Early and late half-life of human chorionic gonadotropin as a predictor of persistent trophoblast after laparoscopic conservative surgery for an ectopic pregnancy

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Early and Late Half-Life of Human Chorionic Gonadotropin as a Predictor of Persistent Trophoblast after Laparoscopic Conservative Surgery for an Ectopic Pregnancy

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EARLY AND LATE HALF-LIFE OF HUMAN CHORIONIC GONADOTROPIN AS A PREDICTOR OF PERSISTENT TROPHOBLAST AFTER LAPAROSCOPIC CONSERVATIVE SURGERY FOR AN ECTOPIC PREGNANCY

La Faculté de médecine, sur le préavis de Monsieur Paul BISCHOF, professeur titulaire au Département de gynécologie et obstétrique, autorise l'impression de la présente thèse, sans prétendre par là émettre d'opinion sur les propositions qui y sont énoncées.

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Doyen

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I. Introduction

Une grossesse ectopique ou extra-utérine (GEU) survient lorsque le blastocyste en développement s'implante dans un lieu autre que l'endomètre de la cavité utérine. La plus commune des localisations extra-utérines est la trompe de Fallope qui concerne 98% de toutes les grossesses ectopiques.

L'incidence des grossesses extra-utérines (GEU) est en augmentation ces trois dernières décennies (Ectopic pregnancy, MMWR 1992; Ectopic pregnancy, JAMA 1995), ceci dans le monde entier, bien qu'apparaisse une stabilisation de l'incidence à 19 pour 1000 grossesses ces 10 dernières années.

Cette augmentation est fortement associée à l'incidence accrue de maladies sexuellement transmissibles et d'infections pelviennes à l'origine d'altérations de la fonction tubaire (Russell 1987; Westrom et al., 1981; Russell 1987; Marchbanks et al., 1988; Hillis et al., 1995-1997; Egger et al., 1998; Kamwendo et al., 2000).

La prise en charge de ces grossesses a changé fondamentalement ces dernières décennies, tout d'abord grâce aux diverses technologies modernes, permettant un diagnostic plus précoce des grossesses ectopiques occasionnant une baisse de la morbidité et mortalité maternelle. Le développement de tests de grossesse à haute sensibilité (dosage de l'hCG urinaire et sérique) et la caractérisation du taux normal d'augmentation de l'hCG (hormone gonadotrophine chorionique) sérique pendant la grossesse associés à des techniques radiologiques plus performantes telle que l'échographie endo-vaginale à haute résolution ont contribué à l'amélioration de l'approche diagnostique.

Ces changements ont permis une prise en charge plus rapide des patientes présentant une GEU, bien avant qu'une rupture tubaire ne survienne, et ont apporté, depuis peu, la possibilité d'un traitement conservateur au niveau de la trompe de Fallope et des ovaires, pouvant être effectué soit par chirurgie laparoscopique, soit par traitement médicamenteux (méthotrexate). Le traitement chirurgical conservateur consiste en une incision de la paroi de la trompe permettant le retrait du matériel de grossesse (salpingotomie), si l'état tubaire le permet. Dans le cas contraire, une salpingectomie (ablation de la trompe) est effectuée.

L'utilisation de ces techniques chirurgicales conservatrices de la trompe engendre un risque, non partagé auparavant par le traitement laparoscopique radical emportant la trompe (salpingectomie), qui est celui de tissu trophoblastique persistant.

Après retrait du matériel de GEU de la trompe ou d'autres localisations, le trophoblaste résiduel généralement dégénère spontanément. Toutefois, malgré une technique chirurgicale méticuleuse, des fragments microscopiques de trophoblaste résiduel peuvent poursuivre leur prolifération, résultant en la persistance d'hCG sériques élevées ou la récurrence de symptômes cliniques (masse annexielle, hémorragie secondaire). Cette situation peut à nouveau mettre en péril la vie de la femme, en raison du risque hémorragique des structures environnant le tissu trophoblastique persistant.

Afin de détecter la présence de trophoblaste persistant, les patientes sont suivies par des contrôles rapprochés et répétés de l'hormone gonadotrophine chorionique. Actuellement, de nombreuses études ont été menées, tentant de déterminer un facteur prédictif caractéristique de trophoblaste persistant et différentes attitudes ont été proposées afin de définir un marqueur précoce, mais le suivi optimal des patientes traitées conservativement pour une GEU n'a encore pas pu être établi.

En l'absence de recommandations concernant une baisse adéquate des valeurs d'hCG permettant d'exclure le risque de trophoblaste persistant, les patientes sont actuellement encore suivies jusqu'à négativation de l'hCG.

Le diagnostic peut être posé pendant le suivi, lorsque les concentrations sériques en hCG mesurées une fois par semaine ou de manière plus rapprochée, montrent un plateau ou une élévation (Vermesh et al., 1988; Pouly et al., 1991; Hagström et al., 1994; Hoppe et al., 1994; Hajenius et al., 1995).

Dans l'idée de réduire l'intervalle de temps nécessaire à l'obtention du diagnostic de trophoblaste persistant, et simultanément diminuer les frais médicaux ainsi que l'anxiété et l'inconfort de la patiente, nous avons entrepris l'étude suivante.

Après un abortus ou un accouchement, l'hCG décroît, dans la circulation sanguine, selon une cinétique de 1er ordre, caractérisée par une première phase de disparition rapide (demi-vie précoce), puis une seconde phase plus lente (demi-vie tardive). Sur la base d'une étude rétrospective effectuée dans notre clinique (Mock et al., 1998), montrant que la 2ème demi-vie de l'hCG (demi-vie tardive) est un meilleur paramètre que la 1ère demi-vie dans le diagnostic de persistance de tissu trophoblastique, nous avons entrepris l'étude prospective suivante.

Pratiquement, le but de notre étude a donc été de déterminer prospectivement si la 2ème demi-vie (demi-vie tardive) de l'hCG représentait un marqueur fiable de la présence de trophoblaste persistant, après chirurgie conservatrice.

Remarque: La participation pratique de l'auteure à l'étude s'est portée sur la plupart des étapes, tant cliniques que théoriques, c'est-à-dire: engagement en temps que médecin-assistante en policlinique et clinique de gynécologie pendant la période de l'étude et participation au diagnostic lors des consultations en urgence des patientes en policlinique et précisément,

intervention chirurgicale effectuée par elle-même chez **19 patientes** inclues dans l'étude; suivi des patientes et relevé des résultats dans le cadre du travail de la policlinique de gynécologie effectué par elle-même (et le Dr. J-L.Anguenot); calculs des demi-vies et des différents paramètres effectué dans sa totalité par l'auteure; dosages de l'hCG effectués au laboratoire d'hormonologie de la Maternité, par l'équipe du laboratoire; relevé des résultats et conclusion tirés par l'auteure; assistance du Prof. P.Bischof pour les calculs statistiques ; article écrit par l'auteure avec l'assistance du Dr. P. Petignat.

II. Introduction: ectopic pregnancy

a) Overview

An ectopic pregnancy is the development of the fertilized ovum outside of the uterine cavity. It can occur in a number of abnormal locations, each with different characteristic growth patterns and treatment options.

The most common sites for an ectopic pregnancy are the following:

1. ampullary (mid) portion of the fallopian tube (80-90%);
2. isthmic (distal 1/3 of the tube) portion of the fallopian tube (5-10%);
3. fimbrial (distal end away from the uterus) portion of the fallopian tube (about 5%);
4. cornual (within the uterine muscle) portion of the fallopian tube (1-2%);
5. abdomen (1-2%); or
6. cervix (less than 1%).

A growing pregnancy requires a large nutrient source (blood supply) and develops many communications with the mother's vascular system. The uterus is uniquely designed to accommodate this development and changes its size and shape dramatically as the pregnancy advances. In the case of an ectopic pregnancy, growth occurs in other surrounding structures which are usually unable to change as readily or provide adequate vascular support and thus are often damaged or "ruptured" by a contained growing pregnancy. In addition, severe hemorraging may result when the ectopic pregnancy outgrows the limits of the space enclosing it and may represent a life-threatening complication for the patient.

Ectopic pregnancies were first described in the 11th century and, until the late 20th century, were considered as an event leading to an inevitable fatal outcome. Initial treatments represented desperate primitive attempts designed to destroy the growing pregnancy without sacrificing the mother's life. During the 19th century, attempts at the surgical management of the condition resulted in a high maternal mortality rate and it was reported that more than 80% of women died from surgery alone. Following this, surgery was rarely performed thereafter.

Since then, several developments in the management of ectopic pregnancies have led to a remarkable success in "saving the mother's life". Further developments have recently resulted in a shift in concern from saving the mother's life to additionally "saving the woman's fertility". The decrease in maternal morbidity and mortality from ectopic pregnancy has been largely due to the development and refinement of :

1. early detection of pregnancy, primarily with the development of sensitive pregnancy tests (hCG assays) and characterization of the normal rate of increase in circulating human chorionic gonadotropin (hCG) concentrations during early pregnancy;
2. more sophisticated radiologic techniques such as high resolution transvaginal ultrasonography;

3. aseptic (sterile) techniques, with surgery now performed in operating rooms with protocols for cleansing, scrubbing and gowning that inhibit transmission of infection;
4. new groups of antibiotics to combat infections due to the major advances in the understanding of infectious diseases and research in antibiotics during the past few decades;
5. anesthetic agents, with new agents allowing increasingly safe administration and a greater understanding of intraoperative patient monitoring.
6. availability of blood or blood products for perioperative transfusions, including advances in terms of blood collection, storage and determination of compatibility with the recipient;
7. surgical techniques which allow to identify and better remove the ectopic pregnancy, such as salpingectomy (to remove the tube) and salpingostomy (discussed below).

At present, advances in the knowledge of the condition have permitted gynecologists not only to better diagnose ectopic pregnancy but, also, to treat it so as to maximize fertility and minimize the risk for a future repeated event. (Ectopic pregnancy,1995; Brzezinski et al., 1994; Yao et al., 1997; Pisarska et al., 1998)

b) Incidence rates and risk factors

A world-side surveillance study of ectopic pregnancies conducted between 1970 and 1993 reported an increasing incidence of the condition (Storeide et al., 1997).

Between 1976 and 1993 in Northern Europe, the incidence increased from 11.2 to 18.8 per 1000 pregnancies (Storeide et al., 1997). In England and Wales, the incidence almost doubled (Report on confidential enquiries, 1994, 1998). In the USA, ectopic pregnancy rates

increased four-fold between 1970 and 1993 (from 4.5/1000 pregnancies to 19.7/1000 pregnancies) (Pisarska et al., 1998; Ectopic pregnancy, JAMA1995).

However, from 1970 to 1993, the mortality rate from ectopic pregnancies dropped almost 90% in the United States (from 35.5/1000 pregnancies to 3.8/1000 ectopics) (Ectopic pregnancy, JAMA 1995). In the United Kingdom, approximately 11,000 cases of ectopic pregnancy per year have been reported (11.5/1000 pregnancies) with four deaths per year (a rate of 0.4/1000 EP) (Report on confidential enquiries, 1994, 1998).

Despite the increased improvement in the mortality rate by the end of this period of time (1979 to 1993), ectopic pregnancies were still the second leading cause of maternal mortality in the USA and accounted for 12% of all maternal deaths in 1987 (Ectopic pregnancy, JAMA 1995).

Ectopic pregnancy commonly occurs in women with impaired tubal function (Russell, 1987). Of the known risk factors, it is believed that an increased number of cases of sexually transmitted diseases, known to damage fallopian tube transport of embryos into the uterus, are responsible for a significant portion of the increased number of cases of ectopic pregnancy in the USA (Westrom et al., 1981; Marchbanks et al., 1988; Hillis et al., 1995-1997; Egger et al., 1998; Kamwendo et al., 2000).

Risk factors for ectopic pregnancy include (Mol et al., 1995-1997; Pisarska et al., 1998):

1. *A prior history of ectopic pregnancy*: when an ectopic pregnancy in the fallopian tube is treated conservatively (by preserving the tube), there is a 10- fold increased risk to have a second ectopic pregnancy. (Skejeldestad, 1998)
2. *A history of surgery on the fallopian tubes or within the pelvis:* when a bilateral tubal ligation is followed by either an unexpected pregnancy (failed tube ligation) or is "reversed" by a tubal reanastomosis (tubal reconstruction) there is an increased risk of a

tubal ectopic pregnancy (McCausland, 1980, 1982; Chow, 1987; Mol et al., 1995). When a woman has a history of pelvic surgery that is associated with significant adhesion formation, such as myomectomy, there is also an increased risk of an ectopic pregnancy.

3. *A history of pelvic infection*. Salpingooophoritis, or Pelvic Inflammatory Disease (PID), is particularly destructive to the fallopian tubes. Chlamydia, a common sexually transmitted disease, and gonorrhea are both able to grow within the fallopian tubes and cause severe damage to the endosalpinx (lining of the inner tubal lumen), agglutination of the mucosal folds in the tube, and peritubal adhesions (scar tissue). The greater the number of pelvic infections, the greater the risk of an ectopic pregnancy. It also appears that the risk of an ectopic pregnancy is enhanced when the woman with the infection is younger and is possibly related to avoiding or otherwise delaying appropriate medical care (Chow Wet al., 1987; Ankum et al., 1996). Other pelvic or lower abdominal infections, such as appendicitis, can also result in pelvic adhesions and result in an increase in the ectopic pregnancy rate.
4. *Use of assisted reproductive technology* such as in vitro fertilization (IVF) and gamete intra fallopian transfer (GIFT)(Ankum et al., 1996).
5. *A history of in utero device (IUD) use* (Mol et al., 1995).
6. *A history of destruction of the uterine cavity or lining*.
7. *A history of diethylstilbestrol (DES) exposure in utero* (Russell, 1987; Ankum et al., 1996; Pisarska et al., 1998).
8. *A history of non-infectious pelvic inflammation* (endometriosis, foreign body).
9. *Smoking* (DeMouzon et al., 1988).
10. *Increased age* (Simms et al., 1997).
11. *Salpingitis isthmica nodosa*.

c) Diagnosis

Early diagnosis of an ectopic pregnancy is critically important in terms of outcome and can be made before the 7th week of pregnancy (i.e., about 4-5 weeks after conception). When an ectopic pregnancy is detected early in development, especially prior to rupture or damage to the surrounding tissue, major morbidity is decreased and the treatment options are enhanced (Cacciatore et al., 1994; Mol et al., 1997).

The different clinical symptoms presented by the patient range from pelvic or abdominal pain with amenorrhea or slight vaginal bleeding at 5 to 6 gestational weeks, to pain radiating to the shoulders, syncope, and shock due to important intra-abdominal hemorrhage later in the course of the pregnancy (Sandra et al., 1993; Pisarska et al., 1998).

There is no uniformly accepted diagnostic protocol for the detection of an ectopic pregnancy and solutions are often combinations of various diagnostic algorithms (Stovall et al., 1990, 1992; Ankum et al., 1993; Pisarska et al., 1998). Some of the common clinical pictures are discussed here.

The early diagnosis of ectopic pregnancy is aided by a high index of suspicion related to the above-mentioned risk factors. In the absence of these, ectopic pregnancy may occur as often as in 1-2% of pregnancies. If multiple risk factors are present, the risk may increase to 25% of pregnancies (Fylstra, 1998).

Sensitive blood hCG assays allow very early diagnosis of pregnancy. Typically, these assays have a sensitivity of 1-5 mIU/ml, thus detecting the occurrence of pregnancy (not the location) approximately 7-8 days after fertilization (a few days prior to a missed menstrual flow). If the hCG assay is negative, generally <5 mIU/ml, complications from an ectopic pregnancy are usually considered to be ruled out (Buster et al., 1995).

The second most common hormone followed in pregnancy is progesterone. Unfortunately, there is a wide overlap between circulating progesterone concentrations in normal intrauterine pregnancy and ectopic pregnancy. Generally, a progesterone concentration of >25 ng/ml is highly correlated (>95%) with a normal intrauterine pregnancy while a concentration <5ng/ml is highly correlated (almost 100%) with an abnormal and nonviable pregnancy. Concentrations between 10 and 20 ng/ml (the most common concentrations) are of little differential value. Progesterone measurements are useful as a single-time screening device but are not useful in patients already identified as being at high risk of ectopic pregnancy (Pisarska et al., 1998).

Serial circulating hCG concentrations are often used to gain insight into the normality of an existing pregnancy. In normal pregnancy, hCG concentrations increase by at least 66% and, more often, 100% in a 2-day period during the first 6 weeks of pregnancy. If the rate of rise is less than 66% over a 2-day period in early pregnancy, this suggests an abnormally growing intrauterine or extra-uterine pregnancy (Buster et al., 1995).

Although there is active research to identify an ectopic pregnancy marker, so far, there are no clinically useful direct tests to confirm a diagnosis. If such a test becomes available, it would certainly revolutionize the diagnosis of this potentially fatal complication of pregnancy.

If concern for an ectopic pregnancy is raised by either the woman's history of known risk factors, pelvic or adnexal pain in early pregnancy, or an abnormal doubling of the hCG concentrations, then additional diagnostic interventions are appropriate.

Transvaginal ultrasonography is a sensitive radiologic test and should be able to detect an intrauterine gestational sac at an hCG concentration of about 1500 mIU/ml, which normally occurs at about 5 weeks of estimated gestational age (EGA) (Barnhart et al., 1994).

The absence of a gestational sac with an hCG concentration >1500 mIU/ml suggests either an abnormally developing intrauterine pregnancy or an ectopic pregnancy (Ankum et al., 1993).

Furthermore, in the study by Cacciatore and coll (1994), an hCG of 1000 mIU/ml combined with the detection of an adnexal mass had a diagnostic sensitivity of 97% and a specificity of 99%. In our clinic, patients having clinical symptoms of ectopic pregnancy are managed by performing first a transvaginal echography, and if the patient's clinical status permits a delay, a quantitative hCG blood test is repeated 48 hours later.

In the absence of pain, evidence of hemoperitoneum (rupture) or cardiovascular instability, a conservative approach is more appropriate if the status and location of the pregnancy is unclear and the pregnancy is desired by the couple. Upon confirmation of an abnormal or ectopic pregnancy, or if the woman becomes less stable, then active treatment must be quickly re-evaluated and selected.

d) Treatment options of ectopic pregnancy

Once the decision has been made to treat a pregnancy as an ectopic pregnancy (or a nonviable intrauterine pregnancy), the physician will attempt to eliminate the potentially dangerous pregnancy to minimise maternal risk and will also try to preserve as far as possible the future fertility potential.

Three primary types of treatments are available for an ectopic pregnancy. These include surgical management, medical management, and expectant management. The most common treatment is surgical.

Surgery allows a rapid and usually definite resolution of the pregnancy and is the preferred treatment for ectopic pregnancy when there is rupture, hypotension, anaemia,

diameter of the gestational sac >4 cm on ultrasonography or persisting pain. Laparoscopy is generally preferred over laparotomy, except when the patient is hemodynamically unstable (Buster et al., 1995). Linear laparoscopic salpingostomy is recommended in ampullary ectopic pregnancy, because the nidation is located between the endosalpinx and the serosa, not in the tubal lumen (Balasch et al., 1994). A longitudinal incision is made by electrocautery, scissors, or laser over the antimesenteric surface of the fallopian tube. Products of conception are removed with suction or forceps. After hemostasis has been achieved, the incision is left to heal by secondary intention. Persistent ectopic trophoblast is the most common complication of laparoscopic salpingostomy and will be discussed below.

Salpingectomy is an alternative to salpingostomy when there is extensive tubal damage, uncontrollable bleeding, or recurrent ectopic pregnancy in the same tube, and when the woman requests sterilization (Brzezinski et al., 1994).

According to the literature, results of subsequent fertility rates after conservative tubal surgery for EP are conflicting, when compared to radical surgery. Some recent reports have shown that conservative tubal surgery had a higher subsequent fertility rate than salpingectomy, with only a slightly higher recurrence of ectopic pregnancy rates (Yao et al., 1997 ; Fernandez et al., 1998 ; Mol et al., 1998). Others observed no significant difference (Clausen, 1996).

In our clinic, as in many others, recommendations to practice conservative salpingostomy were adopted to avoid sterility in the event of subsequent rupture of a pregnancy in the remaining tube. However, this technique carries a risk of persistent ectopic trophoblast, not encountered after salpingectomy.

Medical management primarily involves the use of methotrexate (MTX), a folic-acid antagonist, which has been proned as a way to avoid surgical risks. MTX management results in destruction of the growing pregnancy but is comparatively slow, often taking 4 to 6 weeks

for complete resolution, thus risking rupture of the ectopic pregnancy over this relatively long course of management. Patients with an unruptured EP measuring 4cm or less on ultrasonography are eligible for this treatment but those with larger masses or evidence of rupture are ineligible (Stovall et al., 1991). The outcome of medical therapy now closely matches that of laparoscopic salpingostomy (Buster et al., 1995).

Expectant management is essentially observation and monitoring without active treatment with the knowledge that up to 25% of ectopic pregnancies will resolve on their own. The risk of this treatment option is rupture of the ectopic pregnancy during the observation period.

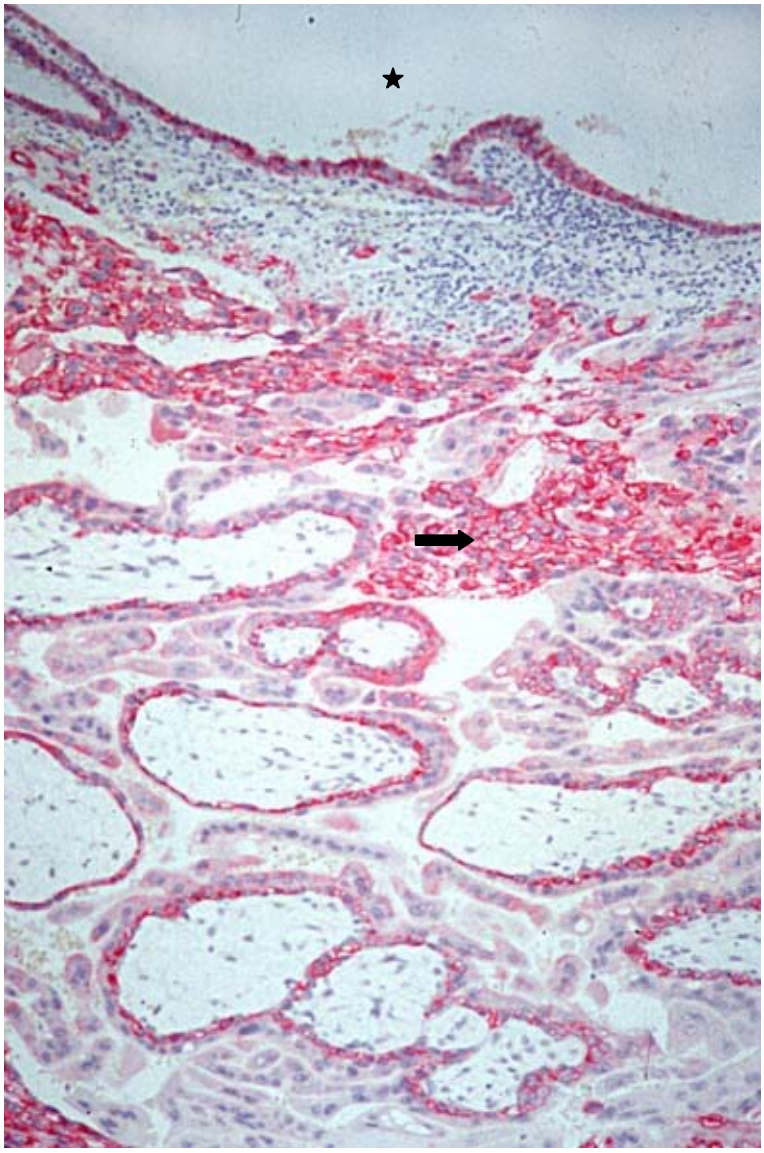
III. Persistent trophoblast after salpingostomy

a) Definition

The development of recent diagnostic tools and protocols and the use of new surgical techniques by laparoscopy to allow a conservative management of the tubes and ovaries have given rise to the risk of persistent trophoblast (DeCherney et al., 1981; Leach et al., 1989; Vermesh, 1989; Zorn et al., 1992). Persistent ectopic trophoblast is the most common complication of laparoscopic salpingostomy and occurs at a frequency of 5-20% as a result of incomplete removal of trophoblastic tissue. It can be defined as a pathological entity, caused by the continual growth of trophoblastic tissue located in the tube which continues to proliferate and, subsequently, causes symptoms or even tubal rupture with intraperitoneal haemorrhage which, generally, requires additional treatment after initial conservative management of the tube (Bell et al.,1987; Vermesh et al.,1988; Stock et al., 1991).

Despite meticulous surgical technique, microscopic fragments of trophoblast are thought to remain after most conservative procedures, especially when trophoblast has invaded the tubal wall (Figure 1, p.16). Fortunately, this remaining tissue usually degenerates after the major trophoblastic mass is removed.

Figure 1



Histological features of a section through a tube (salpingectomy) showing trophoblastic cells invading (arrow) the tubal wall. (Trophoblastic cells were stained by immunohistochemistry with an antibody to cytokeratins using peroxidase as a marker). Tubal lumen (star).

(CK 7 x 100)

b) Diagnosis of persistent trophoblast

To diagnose persistent ectopic trophoblast, patients need serial and close quantitative serum hCG controls; hCG levels should reach undetectable values to ensure disappearance of trophoblastic activity and to exclude the possibility of persistent trophoblast.

Factors known to increase the risk of trophoblast persistence are small ectopic pregnancies (<2 cm diameter), early therapy (<42 days from last menstrual period), and implantation medial to the salpingostomy site (Seifer, 1997; Pisarska et al., 1998).

Many reports have tried to determine the characteristics of predictive factors of persistent trophoblast and different attitudes have been proposed to detect early markers. However, the optimal follow-up of patients treated conservatively for an ectopic pregnancy has not yet been established. To date, no technique offers a 100 % sensitivity to detect persistent trophoblast, a condition that is mandatory, considering the clinical risk incurred by unknown persistent trophoblast. Given the absence of recommendations concerning the threshold representing an adequate decrease of hCG values to allow physicians to rule out the risk of persistent ectopic pregnancy, patients are followed until negativation of hCG levels.

Diagnosis is made during follow-up when hCG concentrations measured once a week or more often show a plateau or a rise (Vermesh et al., 1988; Pouly et al., 1991; Hagström et al., 1994; Hoppe et al., 1994; Hajenius et al., 1995).

In the short term, the cost of salpingostomy is higher than salpingectomy. Not only because patients require close monitoring to ensure disappearance of trophoblastic activity as in any conservative surgery but, also, because additional treatment for persistent ectoic pregnancy is sometimes required.

Indeed, the costs of routine follow-up (medical visits, serum hCG tests, time lost from work) as well as the anxiety over the possibility of persistent trophoblast are important.

We conducted this prospective study with the aim to attempt to reduce this period, and to reduce simultaneously medical costs and patient discomfort and anxiety.

c) Historical perspectives

Persistence of trophoblastic tissue was first described by Kelley et al. in 1979 (Kelley et al., 1979). In a review of 200 conservative procedures conducted between 1953 to 1980, no ectopic persistence was observed (Hallatt, 1986). Five cases were observed in 1985 (Rivlin et al., 1985). Between 1982-1986, four cases were diagnosed among 84 conservative procedures, occurring simultaneously with an increased use of conservative procedures on the tubes. (DiMarchi et al., 1987). Prior to 1986, postoperative hCG conccentrations were not routinely obtained and it is possible that asymptomatic cases of trophoblastic persistence may have remained undetected (DiMarchi et al., 1987). After 1986, the reported incidence of persistent trophoblast following conservative surgery ranged from 3 to 20% when surgery was performed laparoscopically (Vermesh et al., 1988; Pouly et al., 1986; Seifer et al., 1990; Lundorff et al., 1991; Buster et al., 1995; Mock et al., 1998).

d) Treatment of persistent trophoblast

Medical management by systemic MTX injection appears to be ideal for cases with rising or plateauing hCG (Stovall et al., 1991; Seifer et al., 1993; Hoppe et al., 1994).

Further surgery is sometimes necessary or recommended for patients with suspected active intra-abdominal bleeding or poor compliance to follow-up (Pouly et al., 1986; DiMarchi et al., 1987; Vermesh et al., 1988; Seifer et al., 1993).

Expectant management may be followed in stable patients with slowly but steadily declining hCG levels (DiMarchi et al., 1987; De Cherney et al., 1987; Garcia et al., 1987; Vermesh et al., 1988; Hoppe et al., 1994).

The choice of management should be based on serum hCG concentrations, patient's symptoms, and the condition of the involved tube.

IV. Critical evaluation

a) Study aims

After termination of pregnancy, hCG seric concentrations decrease with a first order kinetic, characterised by a rapid disappearance (early $T_{0.5}$), followed by a slow disappearance (late $T_{0.5}$) (Midgley et al., 1968; Rizkallah et al., 1969; Holtz, 1983).

Based on these characteristics of hCG decline, Mock et al. demonstrated in a previous retrospective study conducted in our department that only two hCG measurements (at days 2 and 7) allowed detection of persistent trophoblast with 100% sensitivity, after determination of the late half life (late $T_{0.5}$) of hCG parameters (Mock et al., 1998). In consideration of these results, our clinical procedure is now to control hCG concentrations after conservative laparoscopy at days 2 and 7, and thereafter weekly until complete resolution of hCG.

The aim of our study was to determine prospectively if the late half-life of hCG was a reliable marker in identifying all patients at risk for developing persistent trophoblast following conservative laparoscopic surgery for a tubal pregnancy.

b) Materials and methods

Between June 1997 and September 2000, all patients (n=232) with a suspicion of EP either referred directly by private practitioners or presenting to the Emergency Unit of the Department of Gynecology of the University Hospitals of Geneva were prospectively enrolled in the study. Diagnosis of EP was based on reproductive and surgical history, physical examination, transvaginal ultrasonography, and the quantitative estimation of serum hCG concentration. The flowchart of the study is illustrated in Figure 2, p.25.

Women with an unruptured tubal pregnancy of 3.5 cm or less in greatest dimension, hemodynamically stable, with no presence of cardiac activity, absence of free fluid, and an hCG concentration <10'000 mIU/ml were generally selected for MTX treatment and were excluded. All patients not suitable for medical treatment underwent surgical treatment and were considered as eligible for study entry (n=73). For patients with an isthmic and ampullary localization of the tubal pregnancy, a laparoscopic linear salpingostomy was performed in the antimesenteric border of the tube over the ectopic pregnancy with electrocautery. Trophoblastic tissue was removed, either by grasping forceps or using irrigation and aspiration, and was sent for histological examination. No patient underwent a subsequent suture of the operated tube.

A pre-operative hCG level was obtained as close as possible to the time of surgery (day 0). All patients were then followed according to a fixed protocol including blood sampling (between 08:00 hours and noon) within 24 hours of surgery, followed by samples

taken on days 2, 7, 14, and 21 days post-operatively. This timing could have been modified by two days due to weekends during which no blood samples were taken. Persistent trophoblast was defined as a plateauing or increasing serum hCG concentration.

We used the same mathematical model as used previously in the retrospective study (Mock et al., 1998) to calculate the half-lives of hCG.

The equation was : hCG $T_{0.5}$= 0.6923 x time interval ($t_1 - t_2$) / 2.3 (log10 hCG conc.$_1$ - log10 hCG conc.$_2$), where t_1 and t_2 were the times of sampling as counted from the day of surgery (day 0), and concentrations$_1$ and $_2$ were the concentrations of hCG measured respectively at times t_1 and t_2.

We also reviewed the different clinical and biological characteristics that could be predictive of persistent trophoblast (age, parity, gestity, gestationnal age, hCG values at day 0, 2 and 7, and early $T_{0.5}$).

We have considered as "normal value", a late $T_{0.5}$ ranging between 20.8hrs and 114hrs, and as "pathological value" when it ranged outside these limits.

The range of normal value was the 10th and 90th centile of the log distribution of late $T_{0.5}$ calculated in the previous study mentioned above (Mock et al, 1998).

c) Results

Between June 1997 and September 2000, 232 EPs were diagnosed. A total of 73 patients underwent a salpingostomy by laparoscopy for a tubal EP and fulfilled the inclusion criteria of the study. One hundred and fifty-nine patients were excluded for the following reasons: 75 had salpingectomy (patient's choice or failure of salpingostomy); 70 received systemic medical treatment (MTX); 5 had ovarian or para-ovarian pregnancies; 5 underwent

an expectant management; and 4 presented incomplete data (missing values or lost to follow-up)**.**

The clinical and biological characteristics of women treated successfully (no persistent trophoblast) and unsuccessfully (persistent trophoblast) were similar with regards to age, parity, histology results, presence of foetal cardiac activity, ruptured tube, preoperative value of hCG, and the presence or absence of free peritoneal fluid at the time of diagnosis (initial treatment). None of these variables discriminated statistically between successful and unsuccessful treatment (Table 1, p.26). The preoperative value of hCG was similar in cases of persistent trophoblast, compared with those with a successful conservative surgical outcome. In contrast, the hCG values at days 2 and 7, and the late $T_{0.5}$ were significantly higher in the group of patients with persistent trophoblast (Table 1, p.26).

Sixty-three women were successfully treated with salpingostomy (86%), and 10 presented persistent trophoblast (14%). These lattercases required a second procedure. Nine of the 10 cases presenting persistent trophoblast were identified prospectively on the basis of late $T_{0.5}$, with a mean late $T_{0.5}$ value of –200 +/- 68.8hrs. Among the latter group, patient 3 (Table 2, p.27) was admitted 6 days postoperatively to the emergency service of our clinic in hemorragic shock due to tubal rupture. Her late $T_{0.5}$, calculated with hCG at days 2 and 6, was pathologic and concurred with the clinical evolution. An emergency laparotomy and a second salpingostomy was performed but she presented again with a persistent trophoblast. Finally, a favorable response was achieved after systemic MTX. Patient 7 in the same group (Table 2, p.27) consulted our emergency clinic 9 days following salpingostomy due to recurrent pelvic pain, associated with a hemoperitoneum and hemosalpinx. Similar to patient 3, her late $T_{0.5}$ was pathologic and she underwent a laparoscopic salpingectomy. The remaining seven patients were treated with systemic MTX which allowed complete remission, apart from two

who required a second injection of MTX (Table 2, p.27). Early $T_{0.5}$ only identified 2/10 patients with persistent EP.

One patient had a "normal" late $T_{0.5}$ and was not detected. HCG values after day 7 showed an abnormal evolution (plateauing of hCG values after day 10) and she received a systemic treatment of MTX at day 25.

Thus, by using late $T_{0.5}$, we could determine persistent trophoblast with a 90% sensitivity, a 97% specificity, an 82% positive predictive value, and 98% negative predictive value (Table 3, p.28).

We confirmed, that the late $T_{0.5}$ was significantly different between normal cases and cases with persistent trophoblast and constitutes a better parameter than the early $T_{0.5}$, in women presenting persistent trophoblast (Table 1, p.26 compares successful and unsuccessful treatment).

c) Discussion and Conclusion

Our results confirm the biexponential decline of hCG with an early $T_{0.5}$ of 26.4 +/- 1.3hrs, followed by a late $T_{0.5}$ of 55.8 +/-5.3hrs for patients treated successfully by salpingostomy. We postulated that the determination of an early and late $T_{0.5}$ could identify all patients at risk to develop a persistent trophoblast after conservative surgery. Our objective was to shorten the follow-up period to only two hCG measurements which would certainly be more cost-effective and beneficial for the quality of life of patients.

Unfortunately, the current study does not confirm the promising retrospective results of the previous study (Mock et al., 1998). Late $T_{0.5}$ appears as a good predictor of patients likely to develop persistent trophoblast (90% sensitivity), but its efficacy is not sufficient to identify all patients at risk. We have found no other clinical or biological characteristics as

markers of persistent trophoblast which reached statistical significance, but the small sample size of patients limits statistical power to demonstrate a difference between these variables.

Persistent trophoblast was observed at a rate of 14% in our study, results that concur with recent publications concerning the treatment failure rate of EP (5 to 20%). For the 10 patients with failure after conservative surgery, medical treatment with MTX was administered with success in 8/10 women and only 2/10 women required a second surgery. In our experience, the medical approach using MTX is a good alternative to avoid further surgery.

Many studies, mostly retrospective, have investigated different markers of persistent EP without showing an improved efficacy of the current policy. Different propositions of strategies to improve the latter have been suggested such as performing multicenter prospective studies (Seifer et al., 1997) to standardize different parameters such as experience of operator, type and time of operation, patient selection, improvement of patient compliance to follow-up, the performance of salpingostomy, and to avoid surgery before 6 weeks and practising only fimbrial expression. These propositions need to be evaluated and are not sufficiently appropriate at the present time to justify a change in the management policy of patients presenting with an EP.

In conclusion, the late $T_{0.5}$ value may be used as a predictive "test" to estimate the risk of persistent trophoblast, but cannot formally exclude its existence. Therefore, it is still mandatory to control hCG concentrations after conservative surgery for EP until complete resolution to exclude a late onset of persistent trophoblast. Weekly blood sampling should be performed, or even more regularly if there is any doubt of persistent trophoblast.

Research should continue to seek other possibilities to detect early and late onset of persistent trophoblast and, in particular, further studies are necessary to address the issue of what can be considered as the threshold representing an adequate decrease of hCG values.

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