

Modern Management of Ectopic Pregnancy

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Summary

The incidence can be as 1 in 90 to as low as 1 in 300 conceptions. It is responsible for 6-12% of the maternal deaths.

Methods of diagnosis are history, repeated serum β hCG, repeated vaginal ultrasound with a high resolution probe and pelviscopy or laparoscopy.

The therapeutic regime chosen should provide the patient with the least morbidity while preserving the greatest potential for reproductive function if she so desires.

Conservative treatment can be carried out by laparoscopy or laparotomy. Failure and fertility rates are similar, so laparoscopy is without question the best surgical treatment for ectopic pregnancy.

In our private practice, 84% were treated by laparoscopy and 16% by laparotomy.

Methotrexate, an anti-metabolite first used for the

treatment of gestational trophoblastic disease, is now widely used for the treatment of ectopic gestation. It has been administered systemically and by salpingocentesis, with excellent results.

Persistent ectopic pregnancy occurs in a small percentage of patients treated by salpingotomy or medical therapy.

Introduction

Ectopic gestation is known to occur from 1:90 to 1:300 conceptions. In the last 2 decades, there has been a substantial rise in its incidence for various reasons. The increased incidence of pelvic inflammatory disease (PID), the use of antibiotics for the same, tubal microsurgery for blocked tubes, tubal sterilisation and recanalisation, together with the more widespread use of an IUD may be some of the factors responsible. In addition, ectopic pregnancy occurs in 5-10% of clinical conceptions in an IVF & ET programme. The first human pregnancy following IVF and ET was a tubal pregnancy reported by Steptoe & Edwards. (1976)

Methods of Diagnosis

With the advent of radio immuno assays (RIA) and monoclonal antibody techniques for the estimation of the hormone β hCG, ultrasonography and laparoscopy, 80% or more of tubal pregnancies should be diagnosed before rupture, as compared to the past when only 10-20% were diagnosed before rupture. A positive β hCG of a low titre for the period of gestation with an empty uterine cavity on ultrasound is diagnostic of an ectopic gestation. When serum β hCG is repeated after 48 hr in a normal pregnancy, the titre doubles itself. In an ectopic gestation the titre may increase a little, remain the same or decrease. However, one must remember that 15% of normal pregnancies may have an abnormal hCG rise.

Transvaginal real time ultrasound scanning is the most

informative investigation in patients with suspected EPs. When an intrauterine gestational sac is seen with a foetus, EP can be ruled out, as a combined intra and extra uterine pregnancy is very rare. The presence of a living extrauterine pregnancy; extrauterine gestational sac containing yolk sac or embryo; empty tubal ring and the presence of any adnexal mass other than a simple cyst is diagnostic of EP.

Barnhart et al (1994) described an algorithm consisting of clinical examination, quantitative serum β hCG and transvaginal ultrasound. This protocol diagnosed EPs with a sensitivity of 100% and a specificity of 99% and obviated need for diagnostic laparoscopy.

Management

When surgical intervention is the decision, a diagnostic laparoscopy under general anaesthesia allows the surgeon to thoroughly examine the pelvis. Three ports are usually used, the primary subumbilical 10 mm in size and two additional 5 mm size ports in the iliac fossae. Smaller size primary ports for 4 mm and 5 mm optics which give excellent vision are more often utilised today. The size of the ectopic gestation, its site, whether the tube is ruptured or intact, the condition of the contralateral tube, the presence of a haemoperitoneum and its volume are determined.

The management of ectopic gestation has changed. Before the advent of the above techniques, patients were seen with a chronic pelvic haematocoele or with a haemoperitoneum as an acute abdominal emergency. In maternal mortality records, ectopic gestation was listed high as a major avoidable cause of death. With late diagnosis, the surgical procedure was a laparotomy followed by salpingectomy which jeopardised the patient's reproductive potential. Early detection of tubal gestation brought forth the operations of salpingotomy, tubal resection and microsurgical repair. Semm (1980) and Bruhat (1980) were the first to advocate and publish their experience of operative laparoscopy for ectopic gestation. They showed that whatever was done by laparotomy could be achieved by laparoscopy with minimal trauma, speedy convalescence and a short hospital stay.

The technique of laparoscopic salpingotomy is well documented and illustrated by several authors (Bruhat 1980; Semm 1980). The affected tube is steadied with a grasping forceps; an incision is made in the antimesenteric border of the tube and the products of conception removed. The incision must be made on the proximal part of the swelling as the pedicle of the ectopic formed by the invading trophoblastic tissue is situated at this site. Suction and lavage are done to remove the products of conception. If necessary, a biopsy forceps is used. Haemostasis is secured using bipolar forceps. The suturing of the incision is recommended by the Kiel School (Semm 1987) and the same kept open by the group of workers from Clermont Ferrand (Bruhat 1980).

Serial β hCG estimations are performed postoperatively. A fall to 15% or below of initial β hCG level indicates complete removal of the trophoblastic tissue. If the level is 30-40% of the initial β hCG level it is likely that the trophoblastic tissue is not completely removed; the patient is carefully monitored for persistent EP. Its rate is 5% after laparoscopic salpingotomy.

Discussion

Today laparoscopic treatment is applicable to about 80% of patients with ectopic gestation as it is safe, efficacious cost effective, associated with rapid convalescence and retention of fertility.

Salpingectomy at laparoscopy or laparotomy is necessary when "enough is enough on the tubes". More than 2 EPs in the same tube or irreparable tubal damage from pelvic inflammatory disease (PID).

In the presence of uncontrollable bleeding or extenuating circumstances where neither tube can be saved or one tube has already been removed or irreparably damaged, try and save the uterus and one ovary for IVF.

Wolf et al (1994) have studied the potential limiting factors in Resident Training for laparoscopic management of Ectopic Pregnancies.

They compared 53 consecutive patients with Ectopic

Pregnancies treated surgically in an infertility practice (Group I) with 68 women with ectopic gestation managed in a residency program (group II).

Evaluation at the time of admission showed significantly lower blood pressures, haemoglobin levels and higher pulse rates for the Group II patients than those in Group I. The mean gestational age at diagnosis was greater in Group II than in Group I. Clinical picture was more serious - larger mean gestational mass and a larger haemoperitoneum. Blood transfusion post-operative or intraoperative was 49% in Group II as compared to 13% of Group I. Group I, 83% were managed laparoscopically and in Group II, 24% were managed laparoscopically.

As surgical proficiency is gained only through extensive training. Such experience may not be available for ectopic gestation in a residency program. Special efforts may have to be made to encourage resident participation in care of patients with non-emergency ectopic gestation.

When bleeding from the bed is not controlled by electrocoagulation after removal of the trophoblastic tissue, pressure is applied to stop the bleeding. If still unsuccessful, the vessel in the mesosalpinx arcade may be coagulated. To avoid a salpingectomy and extensive destruction of the tube by endo-coagulation - a laparotomy is advisable.

The tissue of closure of salpingotomy incision was studied by Tulandi & Guralnick (1991). They found no difference in intrauterine pregnancy rate and ectopic pregnancy rate in a randomised trial comparing treatment of ectopic pregnancy by salpingotomy with and without suturing. Of interest intrauterine pregnancy occurred earlier in women whose salpingotomy opening was left unsutured.

Soriano et al (1997) have shown that operative laparoscopy can be performed in patients with ectopic gestation and hypovolemic shock. Thirty three patients of a total of 211 women with ectopic gestation were suffering from hypovolemic shock. After resuscitation laparoscopic salpingectomy using bipolar forceps and scissors was successfully performed in 30 women. Laparotomy was done in 3 women because of technical

difficulties in completing the procedure. Twenty nine out of the 33 women required blood transfusion.

Hypovolemic shock is mentioned as one of the contraindications to laparoscopic surgery. Experience, good instrumentation, careful monitoring during anaesthesia and with blood replacement, the scope of laparoscopic surgery is widened to include patients who were in the past scheduled for a laparotomy.

MTX and Ectopic Pregnancy

Methotrexate, an antimetabolite was first used for the treatment of gestational trophoblastic disease by Li et al. (1956). Actively functioning trophoblastic tissue is extremely sensitive to this drug.

Tanaka et al in 1982 were the first to use methotrexate for treatment of an Ectopic pregnancy. Since then many studies have been published by Ory et al. (1986), Stovall et al (1991), Fernandez et al (1993), Yao & Tulandi (1997), Lindblom (1990) and Goldenberg et al (1992, 1993).

Methotrexate has been administered systemically or by salpingocentesis. Direct injection into the ectopic gestational sac can be done at laparoscopy or by transvaginal route under sonographic control.

The selection criteria for methotrexate therapy are the largest diameter of the unruptured ectopic swelling is 3.5 cm or less. The upper limit of serum β hCG should preferably be less than 5000 mIU/ml. Our limit however was 9000 IU/ml. The patient should have no active renal or hepatic disease, there should be no evidence of leucopaenia or thrombocytopenia.

According to the most widely accepted protocol of Stovall & Ling (1993) the single intramuscular dose is 50 mg/m². They reported a success rate of 94% with minimal side effects.

Response to a single dose of methotrexate therapy may depend not only on the pre treatment level of β hCG but as Stika et al (1996) state, there may be an unpredictable idiosyncratic response in cytotoxic sensitivity to a given

dose of methotrexate. Differences may exist with delivery of the drug to the ectopic site. Schafer et al (1992) have shown that trophoblastic tissue cultures from intrauterine and I.P.s respond differently to in vitro exposure to methotrexate. Some cell cultures from both sources showed no response to methotrexate while ectopic trophoblastic tissue required concentrations approximately 10 fold higher to demonstrate the same suppression of β hCG levels.

Rising hCG concentration is a common phenomenon after methotrexate therapy given locally or parenterally. If this is not known to the surgeon he/she may prematurely decide on surgery and the treatment may be considered a failure. hCG titres return to pre-treatment values only on day 8 after the injection of methotrexate and the return to non pregnant values occurs within a month according to Fernandez & Lelaidier (1993).

Surgically Administered MTX-SAM

Over 10 authors have published their experience with SAM - from 1-100 cases per paper. Only 4 authors have published more than 25 cases. They are Pansky et al (1989), Koor & Koek (1990) Yao & Tulandi (1997) and Fernandez et al (1993).

Others regimes used are MTX 1 mg/kg intramuscularly 4 such daily injections with 15 mg daily of citrovorum factors by mouth for 4 days. Bhatt (1994) have reported on 16 patients given MTX + CV (1 mg/kg X 5 IM and 15 mg X 4 PO) and 19 patients with MTX 50 mg/m² IM single dose. The success rates were 87.5% and 84.2% respectively.

Local injection of methotrexate Vs linear salpingostomy has been compared by Porpora et al (1995). The mean operating time was longer for linear salpingostomy 67 \pm 15min (range 50-90 min) as compared to local MTX injection 32 \pm 5 min (range 25-35 min). The time for serum β hCG levels to disappear was shorter after linear salpingostomy than methotrexate injection (21.1 Vs 36.6 days). When hysterosalpingography was done in the follow up period there was no difference in tubal patency rate

Goldenberg (1993) in a review article on methotrexate therapy of tubal pregnancy mentions that with proper selection of patients success rate of approximately 90% has been achieved.

Toxic effects of methotrexate:

The adverse effects are as a rule dose related. Nausea, vomiting, abdominal distress, ulcerative stomatitis, leucopaenia and elevated liver enzymes may be seen.

Most of these reactions are reversible. Citrovorum factor decreases side effects of the drug but is not routinely used by all workers.

Other drugs tried are Actinomycin D, Potassium Chloride and hyperosmolar glucose.

Interstitial Pregnancy

Interstitial pregnancy is a more appropriate term than cornual pregnancy. It is a rare condition. Its incidence is reported as 2.4% of tubal pregnancies. It occurs 1 in every 2500 - 5000 live births. The mortality rate is 2 to 2.5%. (Mattingly and Thompson 1985).

In view of its life threatening nature, the usual treatment in the past was laparotomy followed by cornual resection or hysterectomy. Tanaka et al (1982) were the first to use Methotrexate for the successful treatment of this condition. Woodland et al (1996) have collected 9 cases from the literature and added one of their own

The transvaginal intrachorionic drug instillation is a simple medicosurgical approach restricted to early viable EP.

Pregnancy after laparoscopic management of an interstitial pregnancy needs close monitoring: the literature is scanty. A case of uterine rupture after 20 weeks gestation has been reported by Weismann and Fishman (1992).

Hysteroscopic removal of an interstitial pregnancy has been described by Cohen et al (1997). A patient with an interstitial pregnancy was treated with methotrexate. Abdominal pain appeared few days later despite a falling

β hCG titre. A laparoscopy and hysteroscopy were done. The cornu contained adhesions, the sac, the embryo and the decidua were removed with the hysteroscopy forceps. There was no bleeding. Diagnostic hysteroscopy 3 months later showed a patent ostium with few adhesions divided easily. Hysterosalpingography (HSG) done later showed a patent tubal ostium.

Ovarian Pregnancy

This is very rare (0.4%), the condition must be differentiated from ovarian attachment of an extruded tubal pregnancy. In true ovarian pregnancy fertilisation occurs within the ruptured follicle. Spiegelberg's criteria for the diagnosis of ovarian pregnancy are 1. the tubes and their fimbriae are separate from the sac 2. the pregnancy sac is in the position of the ovary 3. the presence of ovarian tissue surrounding the sac 4. the sac should be attached to the uterus by the utero-ovarian ligament. Decidual reaction occurs in the endometrium and to a limited degree in the ovarian stroma. Rupture occurs early after 2-3 weeks of a missed period with blood collecting in the Pouch of Douglas and the formation of a haemoperitoneum. Ovarian pregnancy can be treated by wedge resection at laparoscopy using the monopolar electrode or a diagnostic laparoscopy followed by methotrexate therapy (intraovarian or intramuscular).

Cervical Pregnancy

The incidence varies from 1:1000 in Japan to 1:16000 pregnancies as reported by the Mayo clinic. The ovum is implanted in the cervical canal which balloons out and may resemble an abortion. The following criteria are proposed for the diagnosis of this condition - 1. uterine bleeding following a period of amenorrhea without cramping or pain 2. a soft enlarged cervix equal to or larger than the fundus - the so called hour glass uterus 3. the products of conception entirely confined and firmly attached to the endocervix 4. a closed internal os and a partially opened external os.

When separation of the ovum occurs, the bleeding may be excessive from the non-retractile cervix. As the cervix is vascular and fragile, cervical pregnancy has been confused with neoplastic changes. Curettage and packing have been attempted but most often an abdominal

hysterectomy is necessary to control the bleeding. Today local or IM injections of methotrexate is useful and hysterectomy not necessary in most cases.

Heterotopic Pregnancy

The spontaneous occurrence of heterotopic ectopic pregnancy is rare. 1:2600 to 1:30,000 pregnancies (Richards et al (1982). The incidence has increased considerably in patients receiving in vitro fertilisation and embryo transfer. The diagnosis is difficult because of the intrauterine pregnancy and ovarian hyperstimulation; both ultrasound and serum β hCG values are unreliable. The diagnosis is often made after the tubal rupture. Treatment is difficult due to the presence of a viable wanted intrauterine pregnancy.

Expectant Management of Ectopic Gestation

Today with the availability of serum β hCG assays and ultrasound a selected group of patients can be treated expectantly. Probably the most important aspect of this mode of therapy is counselling of the patient and her accessibility to the emergency unit at any point of time should the need rise. The criteria for selection described by Ylostalo et al (1992, 1993) are a falling level of serum β hCG at 2 days intervals, no sign of intrauterine pregnancy, the size of the ectopic pregnancy <4 cm and no signs of rupture or acute bleeding by transvaginal sonography. Over a 3 year period they chose 25% of their cases for expectant management. Of those chosen for expectant management spontaneous resolution occurred in 72% (18% of all ectopic pregnancies). The other 36 patients (28%) were treated by laparoscopic salpingostomy after 2-18 days for various indications, such as pain, plateau or rising serum hCG after an initial fall increased volume of fluid in the pouch of Douglas or increase in the size of the adnexal mass. In one case tubal rupture occurred and was treated by laparoscopic salpingectomy.

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