Pregnancy can either be located at eutopic or ectopic site. Eutopic pregnancy or normal pregnancy is located in normal the intrauterine cavity whereas ectopic pregnancy is located elsewhere, either intrauterine or extraterine in location. The location of intrauterine ectopic pregnancy includes pregnancy at the cornu or the cervix of a uterus. The common location of extraterine ectopic pregnancy is in the fallopian tube. Ectopic pregnancy, especially tubal pregnancy, used to be a leading cause of maternal death due to hemorrhagic shock resulting from rupture at the ectopic implantation site. Clinically, a sexually active woman is suspected to have ectopic pregnancy if she presents with clinical triads, including pelvic pain, bleeding per vagina and adnexal mass. However, medical history and physical examination may or may not always provide useful diagnostic information. The accuracy of the initial clinical evaluation is less than 50%. In the past, a case whose clinical parameters were suggestive of ectopic pregnancy needed close monitoring until the signs of internal hemorrhage were obvious before she received a definite treatment, or she had to undergo exploratory laparotomy, which was too invasive in some cases, to rule out ectopic pregnancy.

It is crucial to localize the site of pregnancy in a woman with potential pregnancy in her first trimester presenting with pelvic pain and/or vaginal bleeding because ectopic pregnancy is among the differential diagnoses of this presentation. Nowadays, owing to the development of highly sensitive pregnancy test (i.e. serum beta-hCG) and high resolution transvaginal ultrasonography (TVS), pregnancy can be confidently diagnosed and localized at a very early gestational age (GA). The minimum level of serum beta-hCG that an ultrasonography can visualize an intrauterine gestational sac (GS) is termed “discriminatory zone”. Although the concept was originally established using transabdominal ultrasonography (TAS), it is now widely accepted that, above the discriminatory cutoff of 1,000-2,500 IU/L, using TVS, a normal intrauterine pregnancy should always be visualized. An absence of such implies an abnormal gestation.  

When serum beta-hCG level is higher than the discriminatory zone and an intrauterine GS cannot be visualized, an ectopic pregnancy is highly suspicious. An early diagnosis of ectopic pregnancy results in a better treatment outcome as the patient can be treated by options other than exploratory laparotomy. The treatment options include expectant management, medical treatment, or minimally-invasive surgery, depending on the patients' condition.

However, when serum beta-hCG level is below the discriminatory zone and there is no pregnancy, either intra- or extra-uterine, visible on TVS, the location of pregnancy cannot be concluded and the patient should be diagnosed as having “pregnancy of unknown location or PUL”. The term PUL was firstly introduced by Cacamore in 1990 and then was adopted by the Royal College of Obstetricians and Gynaecologists of the United Kingdom However, this term is not yet mentioned in the latest version of the International Statistical Classification of Diseases and Related Health Code. It is estimated that that 44-69% of PUL spontaneously resolve. Approximately, one-third of PUL are early developments of intrauterine pregnancies, too small to be visualized under TVS. Over two-thirds of this group, when the location of pregnancy is confirmed after a certain period of followed up, are ongoing viable intrauterine pregnancies. The overall prevalence of ectopic pregnancies in a PUL population varies greatly (8.7-42.8%). The persisting PUL group only accounts for 2% of the total PUL. The persisting PUL group is defined in those women where serum human chorionic gonadotropin (hCG) levels fail to decline and the location of the pregnancy cannot be identified under TVS. The management of PUL is usually by expectant measures if the patient’s clinical signs are stable. Intervention has been shown to be necessary in 23-29%. The followings case series demonstrated 3 patients that were considered to have PUL at some points during the course of management for complicated early pregnancy.

Case 1
A 36-year-old pregnant woman, G4P2012 last 15 years, presented at an emergency room on 20 Jan 2006. Her chief complaint was bleeding per vagina for 1 day. By that time she was pregnant with a GA of 6 weeks and 5 days (last menstrual period was 4 December 2005, and her pregnancy test was positive 11 days before this visit). She had intermittent pelvic cramp for 10 days. The pain became more severe and was localized on the left lower quadrant for 1 day, followed by vaginal bleeding with fresh blood, needing 2 regular sanitary pads in 8 hours. She also passed small amount of tissue through the vagina. Her past medical history included right salpingo-
oophorectomy for benign right ovarian cyst 17 years ago, suctional and curettage for molar pregnancy and post abortion tubal sterilization 12 years ago, and tuboplasty to reverse tubal sterilization 3 months ago. Physical examination revealed normal vital signs (T 36.8°C, P 80 bpm, RR 20/min, BP 120/80 mmHg without postural hypotension) without pallor. The abdomen was soft with mild tenderness at the suprapubic region. Pelvic examination revealed minimal amount of fresh blood in the vagina, congested cervix without cervical excitation pain, normal sized uterus, no adnexal mass, no bulging in the cul-de-sac, and no pelvic tenderness. Other physical findings were unremarkable.

Initial laboratory investigations included CBC (Hb 11.6 g/dL, Hct 34.5%, platelets 264,000/mm³, WBC 8,650/

mm³, N 51%, L 33%) and serum beta-hCG: (211 mIU/ ML). TVS demonstrated hyperechoic endometrium of 9 mm thick without intrauterine gestational sac (Fig 1A), and the well-defined left ovary containing a thick wall hypoechoic cyst of 1 x 2 cm² compatible with corpus luteum (Fig 1B). There was neither abnormal adnexal mass nor free fluid in the cul-de-sac. The initial diagnosis was complete abortion or ectopic pregnancy. The patient was managed expectantly. Serum beta-hCG at 60 hr later was 214 mIU/mL, approximately the same as the initial level. Dilation and curettage (D&C) was performed and 1 table spoon of tissue was obtained. Post operative

Fig 2. Transvaginal sonogram and laparoscopic findings of Case no.2; (a) sagittal view of uterus with type II endometrium of 11.8 mm thick (thin arrow heads) and free fluid in cul de sac (thick arrow head); (b) left adnexa with a simple cyst, c, of 2.8 x 2.5 cm in diameter; (c) laparoscopic findings of pelvic organs, U = uterus, LO = left ovary; (d) laparoscopic picture of left adnexa showing normal left fallopian tube and left ovary containing corpus luteum.

Fig 3. Transabdominal sonogram of Case no.3; (a) sagittal view of uterus with thin endometrium; (b) left ovarian cyst, LT O, of 5.0 x 4.2 cm in diameter; (c) right ovarian cyst, RT O, of 3.1 x 2.6 cm in diameters.

Fig 1. Transvaginal sonogram of Case no.1: (a) sagittal view of uterus with hyperechoic endometrium of 9 mm thick; (b) left ovary with a thick wall cyst compatible with corpus luteum (arrow).

Fig 4. Transvaginal sonogram of Case no.2 on postoperative day 3 shows intrauterine gestational sac (GS) containing yolk sac (arrow head).
course was uneventful. Serum beta-hCG at 24 hours after the D&C was 239 mIU/mL, approximately 13% rising from the initial level. Follow-up TVS revealed no change except that the endometrium thickness was 5 mm. Histopathological report of the curettage revealed proliferative endometrium without chorionic villi. The final diagnosis was suspected extrauterine pregnancy. The patient was treated with single dose intramuscular methotrexate, 50 mg/M². Serum beta-hCG at day 3, 7 and 14 after medical treatment were 88, 20 and 2.5 mIU/mL, respectively. The final location of pregnancy could not be concluded.

Case 2
A 32-year-old registered nurse at Siriraj Hospital, married, P0000 presented at the Outpatient Clinic, Department of Gynecology on 15 Feb 2006. Her chief complaint was severe acute abdominal pain at her left lower quadrant for 4 hours. She had been experiencing pelvic pain, cramping in nature (similar to dysmenorrhea) for 4 days. The pain had been tolerable until the morning of presentation. She did not notice any missing period and had no symptoms related to pregnancy. Her past medical history included appendectomy 10 years earlier, and polycystic ovarian disease (oligomenorrhea/amenorrhea since menarche at 12 years old and polycystic ovaries demonstrated by TVS) diagnosed 4 years ago. She had been taking oral contraceptive pills off-and-on to regulate the menstrual cycles and she finished her last pill package on December 2005 which was followed by a normal period by the end of December. Physical examination revealed normal vital signs (temperature 37.2°C, pulse 88 bpm, blood pressure 110/80 mmHg, and respiratory rate 20 /min), without pallor. The abdomen was soft but presented mild tenderness without guarding or rebound at the left iliac region. Pelvic examination revealed normal vaginal discharge, congested cervix with positive cervical excitation pain, normal sized uterus, ill-defined mass with tenderness at left adnexa, and no bulging in the cul-de-sac. Other physical findings were unremarkable.

Initial investigations included urine pregnancy test (positive), CBC (Hb 12.7 g/dL, Hct 40.2%, platelets 426,000 /mm³, WBC 10,550 /mm³, N 63%, L 28%, Mo 5%), VDRL (non reactive) and antiHIV (negative). TVS demonstrated normal uterus with type II endometrium with minimal amount of free fluid in cul de sac but without intrauterine gestational sac (Fig 2A). There was a cystic structure of 2 cm in diameter at left adnexa (Fig 2B). Serum beta-hCG was 712 mIU/mL. The patient was managed expectantly. Her vital signs were always stable. Eight hours later, her hematocrit dropped to 37% but was stable thereafter. Her abdominal and pelvic signs was somewhat improved. Forty hours from the initial test, serum beta-hCG level increased by 93% to 1,372 mIU/ mL. Follow-up TVS demonstrated free fluid in cul-de-sac, and the change of type II to type III endometrium with slightly increase in the thickness to 1.2 cm but no change in left adnexal cyst. Diagnostic laparoscopy was performed. The operative findings included normal uterus, normal both fallopian tubes, normal both ovaries with corpus luteum of 2 cm at left ovary, and minimal amount of straw colored peritoneal fluid (Fig 2C and 2D). Serum beta-hCG level after operation was 1,857 mIU/mL, (increased by 160% at 49 hr after the initial test) and a follow-up level at 24 hr later revealed a nearly doubling level of 3,431 mIU/mL. Post operative course was uneventful. On post operative day 3, a TVS demonstrated an intrauterine gestational sac with yolk sac, compatible with 4 wk gestational age (Fig 3). The final diagnosis at the time of initial presentation was 3-week intrauterine pregnancy with unexplained pelvic pain.

Case 3
A 33-year-old pregnant woman, G3P1011 last 7 yr, presented at the Outpatient Gynecologic Department on 12 May 2006 with bleeding per vaginam for 1 day. Her gestational age was 6 weeks (last menstrual period was 5 April 2006 and pregnancy test was positive 1 days before the visit). She had continuous dull pelvic pain for 2 days. The pain was worsen and was localized at suprapubic area for 1 day followed by vaginal bleeding, needing only 2 sanitary pads. She did not pass any tissue through vagina. Her past medical history included D&C for abortion 7 years ago. She had never used any contraception. Physical examination revealed normal vital signs (T 36.5°C, P 80 bpm, RR 18/min, BP 120/80 mmHg without postural hypotension) without pallor. Abdomen was soft with mild tenderness at suprapubic region. Pelvic examination revealed minimal amount of fresh blood in vagina, congested cervix with mild cervical excitation pain, normal sized uterus, and bilateral adnexal masses. Both masses were approximately 5 cm in diameter, mobile, not tender, cystic in consistency. There was no bulging in cul de sac, and no pelvic tenderness. Other physical findings were unremarkable.

Initial laboratory investigations included CBC (Hb 12.1 g/dL, Hct 36.2%, platelets 253,000 /mm³, WBC 15,000 /mm³, N 83%, L 10%), and serum beta-hCG (2403 mIU/ML). TAS demonstrated thin endometrium with a thickness of 4.7 mm without intrauterine gestational sac (Fig 4A), and well-defined both ovarian simple cyst measuring 5 x 4 cm and 3.1 x 2.5 cm in diameters at left and right ovary, respectively (Fig 4B and 4C). There was no free fluid in the cul-de-sac. The initial diagnosis was complete abortion or ectopic pregnancy. The patient was managed expectantly. Serum beta-hCG at 48 hr later was 879 mIU/mL, dropping by 64% from the initial level. Laparoscopic cystectomy of both ovarian cysts followed by D&C was performed. The operative findings included normal uterus, normal both fallopian tubes, right ovarian cyst sized 3 cm, and left ovarian cyst sized 5 cm. Both cysts had clear fluid content, thin wall, without solid part. Minimal amount of uterine curetting was obtained. Post operative course was uneventful. The histopathological report using the routine hematoxylin-eosin (H&E) staining revealed: (i) secretory endometrium with decidual reaction without chorionic villi (Fig 5A); and (ii) fibrous connective tissue of ovarian cyst wall (Fig not shown). The pathological section of the uterine curetting was then stained with a
special staining using anti-hCG which finally revealed a few extravillous chorionic cells (Fig 5B). The final diagnosis could be concluded as complete abortion.

**DISCUSSION**

Case number 1 had the highest risk for tubal pregnancy because she had previous tubal surgery. The patient had a reliable GA of 6 wk 5 d which was evidenced by a positive urine pregnancy test by a GA of 4 wk, which is the earliest GA that hCG is detectable in a urine sample. Differential diagnoses of her clinical presentation included abortion and ectopic pregnancy. It was crucial to know the condition of her present pregnancy as soon as possible because the patient had only one fallopian tube; the early diagnosis of ectopic pregnancy would enable the conservative treatment for her only tube. Unfortunately, both the patient’s TVS and her serum beta-hCG (both the initial and the follow-up levels) were not helpful for the differential diagnosis. Moreover, diagnostic laparoscopy, the gold standard for the diagnosis of extraterine pregnancy in the patient with stable vital signs, might not be helpful in this case. The reason was that the patient’s TVS clearly demonstrated left ovary without abnormal adnexal mass implying that the gestational sac was still too small to be seen on ultrasonogram and also under laparoscopy. Besides, a diagnostic laparoscopy in the case with previous laparotomy possessed a risk of injury to internal organs. The histopathology of uterine curettage which revealed proliferative endometrium without chorionic villi confirmed that the pregnancy was not intrauterine by the time of curettage. Moreover, it might never be there, otherwise the curettage should show a residual instead of a proliferative endometrium. Putting together all the information, the serum beta-hCG level which rose after the curettage, the pregnancy was most likely an ectopic pregnancy. Decision of treatment was made after weighing between risk and benefit of expectant management and medical treatment. The medical treatment was chosen and it returned a favorable outcome. However, the exact location of the pregnancy was inconclusive because the pregnancy could not be visualized under ultrasonogram and the patient did not undergo a diagnostic laparoscopy.

Case number 2 had a negligible risk for ectopic pregnancy. Her GA could not be determined from her LMP because of her medical disease (PCOD) making the date of ovulation unpredictable. Retrospectively, the GA by the time of her presentation was approximately 3 wk or a few days after embryonic implantation. Surprisingly, her serum beta-hCG level (712 mIU/mL) was much higher than the average level at this GA (usually less than 50 mIU/mL). The level was rapidly rising to 1,372 mIU/mL which was above a discriminatory zone of 1,000 mIU/mL for high resolution TVS, yet the pregnancy could not be localized. At that moment, the diagnosis was PUL which could have been treated expectantly. The diagnostic laparoscopy was unnecessary then because the patient still had stable clinical signs. A follow-up TVS that demonstrated intrauterine gestational sac 3 days after the laparoscopy indicated that the resolution of the first ultrasound machine was not high enough and the discriminatory zone for that machine must be higher than 1,000 mIU/mL.

Case number 3 also had a negligible risk of ectopic pregnancy. Her clinical presentation and findings was compatible with threatened abortion. Her initial serum beta-hCG level and TAS were compatible with PUL with stable vital signs. Retrospectively, the patient could have been treated expectantly by following serum beta-hCG level and TVS instead of TAS. By so doing, the location of pregnancy could not be concluded but the patient would gain benefit of avoiding the risk of unnecessary surgical intervention. Even having diagnostic laparoscopy and uterine curettage, the location of pregnancy was not easily identified by the routine H&E staining of the curettage. Only after a special staining with anti-hCG was the extravillous chorionic cells identified and the final diagnosis of complete abortion could be concluded.

A combination of a highly sensitive serum beta-hCG test and a high resolution TVS is a useful tool for early diagnosis of ectopic pregnancy. Nevertheless, this tool can be misleading and causes confusion if there is not adequate information and comprehension regarding both the clinical data and the performance of the tool. Different models of ultrasound machine have different resolution and different discriminatory zone. Therefore, it is necessary to find out the discriminatory zone for each ultrasound machine in order to accurately identify the location of pregnancy, as a consequence, both an unnecessary and a delayed operations can be avoided.

**REFERENCES**