"A Pregnant Pause": K-Kase for K-B (Educational Exercise)
In the K-B mailing, we presented the following scenario and question related to specimens K-09 and K-10:

The laboratory receives a second specimen from the same patient for human chorionic gonadotropin (hCG).

The patient is a 28 year-old woman whose last menstrual period was 6 weeks prior to her recent visit to the emergency department. She arrived complaining of spotty vaginal bleeding and slight abdominal discomfort. After two successful pregnancies, she had requested bilateral tubal ligation, which was performed one year earlier. Her subsequent menstrual history has been unremarkable. Mild bilateral adnexal tenderness was noted on physical exam. Serum hCG was measurable (see below) but no gestational sac was observed by transvaginal ultrasonography. The patient was told that she was pregnant and that ectopic pregnancy was suspected. She was discharged from the emergency department but told to return immediately if she experienced any increase in her abdominal discomfort. She was also asked to return in 2 days to have her blood drawn again for serum hCG.

Review the results your laboratory obtained for hCG for specimens K-09 and K-10. Assume that K-09 is the specimen from the patient's initial visit and K-10 is the specimen drawn 2 days later. If the medical team calls to inquire whether the results support the diagnosis of ectopic pregnancy, what would be the best response?

This appears to be a normal intrauterine pregnancy.
This appears to be an ectopic pregnancy.
This appears to be a non-viable pregnancy.
This may be a non-viable pregnancy and serum progesterone should be tested.
This may be a non-viable pregnancy and transvaginal ultrasonography should be repeated.

Results and Discussion
Normally, hCG levels rise briskly during the early part of the first trimester. The differential diagnosis of disorders associated with persistently low hCG levels is fairly short and includes non-viable pregnancy (or, even, early loss); ectopic pregnancy; trophoblastic disease (with abnormal hCG production, usually with very high levels); "phantom" hCG (usually due to heterophilic antibodies) and pituitary hCG (usually very low levels).

A single hCG level by itself usually does not provide enough information unless paired with transvaginal ultrasound. Even then, repeat hCG and ultrasound in 2-3 days may be needed to confirm a diagnosis. A gestational sac should be visible by ultrasound by the time hCG levels rise above 2000 mIU/mL (usually between 5-6 weeks gestational age). When the hCG is less than 2000 mIU/ml, serial levels are frequently helpful to diagnosis abnormal intrauterine pregnancy and ectopic pregnancy. Lack of doubling after 48-72 hours is strong evidence of a non viable pregnancy.

The overall method means for specimens K-09 and K-10 were 727 and 1034 mIU/ml, respectively. Of the 2086 laboratories participating in the K-B survey, 1079 contributed an answer to our hypothetical case with the following results.

A. This appears to be a normal intrauterine pregnancy.

Only 7% of the respondents chose this answer. Gestational age by LMP dates can be fraught with error but it seems very unlikely that this patient, with a history of tubal ligation, would have a normal intrauterine pregnancy with such relatively low levels of hCG that did not show an appropriate increase over 2 days.

B. This appears to be an ectopic pregnancy.
C. This appears to be a non-viable pregnancy.

Combined, 60% of respondents decided that the lack of increase in hCG was consistent with an abnormal pregnancy, either ectopic (54%) or non-viable intrauterine (5%). It would be difficult to differentiate the two at this point, although the absence of a gestational sac and the history of previous tubal ligation increases the likelihood of a tubal pregnancy.

If the HCG is elevated and no gestational sac or fetal pole can be seen, then the possibility of an ectopic pregnancy should always be entertained. Tubal pregnancies may be identified by ultrasound on initial presentation or might only be apparent on repeat ultrasound or laparoscopy. A significant proportion (5-10%) of women evaluated in the ED setting with symptoms associated with pregnancy loss (vaginal bleeding, cramping, syncope, etc.) will be found after evaluation to have an ectopic pregnancy. Previous tubal ligation increases the risk of ectopic tubal pregnancy but these patients frequently never suspect that there are pregnant until rupture has occurred or is imminent.

D. This may be a non-viable pregnancy and serum progesterone should be tested.

Only 14% chose this response. If the early first trimester trophoblast is abnormal, hCG is deficient in terms of its ability to maintain the corpus luteum of pregnancy and progesterone levels are low. Several studies have indicated that a single progesterone level may be predictive of non-viable pregnancy, but until recently, this test was not widely available on automated immunoassay analyzers and thus has not gained widespread clinical use.

E. This may be a non-viable pregnancy and transvaginal ultrasonography should be repeated.

Ultrasound findings are much more accurate than serial hCG levels when assessing pregnancy viability after 5-6 weeks gestation and 19% chose this response. In a normal pregnancy at 6 weeks gestational age, transvaginal ultrasound should show a gestational sac and possibly even a fetal pole that can be measured. However the ultrasound should be interpreted with caution if the HCG is less than 2000 mIU/mL since gestational age by LMP is frequently inaccurate and a single low hCG with an absent gestational sac may be due to incorrect dating. A transvaginal ultrasound or, if appropriate, a pelvic ultrasound may also be able to detect an ectopic pregnancy.

In summary, the consensus is that this scenario should be considered an abnormal pregnancy, probably an ectopic tubal pregnancy. Other disorders in the short list of differential diagnoses are less likely, given the clinical history and findings. Trophoblastic disease is usually associated with an intrauterine mass and extremely high hCG levels (as high as 2,000,000 mIU/mL). "Phantom hCG" refers to persistent mild elevations of hCG (up to 900 mIU/mL) which do not rise appropriately and may lead physicians to treat patients with cytotoxic chemotherapy for trophoblastic disease when in reality no true hCG or trophoblast disease is present. With phantom hCG, low levels of hCG can be detected in serum by multiple different assays but there may be as much as a five fold difference in values and levels may not decrease appropriately on dilution. Importantly, no hCG is

detected in the urine since the heterophilic antibodies which cause the falsely elevated results are not present in urine. A standard urine pregnancy test will be negative in these cases.

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Read more about it !
Cole LA et al: Gestational trophoblastic diseases: 4. Presentation with persistent low positive human chorionic gonadotropin test results. Gynecol Oncol 2006; 102: 165-172.

NOTE: *K-Kases are educational exercises using CAP proficiency testing specimens to mimic real-life laboratory situations. Participation is optional. Responses will not be graded and will not be included in the individual laboratory evaluations.*