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Ectopic Pregnancy-
Etiology, Modern Diagnostic and therapeutic approach.

Diploma thesis

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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.

In Prague on March 31th, 2009

Anders Norvik

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Summary

Ectopic pregnancy can be a life-threatening condition occurring in women all over the world. Over the past decades there has been a fluctuation in the incidence of the condition. This can be explained by factors like changing incidence of PID in the population, changing habits in contraceptive (IUD) use and increased diagnostic abilities.

The clinical picture of ectopic pregnancy can be very individual and the doctor must therefore always have a high suspicion towards the diagnosis in a fertile woman, independent of symptoms.

The presenting signs and symptoms range from a completely asymptomatic woman to a woman presenting with an acute abdomen and shock. The symptoms most commonly reported are abdominal pain, vaginal bleeding or spotting and amenorrhoea can also be present.

The cornerstones in the diagnosis, together with history and physical examination, are ultrasound and hCG levels in serum. Despite the big progress in diagnosing the condition there can be cases where the physician will feel unsure about the diagnosis.

Complication that we fear the most is rupture. It can lead to death. Since this is a outcome we don't want, it is necessary to increase the awareness among doctors and nurses and always think of the condition when presented with a woman in her fertile age.

Introduction

Ectopic pregnancy can be a medical emergency. It is still the number one killer of pregnant women in the western world. The mortality has been reported to vary between 0.97 per 1 000 000 people in South-Africa, 0,22 in Norway, 0,10 in the Czech republic, 0,03 in Canada and 0.02 in the UK⁴².

Ectopic pregnancy is defined as implantation of a fertilized egg outside the uterine corpus, most commonly in the fallopian tubes. The basic problem in ectopic pregnancy is that the site where the embryo is implanted is not able to develop in the same phase as the embryo. This can lead to rupture of the organ it is implanted into and this leads to great bleeding. It is therefore an important condition all healthcare personnel should have some basic knowledge of. All physicians, no matter what speciality, should be very aware of the diagnosis and always have a high suspicion when presented with a woman in her reproductive age with abdominal pain, gynaecological problems or in worst case, haemodynamic instability and signs of acute abdomen.

I have focused my Diploma work on the epidemiology, risk factors, prevention, possible causes, diagnosis and treatment of ectopic pregnancy.

My discussion will be based on articles found through searches in PubMed and I have used them in order to build up under arguments for and against different aspects of ectopic pregnancy. I have tried to be as balanced and informative as I can. My approach in obtaining sources has not been of a methodological character and has been based on what I thought would be relevant for my discussion. All my sources will be listed at the end of my work.

1. Epidemiology and risk factors

Ectopic pregnancy(EP) is a condition that occurs in women all over the world, during their whole period of reproductive age.

Today the overall incidence of EP is somewhere between 100-175 per 100 000 women aged 15-44 in the western world. It is most common in women aged 35-44 years in USA, France Sweden and others while in Norway it is most commonly seen in the age group 25-34 years. The risk factors of EP are many. The most common risk factor is a history of previous infections. Other risk factors are smoking, previous surgery, previous EP and others. In the following discussion I will look closer at changes in the incidence over the last decades and risk factors for ectopic pregnancy. My findings will be further discussed in the section Discussion.

1.1 Incidence

The incidence of EP was increasing in most industrialized countries during the 70's and 80's and then stagnating or declining during the 90's.

In a Swedish study (1) the authors show the trend of EP in women from 15-54 in the time period 1970-1997. The data was collected from a Swedish area with 120 000 inhabitants. They divided the period into smaller periods of 5 years. Their results showed that in the period from 70-74 there was a sharp increase in EP from 7.7 per 1000 pregnancies to 13.4. Over the next 15 years the situation was quit stable with a slight increase and the trend changed in the late 80's/early 90's with a decrease in incidence with 30% by 1997 back to approximately 8%. The same trend was also seen in USA during the period of 1980-1999(2, 10), in New South Wales between 1993 and 1998 (3) and in France it the period 1992-1997(4).

Two studies performed in Norway show a bit different trend (5, 6). One was carried out between 1976 and 1993 and it showed that the incidence rose during all 3 periods (the 18 years was divided into 6 years periods). The other study done in Norway (6), women from 15-44 years of age from 1970 to 1993 showed the same trend, with an increase of incidence throughout the period. Studies involving the period from 1990 to 2001 (7), show that also Norway catches on the trend of decrease seen in Sweden and other countries in the 80s. This turning-point is not seen before 93/94.

After seeing the decreasing incidence during the 90's, J. Thorburn from Sweden stated in 1995 that the epidemic "seemed" to be over (8). This statement was argued against in a French study from 2004 (9). Here the incidence of EP was studied between 1992-2002 using material from the Auvergne register(see below). Even though we can see an overall decrease in incidence during this period there is an increase in EP due to reproductive failure compensated by a decrease in EP due to contraceptive failure (we should distinguish the two due to different risk factors). Therefore we see that the incidence might be on the rise again. The decrease in EP due to contraceptive failure is due to changes in use of contraceptives. Women don't use IUDs so often anymore.

The Auvergne register is a collection of data where all women, in the age group 15-44 from a certain area of France with previous EP are included. The information collected by the register concerns socio-demographic characteristics, sexual, gynaecological, reproductive and surgical history, conditions at conception(use of contraception, ovulation induction, IVF), smoking habits, result of serological tests for *Chlamydia Trachomatis*, characteristics for the EP(site, tubal rupture, haemoperitoneum) and treatment given. It has been used in many French studies on ectopic pregnancy

Even though the changes in EP incidence have been quite uniform throughout the western world there can be big differences among different ethnic groups. This can be illustrated by a study from California in USA (10). Calderon and his colleagues looked at the incidences of EP among different ethnic groups from 1991 till 2000. African American women were those with the highest incidence of ectopic pregnancy (29.5/1000 – 21.6/1000 pregnancies during the time period), Hispanics had the lowest incidence(9.4 – 7.2/1000) and Asians were between white women and Hispanics. White women were used as controls (18.9-10,3/1000). This is a quite interesting finding, since the Hispanics and Afro-Americans come from similar socioeconomic levels of the American society. The differences can not be blamed on poverty and low living standard then. Apparently there are big differences inside the Hispanic group depending on the origin of the people. The majority of Hispanic people in California come from Mexico. If we look at the Puerto-Ricans in New York, also representing the Hispanics, they share the same incidence as the afro-American women in California understating again the diversity among the American population. Despite the big differences the same age groups were dominating the statistics across the races (35-44yoa).

1.2 Risk Factors

A French retrospective study (11), using data from Auvergne register, were in 2002 able to review a lot of different risk factors in relation to EP(see table 1). They obtained data from the period 1993-2000 including women aged 15-44 with EP. Women being on contraceptives (IUDs mainly) at the time of conception were excluded from the study since there is no correlation between other risk factors and EP in this group. They found 803 cases of EP and had a group of 1,683 controls.

The main risk factors were divided into four different groups:

1. Socio-demographic characteristics.
2. Surgical, gynaecologic and obstetric history.
3. Potential exposure to infectious factors and.
4. Contraceptive history and fertility markers.

In group one they found that only age and smoking had impact on the risk of getting EP. Educational level on the other hand has no influence on the risk(OR=1.0 – 1.1). The risk related to age, judged by the odds ratio, is increasing with the age of the woman where women over 40 have the highest risk(OR=5.7). The same relation is seen with smoking. Here the number of cigarettes smoked per day dictates the risk.

Moving on to group number two we see that prior deliveries, prior ectopic pregnancies, spontaneous abortions/ induced abortions, ruptured appendixes and prior tubal surgery all increases the chance of EP. Furthermore, when looking at induced abortions we see that medically induced abortions (OR=2.6) imply a higher risk for EP than what surgical abortion do (OR=1,4 CI=1.1 – 1.8, the CI excludes this factor as a risk).

In group three we see clearly a correlation between infection and higher risk of EP, where the highest risk is seen among ladies with a history of STD with confirmed PID. Other measures related to infections, like age at first intercourse and number of sexual partners also backup under this statement. The less partners and the higher age of debut give less chances to get an STD and a lower risk for EP the way I see it.

The last group concerning contraceptive history and fertility markers shows that oral contraceptives decrease the risk of EP while IUD's increases the risk. A prior history of infertility also increases the risk for EP.

Variables	OR*	CI*	p value
Woman's age (years)			
<20	0.6	0.2, 2.1	
20–24	0.9	0.7, 1.3	
25–29	1		0.01
30–34	1.3	1.0, 1.7	
35–39	1.4	1.0, 2.0	
<u>≥40</u>	<u>2.9</u>	1.4, 6.1	
Smoking			
Never	1		<0.001
Past smoker	1.5	1.1, 2.2	
1–9 cigarettes/day	1.7	1.2, 2.4	
10–19 cigarettes/day	3.1	2.2, 4.3	
<u>≥20 cigarettes/day</u>	<u>3.9</u>	2.6, 5.9	
Prior spontaneous abortions			
None	1		0.02
1–2	1.2	0.9, 1.6	
≥3	3.0	1.3, 6.9	
Prior induced abortions			
None	1		0.05
Surgical only	1.1	0.8, 1.6	
Medical (or medical and surgical)	<u>2.8</u>	1.1, 7.2	
Appendectomy			
No, or unruptured appendix	1		0.20
Yes, ruptured appendix	1.4	0.8, 2.4	
Prior sexually transmitted diseases			
None	1		<0.001
Yes, without salpingitis	1.0	0.8, 1.3	
Yes, with probable pelvic inflammatory disease	2.1	0.8, 5.4	
<u>Yes, with confirmed pelvic inflammatory disease</u>	<u>3.4</u>	2.4, 5.0	
Prior tubal surgery			
No	1		<0.001
Yes	<u>4.0</u>	2.6, 6.1	
Previous use of oral contraceptive			
No	1		0.03
Yes	0.7	0.5, 1.0	
Previous use of intrauterine device			
No	1		0.10
Yes	1.3	1.0, 1.8	
History of infertility			
No	1		<0.001
<1 year	2.1	1.2, 3.6	
1–2 years	2.6	1.6, 4.2	
<u>≥2 years</u>	<u>2.7</u>	1.8, 4.2	

Table 1: Main risk factors for ectopic pregnancy by final logistic regression analysis (random effects model), register of the Auvergne region, France, 1993–2000 (10) * OR, odds ratio; CI, confidence interval (11).

1.3 Prevention of ectopic pregnancy.

Having now spoken about risk factors of EP I can move on to talk about prevention of EP. The only two ways of doing this, at least in relation to the risk factors, is decreasing smoking in the population and decreasing the amount of STD's in the population.

A Swedish study (1) has shown a correlation between the incidence of PID and EP in a population. They looked at the period from 1970 to 1997 using data from admissions at the department of obstetrics and gynaecology in Orebro Medical Centre Hospital. We know when looking at the risk factors above that PID is a strong risk factor for later development of EP. This can again be transformed into saying that the incidence of PID is reflected in the incidence of EP. The rise of PID during the 60s and early 70s correlates with the rise of EP during the late 70s and early 80s in USA and Europe. Table 2, from the Swedish study, understates the trend in late 70s 80s and 90s.

Table 2 : Incidence of ectopic pregnancy and pelvic inflammatory disease in the time period 1970–1997 (1).

Time periods	EP per 1000 women		PID per 1000 women	
	≤24 y.	≥25 y.	≤24 y.	≥25 y.
1970-4	0.49		5.95	1.45
1975-9	0.97	0.84	7.75	1.71
1980-4	0.68	1.17	4.52	1.41
1985-9	0.73	1.59	3.39	1.01
1990-4	0.88	1.23	1.55	0.63
1995-	0.33	1.05	0.74	0.46
1996-	0.33	0.94	0.41	0.51
1997-	0.25	0.78	0.67	0.43

We see that the highest incidence of PID is in women below 25 years. The highest incidence of EP is seen in those over 25 years of age. Furthermore we see that when the PID drops in women aged less than 25 years we also see a decrease in the EP for the

same age group while the incidence of EP is unaffected in those over 25 years. We also see that after some periods of drop in PID among those under 25 years the incidence of EP starts to decrease in those over 25 years. This points out a correlation between EP and PID. Even thou the author discusses the weaknesses in an ecological study and the fact that the data was only gathered from one region of Sweden, he is still of the opinion that the findings are true for Sweden and that the study builds up under his point.

In Sweden they screen for Chlamydia in their female population. An ecological analysis (12) was conducted using data from Uppsala Chlamydia database and discharge data from University Hospital in Uppsala. The authors state that the screening program for Chlamydia has been effective in decreasing the incidence of Chlamydia among the Swedish population. They conclude with that a declining incidence of Chlamydia is correlated with a

decreasing incidence of EP. This implies that EP can be prevented on national basis through screening and treating the population for Chlamydia.

Another Swedish(13) study done to compare the chlamydial infections and EPs in Uppsala county and South East Thames Region. They found a decline in both chlamydial infections and ectopic pregnancies in Uppsala, where screening for Chlamydia is done. In the SE Thames region on the other hand there was an increase in both conditions in the same time period. This again understates the argument for screening the population for Chlamydia. They have now introduced Chlamydia screening in UK and studies are underway to determine the efficacy of this.

Based on these three studies we can see a much clearer link between EP and PID.

From a preventive point of view this means that EP can be prevented through informing the population of the importance of safe sex. Further we see that a national screening program for Chlamydia can decrease the incidence of EP since this measure will decrease the prevalence and incidence of Chlamydia in the population.

Risk for EP would be decreased by stopping smoking as well. Hence a smoking stop could prevent future EPs.

A study from Nederland looked at the possibilities of screening symptom-free women with an increased risk of ectopic pregnancy for EP. They concluded that screening would decrease the amount of ruptured EPs, but at the expense of a large group of false positives (21).

2. Pathology and pathogenesis of Ectopic pregnancy.

2.1 Location

The most common implantation site for Ectopic pregnancies is the ampullary part of the Fallopian tube. A French study reviewed the locations of EP and factors determining the location of EP in 1800 cases over 10 years. They collected data from the Auvergne register. The results showed that 95.5% of all EPs studied were located in the fallopian tubes, 73% of these were located in the ampullary part of the tubes, 3.2% was ovarian and 1.3% was abdominal. In all, only 4.5% of all EPs studied were extratubal. No cervical EPs were found, understating the fact that this type is extremely rare.

Further, the majority of ampullary EPs are located intraluminary with preservation of tunica muscularis while the majority of isthmic EPs are located extraluminary with disruption of the muscular layer. This is due to the differences seen in the anatomy of the two parts and the reason why rupture is more common in isthmic pregnancies.

A study from 2007 reviewed EPs with unusual locations (18). I have summarized the study in the following paragraph.

Interstitial pregnancy is a form of tubal pregnancy that account for only 1-3% of all ectopic pregnancies. Because of its muscular surroundings these pregnancies can reach 2nd trimester. Rupture of such an advanced gestation is catastrophic for the mother and carries a high mortality rate.



Ovarian EP is a very rare entity (figure 1). It is classified as primary or secondary. Primary means that the ovum is fertilized inside its follicle. Secondary occurs when the ovum is fertilized inside the tube, but refluxes and inserts on the ovary.

Figure 1: Ovarian pregnancy.

On the contrary to tubal pregnancies, infections and IUDs are not the cause of ovarian pregnancies. Here there are conflicting findings thou. It has been speculated in whether ovarian pregnancies are caused by IVF, embryo transfer or ovary stimulation, but there are no

clear links between the entities so ovarian pregnancy seems like a completely random event(17).

Abdominal EPs are also rare. They can be found in the cul-de-sac, on the omentum, broad ligament, bowel and spleen. The foetuses can grow to a large size and may be viable when discovered, complicating their management. Causes of abdominal EPs are not clear, but they have been seen after IVF and can be a secondary event of tubal pregnancies.

Cervical Ectopic pregnancy accounts for less than one percent. Predisposing factors are thought to be previous instrumentation of the cervical canal, anatomic anomalies (myomas, synechiae) IUDs, IVF and DES exposure.

Maybe the rarest form of Ectopic pregnancy is found intramurally or in Caesarean scars. It has been proposed that these pregnancies enter the caesarean scar trough micro-fistulas. Little is known about them.

2.2 Causes

The most common cause of implantation in the tube is some tube pathology. This pathology can have occurred after surgery (f.ex sterilization with electrocoagulation and subsequent fistula formation), previous infections or it can be due to endometriosis. In a study (16) of tubal pathology in EP, 92% of tubes had some kind of pathology. In case of ampullary EP, the dominant pathology was chronic salpingitis, but endometriosis was also found. In case of isthmic EP the same study concluded with that all tubes had some pathology. Again chronic salpingitis predominated and endometriosis was found as cause as well. Women with prior damage to their tubes had a tendency to carry their EP in the proximal part of the tube while women with an IUD showed a tendency to carry it in the distal part of the tube. This has also been the conclusion of other studies. Raziel examined 20 ovarian EPs in a study published in 1990. He saw that in 18 of the women an IUD was present at the time of conception. Sandvei found the same tendency when reviewing 25 ovarian EPs. 68% of the ladies had an IUD at the time of conception.

A study published in January 2009 investigated the physiology behind ovum propulsion in the oviducts and looked at the effect of *Chlamydia muridarum* on mice oviducts (15). They found, in contrast to earlier believes, that cilia beating in the oviducts are not sufficient to propel an oocyte. The cilia can propel small cellular debris with a size of 15-25µm but the ovum with its diameter of approximately 70-90µm also need help from the

spontaneous contraction of the myosalpinx. They further hypothesized that interstitial cells of Cajal (pacemaker cells in GIT that are also found in human and mice oviducts) work as pacemakers in the contractions of the oviducts, helping propulsion of the oocyte. They found that infections with *C. muridarum* disrupts the network of Cajal cells and abolishes the spontaneous pacemaker activity. This again leads to hydrosalpinx or pyosalpinx and the long term effect would be scarring and occlusion of the Fallopian tube. These changes could lead to infertility but also abnormal implantation of the oocyte in the tube.

Clomiphene citrate has also been examined as a cause of EP but the results have been equivocal and non-conclusive so far. The higher incidence of EP in these patients could be due to their infertility, another risk factor for EP. It has been discussed whether there is a higher incidence of chromosomal abnormalities in fetuses with Ectopic location, but this has been found improbable by studies.

Event thou we now know a lot of risk factors and causes of ectopic pregnancy many cases of EP still present without obvious risk factors or causes. There is still a lot of work to be done on this field.

3. Clinical presentation and diagnosis of ectopic pregnancy.

3.1 Signs and symptoms.

The presentation of EP has classically been described as the triad of abdominal pain, amenorrhoea and vaginal bleeding in the 1st trimester. Nothing is typical in medicine and less than 50% present with this triad. It is important to diagnose this condition early in order to decrease both maternal mortality and morbidity.

The so called asymptomatic EP can be found when evaluating a woman for possible pregnancy or during a normal routine check-up. It is usually at a very early stage when still asymptomatic.

Later the woman may present with a history of sporadic spotting. She may have abdominal pain, cervical motion tenderness, adnexal tenderness and an adnexal mass can be felt on bimanual palpation (rare). There may or may not be a rupture at this point. The most serious presentation is when the woman has severe sharp abdominal pain, shows signs of acute abdomen (rebound tenderness, guarding, diaphragmatic irritation) and is hemodynamically unstable. These are signs of rupture and severe intraperitoneal bleeding. The woman's life is at danger and she is in need of immediate surgical interventions.

3.2 Diagnostic work-up.

When not presented with a surgical emergency (hemodynamically stable patient) it is important to do a thorough diagnostic work-up of the patient. This work-up should consist of history taking with focus on risk factors, a physical examination, transvaginal ultrasound and repeated hCG measurements. When deciding to treat a woman for EP it is necessary to be as sure as possible of the diagnosis. This is because many women with normal viable pregnancies can present with the same symptomatology as a woman with EP. As I understand the literature, it can sometimes be very difficult and confusing to differ the two.

3.2.1 Physical Examination.

Studies have been done to investigate the sensitivity of history and physical examination when trying to diagnose EP. A study conducted by Dart RG and colleagues in 1999 (25) looked at patients admitted with abdominal pain or vaginal bleeding and a positive hCG level, excluding those with a ultrasound at a previous visit or a uterus bigger than 12 weeks by manual examination. 441 patients were admitted with the symptoms listed above.

Only 57 of them had EP. They found that a history of moderate to severe lateral pain of a sharp character increased the risk for EP this would also a history of IUD, infertility, prior pelvic surgery or tubal surgery do. On the other hand, pain located in the midline decreased the risk of EP. Further they found that the presence of peritoneal signs, cervical motion tenderness or lateral or bilateral abdominal or pelvic tenderness increased the risk of EP. A uterine size larger than 8 weeks by manual examination decreased the risk for EP. He concluded that no combination of history clues and physical examination findings could confirm nor exclude a diagnosis of ectopic pregnancy. A similar study conducted by Buckley RG and colleagues in 1999 (26) grouped the patients, that were in their 1st trimester with abdominal pain or vaginal bleeding, into a high risk group(peritoneal signs or cervical motion tenderness), a intermediate risk group(presence of pain or tenderness, other than midline cramping, plus absence of fetal heart tones and absence of tissue at the cervical os) and a low grade risk group(neither high or intermediate). 915 patients was admitted. 845 had IUP, 70(7,6%) had EP and 18 was lost to follow up. He found that on basis of the EP prevalence(7.7%) in the admitted group the risk of EP in a patient being in the low risk group was less than 1%. It was 7% for a patient classified as intermediate risk and 29% for a patient classified in the high risk group. The conclusion of his study was that this could be a useful prediction model when estimating risk. A study done by Mol BW and colleagues (27) concluded with pretty much the same conclusion, PE in EP does not have a very high predictive value.

In a review of 147 cases from 1982(19) it was found that 98,6% of patients presented with abdominal pain, 74,1% had amenorrhoea and irregular vaginal bleeding was reported by 56,4% of the patients. As for physical symptoms, the most common ones were abdominal tenderness and adnexal tenderness present in 97.3 and 98% of patients respectively. It is important to note that of the 147 patients 115 (78.2%) of them presented with rupture prior to admission. This is a very high proportion of the patients. This proportion has decreased since then. In a study, looking at risk factors associated with rupture of EP in the period from 01.01.1995 to 03.01.2002, 738 patients were identified, and only 439 (59%) presented with rupture of the EP (20). I expect it to be even less now and this change leads again to a change in the average symptoms at presentation

3.2.2 hCG and its changes in ectopic pregnancy

When dealing with a woman in her reproductive age with abdominal pain it is always important to confirm or exclude pregnancy. Pregnancy is easiest excluded by an hCG measurement. hCG is detected in urine and blood serum from one week before expected menstruation and increases throughout pregnancy. It can be detected down to 5 IU/L in serum and down to 25 IU/L in urine. In case of a negative result, we can with very high probability exclude EP and in case of a positive hCG test, EP should be high on the list of differential diagnoses. The hCG level and the changes of the hCG level can be of great help when evaluating a patient for EP. There have been many different studies looking at the value of the quantitative aspect of hCG level.

A study done by Kohn and colleagues (28) compared the level of hCG in women with EP, abnormal intrauterine pregnancy (IUP) and normal IUP. He reviewed 730 cases where 96 were EP, 253 had an abnormal IUP and 381 had a normal IUP. He found that the distribution of hCG in the group of abnormal IUP and EP was similar and much lower than the hCG level in normal IUPs. He found that a level less than 1500 IU/L more than doubled the odds of EP. 158 patients had hCG levels less than 1500 IU/L, 40 of these had EP and only 25(16%) of them had normal IUP. This means that the likelihood of a normal pregnancy is very low at these levels.

Kaplan BC and colleagues conducted a similar study and found that patients with an hCG value of less than 1000 IU/L had a four fold increase in EP risk.

Another aspect to hCG measurement is serial measurement. An increase of at least 66% percent is seen over 48 hours is a good indication of viability.

Dart RG and his colleagues did a study to try and find the predictive value of changes in hCG in patients with symptoms suggestive of ectopic pregnancy, but with an indeterminate transvaginal ultrasound findings. The patients were divided into four groups based on the rate of change in hCG over 48 hours (increase by more than 66%, increase by less than 66%, decrease by less than 50% and decrease by more than 50%), further the four groups was subdivided depending on whether the uterine cavity was empty at US examination. In all 307 patients entered the study. They identified 3 main risk groups. The group with the biggest risk of EP was those with an empty uterus at US and hCG values increasing by less than 66%, patients with hCG that decreased by less than 50% with an empty uterus and patients with hCG values increasing more than 66% with an empty uterus. Patients with a decrease of more than 50% irrespective of US findings showed the smallest risk. The study concluded with that

changes in serial hCG measurements in patients with indeterminate US is predictive of ectopic pregnancy. Not only does this study show the importance of hCG, but also the importance of hCG together with US in the diagnosis of EP.

Many different serum markers for EP have been studied. Progesterone is one of these. A meta-analysis looked at 26 different studies, trying to find some progesterone levels that could distinguish between ectopic pregnancy and non-ectopic pregnancy and between viable and non viable pregnancy(23). They found that a single measurement of serum progesterone level could not discriminate between ectopic and non-ectopic pregnancies. It could identify patients at risk though, and indicate further follow-up. Progesterone levels were also found to be reliable when evaluating the viability of the pregnancy, where values below 5ng/ml indicated non viable pregnancy and values above 22 indicated viable pregnancy. Together with serum hCG, serum progesterone can have prognostic values. Patients with progesterone levels below 10ng/ml and hCG levels below 1500 IU/L are most likely to demonstrate a spontaneous resolution of an EP(24).

Another marker produced during pregnancy is PAPP-A. It has been demonstrated that the levels of PAPP-A is lower in patients with EP and intrauterine abortions compared to those with normal pregnancies. Again we are not able to diagnose EP based on this substance(24). Other substances like VEGF, creatinine kinase and CA 125 has also been studied to find their value in evaluating the probability of EP but the different studies conducted do not come to the same conclusion, rendering these substances unable to help in diagnosing EP for now.

3.2.3 Ultrasound and ectopic pregnancy.

Ultrasound is a maybe the most important tool in diagnosing EP. With the introduction of transvaginal US we are now able to be more precise and accurate at an earlier stage when diagnosing normal pregnancies and other abnormalities. An ovoid collection of fluid adjacent to an endometrial stripe is regarded as a normal gestational sac. This finding can be visualized at 5 weeks of gestation. The yolk sac appears when the gestational sac is 8mm or more in diameter, usually during the 5th week. Cardiac activity can usually be seen by 6 - 6.5 weeks. A study from the 80s found that there was a level/zone at which a normal pregnancy could be seen on ultrasound (30). This threshold has decreased with the improvement in ultrasound machines. It used to be 6500 IU/L for transabdominal US, but with transvaginal US we can see the fetus at levels down to 1000- 2000 IU/L depending on the machine used and the experience of the ultrasonographer. The same study stated that a hCG level above 6500 IU/L

and an empty uterus implied an EP, while a level below 6500 IU/L and an empty uterus could not be used to either confirm nor discard EP or normal IUP. Later studies have challenged this study by finding that indeterminate US and hCG above threshold level is not always equal to EP.

So what do we look for when trying to diagnose ectopic pregnancy? In a study from 1990 Fleicher and his colleagues looked at the prevalence of the different US signs in 50 EPs. He looked for the following signs: endometrial thickening (more than 12 mm anteroposterior dimension, which is expected for a mid-secretory phase endometrium), a “pseudosac (figure 2 and 3),” fluid in the cul-de-sac, dilated tube, corpus luteum (figure 4), non-specific adnexal mass, and tubal ring (figure 5) (with or without yolk sac or embryo, or embryo with or without heart activity). All of these findings were found in the different cases and many of the findings were found together in single cases.

The three most common findings were thickened endometrium (43%), tubal ring in the adnexa (49%) and simple fluid in the peritoneal cavity (47%).

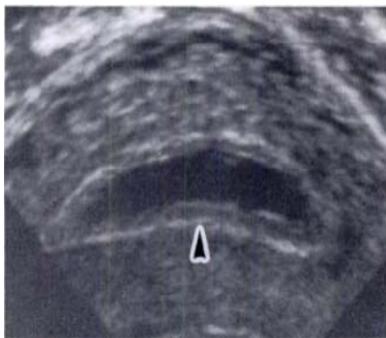


Figure 2: Transvaginal US of an 8-week ectopic pregnancy shows decidualized endometrium or pseudosac (arrow head) surrounding hypoechoic intraluminal fluid

A study conducted by Condous and colleagues found these ratios among ultrasound findings: 57.9% had an inhomogeneous mass (so called blob sign), 20.4% had a hyper-echoic ring around the gestational sac and 13.2% had an embryo with or without cardiac activity (32, study discussed in more detail below)

As said, finding an intrauterine pregnancy usually excludes EP, this is not valid for women with heterotopic pregnancy. This is a twin pregnancy where one is intrauterine and the other is ectopic.



Figure 3: Transvaginal US shows a pseudosac containing echogenic fluid*.



Figure 4: Transvaginal US from a patient whose ectopic pregnancy had caused the tube to rupture shows a corpus luteum (arrow), which is surrounded by clotted blood in the cul-de-sac.



Figure 5: Transvaginal sonogram of tubal ring (arrow) surrounded by fluid in an unruptured pregnancy.

It is very rare and said to be found in 1/6000 – 1/40 000 pregnancies. In the setting of assisted reproduction though, the frequency of heterotopic pregnancy is 1/100 and should be kept in mind!

Another study found that it was better to use the gestational age than the level of hCG when assessing the risk for EP(31). They concluded with that failure to detect the gestational sac 24 days or more after conception was “a presumptive evidence of an ectopic pregnancy”. This age is not always known and hCG value is still very important in evaluating these patients.

So how reliable is the ultrasound as a single measure in diagnosing EP? A study conducted by Condous G and his colleagues showed that 90.9% of all EPs could be diagnosed before surgery(32). It was a large study. 6621 women underwent transvaginal ultrasound. The diagnosis of EP was defined as any of these 3 ultrasound signs were seen in the adnexal region:

- an inhomogeneous mass or blob sign adjacent to the ovary and moving separately from the ovary;
- a mass with a hyper-echoic ring around the gestational sac or bagel sign;
- a gestational sac with a fetal pole with or without cardiac activity.

After diagnosing EP by ultrasound the patient was sent for laparoscopy and final diagnosis was made. Of the 152 laparoscopies performed, 9 were negative. Thirteen of the 143 confirmed EPs was not seen on transvaginal ultrasound (TVU) prior to laparoscopy. The sensitivity and specificity of the TVU in this study was 90.9% and 99.9% respectively. We could discuss whether the old age of the pregnancies at presentation (average 48.3 days and hCG 6997.4 IU/L) affected the high sensitivity and the high specificity. The author says that it could be, but in this study they were not able to influence this since the data was collected from a walk-in clinic in London where the patients came on own initiative. The person conducting the TVU examination did not know the result from the hCG test when doing the US so he was not affected by this. Other studies have come to the same conclusion with similar sensitivity and specificity(33, 34). One conducted in 1990 found a sensitivity of 93% and a specificity of 99%. Another study conducted in 1998 found a sensitivity of 87% and a specificity of 94%.

There has also been some discussion in the society of gynecologists and obstetricians whether magnetic resonance has a place in diagnosing EP. Some authors have stated that MR imaging is not usually essential for diagnosis. Others have stated that MR imaging is useful

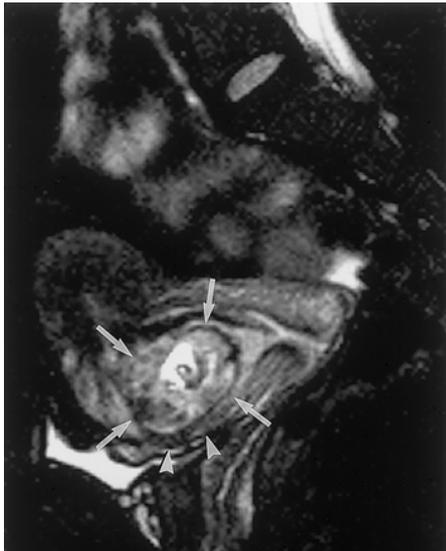


Figure 6: MRI of an myometrial pregnancy in a cesarean section scar in a 26-year-old woman.

for specific diagnosis of rare or complicated forms of ectopic pregnancy, such as abdominal pregnancy, interstitial pregnancy, myometrial pregnancy (fig. 6), and cervical pregnancy, when the results of US are insufficient or inconclusive (from and colleagues 2002).

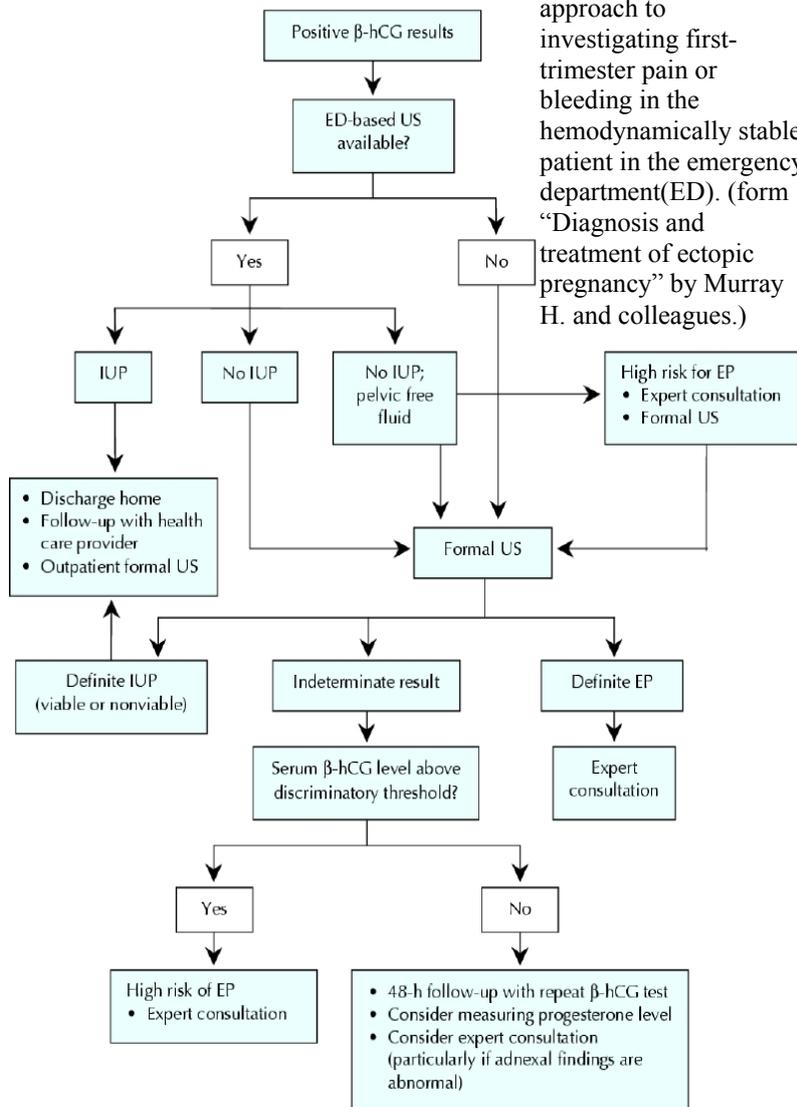
An American decision analysis compared 6 different diagnostic algorithms and found that ultrasound followed by hCG analysis resulted in the best outcomes (22). The author argued that the approach described above saved diagnostic time and no potential EPs were missed as opposed to the approach with hCG

first and then ultrasound after.

We must remember that this analysis is only a theoretical analysis and does not reflect real life in a good way.

As far as I will practice my medicine in the future all women with abdominal pain and vaginal bleeding in the emergency room will get an hCG measurement first and regardless of the result they will also get a transvaginal ultrasound. This because in real life such a presentation is not only due to pregnancy or EP, as it was in this analysis, but also diagnoses like abortion, myomas, ovarian torsion, ruptured corpus luteum cyst and tubo-ovarian abscess.

Figure 7: Recommended approach to investigating first-trimester pain or bleeding in the hemodynamically stable patient in the emergency department (ED). (from "Diagnosis and treatment of ectopic pregnancy" by Murray H. and colleagues.)



4. Treatment of Ectopic pregnancy.

In the past the only treatment option for ectopic pregnancy was surgery. As medicine has evolved and our surveillance possibilities with hCG and transvaginal ultrasound has increased, less invasive treatment options are now available. Depending on the clinical presentation and compliance of the mother we can choose from expectant management, treatment with Methotrexate and surgery(table from lancet).

4.1 Surgery in ectopic pregnancy.

Surgery is the most common approach in a patient with EP. The surgical approach chosen depends on the patients clinical status(35). If the patient is hemodynamic instable, has signs of an acute abdomen and the surgeons lacks experience with laparoscopy or if the laparoscopic approach will be too difficult, the laparotomic approach will be preferred. This is rarely done today.

In case of laparoscopic approach we can perform conservative surgery, which includes salphingostomy(used in ampullary EPs) segmental resection of the isthmus or fimbrial expression(fig.7).

The more radical approach, salpingectomy, is reserved for patients with uncontrollable bleeding, extensive tubal damage, recurrent EPs in the same tube or if sterilization is desired by the patient. It is done less commonly these days. There are today no randomized studies comparing salpingostomy and salpingectomy. A review of 40 non randomized studies found that the subsequent fertility and rates of recurrent EP were the same for the two approaches(38).

The salphingostomy is done by a linear longitudinal incision by electrocautery, laser or scissors on the antimesenteric side of the bulging mass in the tube (fig. 8)). The products in

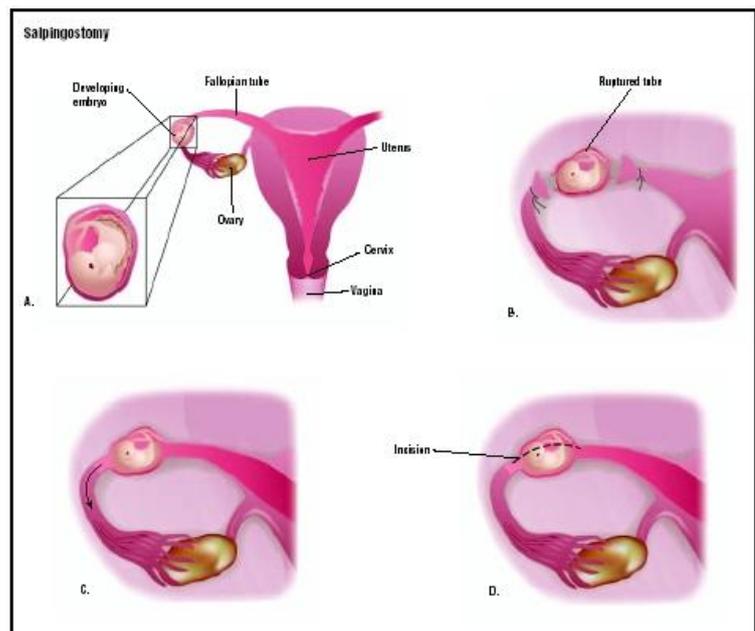


Figure 7: Treatment of tubal pregnancy a) location of tubal pregnancy, b) segmental resection, c) milking of tube (not done today), d) salpingostomy (most commonly done)



Figure 8: Incision at the anti-mesosalpingeal border the tube are so removed(fig. 9). Hemostasis is achieved and the incision is left for secondary healing.

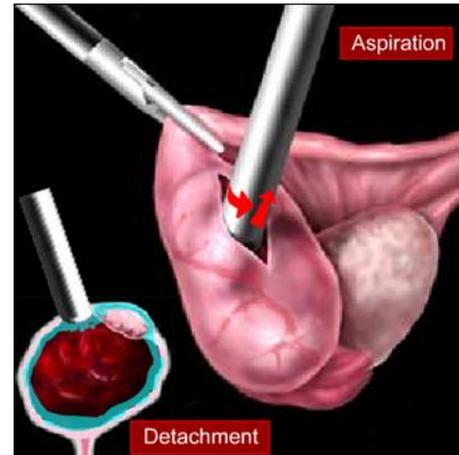


Figure 9: Extraction of tube content.

Segmental excision is done by excising the segment of the tube that contains the EP (isthmic part). Then after the excision the ends of the tubes are anatomised by microsurgical techniques during the operation or later.

4.2 Methotrexate, the medical alternative.

Metotrexate is the second option in treating EP. Metotrexate is a folic acid antagonist that inhibits synthesis of purines and pyrimidines. This interferes again with DNA synthesis and cell multiplication, something that is crucial for rapidly dividing cells like trophoblasts. Administered to the well selected patient it has a success rate up to 94%(39). The criteria for Methotrexate administration are as follow:

- Hemodynamic stability.
- Ability and willingness of the patient to comply with post-treatment monitoring.
- Pretreatment hCG concentration less than 5000 IU/L.
- Absence of ultrasound evidence of fetal cardiac activity.

There are two main regiments of administration of Methotrexate, the single dose and multiple dose regimen. In the multiple dose regimen Methotrexate(1mg/kg IM) is given together with Leucovorin(Folic acid for protection of normal cells, 0,1mg/kg) on alternate days. When we can see a fall in hCG by more than 15% over 48 hours we can stop giving Methotrexate. It is still necessary to continue weekly follow-up of hCG until it is no longer detected in serum. In this regimen the treatment varies according to the response and we can give a maximum of 4 doses before the treatment is considered a failure.

Local approaches instead of systemic approaches have also been tried. The agents used have been MTX, prostaglandins, hyperosmolar glucose, potassium chloride and saline. Local MTX treatment has the advantage that it offers less systemic toxicity. Despite this it is a disadvantage that you need laparoscopic or ultrasound guidance when applying the agent. This approach has also shown to be less effective than the systemic approach. The others have also shown poor results when compared to our more established approaches.

4.3 Expectant management.

The last and probably rarest used approach to treatment of EP is expectant management. The philosophy behind this approach is that some early EPs will regress spontaneously without any further interventions. It is used in women with low hCG and pregnancy of unknown location. It is necessary to keep a tight follow-up of the patient and the patients hCG level when choosing this alternative.

4.4 A comparison of the different treatments

4.4.1 Laparotomy versus laparoscopy.

A meta-study looked at all the different studies that concerned treatment of EP(36). The studies comparing laparoscopy and laparotomy found that laparotomy was more successful than laparoscopy. This was mainly due to persistent trophoblastic tissue in the laparoscopy group. The cost of laparoscopy was much lower than of laparotomy. A study done by Gray and his colleagues found a similar relationship(37). The success rate of laparotomy was higher due to higher rates of remaining trophoblastic tissue in the tubes in the laparoscopy group(95% vs. 81%). Laparoscopy was found to be cheaper for the hospital. The reason it was cheaper was due to shorter operation time(88min vs. 105min) and shorter stay in hospital(5 days vs. 2 days). The patients in the laparoscopy group did require a second operation more frequent due to remaining trophoblastic tissue, but this did not add up to the other expenses seen in the laparotomy group. Other studies(36) have found that the laparoscopy group suffers less blood loss(79ml vs. 195ml) and has a shorter convalescence time(11 vs. 24 days). This illustrates that laparoscopy is better for the patient and cheaper for the society since it does not have to pay sick leave money and so on. Gray argued against

these findings and said that they were partly biased since they were not randomized and that this caused different outcomes.

Today laparoscopy is the most commonly used approach in the developed world.

4.4.2 Salpingostomy versus multiple dose Methotrexate.

A review paper by Mol and colleagues (36) compared multiple dose MTX with laparoscopic salpingostomy. They found that the success rate was about the same with the two approaches. And the subsequent fertility rate was the same. Medically treated women though, had more limitations in physical abilities, reduced social functioning, had worse health perception, less energy, more pain and were more depressed after the treatment than what surgically treated women were.

4.4.3 Salpingostomy versus single dose Methotrexate.

When looking at the differences between single dose MTX and laparoscopic salpingostomy they found that the medical treatment was significantly less effective than the surgical treatment(36). This time the MTX group showed less physical limitations than the operation group. The psychological function and the subsequent fertility were found to be the same in the two groups. Treatment with MTX was cheaper than the operative approach.

4.4.4 Single dose versus multiple dose Methotrexate.

In a metaanalysis from 2003 the different approaches were compared(40). They searched the literature looking for studies and cases of ectopic pregnancy treated with Methotrexate either with single or multiple dose regimen. They used strict criteria for using the studies they found. No studies have compared the two regimens before Barnhart's study. They reviewed in all 1327 cases of ectopic pregnancy treated with Methotrexate. A total of 1067 women were treated with the single dose regimen and 260 women were treated with the multidose regimen. They found that the overall success rate of Methotrexate was 89%(failure was defined as abandonment of medical therapy after initiation). The single dose regime was found to be less effective (88.1%) than the multidose regime(92.7%). It was found that an increasing hCG level correlated with an increasing failure rate. Another factor that influenced the success rate was cardiac activity in the embryo. Cardiac activity was associated with a higher failure rate. The hCG level was in average 2778 IU/L in the single dose group and 5023 IU/L in the multiple dose group showing that the cases in the multiple dosing group was

less suitable for Methotrexate therapy. Despite this, there was a higher success rate in this group.

The single dose(31.3%) approach had less side effects than the multiple regimen(41.2%) had. The most common side effects were nausea, vomiting, alopecia and abdominal pain.

Abdominal pain is one of the unexplainable side effects of Methotrexate. The incidence of abdominal pain was similar in the two groups. Most patients with abdominal pain were readmitted for observation since this can also be a sign of tubal rupture. It was found that the presence of side effects was associated with a lower failure rate.

The author argued for “single dose” being a misnomer. He found that of those being in the single dose group, 14.5% of the women got more than one dose. Of the women receiving multiple doses 53.5% got 4 or more doses and 6.8% received more than one course(4 doses). He concluded with that the multiple dose regimen was more effective than the single dose, but the single dose regimen was more convenient for patient and doctor and it had less side effects. The biggest weakness of this study is that it contains no randomized studies. This could have led to the policy of assigning the patients with the poorest prognosis to the multiple regimen.

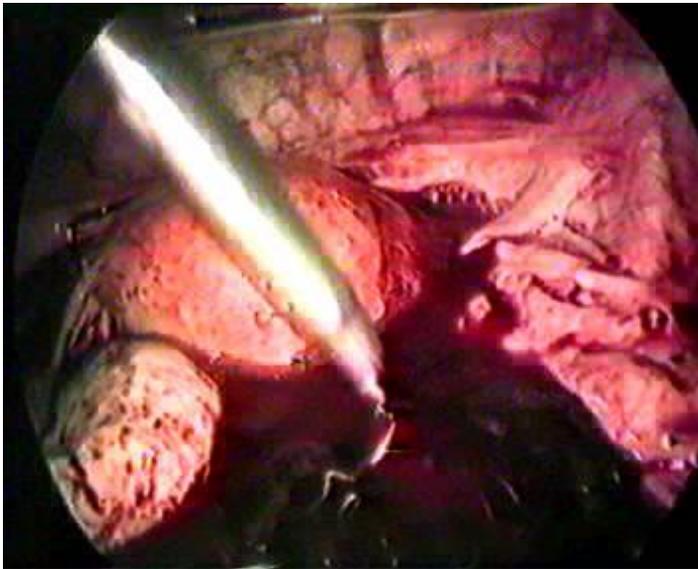
A randomized study done by Alleyassin and colleagues in 2006 found similar numbers, but he concluded with that the differences were statistically insignificant. His study included 108 EPs that fulfilled the criteria for Methotrexate(MTX). Unfortunately I did not have access to the full text so I could only extract information from the abstract.

4.4.5 Expectant management versus low dose Methotrexate.

The meta-analysis I discussed above also compared expectant management with systemic MTX therapy(36). They found no significant difference between the two strategies in regard of success. It must be said that the doses of MTX was lower than normal. The average hCG level in the study reviewed was low (211 IU/L in the expectant group and 395 IU/L in the MTX group). This was a double blind placebo controlled study, so the results are quite reliable.

5. Complications of ectopic pregnancy and its treatments.

The complications of ectopic pregnancy are not many. The most feared complication of EP itself is rupture of the tube(fig. 10).



This leads to intra-abdominal haemorrhage, shock development and the patient presents with signs of an acute abdomen. This is a medical emergency that requires immediate surgical interventions. This is the most common cause of death due to EP.

Figur 10: Hemoperitoneum due to ruptured ectopic pregnancy.

As we see in the section of risk factors we see that previous EP and surgery of the tubes predisposes to having a subsequent EP. So a complication of EP and its treatment could also be ectopic pregnancy.

A complication of EP treatment could be remaining trophoblastic tissue. This is seen after salpingostomy and was commonly seen after milking the tube for the EP(the reason why it was abandoned). This causes return or continuing of symptoms and we will not observe a fall in hCG back to zero. This requires a new exploration and salphingectomy. Often MTX is given during the surgery as prevention of remaining trophoblastic tissue.

There have been studies conducted on fertility after EP. A French study looked at the differences between fertility after EP in those who used IUD at the time of conception(contraception failure) and those who did not use IUD at the time of conception. They found that non of the IUD users experienced recurrent EPs whereas 10% of the non-users experienced a new ectopic pregnancy. The fertility rates between the two groups where not significant but the rate of miscarriages was significantly higher in the IUD non-user group(26%) than in the user group(5%). Another difference was that all of the pregnancies in the user group was spontaneous while many of the pregnancies in the non user group was achieved by IVF techniques.

6. Discussion.

The changes in EP seen during the 70s and 80s could be accredited the increasing incidence of chlamydial infections seen in the 60s and 70. This is only a part of the big picture thou. We must also remember that the diagnostic abilities increased in the same period. We were able to detect clinically silent EPs that were not detected before. French studies have pointed towards the fact that the use of IUDs among the population increased. This changed to a decrease in the 90s. Another factor could also be the increasing use of laparoscopy, which can lead to adhesions and this again could predispose to EP.

An interesting Finnish study (14) points to the effect of demographic changes. They conclude with, together with the factors mentioned above, that the so called “baby-boom” seen after the Second World War(1945-1954) also contributed to the increase seen in the 70s, the time when the babies of the “baby-boom” reached their fertile age. Williams obstetrics also points out increased use of assisted reproduction and increase in numbers of abortions.

We saw in France, during the period of 1992 – 2002, that there was a decrease in the overall incidence of EPs. This was due to and decrease in the incidence of EP due to contraceptive failure. Despite this there was an increase in EP incidence due to reproductive failure. As seen above reasons for this could be many but as we have seen it can be related to the changes in incidence of Chlamydia and other STDs in the population. Changes like this could be a warning sign. It may signal that the incidence of Chlamydia is on the rise in the population again. If we look to Sweden and the UK, it is possible to introduce a screening program for Chlamydia. This would decrease the amount of STDs in the population and its consequences. Most countries still don't have such a program. There may be many reasons for this, cost and little knowledge of the effect may be some of them. Despite maybe not having such a program, we as doctors can increase the awareness, among ourselves in regard of EP and among our patients in regard of contraceptives. We should inform, both boys and girls, men and women about the importance of using a condom when having sex with strangers. This is not only due to risk of subsequent EP, but also other conditions like decreased fertility (which in fact is very much related to EP), but maybe mostly due to AIDS, a killing disease. We can also inquire about the possibility of Chlamydia when doing routine checkups of women and not hold back on testing when the woman wants this. Even when she is asymptomatic. Another thing that could be done is to encourage the woman to see her doctor soon after

thinking she is pregnant. In this way EP can be discovered before it becomes symptomatic. We can then choose less invasive options for treatment.

As tubal rupture becomes less and less seen the symptomatology of EP has changed from that of the very serious “rupture presentation” to that of an incidental finding on a routine check-up.

Based on the studies done to investigate the symptomatology of EP we can say that physical examination is not a very reliable part in the final diagnosis of EP. We see a big variety in presentation of the condition. Because of this, it is very important for the physician to have a high level suspicion towards the condition and not expect to always be presented with the described symptomatology.

It is important to communicate this message to doctors that deal with young women in their fertile age. In this way the condition can be discovered earlier and this will decrease both mortality and morbidity among the ladies.

Is the physical examination useful at all then when diagnosing EP? Please don't get me wrong, physical examination is always important. It is important to consider the whole clinical picture and physical examination and history is an important part of this. The history and the physical examination are important in guiding the physician down the correct road in order to reach the correct diagnosis. So what I'm trying to say is that physical examination is important, but the absence of either abdominal pain, amenorrhea or spotting does not exclude the diagnosis of ectopic pregnancy.

The studies done on hCG and its changes in EP and other conditions have helped us a lot in clinical decision making. Despite our broad knowledge of its value we can still not rely 100% upon its values. Especially these gray-zone values. This is because even levels seen in normal physiological situations can stray into the pathological levels seen in disease. A study done to investigate hCG changes in normal IUPs showed that there was a variation in changes of hCG from 53% to 228% at 48 hours (29). We can not say anything about the location of the pregnancy either (intrauterine or extrauterine). This result stresses that we should be careful in interpreting it and our decisions should not be based solely on the hCG value. Normal intrauterine pregnancies have been terminated due to this. When combined with transvaginal ultrasound the value of the two tools increases. It has classically been said that when the hCG value is over the discriminatory zone and no intrauterine pregnancy(IUP) can be seen on US examination it is very predictive of an EP. Condous et. al. argued that it would

be better to focus on trying to find the EP instead of relying on presumptions. If the doctor can find the EP this is a confirmation that treatment for EP is indicated. Sometimes the ultrasound findings are equivocal. In those situations it is good to lean on a detailed history (with focus on risk factors), physical examination and hCG values. If the diagnosis are still unclear and the patients symptomatology is stable it is possible to use an expectant approach with close follow up and repeated hCG, TVU and PE. We do not want to end a normal IUP, something that can happen if we act too quickly.

Despite the sometimes difficult cases the options for diagnosing EP quick and fairly reliable. Still we must remember that the only diagnostic measure which can diagnose EP with 100% certainty is laparoscopy with a histological confirmation.

When it comes to treatment of ectopic pregnancy, it would be best if we could individualize our treatment of our patients. In this way we can get the best of both the medical and surgical world. Here it is important to stress that if we suspect rupture, surgery is the only option. For the other patients without rupture MTX or even expectant management can be an option. These treatment options could be viewed as simpler options compared to surgery since they take less hospital beds less time from the doctor and it offers bigger freedom for the patient. The medical treatment does have some toxicity which is quite high, especially for the multidose regimen with both physical and psychological problems after treatment. This is not seen so commonly in the single dose regimen, but this approach fails more often and there is a need for more doses. Failure could lead to further development of the fetus and subsequent rupture. It is therefore absolutely necessary to have a close follow-up of these patients. Surgery on the other hand offers a lower failure rate and a definite diagnosis. It is more expensive and time consuming and it carries the risks of anaesthesia and intraoperative complications that can be fatal in some instances. There has been found no differences in subsequent fertility with the two approaches. Due to these positive and negative features of the different treatments, I believe that there is some differences in the approaches to EPs at different hospitals. The specialists often choose the treatment that they feel more comfortable with and according to the tradition at the hospital. There is no answer to what approach is the best so far.

When addressing the complications of ectopic pregnancy I can not mention the fact that early diagnosis decreases chance of rupture too many times.

We see that EP may lead to decreased fertility. In my eyes this decreased fertility is not a consequence of EP, but EP is a consequence of decreased fertility.

7. Conclusion.

Despite the big progress that have been made in understanding, diagnosing and treating ectopic pregnancy during the last decades, ectopic pregnancy is still among the most common causes of maternal death. The awareness among health care workers need to increase in order to decrease mortality and morbidity of this relentless condition.

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