INTRODUCTION

The more liberal use of home pregnancy tests and access to early pregnancy Assessment units (EPAU) have led to an increase in the number of women undergoing early transvaginal ultrasound scans (TVS) to locate, date and confirm viability of their pregnancy. This approach has resulted in more women being diagnosed with a pregnancy of unknown location (PUL) or inconclusive scan (an empty uterus and no adnexal mass on TVS). This group of women is defined as having a positive pregnancy test and no sign of intra or extrauterine pregnancy on TVS ***(Gevaert O et al., 2006)***.

Assessment of early pregnancy is indicated in women with clinical symptoms suggestive of miscarriage or ectopic pregnancy. With transvaginal ultrasound, it is possible to visualize early pregnancy in the majority of women ***(Bateman B et al., 1990)***.

Failing intrauterine pregnancies are regarded as a common gynecological cause of abdominal pain and vaginal bleeding, which should be distinguished from ectopic pregnancy ***(Condous G et al., 2006)***. Therefore, several methods including clinical and sonographic evidence have been proposed to aid in

deferential diagnosis between these two conditions ***(Bourne T et al., 1997)***.

Pregnancy causes a choriodecidual reaction in the endometrium, producing the sonographic appearance of the echogenic trophoblastic endometrium. Therefore, one could hypothesize that because the endometrial decidual response depends on the gestational hormonal milieu, a thin endometrial thickness may predict abnormal pregnancy outcome at an early gestational age ***(Dart R et al., 1999)***.

Some studies showed that the thinnest endometrial measurements are seen in patients with ectopic pregnancies **(Spandorfer S et al 1996)**. However, their enrolment criteria limited patients to those with β-human chorionic gonadotrophin (β-hCG) levels <1500 mIU/mL. Other studies found no threshold for endometrial thickness to distinguish among patients with ectopic pregnancy, spontaneous miscarriage or early IUP ***(Mol B et al., 1999), (Mehta T et al., 1999), (Banerjee S et al., 1999), (Seeber B et al., 2007), (Condous G et al., 2005) and (Col-Madendag I et al., 2010)***.

The relative proportions of PULs are determined by many factors, with the quality of ultrasound examination probably

being the most important one. There is a consensus that modern early pregnancy units should strive to maintain a PUL rate of 15% or less. This is still a relatively high figure, and management of women with PUL therefore forms a significant part of the workload in most early pregnancy units ***(Condous G et al., 2006)***.

AIM OF THE WORK

The aim of our study was to determine whether endometrial thickness at the time of initial presentation can be used to predict normal intrauterine pregnancy or not.

Chapter 1:
DEFINITION, INCIDENCE AND CLINICAL TYPES OF PREGNANCY OF UNKNOWN LOCATION

PUL can be defined as:

1- When serum levels of β-hCG are below the discriminatory zone (<1000 mIU/m L) and there is no pregnancy (intra or extrauterine) is visualized on transvaginal ultrasound scan ***(Cacciatore B et al., 1990)***.

2- Whenever there is no sign of either intra or extrauterine pregnancy or retained products of conception on transvaginal ultrasound, despite a positive pregnancy test ***(Rulin M et al., 1993)***.

3- ***(Condous G et al., 2006)*** defined the PUL as a situation in which there is a positive pregnancy test with no signs of intra or extrauterine pregnancy on transvaginal sonography (TVS).

4- ***(Kirk E et al., 2006)*** defined the PUL as it's a descriptive term used to classify a pregnancy when a woman has a positive pregnancy test, but no pregnancy can be visualized on TVS.

5- ***(Cordina M et al., 2011)*** defined the PUL as it's a clinical situation when transvaginal ultrasound examination fails to identify an intrauterine or ectopic pregnancy in a woman with a positive pregnancy test.

The majority of women with PULs attend for ultrasound examination after miscarriage, when the pregnancy test is still positive, but when there is very little or no trophoblast left within the uterus.

PUL is estimated to represent 8-31% of the pregnancies ***(Banerjee S et al., 1999), (Banerjee S et al., 2001), (Cacciatore B et al., 1988), (Condous G et al., 2004), (Hahlin M et al., 1995) and (Hajenius P et al., 1995)***.

Clinical outcomes of PUL:

1-Failing pregnancy of unknown location (FPUL): The majority of PULs fails and resolves spontaneously (44–69%). This failing PUL group is also known as trophoblast in regression and are never visualized using TVS; an indeterminate proportion of these are failing ectopic pregnancies as well as failing IUPs ***(Banerjee S et al., 2001).***

2-Intrauterine pregnancy (IUP): Approximately one-third of PULs are early developing IUPs, too small to visualize on TVS. Over two thirds of this group, when followed up after

confirmation of location, are ongoing viable IUPs ***(Condous G et al., 2005)***.

3-Ectopic pregnancy (EP): The overall prevalence of ectopic pregnancies in a PUL population varies greatly (8.7–42.8%) ***(Condous G et al., 2005)***. Whenever sonographic skills are highly developed; the majority of PULs will not have an underlying ectopic pregnancy. In highly specialized scanning units one can expect to have low rates of ectopic pregnancy (8.7–14%) ***(Banerjee S et al., 2001)***. In these units, the diagnosis of an ectopic pregnancy is based on the positive visualization of an adnexal mass using TVS, rather the absence of an intrauterine gestational sac. A recent study demonstrated clearly the capability of TVS when used as a single test to positively identify an ectopic pregnancy where present ***(Condous G et al., 2005)***. Although few clinicians would use ultrasound evidence of extrauterine pregnancy as the primary way to diagnose ectopic pregnancies, data suggest that ultrasound is a reliable diagnostic tool. In the aforementioned study, 90.9% of ectopic pregnancies were correctly diagnosed pre-operatively using TVS alone ***(Condous G et al., 2005)***. Other studies report between 87 and 93% of ectopic pregnancies being identified using TVS prior to surgery ***(Cacciatore B et al., 1999)***.

4-Persisting pregnancy of unknown location (PPUL): The persisting PUL group only accounts for 2% of the total PULs. The persisting PUL group is defined in those women where serum human chorionic gonadotrophin (β-hCG) levels fail to decline and the location of the pregnancy cannot be identified using TVS. The serum hCG levels tend to be low (<500 mIU/mL) and reach a plateau. These PULs behave biochemically like ectopic pregnancies and almost certainly represent ultrasonically missed ectopic pregnancies ***(Condous G et al., 2004)***.

Chapter 2:

Diagnosis of pregnancy of unknown location

Early pregnancy assessment units (EPAU) should be generally available, easily accessible, comprehensive and ideally sited in a dedicated area with appropriate staffing. There should be direct access for selected patient groups ***(Rulin M et al., 1993)***.

To be effective, an early pregnancy assessment unit (EPAU) requires an efficient appointments system, an appropriate setting, ultrasound equipment (including transvaginal probes) and easy access to laboratory facilities for rhesus antibody testing and selective serum human chorionic gonadotrophin (hCG) and progesterone estimation. The service should be available on a daily basis during the normal working week, although many units offer an additional limited service at weekends. Standardized information leaflets, referral and discharge letters should be available and regularly reviewed. Certain patient groups, such as women who have had a previous ectopic pregnancy and those with repeated or recurrent miscarriage, can be offered future access to the service by direct self-referral via the appointments system ***(Condous G et al., 2003)***.

1- Clinical factors in the Diagnosis of PUL

I. Triage of patients with early pregnancy complications before ultrasound:

The aim was to develop and evaluate a score system usable by emergency room (ER) nurses for the triage of patients with early pregnancy complications. Potential dangerous conditions (ectopic pregnancy, septic abortion and sever bleeding) should be recognized by the ER nurses and referred to the gynecologist immediately. Women with mild pain and light bleeding can be referred for later ultrasound (US) examination. US examinations in very early pregnancy were intended to be postponed to minimize the number of pregnancies of unknown location (PUL). The following scores were used: no bleeding = 0, menses-like bleeding = 1, severe bleeding = 2, no pain = 0, light pain = 1, severe pain = 2, no fever = 0, fever above 37.5◦ Celsius = 2. Sum of scores for bleeding + pain + fever exceeding 2 should lead to contact with the gynecologist. Information focused on which symptoms to observe and when contact with a physician is necessary. Evaluation of ER score charts was done on 116 patients. The women were aged 15–44 years, gestational age range 4–16 weeks. The Result was 96 women (83%) had scores less than 2, suggesting no need for treatment. 20 women (17%) had scores of 2 or more, 17 women had US in the ER diagnosing: 6 viable pregnancies, 5 PULs, 3

abortions, 2 intrauterine gestational sacs and 1 missed abortion. This study is concluded that emergency room score system for early pregnancy complications was useful. The majority of women did not need ultrasound in the ER; however the score system was not applied in women with obvious need for emergency treatment ***(Zingenberg H et al., 2006)***.

A scoring system based on symptoms at presentation has value to stratify risk and influence the intensity of outpatient surveillance for women with pregnancy of unknown location but does not serve as a diagnostic tool ***(Barnhart Ket al., 2012)***.

II. A British study was done in 2004 to show if clinical factors and ultrasonographic findings can be useful in the prediction of outcome of (PUL) or not:

This Prospective study was done on 196 consecutive women classified as PULs. Final classification as: FPUL, IUP and EP. Each woman classified as PUL had historical, clinical and ultrasound data collected. Historical data included age, gestation and risk factors for EP. Clinical data included amount per vaginal bleeding (PVB), abdominal tenderness and localization of the tenderness. Ultrasonographic data included endometrial thickness (ET), character of midline echo, presence or absence of free fluid in pouch of Douglas (POD) and site-specific tenderness on transvaginal scan (TVS). The greater the PVB the higher likelihood failing PUL. Presence of abdominal

tenderness did not correlate with outcome. Uterine site-specific tenderness was significantly greater in failing PULs. Adnexal tenderness did not differ significantly between the three groups. Vaginal bleeding and uterine site-specific tenderness are important variables in predicting failing PULs. As the vast majority of PULs is asymptomatic at presentation, it is not surprising that historical and clinical factors do not seem to vary between the three outcome groups ***(Kirk E et al., 2004)***.

Other study concluded that Examination and ultrasonographic information did not significantly improve the performance of logistic regression models in the prediction of PUL outcome. When approaching women with a PUL, biochemical data alone, and in particular the hCG ratio (hCG 48hrs/hCG 0hr), can be used to predict PUL outcome with a high degree of certainty **(Condous et al., 2006)**.

2-Biochemical markers in diagnosis of PUL

I. β-hCG and Progesterone in diagnosis of PUL:

The majority of women attending an EPAU can be managed using urine based hCG tests. Modern monoclonal antibody based kits can detect hCG at 25 mIU/mL, a level reached 9 days post conception. At levels above 1500 mIU/mL, an ectopic pregnancy will usually be visualized with TVS **(Condous G et al., 2005)**. However, the importance of levels

that plateau below 1000 mIU/mL must be recognized. In these cases, pregnancy of unknown location and miscarriage are both possible outcomes. The potential for rarer diagnoses, such as gestational trophoblastic disease or cranial germ cell tumor, must be considered although, in these cases, serum hCG levels are likely to be greater than 1000 mIU/mL ***(Condous G et al., 2005)***.

- **β-hCG discriminatory zone:**

Diagnosis of pregnancy is made by measuring the serum or urine hCG. The hCG is often positive before US can detect a pregnancy. The discriminatory zone for hCG is the serum level above which a gestational sac should be visualized by ultrasound examination if an IUP is present ***(Ankum W et al., 1993)***.

At most institutions, the hCG discriminatory zone is 1500 to 2000 mIU/mL with TVS. The level is higher [6500 mIU/mL] with transabdominal scan (TAS). It was reported that a serum hCG of greater than 6500 mIU/mL and the absence of an intrauterine gestational sac on TAS had a sensitivity of 100% and a specificity of 96% for the prediction of ectopic pregnancy. This is a general threshold and may vary across women and with multiple gestations. However, if an IUP is not seen at this level and the patient is stable and has a desired pregnancy, hCG testing and US should be repeated within 48

hours. Since factors such as the margin of error of hCG measurement, multiple gestation, or recent pregnancy may elevate the hCG, and the quality of US is variable, there is no established maximum hCG at which a patient with no IUP on US should be treated for ectopic pregnancy without further evaluation. As an example, in a retrospective series of 35 women with an hCG greater than 2000 mIU/mL and no IUP on US who were managed expectantly, all had an IUP at follow-up US ***(Shalev E et al., 1998)***.

- **Variation in the discriminatory zone did not significantly improve the detection of ectopic pregnancy:**

Ninety-three % of ectopic pregnancies will be visualized on transvaginal sonography. Currently, hCG levels are greater than a given discriminatory zone, one should always expect to see an intrauterine gestation; in the absence of this, an ectopic pregnancy must be excluded. Various serum hCG discriminatory zones are currently used for evaluating the likelihood of an ectopic pregnancy (EP) in women with a pregnancy of unknown location (PUL). Discriminatory zones of serum hCG > 1000 mIU/mL, 1500 mIU/mL and 2000 mIU/mL for the detection of EP in such women were evaluated by ***(Condous G et al., 2005)*** through their prospective study .All PUL had serum hCG measured at presentation. All women were followed up with TVS until a diagnosis was established: failing PUL, intrauterine pregnancy, EP or persisting PUL.

Three different discriminatory zones (1000 mIU/mL, 1500 mIU/mL and 2000 mIU/mL) were evaluated for predicting EP. 5544 consecutive women presented to the Early Pregnancy Unit. 568 PUL were diagnosed and 41 were lost to follow up. 527 PUL analyzed: 300 (56.9%) failing PUL, 181 (34.3%) IUP, 37 (7.1%) EP and 9 (1.7%) persisting PUL. The sensitivity and specificity of hCG > 1000 mIU/mL to detect EP were 21.6% and 87.3% respectively. The sensitivity and specificity of hCG > 1500 mIU/mL to detect EP were 18.9% and 93.4% respectively. The sensitivity and specificity of hCG > 2000 mIU/mL to detect EP were 13.5% and 95.2% respectively, so for the prediction of ectopic pregnancy in women with PULs ,it found that the sensitivity for the detection of ectopic pregnancy decreases as the discriminatory level of hCG increases and varying in the discriminatory zone did not significantly improve the detection of ectopic pregnancy. Therefore this alone cannot be used to diagnose ectopic pregnancies ***(Condous G et al., 2005)***.

It was concluded that, when there is a PUL, it is the change in serum hCG over time (hCG ratio = hCG 48hrs/hCG 0hr) that is important rather than any absolute initial serum value of hCG, as some ectopic pregnancies have relatively low serum hCG levels. In contrast, a significant proportion of failing PULs and early IUPs in PUL populations have high serum hCG levels at presentation and may undergo unnecessary