CHARLES UNIVERSITY IN PRAGUE

THIRD FACULTY OF MEDICINE

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Ectopic pregnancy

"Etiology, modern diagnostics and therapeutic approach"

Prague March 2010

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Master's programme of study

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Date and year of defence: March 2010

Written Declaration

I declare that I completed the submitted work individually and only used the mentioned sources and literature. Concurrently, I give my permission for this diploma/bachelor thesis to be used for study purposes.

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ABSTRACT

Ectopic pregnancy should be considered a relevant public health indicator that presents as an acute emergency and life threatening event.

Despite the fact that that early diagnosis have led to decreased mortality rates and conservative laparoscopic treatments have enabled outcomes, ectopic pregnancy is a leading cause of maternal mortality and morbidity that is responsible for thousands of hospital admissions, surgical interventions and blood transfusions.It accounts for a sizeable proportion of infertility and ectopic recurrence, and it is a cause of up to 10% of all maternal deaths.[1]

INTRODUCTION

An ectopic pregnancy or extrauterine pregnancy is one in which the blastocyst implants anywhere other than the endometrial lining of the uterine cavity.

98% of ectopic pregnancies implant in the fallopian tube, with 80% occurring in the ampullary segment. Other locations include, but are not limited to, the ovary, cervix, and abdomen. In some form they account for 1.3% to 2% of reported pregnancies in the United States.[2]

Ectopic pregnancy was life-threatening in the past, today we can diagnose it earlier because of new ability to detect the ß- subunit of human chorionic gonadotropin (hCG) combined with high-resolution transvaginal sonography (TVS) which has reduced this threat.

The incidence of ectopic pregnancy has increased consistent with the rise in chlamydial infections.[2]

The increase is also in relation to improved methods of diagnosis and reporting.

Ectopic pregnancies still remain an important cause of morbidity and mortality worldwide.[2]

Incidence of ectopic pregnancy . Table 1[2]

Location	Natural conception	Incidence
Fallopian tube		98%
Ampulla		80%
Isthmus		12%
Fimbria		6%
Cornua		2%
Abdominal		1-2%
Ovarian		<1%
Cervical		0.15%

Location	Conception after assisted reproductive technologies	Incidence
Ampullary		93%
Tubal		82%
Cornual		7%
Ovarian/abdominal		5%
Cervical		1.5%

Epidemiology

Ectopic pregnancy has increased worldwide in its incidence. A study done have reported a three fold increase in Finland from 1966 to 1985 while Center for disease control (CDC) in USA reported a four fold increase in its incidence from 1970 to 1983 from 4.5 to 16.18 per 1.000 pregnancies. At the same time however the fatality rate decreased from 35.5 to 3.8 per 10.000 ectopic pregnancies-a decrease of 90%. Presently in the UK, ectopic pregnancy accounts for 11.5 % of all maternal deaths.[4]

Several factors may explain the trends of the increase of ectopic pregnancy.[1]

A higher prevalence of risk factors, like sexually transmitted diseases leading to pelvic inflammatory disease. A lower prevalence of protective factors, like lack of protection during sexual intercourse, having many sexual partners and an early sexual debut.[1]

The control of ectopic pregnancy have improved in the last 30 years. Awareness among health care providers may lead to more complete reporting of this condition.

The use of modern technology like laparoscopy, ultrasound examination and assay for human chorionic gonadotropin may permit early diagnosis of some ectopic pregnancies that would have gone unrecognised in the past.[1]

In recent years, many women have postponed bearing children until later reproductive life when the risk of ectopic pregnancy is greatest[5].

It is a big variation in reported incidence of ectopic pregnancy between developed and developing countries. [1]

In a study done in 2004, African countries were reported to have the highest incidence of ectopic pregnancy (0.5-2.3% of live births) and the lowest incidence where reported in Asia and Middle East during the same time period (0.4-0.6% of live births).[1]

Incidence of EP in England-Wales is reported as 12,4 per 1000 pregnancies between 1994-1996.

In Beijing and China the incidence is reported as 0.50 per 1000 women of reproductive age. Whereas in Nigeria incidence of ectopic pregnancy is reported as 4%.

In the United States it has been estimated that about 40 women die annually as a result of ectopic pregnancy, about 0.8 deaths per 1000 cases.

Moreover, this relative risk of death from ectopic pregnancy is 10 times the risk of death from childbirth and 50 times the risk of legally induced abortion.

In developing countries, it is a problem that maternal deaths are frequently underreported, resulting in the omission of numerous patients who died before receiving any treatment, including those who died due to EP.[1]

In Europe and the United States the rate of ectopic pregnancy is increasing.[6]

Two factors that can explain this is the recent increase in both chlamydial infections and cigarette smoking. These two factors explain 60% of cases of ectopic pregancies in French women of reproductive age. The currency of Chlamydia Trachomatis infection increased 23% between 1998 and 2002 and the number of woman smoking at age 15-44 increased by 8.2% between 1995 and 1999.[6]

The increased incidence of Chlamydia.Trachomatis infection is also observed in the middle of the 1990s in the Netherlands, Finland and Sweden.

An increase in the currency of cigarette smoking in women in reproductive age has been observed in Germany, Switzerland, Spain, Finland, Poland and Russia and this can be related to the increase in ectopic pregnancies.[6]

Ectopic pregnancy is responsible for thousands of hospital admissions, surgical interventions and blood transfusions.

I want to demonstrate some numbers related to the incidence of ectopic pregnancies in the tables below. This is a retrospective study of the incidence in different countries in the world.[7]

The crude rate of ectopic pregnancy per 1000 reported pregnancies rose [7]

- from 5.8 to 11.1 during 1962-1977 in Sweden
- from 5.7 -9.3 during 1971 -1980 in Canada
- from 4.5 to 16.8 during 1970-1987 in the USA
- from 3.22 to 5.9 during 1968-1974 in Norway

Indicence of ectopic pregnancy per 100 reported pregnancy:Table 3[7]

Country	Type of study	Setting	Time	Incidence of EP/100 reported pregnancy
England & Wales	Retrospective	Population based	1994 - 1996	1.24
Hungary	Retrospective	Population based	1995	0.64
France	Retrospective	Hospital based	1992	1.58
Ireland	Retrospective	Hospital based	1996	0.83
USA	Retrospective	Population based	1992	2.0
Mexico	Retrospective	Hospital based	1992-1995	2.06
Pakistan	Retrospective	Hospital based	1997-1999	1.3

Incidence of ectopic pregnancy per 100.000 women aged 15-44:Table 4

Country	Type of study	Population based	Time	Incidence of EP/100.000 women aged 15-44
Finland	Retrospective	Population based	1994	155
Norway	Retrospective	Hospital based	1988-1993	154
Sweden	Retrospective	Population based	1991	149

Incidence of ectopic pregnancy per No. of delivery:Table 5

Country	Type of study	Setting	Time	Incidence of EP/ No.delivery
China	Retrospective	Hospital based	12 years	1:52
India	Retrospective	Institutional based	1988-1993	1:160

Incidence of ectopic pregnancy per 1000 delivery:Table 6

Country	Type of study	Setting	Time	Incidence of EP/ 1000 delivery
UK	Retrospective	Institutional based	1990-1994	5.9
Saudi-Arabia	Retrospective	Hospital based	3&1/2 year	7.4
Ghana	Retrospective	Hospital based	1991-1993	39.3
Cameroon	Retrospective	Hospital based	1992	11.0

Summary of the incidence per denominator:Table 7

Incidence	Denominator
0.6-2	100 reported pregnancy
8-40	1000 delivery
152-160	1: number of delivery
149-155	100.000 women aged 15-44

ETIOLOGY

There are multiple factors that can contribute to ectopic pregnancy. Anything that impede the migration of the embryo to the endometrial cavity could predispose women to ectopic gestation. Pelvic infection is one of the explanations for the increasing number of ectopic pregnancies; however most patients presenting with an ectopic pregnancy have no identifiable risk factors. The following risk factors have been linked with ectopic pregnancy.[3]

Pelvic inflammatory disease

Antecedent infection caused by Chlamydia Trachomatis is the most common cause of ectopic pregnancy. The clinical presentations in the patients with chlamydial infection can range from asymptomatic cervicitis to salpingitis and florid pelvic inflammatory disease (PID) More than 50% of women who have been infected are unaware of the exposure.

Infection with Neisseria gonorrhoea also increase the risk of ectopic pregnancy. A history of salpingitis increases the risk of ectopic pregnancy 4 fold.

The incidence of tubal damage increases after successive episodes of PID (i.e, 13% after 1 episode, 35% after 2 episodes, 75% after 3 episodes)[3]

History of prior ectopic pregnancy

If a patient had one ectopic pregnancy earlier the patient obtain a 7- to 13 fold increase in the likelihood of another ectopic pregnancy.

A patient with prior ectopic pregnancy has a 50-80% chance of having a subsequent intrauterine gestation, and a 10-25% chance of future tubal pregnancy.[3]

History of tubal surgery and conception after tubal ligation

A patient who previously underwent a tubal surgery have an increased chance of acquiring ectopic pregnancy.

Salpingostomy, neosalpingostomy, fimbrioplasty, tubal reanastomosis, and lysis of peritubal or periovarian adhesions are among the surgeries that carry a higher risk of subsequent ectopic pregnancies.

Pregnancy after a previous tubal ligation increases the risk of developing ectopic pregnancy. Of those women who conceive after a tubal ligation thirty-five to 50% are reported to experience an ectopic pregnancy.

Bipolar cautery failure is more likely to result in ectopic pregnancy than occlusion using suture, rings or clips. Failure is related to fistula formation that allows sperm passage.

Tubal sterilisation can predispose to ectopic pregnancy, and usually occurs 2 or more years after sterilization.[3]

Use of fertility drugs or assisted reproductive technology

Induction of ovulation with clomiphene citrate or injectable gonadotropin therapy has been linked with a 4-fold increase in the risk of ectopic pregnancy in case control study. Multiple eggs and high hormone levels may be significant factors.

One study done on infertility patients shows that luteal defects have a statistically higher rate of ectopic pregnancy than patients where infertility is caused by anovulation.

When the patient has used assisted reproductive techniques to conceive, the risk of ectopic pregnancy and heterotopic pregnancy (ie. Pregnancies occurring simultaneously in different body sites) dramatically increases, such as in vitro fertilization (IVF) or gamete intrafallopian transfer (GIFT) .

The ectopic pregnancy rate was 4.5% in a study of 3000 clinical pregnancies achieved through in vitro fertilization, which is more than double the background incidence.

Studies have furthermore demonstrated that up to 1% of pregnancies achieved through IVF or GIFT can result in heterotopic gestation, compared to an incidence of 1 in 30.000 pregnancies for spontaneous conceptions.[3]

Use of an intrauterine device

Traditionally it was thought of as a risk factor if the patient used copper-containing or progesterone intrauterine device.

Today it is confirmed that the progesterone IUD has a rate of ectopic pregnancy higher than that for women not using any form of contraception, but the modern copper IUD does not increase the ectopic pregnancy risk.

On the other hand if the woman ultimately conceives with an IUD in place there is a 3-4% incidence of ectopic pregnancy.[3]

Increasing age

Age is a contributing factor to ectopic pregnancy and the highest rate occurs in women aged 35-44 years.

The risk of developing an ectopic pregnancy is a 3-4 fold increase compared to women aged 15-24 years.

An explanation to this can be the myoelectrical activity in the fallopian tube, which is responsible for tubal motility. Loss of this myoelectrical activity along the fallopian tube may be a result of aging. [3]

Smoking

It is documented that cigarette smoking is shown to be a risk factor for developing an ectopic pregnancy. The elevated risk in a smoking woman to develop an ectopic pregnancy is ranging from 1.6 – 3.5 times that of non-smokers. The amount of cigarettes the woman smokes can also have some influence..

Laboratory studies in humans and animals have postulated several mechanisms by which cigarette smoking might play a role in ectopic pregnancies, these are: **delayed ovulation, altered tubal and uterine motility, or altered immunity.**

Nevertheless, no study has to date supported a specific mechanism by which cigarette smoking affects the incident of ectopic pregnancy.[3]

Salpingitis isthmica nodosum

This is a condition of the fallopian tube characterized by nodular thickening of the tunica muscularis of the isthmic portion of the tube enclosing glandlike or cystic duplications of the lumen..

Histopathological sections taken from the fallopian tube have manifested that approximately 50% of patients that underwent salpingectomy for ectopic pregnancy have evidence of salpingitis isthmica nodosum.

Salpingitis isthmica nodosum has an unclear etiology, but mechanisms included are postinflammatory and congenital as well as acquired tubal changes such as observed with endometriosis.[3]

Other

Increased incidence of ectopic pregnancy can be associated with other risk factors like: Previous diethylstilbestrol (DES) exposure, a T-shaped uterus, prior abdominal surgery , failure with progestin-only contraception, and ruptured appendix.[3] (E medicine)

Risk factors

- Previous salpingitis
- Previous infertility
- Previous ectopic pregnancy and tube surgery
- Failing of contraception in relation to the use of copperspiral
- Failing of contraception in relation to sterilisation.
- Ovulation induction
- Smoking
- Diethylstilbestrol exposure and advanced age[2]

Location of ectopic pregnancies

Tubal Ectopic Pregnancy

Without intervention, the natural course of tubal pregnancy can lead to tubal abortion , tubal rupture, or spontaneous resolution. This tissue can then either regress or reimplant in the abdominal cavity. Tubal rupture is associated with significant intra-abdominal bleeding, often necessitating surgical intervention.[2]

Ovarian Pregnancy

Ectopic implantation of the fertilized egg in the ovary is rare. The recent increased incidence is likely due to improved imaging modalities. Risk factors are similar to those for tubal pregnancies. Diagnosis is based on the classical sonograph description of a cyst with a wide echogenic outer ring on or within the ovary.[2]

Interstitial Pregnancy

Also termed **cornual pregnancy**, interstitial pregnancies implant in the proximal tubal segment that lies within the muscular uterine wall.

Swelling lateral to the insertion of the round ligament is the characteristic anatomic finding. A pregnancy that implants in the cornual segment of the tube tends to present several weeks later in pregnancy , because the muscular cornu of the uterus is better able to expand and accommodate an enlarging pregnancy.

As a result, rupture of cornual (isthmic) pregnancy typically occurs between the eight and sixteenth gestational weeks, and is often associated with massive hemorrhage, frequently requiring hysterectomy. Mortality rates are quoted as a high as 2.5%.[2]

Cervical Pregnancy

Cervical pregnancy occurs in 1 in 9000 to 12.000 pregnancies, when the ovum implants in the cervical mucosa below the level of the histologic cervical internal os.

A risk factor unique to cervical pregnancy is a history of dilation or curettage, seen in nearly 70% of cases.

Two diagnostic criteria are necessary for confirmation of cervical pregnancy:

1) The presence of cervical glands opposite the placental attachment site, and

2) A portion of or the entire placenta must be located below either the entrance or the uterine vessels or the peritoneal reflection on the anterior and posterior uterine surface.

Medical management can be used if the previously described criteria are met.[2]

Heterotopic Pregnancy

Heterotopic pregnancy (coincident or combined pregnancy) is the coexistence of an ectopic and intrauterine pregnancy.

The incidence was previously estimated to be 1 in 30.000 pregnancies figuring incidences of dizygotic twinning and ectopic pregnancy of 1% each.

As a result of assisted reproduction, however, the rate of heterotopic pregnancies has increased to 1 in 100 pregnancies.

Mechanisms that have been proposed to explain this include:

1) Hydrostatic forces delivering the embryo into the cornual or tubal area

2) The tip of the catheter directing transfer towards the tubal ostia;or

3) Reflux of uterine secretions leading to retrograde tubal implantation. In addition to the option of surgical management of the ectopic pregnancy while attempting to not disturb the intrauterine pregnancy, medical therapy in which potassium chloride can be injected into the pregnancy sac is a consideration.[2]

Methotrexate is contraindicated due to potential debridemental effects on the normal pregnancy.

Abdominal pregnancy

The estimated incidence of abdominal pregnancy ranges from 1 in 10.000 to 1 in 25.000 live births. Abdominal pregnancies may result from primary implantation onto the peritoneal surface or secondary implantation via tubal rupture or tubal abortion . Physical findings and symptoms are widely variable, depending on gestational age and site of implantation. Diagnosis is confirmed primarily by ultrasonography.

Abdominal pregnancy is usually discovered long before fetal viability and removal of the pregnancy is the mainstay of therapy. Survival of the fetus occurs in only 10% to 20% of cases; up- to one half of those surviving have significant deformity . The patient is given the option of continuing the pregnancy to fetal viability with operative delivery , or operative termination of the pregnancy at the time of diagnosis. In either case, removal of the placenta is usually not attempted because of the risk of uncontrollable hemorrhage.[2]

Symptoms

Because of the availability of early pregnancy testing, the ability to diagnose ectopic pregnancy before rupture-even before the onset of symptoms-is not unusual.

The classic symptoms associated with ectopic pregnancy are amenorrhea followed by vaginal bleeding and abdominal pain on the affected side. However there is no constellation of symptoms that are diagnostic.

Other pregnancy discomforts, such as breast tenderness, nausea and urinary frequency, may accompany more omnious findings. Also included is shoulder pain worsened by inspiration, which is caused by phrenic nerve irritation from subdiaphragmatic blood, or vasomotor disturbances such as vertigo and syncope from hemorrhagic hypovolemia.

As long as the placental hormones are produced, there is usually no vaginal bleeding. Irregular vaginal bleeding results from the sloughing of the decidua from the endometrial lining.[2]

Vaginal bleeding in patients with an ectopic gestation may range from little or none to heavy, menstrual like flow. In some patients, the entire " decidual cast" is passed intact, simulating an spontaneous abortion.

Histologic evaluation of this tissue confirms whether placental villi are present. In any patient with a positive pregnancy test result, whenever evaluation of tissue passed spontaneously or obtained by curettage does not demonstrate villi, an ectopic implantation should be assumed to be present until proven otherwise.

Many women with a small unruptured ectopic pregnancy may have unremarkable clinical findings. Nevertheless, the diagnosis should be considered strongly when any of the above symptoms are reported by reproductive age women, especially those with risk factors for an extrauterine pregnancy.[2]

Clinical findings

Abdominal and pelvic findings are notoriously scant in many women before tubal rupture.

Prior to rupture, the diagnosis of an ectopic pregnancy is primarily based on laboratory and ultrasound findings.

With rupture, however, nearly three-fourths of women will have marked tenderness on both abdominal and pelvic examination, and pain is aggravated with cervical manipulation.

A pelvic mass including fullness posterolateral to the uterus, can be palpated in about 20% of women.

Initially, the ectopic pregnancy may feel soft and elastic, whereas extensive hemorrhage produces a firmer consistency.

Many times, discomfort precludes palpation of the mass. Avoidance of pelvic examination may actually help avert iatrogenic rupture.[2]

Fever is not expected, although a mild elevation in temperature in response to intraperitoneal blood may occur. A temperature of 38% may suggest an infectious cause to the patients symptoms.

Abdominal distention tenderness, with or without rebound, rigidity or decreased bowel sounds may be seen in cases of intra-abdominal bleeding.

Abdominal tenderness is variable; it is present in 50% to 90% of patients with ectopic pregnancies. Cervical motion tenderness caused by intraperitoneal irritation and adnexal tenderness are commonly found. An adnexal mass is present in roughly one-third of cases, but its absence does not rule out the possibility of an ectopic implantation. The uterus may

enlarge and soften throughout the first trimester, thus simulating an intrauterine pregnancy. A slightly open cervix with blood or decidual tissue may be found and mistaken for a threatened/or spontaneous abortion.[2]

Differential diagnosis

Symptoms of ectopic pregnancy can mimic multiple entities.

Early pregnancy complications (threatened, incomplete, or missed abortion), placental polyp, or hemorrhagic corpus luteal cyst are difficult to diagnose.Moreover, early bleeding occurs in about 20% of women with normal pregnancies.

A number of nonpregnancy-related disorders, such as appendicitis and renal calculi, can mimic ectopic pregnancy.

The rapid and accurate diagnosis of ectopic is imperative to reduce the risk of serious complications or death.

Up to half of the women who have died as a result of ectopic pregnancy had a lag in treatment because of delayed or inaccurate diagnoses.

Any sexually active woman in the reproductive age group who presents with pain, irregular bleeding, and/ or amenorrhea should have ectopic pregnancy as part of the initial differential diagnosis.[2]

Diagnostic procedures

High resolution transvaginal sonography and serial serum ß-hCG

The most valuable diagnostic aids to confirm the clinical suspicion of an ectopic pregnancy is with **high resolution transvaginal sonography and serial serum ß-hCG** .

The initial assessment in the otherwise hemodynamically stable patient must include a pregnancy test.

A negative pregnancy test excludes the possibility of ectopic pregnancy. Urinary pregnancy tests which detect hCG levels to 20 IU/L , are now commonly available. These tests detect hCG as early as 14 days after conception and are positive in more than 90% of cases of ectopic pregnancy. Serum assays can detect the presence of hCG as early as 5 days after conception, that is, before the missed menstrual cycle; however, because they require additional time and expertise to perform, they are often not used in a potentially emergent clinical setting.

If a positive pregnancy test is found when ectopic pregnancy is suspected, the remainder of the workup should focus on evaluating the viability and location of the pregnancy.

In normal pregnancies , serum ß-hCG levels rise in a log-linear fashion until 60 or 80 days after the last menses, at which time values plateau at about 100, 000 IU/L. During this period a 66% or greater increase in serum ß-hCG levels should be observed every 48 hours. Approximately 15% of normal intrauterine pregnancies are associated with less than a 66% increase in hCG , and 17% of ectopic pregnancies have normal doubling times. [2]

Deviation from this pattern should raise suspicion for a pregnancy that is not proceeding normally, including ectopic pregnancy.

Although inappropriately rising serum ß-hCG suggests (but do not diagnose) an abnormal pregnancy, they do not identify its location

A key adjunct to serial quantitative levels of hCG is pelvic ultrasonography. High-resolution ultrasonography has revolutionized the clinical management of women with a suspected ectopic pregnancy.

Using transvaginal ultrasonography, a gestational sac is usually visible between 4 1/2 and 5 weeks from the last menstrual period, the yolk sac appears between 5 and 6 weeks , and a fetal pole with cardiac activity is first detacted at 5 1/2 to 6 weeks.

With transabdominal sonography these structures are visualized slightly later.

Each institution must define a ß-hCG discriminatory value, that is , the lower limit of hCG at which an examiner can reliably visualize pregnancy on ultrasound. The more sensitive transvaginal ultrasonography should show the pregnancy by the time the hCG level is 1000 to 2000 IU/L.

Transabdominal ultrasonography should be able to identify an intrauterine gestation by the time the hCG level reaches 5000 to 6000 IU/L.[2]

Accurate diagnosis by sonography is three times more likely if the initial ß-hCG level is above this value. The absence of uterine pregnancy with ß-hCG levels above the discriminatory value signifies an abnormal pregnancy; ectopic, incomplete abortion , or resolving completed abortion.

Care must be taken to differentiate between a uterine gestation and a pseudogestational sac. This one-layer sac is the result of an intracavitary fuid collection caused by sloughing of the decidua typically situated in the midline of the uterine cavity, whereas a normal gestational sac is eccentrically located.[2]

Serum progesterone

Serum progesterone concentration has also been used as as screening test for ectopic pregnancy . There is minimal variation in serum progesterone concentration between 5 and 10 weeks`s gestation , thus a single value is sufficient.

A serum progesterone level of < 5 ng / ml has been used to identify a non-viable pregnancy with near-perfect specificity and with sensitivity of 60% .

Conversely a serum progesterone of > 20 ng has a sensitivity of 95% with a specificity of approximately 40 % to identify a healthy pregnancy

Serum progesterone values cannot differentiate between an ectopic and intrauterine pregnancy.[2]

Curettage of the uterine cavity can also help rule out ectopic pregnancy but should only be undertaken after the possibility of interrupting an intact pregnancy has been considered.

Identification of chorionic villi in tissue samples identifies an intrauterine location of the pregnancy and essentially rules out ectopic pregnancy.

The presumptive diagnosis of ectopic pregnancy is reportedly inaccurate in nearly 40% of cases without histologic exclusion of a spontaneous pregnancy loss. The **Arias-Stella reaction**, a hypersecretory endometrium of pregnancy seen on histologic examination, occurs with both ectopic and intrauterine pregnancies and, therefore, is not useful in identifying an ectopic pregnancy.[2]

Culdocentesis can identify **hemoperitoneum** , which may indicate a ruptured ectopic pregnancy, although it is also consistent with other causes such as a ruptured corpus luteum cyst.

An 18-gauge needle is inserted posterior to the cervix , between the uterosacral ligaments, and into cul-de-sac of the peritoneal cavity. Aspiration of clear peritoneal fluid (negative culdocentesis) indicates no hemorrhage into the abdominal cavity but does not rule out an unruptured ectopic pregnancy .

Aspiration of blood that clots can indicate either penetration of a vessel or such rapid blood loss into the peritoneal cavity that the blood clot has not had time to undergo fibrinolysis..

Nonclotting blood is evidence of hemoperitoneum (positive culdocentesis) in which the blood clot has undergone fibrinolysis. If nothing is aspirated (equivocal or nondiagnostic culdocentesis) , no information is obtained.[2]

Purulent fluid suggests a number of infection-related causes, such as salpingitis or appendicitis. Because no finding on culdocentesis can definitively confirm the presence or absence of ectopic pregnancy, its use in clinical practice has declined.

When used, the primary utility of culdocentesis is that a positive culdocentesis identifies blood in the peritoneal cavity and confirms the need for further evaluation to identify the source of the bleeding.

The most accurate technique of identifying an ectopic pregnancy is by direct visualization, which is done most commonly by laparoscopy. Even laparoscopy, however has a 2% to 5% misdiagnosis rate. For example, an extremely early tubal gestation may not be identified because it may not distend the fallopian tube sufficiently to be recognized as an abnormality (false-negative)

Conversely, a false positive diagnosis may result from a hematosalpinx (blood in the fallopian tube) being misinterpreted as an unruptured ectopic pregnancy or tubal abortion.[2]

Management

Management may be either surgical or medical, depending on a variety of factors. Surgery may be minimal or extensive, depending on the gestational age of the pregnancy and other factors. Due to the inherent risk of each; medical therapy is preferred over surgery in appropriate patients.[2]

Medical Management:

Methotrexate is the medical treatment used as an alternative to surgical therapy.

Methotrexate is a folic acid antagonist that competitively inhibits the binding of dihydrofolic acid to dihydrofolate reductase, which in turn reduces the amount of active cellular metabolite, folinic acid.

The best candidate for medical therapy is the woman who is asymptomatic, motivated, and who has resources to be compliant with follow-up. Relative and absolute contraindications for medical management are listed in the table below.[2]

Table 2 - Contraindications to medical therapy for ectopic pregnancy [2]:

Absolute

- Breastfeeding
- Overt or laboratory evidence of immunodeficiency
- Alcoholism , alcoholic liver disease, or other chronic liver disease
- Preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, or thrombocytopenia, or significant anemia
- Known sensitivity to methotrexate
- Active pulmonary disease
- Peptic ulcer disease
- Hepatic, renal, or hematologic dysfunction

Relative

- Gestational sac greater than 3.5 cm
- Embryonic cardiac motion[2]

Factors that can be assessed in predicting the success of medical therapy include initial ß-hCG level, size of ectopic pregnancy is determined by TVS, and the presence or absence of fetal cardiac activity.

The initial serum ß-hCG level is the single best prognostic indicator of treatment success in women given single-dose methotrexate.

An initial serum value < 5000 IU/L is associated with a success rate of 92% whereas an initial concentration > 15.000 IU/L has a success rates of 68%.

Although there are few data concerning the effect of ectopic pregnancy size on success rates with methotrexate, many early trials used " large size " as an exclusion criterion.

Success rates with singledose methotrexate were 93% in cases with ectopic masses < 3.5 cm.

Cardiac activity and size greater than 3.5 cm are considered relative contraindications to medical management because these findings are associated with a lower success rate.

The most common side effects of methotrexate include nausea, vomiting, diarrhea, gastric distress, dizziness and stomatitis.

Intramuscular methotrexate given as single dose has been the most widely used medical treatment of ectopic pregnancy . Close monitoring is imperative.[2]

A serum ß-hCG level is determined before administering methotrexate and is repeated on days 4 and 7 following injection.

Levels may continue to rise until day 4. Comparison is then made between the day 4 and the day 7 serum values.

If there is a decline by 15% or more, weekly serum ß-hCG levels are measured until they are undetectable.

If the ß-hCG levels does not decline, the patient may require either surgery or a second dose of methotrexate if no contraindications exist.

If there is an adequate treatment response , hCG determinations are reduced to once a week.

An additional dose of methotrexate may be given if ß- hCG levels plateau or increase in 7 days.

Surgical intervention may be required for patients who do not respond to medical therapy.

During the first few days following methotrexate administration , up to half of women experience abdominal pain that can be controlled with nonsteroidal inflammatory drugs. This pain presumably results from tubal distention caused by tubal abortion or hematoma formation or both.[2]

Surgical management

Conservative surgery has replaced the standard laparotomy due to the ability to make earlier diagnosis and improvements in microsurgical techniques.

The conservative surgical approach include linear salpingostomy and milking the pregnancy out of the distal ampulla.

The more radical approach includes resecting the segment of the fallopian tube that contains the gestation with or without reanastomosis.

Laparoscopy is a favored approach. In hemodynamically unstable patients or patients with cornual ectopic pregancies laparotomy is used. It is also a preferred method for surgeons who are inexperienced in laparoscopy and in patients where laparoscopic approach is difficult.(e.g secondary to the presence of multiple dense adhesions, obesity or massive hemoperitoneum).

Laparoscopic treatment result in fewer postoperative adhesions than laparotomy. Blood loss and the need for analgesia is less after a laparoscopic approach. Laparoscopy also reduces cost, hospitalization and convalescence period.

In ampullary unruptured ectopic pregnancies , linear salpingostomy along the antimesenteric border to remove the products of conception is the procedure of choice.[3]

Intraoperative details[3]

Salpingectomy is indicated in the following situations:

- The ectopic pregnancy has ruptured
- Future fertility is not desired
- There is a sterilisation failure
- It is a previously reconstructed tube
- Sterilization is requested

- Hemorrhage continues after salpingotomy
- The ectopic pregnancy is in the blind-ending distal segment after partial salpingectomy
- There is chronic tubal pregnancy.

If there is absence of any of these indications, salpingotomy may be performed instead.[3]

Women who are hemodynamically stable and in whom there is a small tubal diameter, no fetal cardiac activity ,and serum ß-hCG concentrations < 5000 IU/L have similar outcomes with medical or surgical management.

Conservative surgical techniques maximize preservation of the fallopian tube.

If removal is done through the laparoscope, definitive diagnosis and treatment can be accomplished at the same operation with minimal morbidity, cost and hospitalization.

In a **linear salpingostomy**, the surgeon makes an incision on the fallopian tube over the site of implantation, removes the pregnancy, and allows the incision to heal by secondary intention.[2]

A **segmental resection** is the removal of a portion of the affected tube.[2]

Salpingectomy is removal of the entire tube, a procedure reserved for those cases in which little or no normal tube remains.

When conservative surgery or nonsurgical treatment is used, the patient must be followed post therapy with serial quantitative ß-hCG levels to monitor regression of the pregnancy .

Subsequent surgery or methotrexate therapy is needed if trophoblastic function persists as evidenced by persistent or rising levels of Hcg.

Rh-negative mothers with ectopic pregnancy should receive Rh-immune globulin to prevent Rh sensitization.[2]

Fertility after treatment

Conservative surgery restores tubal patency in over 80% of cases. We can see in general that the ratio of intrauterine to recurrent ectopic pregnancy is about 6:1 but it rises to about 10:1 if the other tube appears normal.

After one ectopic and tubal sparing surgery we can see that the subsequent delivery rate is about 55-60%. The recurrent ectopic rate is about 15% and the infertility rate is about 25-30%.

If the other tube is absent or blocked there is a subsequent delivery rate of about 45-50%. The recurrent ectopic rate is about 20% and the infertility rate is about 30-35%.

If a patient had 2 or more ectopic pregnancies and conservative surgery the subsequent delivery rate is about 30%. The recurrent ectopic rate is about 20-30% and the infertility rate is about 40-50%.

The more ectopic pregnancies a woman has the more difficult is it to have live births without IVF treatment.[8]

Prevention

Ectopic pregnancy cannot be prevented but the contributing factors leading to it can.

Risk factors like early sexual debut, multiple sexual partners, no use of condom as protection during intercourse, can all lead to the infection by sexually transmitted diseases and pelvic inflammatory disease which can cause ectopic pregnancy.

It is important that young people get information about these risk factors at an early age. Health workers should provide this information to teachers, parents and other adults who can bring the information to the young adults.

The most common sexually transmitted diseases like Chlamydia Trachomatis and Neisseria Gonorrhoea can be avoided if a person practises safe sex. The use of a condom is an important prevention tool against pelvic inflammatory disease.

Screening for sexually transmitted diseases is also an important factor that decreases the incidence of pelvic inflammatory disease.

Good screening procedures of sexual transmitted diseases like Chlamydia and Gonorrhea is a contributing factor to prevention. It is important to inform the people about the importance of regular screening in order to avoid evolving of the disease. Any person who had unprotected sexual intercourse with a person that he or she is not in a relationship with should undergo an STD test.

Once diagnosed with a STD, the person has a moral and legal duty to inform all recent sexual partners.

Surgeries of the reproductive system, bowels, or lower abdomen are often complicated by excessive scarring and adhesions. Therefore, the surgeon should always use the best approach available to minimize all possible risks.

A pregnant woman with increased risk of having an ectopic pregnancy, should go to see a specialist in the hospital after evidence of positive pregnancy test. This makes the physician able to follow up the pregnancy and look for abnormalities. The screening includes the measurement of ß-hCG concentrations and transvaginal ultrasonography. These two methods have a sensitivity of 84-88% and specificity of 100%.[3]

Smoking is also a contributing factor to the incidence of ectopic pregnancy. If the women change their smoking habits, they can decrease their chance of developing ectopic pregnancy as well.

Age is also a risk factor and should be taken into account. Good family planning could be a prevention tool for appropriate timing of conception.

In developing countries the situation is very different from that of developed countries.

In the developing countries, missing education in the general population leads to lack of information about prevention of sexually transmitted diseases. The economic status is also poor and health care is not optimal. There are big distances from hospital to hospital and women do not get help fast enough in emergency situations such as ruptured ectopic pregnancy.

Very important is also that the woman seeks help and that health professionals give help as fast as possible in situations like ruptured ectopic pregnancy. Health care workers should be

trained to look for risk factors in the anamnesis of their patient and also include ectopic pregnancy into differentials when a woman comes to the hospital.

A ruptured ectopic pregnancy should be treated as a life threatening event. The time it takes for the woman to get to the hospital is an important factor, availability of hospitals with trained staff is also necessary to decrease the morbidity of ectopic pregnancy.

Conclusion

Ectopic pregnancy is a major cause of maternal mortality and morbidity. It is a common and serious problem for the woman.

Nowadays, good technology like laparoscopy, transvaginal ultrasound and ß-hCG is available to detect the ectopic pregnancy in such an early state that it decreases the mortality rate drastically.

Conservative surgery has taken over for the laparotomic approach since it is less invasive, less time consuming and more cost effective.

A meta-analysis of medical versus surgical therapy for ectopic pregnancy was published in Human Reproduction Update 2008 and The Cochrane Collaboration. Results of this study indicated that laparoscopic surgery for ectopic pregnancy was the most cost-effective approach. Medical therapy using methotrexate was also cost effective for beta-hCG levels less than 3000 mIU/mL. Both approaches were found effective in appropriately selected patients with adequate follow-up.[3]

The rate of ectopic pregnancy is increasing in different parts of the world due to the increased incidence of infection with Chlamydia trachomatis and Neisseria.Gonorrhoea.

Women today have more sexual partners and an earlier sexually debut than before. It also takes longer time for a woman nowadays to settle down with one man and that means she will have several sexual partners during her young reproductive life and has a bigger chance of detecting some form of STD.

Globalisation has also led to an increased rate of people travelling, so the sexual transmitted diseases does not stay in one country but crosses borders and get imported around the world.

Use of the contraception pill can make women and men forget that the pill is a protection against pregnancy but not for sexually transmitted diseases.

Increased incidence of smoking women also shows a relationship with the increased rate of ectopic pregnancy in Europe today.

The women can also make a choice to get pregnant later in life than earlier and this again lead to higher maternal age and higher risk of ectopic pregnancy.

The difference between the developed world and the developing world is also important to take a look at.

In the developed world we can see that the incidence increases but that the mortlity has decreased. In the developing world the mortality rate is extremely high due to the lack of proper health service.

In the developing world, the lack of general education , political infrastructure and the high incidence of poverty are factors that influence the low incidence of protection during sexually intercourse, screening for ectopic pregnancy and emergency service in critical situations.

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Ectopic Pregnancy Updated: Aug 2, 2009
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