

## Chapter 2

# Discriminatory Serum hCG Level for Ectopic Pregnancy

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### Case Study

A 38-year-old patient was admitted for suspected ectopic pregnancy after in vitro fertilization (IVF) treatment for male factor infertility. Three embryos were transferred 16 days prior to her admission. Serum beta-hCG measurement 4 days before her admission was 3200 mIU/mL and repeat testing 2 days later demonstrated a beta-hCG level of 2980 mIU/mL. She was hemodynamically stable, with very mild right abdominal pain. Transvaginal ultrasound (TVUS) revealed enlarged ovaries with multiple corpora lutea and a small amount of fluid in the cul-de-sac. The right fallopian tube seemed distended. Beta-hCG level on admission was 3000 mIU/mL. With the possibility of a right ectopic pregnancy, the consulting gynecologist prescribed methotrexate.

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## My Management

- a. Agree with the consulting gynecologist to administer methotrexate
- b. Repeat serum hCG measurement and perform ultrasound in 2–3 days
- c. Perform laparoscopy

## Diagnosis and Assessment

In women who conceive via assisted reproductive technique (ART), the risk for ectopic pregnancy may be increased as much as twofold [1]. These women are at risk for an ectopic gestation. Ultrasound findings of a gestational sac with a yolk sac, embryo, or cardiac activity outside the uterus provide a definite diagnosis of an ectopic pregnancy, and immediate treatment is justified. Our patient had a complex adnexal mass or fluid in the cul-de-sac; it suggests the probability of an ectopic pregnancy, but is not diagnostic [2]. When a pregnancy of unknown location (PUL) is diagnosed, the possibilities include an abnormal intrauterine pregnancy (collapsed, aborted, or simply underdeveloped) or an ectopic pregnancy (too small for recognition by TVUS or aborted). The possibility of a heterotopic gestation should be entertained especially in pregnancies resulting from ART [3]. Only 7–20% of the women with an initial diagnosis of a PUL will eventually be diagnosed with an extrauterine pregnancy [4].

The serum hCG level can assist in determining the location and normal development of a pregnancy. The levels can help determine whether an intrauterine sac should already be seen by ultrasound. The cutoff for the diagnosis of an intrauterine pregnancy using transabdominal ultrasonography is 6000–6500 IU/L [5]. With the use for transvaginal transducers, the discriminatory zone for the diagnosis is 1500 IU/L. This threshold level depends on the experience and skill of the examiner and the type of transducer used.

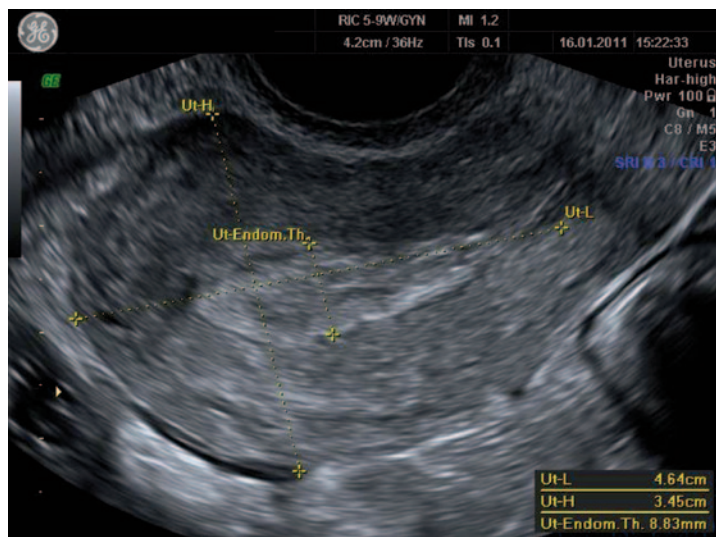
The reported sensitivity and specificity of hCG > 1000 IU/L in the detection of ectopic pregnancy when no intrauterine pregnancy

is visible is 21.7 and 87.3%; for an hCG level of  $>1500$  IU/L these values are 15.2 and 93.4%, and for an hCG level of  $>2000$  IU/L they are 10.9 and 95.2%, respectively [6]. Raising the threshold to 2000 IU/L increases the specificity and minimizes the number of false positive errors, but may also delay the diagnosis of an ectopic pregnancy. The contribution of TVUS when beta-hCG is below 1500 IU/L in diagnosing intra- and extrauterine pregnancies is small, with sensitivities of 33 and 25 %, respectively [7].

Serum hCG value above the discriminatory zone (1500 IU/L) and no intrauterine sac on TVUS strongly suggests an extrauterine pregnancy, but is still not diagnostic. Several possible scenarios are possible in such cases:

1. A complete abortion with rapidly declining beta-hCG levels.
2. An incomplete abortion with an indiscernible intrauterine sac.
3. A normally developing intrauterine multiple gestation. In women with an intrauterine multiple pregnancy, the serum hCG level could be higher than 1500 mIU and yet ultrasound examination would not reveal an intrauterine pregnancy. Previously, levels of over 9000 IU/L have been described for intrauterine triplet pregnancies unobserved by TVUS [8]. In this case, declining beta-hCG levels may be due to a poorly developed single gestation in a multiple-gestation pregnancy.
4. A heterotopic pregnancy with a normally developing intrauterine pregnancy along with an extrauterine pregnancy.
5. Several additional factors can contribute to nonvisualization of an intrauterine singleton pregnancy with levels above the discriminatory value. These include obesity and intrauterine pathologies, such as fibroids, adenomyosis, and endometrial polyps [8]. Accordingly, in minimally symptomatic women with a low risk for an ectopic pregnancy, even when the hCG level is above the discriminatory zone and no intrauterine pregnancy is visible on TVUS, a repeat hCG level in 2 days is recommended. This type of watchful waiting can decrease the number of patients treated with methotrexate unnecessarily. More importantly, it could be harmful to an intrauterine pregnancy [9].

In patients with a beta-hCG level below the discriminatory zone, the absence of an intrauterine sac is inconclusive. We recommend serial



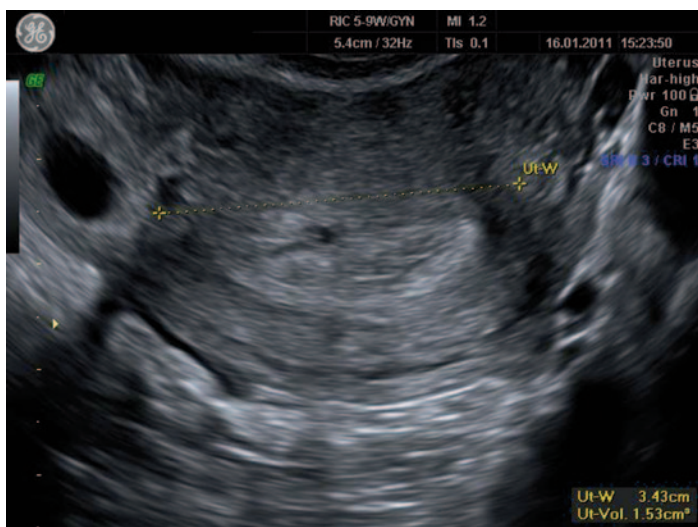
**Fig. 2.1** Longitudinal view demonstrating regular thickened endometrium

measurements of hCG levels at 2-day intervals until the discriminatory zone is reached and the diagnosis is established [10]. Interassay variation of hCG between different laboratories is up to 15%.

Our patient had hCG values above the discriminatory value for intrauterine pregnancies. The probability of an ectopic pregnancy is high, but the possibility of a concomitant intrauterine pregnancy or a multiple gestation pregnancy cannot be ruled out (Figs. 2.1 and 2.2).

## Management

The patient presented is hemodynamically stable and is mildly symptomatic, with minimal abdominal discomfort. TVUS fails to reveal a gestational sac, and the diagnosis of PUL should be made. There is no need for an emergency laparoscopy and the early administration of methotrexate could be redundant and even harmful.



**Fig. 2.2** Transverse view demonstrating intrauterine pseudosac and isthmic tubal pregnancy to the *left* of the uterus. (These two ultrasound pictures (Figs. 2.1 and 2.2) were taken from the same patient. Longitudinal view demonstrates a normally appearing luteal phase endometrium while the transverse view reveals a pseudosac and a clearly visible ectopic pregnancy in the isthmic portion of the fallopian tube. With beta-hCG levels of 1500 IU/mL this ectopic pregnancy could easily have been missed. (Courtesy Arnon Agmon, MD)

Repeating beta-hCG and performing TVUS if needed two days afterwards would be the recommended course of action. Even if an extrauterine pregnancy becomes evident during follow-up, methotrexate may or may not be the preferred treatment. According to a recent study performed by our group, 40% of extrauterine pregnancies will resolve spontaneously with watchful waiting [11], making the administration of methotrexate redundant. By follow up with beta-hCG and TVUS several possibilities may arise:

1. Values of beta-hCG will rise and a multiple intrauterine pregnancy will be seen on TVUS. In this scenario the administration of methotrexate may harm the developing fetuses, as this drug is teratogenic.

2. Values of beta-hCG will rise and a heterotopic pregnancy is seen on TVUS. In this case the decision to treat conservatively versus surgical removal of the ectopic pregnancy depends on its location and the patient's hemodynamic stability [12, 13].
3. Values of beta-hCG will rise and a repeated TVUS will reveal a tubal pregnancy without intrauterine pregnancy. In this case administration of methotrexate versus laparoscopic management will depend on hemodynamic stability, hCG value, and the existence of extrauterine cardiac activity.
4. Values of beta-hCG will rise above the discriminatory zone, but at an abnormal rate, and yet TVUS will remain inconclusive as to the location of the pregnancy. Here, medical treatment can be offered safely, but a presumed diagnosis of an extrauterine pregnancy will be inaccurate, making methotrexate treatment needless in 40% of the cases [14].
5. Values of beta-hCG will plateau. Methotrexate administration should be considered.
6. Values of beta-hCG will steadily decrease. In the absence of any significant change in clinical status, expectant management by watchful waiting is the recommended treatment, with success rates of 90 and 60% in women with hCG concentrations below 2000 IU/L and over 10,000 IU/L, respectively [15].

## Outcome

The patient received an intramuscular injection of a single dose of methotrexate (day 0). On day 4, the serum hCG level was 5000 IU/L. An ultrasound was performed and to the gynecologist's surprise, it revealed a heterotopic pregnancy with a right tubal chorionic sac and yolk sac and an intrauterine gestational sac. Due to the developing extrauterine gestation, a laparoscopic right salpingectomy was performed. Understanding the risks associated with methotrexate exposure during pregnancy, the patient opted to terminate the intrauterine pregnancy.

## Clinical Pearls/Pitfalls

- The discriminatory values of serum hCG for the diagnosis of an intrauterine pregnancy are not always reliable.
- Serum hCG value above the discriminatory zone and no intrauterine sac on TVUS is not diagnostic of an extrauterine pregnancy.
- When hCG level is above the discriminatory value of 1500 IU/L, but no intrauterine pregnancy is visible on TVUS, options such as a complete/incomplete abortion, multiple gestation, or heterotopic gestation should be considered.
- Obesity and intrauterine pathologies can obscure an early intrauterine pregnancy.
- A beta-hCG level below the discriminatory zone in the absence of an intrauterine sac is inconclusive. In hemodynamically stable patients, repeated beta-hCG and TVUS exams are recommended.
- Interassay variation in beta-hCG values exists. In hemodynamically stable patients, serial values should be obtained before treatment is offered.
- Failure to recognize an intrauterine pregnancy may be more harmful than delaying diagnosis of an extrauterine pregnancy.
- Watchful waiting in patients with declining beta-hCG levels prevents redundant administration of methotrexate.

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