed on clinical features alone (Tuomivaara et al., 1986). The clinical signs and symptoms of ectopic pregnancy overlap with those of other surgical and gynecological conditions, such as threatened or incomplete miscarriage, pelvic inflammatory disease, ruptured or haemorrhagic corpus luteal cyst, salpingitis, adnexal torsion, degenerating fibroid, dysfunctional uterine bleeding, endometriosis and appendicitis.

The first clinical symptom of ectopic pregnancy is usually pain. This is present in 95% of cases, while 80% have amenorrhoea and 50% experience abnormal vaginal bleeding. The presentation may be acute, subacute or silent. In acute cases associated with tubal rupture there may be massive i.p. haemorrhage, causing acute abdominal pain, circulatory collapse with hypotension and tachycardia. In such patients, immediate laparotomy is necessary with salpingectomy being mandatory to arrest the bleeding.

The most common situation is of a subacute presentation with amenorrhoea, abdominal pain and sometimes irregular vaginal bleeding. If rupture or tubal abortion occurs gradually, the symptoms are less dramatic, and the diagnosis may be missed. Similarly, the development of ovarian hyperstimulation syndrome (OHSS) subsequent to assisted conception treatment may mask the symptoms of an ectopic pregnancy (Thakur and El-Menabawey, 1996; Paulson and Lobo, 1998).

Diagnostic tests

The morbidity and mortality associated with ectopic pregnancy are directly influenced by the time interval between the onset of symptoms and the start of treatment (Department of Health, 1998). Thus the prospect of early treatment is dependent on maintaining a high index of suspicion and the deployment of a few additional diagnostic tests, dictated by local availability and costs.
Biochemical tests

**Human chorionic gonadotrophin (HCG)**

HCG may be detected in the urine as early as 14 days post-conception by sensitive enzyme-linked immunosorbent assays (detection limits 25–50 IU/l; sensitivity 98–100%) (Armstrong et al., 1984; Kingdom et al., 1991; Speroff et al., 1994). It can be detected in the serum 6–7 days post-conception by immunometric radioassays (detection limits <5 IU/l; sensitivity 100%) (Lenton et al., 1982; Speroff et al., 1994). Early normal intrauterine pregnancies are associated with a doubling of serum HCG concentrations every 1.4–2.1 days (Kadar et al., 1981; Pittaway et al., 1981). An ectopic pregnancy produces less HCG than a normal intrauterine pregnancy, which has the effect of prolonging the HCG doubling time (Check et al., 1992; Heiner et al., 1992). However, 15% of normal pregnancies will have an abnormal doubling time and 13% of ectopic pregnancies will have a normal doubling time (Ling and Stovall, 1994). Therefore, in order to increase the sensitivity of quantitative HCG, a discriminatory zone has been described, whereby an HCG titre of 1000–1500 IU/l will be associated with the presence of an intrauterine sac on transvaginal ultrasound (6000–6500 IU/l for transabdominal ultrasound) (Kadar et al., 1981; Keith et al., 1993). Several prospective studies employing diagnostic algorithms, including clinical symptoms, quantitative serum HCG and transvaginal ultrasound, have shown a diagnostic sensitivity of this discriminatory zone for ectopic pregnancies of 95–99% and a specificity of 95–100% (Fernandez et al., 1991a; Ankrum et al., 1996b).

Kadar and Romero (1988) were among the first to address the problem of distinguishing ectopic pregnancy from spontaneous abortion on the basis of falling HCG concentrations over a 48 h period. In their study, if the half-life of HCG was <1.4 days, then a complete abortion was likely and the patient was best managed expectantly. If the half-life was >7 days, then an ectopic was likely. Thus, contrary to popular belief, falling HCG concentrations are not synonymous with spontaneous abortion, and can be used to distinguish spontaneous abortion form ectopic pregnancies, provided the half-life of HCG is calculated.

In IVF patients, since more than one embryo is usually transferred, and more trophoblastic tissue may be present to produce HCG, an extra 2 or 3 days are required for a sac to become visible. Okamoto et al. (1987) were the first to report on the accuracy of serum β-HCG measurement in the diagnosis of ectopic pregnancies after IVF/embryo transfer. They reported a 100% sensitivity and a 68% specificity when comparing 88 viable intrauterine pregnancies with nine ectopic pregnancies. A serum HCG concentration of >295 IU/l on day 16 post-embryo transfer was reported to give a 90% chance of intrauterine implantation (Smith et al., 1982).

Mol et al. (1997) evaluated the discriminative capacity of transvaginal sonography in combination with HCG measurement in the diagnosis of ectopic pregnancy after IVF/embryo transfer, and found that whenever the serum β-HCG concentration on day 9 after embryo transfer was >18 IU/l, the pregnancy was always intrauterine and viable. Therefore, they concluded that transvaginal sonography can be postponed until 5 weeks after embryo transfer, except for patients with abdominal pain and/or vaginal bleeding, or in patients with a serum β-HCG concentration of <18 IU/l.

**Serum progesterone**

Serum progesterone concentrations are lower in ectopic than in normal intrauterine pregnancies (Johansson, 1969; Radwanska et al., 1978; Milwidsky et al., 1984; Mathews et al., 1986). Whether ectopic implantation causes the shutdown of progesterone by the corpus luteum or whether low progesterone concentrations actually lead to ectopic implantation is still uncertain, although the electrophysiological studies of Pulkkinnen and Jaakkola (1989) suggest the latter may be the case.

To investigate the diagnostic accuracy of serum progesterone in the diagnosis of ectopic pregnancy, Yeko et al. (1978) identified a cut-off value of 15 ng/ml to differentiate between viable and non-viable pregnancies. On the same notion, McCord et al. (1996) advised that when the serum progesterone is >17.5 ng/ml, patients thought to be at risk of ectopic pregnancies could reasonably be followed without ultrasound or further invasive diagnostic studies. The sensitivity of serum progesterone values <15 ng/ml to distinguish between normal pregnancies and ectopic gestation is ~80% (Buck et al., 1988), with false-positive rates of ~10% (Stovall et al., 1989).

In patients clinically suspected of having an ectopic pregnancy, a progesterone concentration of <20 ng/ml suggests early pregnancy failure, whatever the gestational age (Sauer et al., 1989). In their study of 135 patients who suffered ectopic pregnancies following IVF/embryo transfer, Marcus et al. (1995) found that the mean plasma progesterone concentration was significantly lower than that of patients with normal singleton pregnancies. On the other hand, other investigators, (Ling and Stovall, 1994; Speroff et al., 1994) found serum progesterone concentrations did not appear to increase the diagnostic sensitivity.

Other hormones, such as pregnancy-associated plasma protein A (PAPP-A), have been evaluated as possible ancillary diagnostic tests in suspected ectopic pregnancies (Tornehave et al., 1987). The two major proteins synthesized by the human endometrium; progesterone-dependent endometrial protein (pectopic pregnancies ) and insulin-like growth factor binding protein (IGF-bp) have also emerged as candidates as biochemical markers of ectopic implantation (Ruge et al., 1991; Pedersen et al., 1991).
Ultrasound

The role of ultrasonography in suspected ectopic gestation is to diagnose and localize the pregnancy. The image resolution and patient acceptance of transvaginal ultrasonography are considerably better than that of transabdominal ultrasound (Bateman et al., 1990). In order of appearance, a normal intrauterine sac should contain a yolk sac and embryonic echoes with visible heart activity at days 33, 38 and 43 from the last menstrual period respectively (Cacciapuoti et al., 1990).

There are three sonographic features of tubal pregnancy as seen by a vaginal transducer. First, the demonstration of a live embryo within a gestational sac in the adnexa. This remains the gold standard for the sonographic diagnosis of ectopic pregnancy. It typically appears as an intact, well-defined tubal ring (the ‘doughnut’ or ‘bagel’ sign) in which the yolk sac and/or the embryonic pole, with or without cardiac activity, are seen within a completely sonoluent sac. An ectopic embryo/fetus is reported to be seen in 12–20% of cases with vaginal ultrasound (DeCrespigny, 1988; Stabile et al., 1988). The second transvaginal sonographic appearance of tubal pregnancy is that of a poorly defined tubal ring, possibly containing echogenic structures (Dodson, 1991; Atri et al., 1996). Typically, the pouch of Douglas also contains fluid and/or blood. These features are consistent with a tubal pregnancy that is aborting. The third typical sonographic picture is the presence of varying amounts of fluid in the pouch of Douglas, representing rupture of the tubal pregnancy (Nyberg et al., 1991).

Arguments persist as to whether or not a pseudogestational sac is seen using transvaginal ultrasound. In the experience of some (Timor-Tritsch et al., 1988), a pseudogestational sac is not visible when a tubal gestation is detected. Others admit that it may be difficult, even with transvaginal sonography, to evaluate an intrauterine sac <4 mm in diameter. However, in the absence of an eccentric placement of a gestational sac within the endometrial cavity (which is the hallmark of a normal intrauterine pregnancy), a pseudogestational sac should be suspected (Cacciapuoti et al., 1990).

Despite recent advances in sonographic techniques and better patient acceptability of the transvaginal method of scanning, considerable expertise is still needed for image interpretation. Of particular difficulty is the diagnosis of heterotopic pregnancy, which is fraught with potential pitfalls and is often delayed (Bello et al., 1986). To be conclusive, the diagnosis requires the demonstration of a foetus or a gestational sac both in and outside the uterus. Thus, establishing the existence of an intrauterine pregnancy by ultrasound, although reassuring, does not rule out a co-existing ectopic pregnancy (Hayes and Haley, 1984; Goldman et al., 1992). Correct pre-operative diagnosis of ovarian pregnancies is equally difficult, being confused with corpus luteal cysts (Tan and Yeo, 1968; Raziel et al., 1990).

Colour and pulsed Doppler techniques may complement endovaginal sonographic findings, but they should be performed only after a thorough real-time evaluation of the adnexal region (Atri et al., 1996). Whilst Speroff et al. (1994) indicated that the use of colour Doppler imaging should only be confined to research trials to increase the sensitivity of transvaginal ultrasonography, others (Chew et al., 1996; Abramove et al., 1997) found that it failed to improve on the results of transvaginal B-mode sonography in the detection of ectopic pregnancy.

Other methods

Culdocentesis (Ling and Stovall, 1994; Speroff et al., 1994) and uterine curettage (Speroff et al., 1994; Ramirez et al., 1996) have limited use in the diagnosis of ectopic pregnancy.

Laparoscopy

Laparoscopy as a method of diagnosing ectopic gestation has been used since 1937, when Hope reported the first 10 cases (Hope, 1937). When laparoscopy became a routine procedure it facilitated the early diagnosis of ectopic pregnancy and in up to 40% of cases laparotomies were avoided. The development of a very sensitive radioimmunoassay for β-HCG, together with the use of ultrasound, has again changed our ability to diagnose ectopic pregnancies. Under these circumstances, the role of laparoscopy nowadays has moved from being a diagnostic tool (false negatives 3–4%; false positives 5%) (Ling and Stovall, 1994) to become a treatment modality only (Barnhart et al., 1994; Ankum et al., 1996b).

Treatment

Early diagnosis of unruptured ectopic pregnancy (Figure 1) allows for conservative medical or invasive surgical therapy. The recurrent ectopic pregnancy rates after radical and conservative management are similar (10–22%), while the intrauterine pregnancy rate in subsequent pregnancies is 60% after conservative tubal surgery, 87% after medical treatment and 40% after salpingectomy (Vermesh et al., 1989; Rulin, 1995). Therefore, a conservative therapeutic approach should be attempted in patients with an ectopic pregnancy who desire future fertility and are haemodynamically stable at presentation.

Surgical treatment

Laparoscopy versus laparotomy

Laparoscopic salpingostomy (Figure 2) is rapidly replacing laparotomy for most cases of tubal ectopic pregnancy. In modern practice, the prevalent opinion is that laparotomy
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should be performed only in cases in which the laparoscopic approach is difficult or the patient is haemodynamically unstable (Baumann et al., 1991; Lundorff et al., 1991; Murphy et al., 1992). The advantages of the laparoscopic approach have been well-documented in terms of shorter hospital stay (Kouam et al., 1996), fewer post-operative analgesic requirements (Lundorff et al., 1991), reduced cost (Gray et al., 1995; Garry, 1996) and a lower risk of adhesion formation (Tuomivaara and Kaupilla, 1988). Recently, ovarian ectopic pregnancies have also been reported to be managed laparoscopically with variable success (Hage et al., 1994; Seinera et al., 1997).

Laparoscopic salpingostomy versus laparoscopic salpingectomy

In a patient with a diseased tube or a damaged contralateral tube, the question arises as to whether laparoscopic treatment should be by salpingectomy or salpingostomy. In patients where the contralateral tube is diseased, but nevertheless patent (Tuomivaara and Kaupilla, 1988; Silva et al., 1993; Bronson, 1997) the post-operative chances of conception are not significantly different whether treatment is by salpingectomy or salpingostomy. This finding is important since laparoscopic salpingectomy poses a number of advantages compared with salpingostomy. It is more simple, requiring no specific equipment (Dubuisson et al., 1996) and does not carry the risk of leaving intra-tubal residual trophoblastic tissue. Subsequent persistent trophoblast has been reported to occur in 15–20% of cases following laparoscopic salpingostomy (Vermesh et al., 1989; Murphy et al., 1992; Buster and Carson, 1995; Kouam et al., 1996). Since persistent trophoblast tends to be found in the proximal portion of the tube, it is recommended that suction irrigation should be used to flush the gestational products out of the tube. In addition, it is advisable to perform weekly β-HCG measurements as a follow up after surgery. The average time for β-HCG concentrations to become undetectable is 4 weeks (Ling and Stovall, 1994). It is encouraging that the pregnancy rate does not seem to be decreased after persistent ectopic pregnancy (Seifer et al., 1994).

Interestingly, a randomized prospective study has shown that the reproductive outcome after conservative treatment by salpingostomy is comparable, whether carried out by laparoscopy or laparotomy (Vermesh and Presser, 1992). The reported subsequent intrauterine pregnancy rates vary from 23 to 70% and the incidence of recurrent ectopic pregnancies ranges from 10 to 30%. These wide variations are largely due to differences in reporting characteristics. However, by using the number of women who desire pregnancy after the procedure as the denominator, ~35% of women will have a subsequent intrauterine pregnancy and 15% will have a repeat ectopic gestation (Lavy et al., 1987). Women undergoing IVF must, therefore, be informed of the risk of ectopic pregnancy (Agrawal et al., 1996; Chen et al., 1998), even if they have had bilateral salpingectomy, since cornual implantation can still occur (Manhes et al., 1983).

Hysteroscopic resection

Diagnostic hysteroscopy has been used in the management of cervical pregnancy. Roussis et al. (1992) used the hysteroscope to visualize a cervical pregnancy 40 days after failed systemic methotrexate treatment. As hysteroscopy confirmed minimal vascularity in the endocervical canal, they proceeded with suction aspiration of the trophoblastic tissue. Ash and Farrell (1996) also described hysteroscopic resection of a cervical pregnancy and concluded that operative hysteroscopy permits complete resection of a cervical pregnancy. When it is successful, this treatment should result in prompt resolution of the ectopic pregnancy, thus avoiding the need for a prolonged follow up or hysterectomy. Hysteroscopy has also been used successfully to diagnose and treat interstitial ectopic pregnancy (Laury, 1995; Alexander et al., 1996).

Medical treatment

Although operative laparoscopy has substantially fewer complications than laparotomy (Lundorff et al., 1991; Murphy et al., 1992) there remains an irreducible minimal degree of morbidity intrinsic to surgery and anaesthesia. Though they are not yet standard therapy in many centres, medical treatments can greatly reduce this morbidity, and consequently there is increasing interest in using them. To supplant surgery, however, medical therapies must match the success rates, low complication rates,
and subsequent reproductive potential achieved with laparoscopic operations. This appears to have been achieved (Stovall, 1995; Alexander et al., 1996).

The first case report describing the use of medical therapy for tubal pregnancy appeared in 1982 (Tanaka et al., 1982). Observational studies in the mid-1980s used, with varying success, methotrexate (Leach and Ory, 1989), prostaglandins (Husslein et al., 1988; Lindblom et al., 1990), actinomycin (Altaras et al., 1988), hyperosmolar glucose (Lang et al., 1990), and anti-HCG antibodies (Frydman et al., 1987). Potassium chloride (Robertson et al., 1987; Aboulghar et al., 1990) is particularly useful in the treatment of heterotopic pregnancy, as it has no effect on the intrauterine fetus(s). Mifepristone (RU486) (Kenigsberg et al., 1987), an oral progesterone antagonist abortifacient with low toxicity, was ineffective except in combination with methotrexate (Gazvani et al., 1998). Although treatments given systemically have proved most practical, several of these agents have been injected into the ectopic gestational sac under laparoscopic or ultrasound guidance or by hysteroscopic intratubal cannulation.

**Methotrexate**

A folic acid antagonist, methotrexate inhibits the spontaneous synthesis of purines and pyrimidines, thus interfering with DNA synthesis and the multiplication of cells (Chu et al., 1990). Actively proliferating trophoblast was shown to be vulnerable to methotrexate treatment of gestational trophoblastic disease (Sand et al., 1986; Leach and Ory, 1989).

Haemodynamically stable patients with ectopic pregnancy, in which the mass is unruptured and measures ≤4 cm in diameter by ultrasound, are eligible for treatment with methotrexate (Stovall et al., 1990, 1991b; Darai et al., 1995a). Patients with ectopic pregnancies with larger masses, cardiac activity within the adnexal mass, or evidence of acute intraperitoneal bleeding are ineligible for methotrexate therapy (Stovall et al., 1990, 1991a,b; Kooi and Kock, 1992).

Tanaka et al. (1982) first reported the treatment of ectopic pregnancy using methotrexate in 1982. Since then, methotrexate has been used widely for unruptured ectopic pregnancies (Pansky et al., 1989; Alexander et al., 1996; Súka et al., 1996). It can be given systemically (orally, i.v. or i.m.) (Pansky et al., 1989; Balasch et al., 1992; Stovall and Ling, 1993), or by local injection under laparoscopic control (Lindblom et al., 1987; Stovall et al., 1989; Zakut et al., 1989; Kojima et al., 1990), or under ultrasound guidance (Feichtinger and Kemeter, 1987; Aboulghar et al., 1990; Menard et al., 1990; Tulandi et al., 1992; Fernandez et al., 1993, 1994; Pérez et al., 1993; Darai et al., 1995b).

**Systemic methotrexate**

Oral methotrexate cannot generally be recommended and is rarely used for the treatment of ectopic pregnancy. More commonly, methotrexate has been used in multiple i.m. doses or in single doses, in a schedule of 0.5–1.0 mg/kg every other day for 5–7 days (Farabow et al., 1983; Fernandez et al., 1994), or 50 mg/m² of body surface area (Stovall et al., 1991a).

Transient pelvic pain frequently occurs 3–7 days after the start of methotrexate therapy. This pain is presumably due to tubal abortion and normally lasts 4–12 h (Stovall et al., 1990, 1991b). Perhaps the most difficult aspect of methotrexate therapy is learning to differentiate between the transient abdominal pain of successful therapy from that of a rupturing ectopic pregnancy (Figure 3). Objectively, surgical intervention is necessary when the pain is associated with tachycardia, hypotension or a falling haematocrit.

The reported outcome of systemic methotrexate treatment of ectopic pregnancy compares favourably with that of laparoscopic salpingostomy (Tanaka et al., 1982; Miyazaki, 1983; Ory et al., 1986; Haans et al., 1987; Ichinoe et al., 1987; Sauer et al., 1987; Bryrjalsen, 1991; Stovall et al., 1991b; Prevost et al., 1992; Isaacs et al., 1996; Maymon and Shulman, 1996). A success rate (i.e. patients who did not need subsequent therapy) of 90–95% has been achieved, with a non-response rate and/or tubal rupture rate of 3–4% (Lipscomb et al., 1998). Of the women followed, 71% subsequently became pregnant, with 11% of those pregnancies being ectopic (Slaughter and Grimes, 1995). More recently, Fernandez et al. (1998) compared methotrexate treatment with laparoscopic salpingectomy in a prospective randomized study. They found that medical treatment was associated with a significantly shorter post-operative stay, but HCG values...
returned to normal concentrations more rapidly after laparo-scopic treatment. Spontaneous reproductive performance was similar in both groups, but overall rates of intrauterine pregnancy were higher and repeat ectopic pregnancies lower after methotrexate treatment. They concluded that in selected cases of ectopic pregnancy, methotrexate treatment appeared as safe and efficient as conservative treatment by laparoscopy and was associated with improved subsequent fertility.

In the search for a more potent alternative to a single i.m. injection of methotrexate for unruptured ectopic pregnancy, combination therapy was suggested. Gazavani et al. (1998) randomized 50 patients with unruptured ectopic pregnancies to receive a single i.m. injection of 50 mg/m² body surface methotrexate alone or in combination with 600 mg of oral mifepristone. The success rates for treatment arms were similar, however, median administration to resolution times was shorter and a second injection or laparotomy was less likely to be needed in the combination group.

**Local methotrexate**

In 1987 Feichtinger and Kemeter reported the direct injection of methotrexate under transvaginal ultrasound guidance. They instilled 1 ml (10 mg) of methotrexate into the ectopic gestational sac and resolution occurred within 2 weeks. Direct injection delivers concentrations of methotrexate to the implantation site which are many times higher than those achieved with systemic administration. Thus there is less systemic distribution of the drug, a smaller therapeutic dose, and less toxicity.

Injection of methotrexate into the gestational site under laparoscopic guidance is performed with varying dosages, ranging from 5 to 100 mg, and the amount of normal saline diluent may range from 0.8 to 10 ml. On the other hand, direct injection under ultrasound control is preferable, as it enables treatment on an outpatient basis, with neither general anaesthesia nor laparoscopy being required (Goldenberg et al., 1993). But this may also be offset by the risk of accidental damage to other pelvic organs and the requirement for specialized invasive training.

Systemic and intratubal methotrexate were shown to have similar efficacy and resulted in comparable subsequent pregnancy rates (Kooi and Kock, 1990; Fernandez et al., 1993). Nevertheless, the success rate of local injection of methotrexate is highly dependent on the proper selection of patients (Goldenberg et al., 1993). The success rate for direct methotrexate injection under ultrasound guidance ranges from 70 to 95% (Feichtinger and Kemeter, 1987; Menard et al., 1990; Fernandez et al., 1991b; Tulandi et al., 1992; Darai et al., 1995b) and between 43 and 100% under laparoscopic control (Kojima et al., 1990).

In an effort to find a more effective and safe method for the local injection of methotrexate, Fujishita et al. (1995) prepared a suspension of methotrexate dissolved in lipidol with phosphatidylcholine added as a dispersing stabilizer to maintain the high tissue concentration and to prolong the effect. Their results showed that this suspension seems to be more effective than methotrexate solution alone.

The side-effects of local methotrexate therapy include: gastrointestinal disorders, liver dysfunction, bone marrow suppression, opportunistic infections, blood dyscrasias, reversible alopecia, persistent haematosalpinx and methotrexate-induced lung disease. These side-effects are infrequent and in the shorter treatment schedules used in ectopic pregnancies and can be attenuated by the administration of leucovorin (macrophage colony stimulating factor) (Leach

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**Figure 3.** Transvaginal ultrasound depicting a heterotopic pregnancy with fluid in the pouch of Douglas (see dark area adjacent to the uterus).

**Figure 4.** Transvaginal ultrasound depicting a pseudogestational sac within the uterus.
and Ory, 1989; Stovall et al., 1991a,b; Issacs et al., 1996). Extensive experience with methotrexate in gestational trophoblastic disease has diminished concern about the risks of subsequent neoplasia, increased abortion rates and fetal congenital anomalies (Ross, 1976). Nevertheless, it is true to assume that most patients can expect a low risk of mild complications. Although Stovall and Ling (1993) reported no significant side-effects in patients treated with local or systemic methotrexate, Kooi and Kock (1992) observed that 2% of their patients treated with topical methotrexate developed some side-effects, compared with 21% treated systemically. On the other hand, Glock et al. (1994) reported mild side-effects in 34% of their 35 patients, while Fernandez et al. (1993) reported mild side-effects in three out of 100 patients. Sufficient to say that, although generally safe and effective, methotrexate should be used with the utmost care in the treatment of ectopic pregnancy.

Methotrexate treatment, administered either systemically or locally, has been reported to be less satisfactory as a primary treatment of cervical pregnancy than of tubal pregnancy. Some authors claimed that their cases failed initial methotrexate treatment and required additional interventions, including suction curettage (Mantalenakis et al., 1995), salvage chemotherapy with the same agent (Kaplan et al., 1990; Hung et al., 1996), feticide with intra-amniotic injection of potassium chloride (Kung et al., 1995), angiographic immobilization (Cosin et al., 1997), ligation of bilateral uterine arteries (Wolcott et al., 1988) or even hysterectomy (Dall et al., 1994). Hung et al. (1998) conducted a Medline search to identify the clinical factors that might lead to an unsatisfactory outcome of primary methotrexate treatment in cases of cervical pregnancy. They concluded that systemic administration of low dose methotrexate is ideal for patients who are clinically stable with cervical pregnancies of <9 weeks gestation and serum HCG concentration of <10 000 IU/l. If embryonic cardiac activity is evident, concomitant feticide must be performed to minimize the potential risk of methotrexate treatment failure.

**Expectant management**

The concept of expectant management is not new. Lund (1955) randomized patients to receive expectant management or surgical treatment. Among 114 patients randomized to be treated expectantly, the success rate was 57%. However, most of the patients who failed expectant management returned with significant symptoms including haemoperitoneum, or cardiovascular collapse. Criteria for expectant management are similar to those for medical treatment, including falling β-HCG titres (Garcia et al., 1987; Speroff et al., 1994; Yao and Tulandi, 1997). Nowadays, as a consequence of the improvement in diagnostic serial serum β-HCG assays, combined with the availability of high-resolution transvaginal sonography, expectant management of unruptured ectopic pregnancies has become safer. When the β-HCG concentration is <1000 IU/l and the plasma progesterone <5 ng/ml, spontaneous resolution occurs in 74% of cases of ectopic pregnancies with expectant management (Darai et al., 1995a). A review of 10 prospective studies of expectant management reported success rates of 46.7–100% (Yao and Tulandi, 1997). Generally speaking, there is a decreased chance of successful expectant management the higher the initial serum β-HCG concentrations are (Adoni et al., 1986). As there is no certain limit below which tubal rupture will not occur, we believe, as others do (Mascarerhas et al., 1997; Lipscomb et al., 1998), that methotrexate treatment may be a more appropriate alternative.

**Conclusions**

Although the mortality from ectopic pregnancy has decreased due to earlier diagnosis and more medical treatment, ectopic pregnancy is still a common cause of maternal morbidity and mortality. Recent advances in the measurement of quantitative serum β-HCG and progesterone, together with the development of high-resolution ultrasound scanning, has improved the rate of early diagnosis of ectopic pregnancy and had made it possible in most cases to diagnose extra-uterine pregnancy without resort to laparoscopy.

Several options exist today for the treatment of ectopic pregnancy. The chosen treatment depends on the size and site of the ectopic, the expertise and facilities available and the general condition of the patient. Successful outcome after medical treatment could be perfected by improved selection of patients. Although methotrexate is generally safe and effective, it should be used with the utmost care in the treatment of ectopic pregnancy.

Surgical treatment is increasingly carried out by laparoscopy, which is effective in decreasing morbidity and mortality, but of unproved benefit in subsequent reproductive outcome. Laparotomy remains necessary in emergency cases, with haemodynamic instability and with exceptional locations, such as abdominal, cervical or interstitial pregnancies. There is no definitive answer on whether laparoscopic surgery or methotrexate should be first line of treatment. This question can only be answered by carrying out a large multicentre trial. Ultimately, breakthroughs in the understanding of the mechanism of implantation and in the natural history of the disease will provide advances in treatment options. Meanwhile, increased vigilance and application of technological advances should ensure early diagnosis and less invasive therapy achieving a continued reduction in the mortality and morbidity of ectopic pregnancy.
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