

**“STOP USING THE HCG DISCRIMINATORY ZONE OF 1,500 TO 2,000 MIU/ML TO GUIDE INTERVENTION DURING EARLY PREGNANCY”**

ROBERT L. BARBIERI, MD  
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**Defining “abnormal rise” is the elephant in the room**

It was refreshing to read Dr. Barbieri’s recent editorial on the management of ectopic pregnancies based on human chorionic gonadotropin (hCG) levels. However, I feel there’s an elephant in the room. The phrase “abnormal rise” is not clearly defined, even though countless texts and review articles continue to use the phrase. In fact, many authors include a flow chart in which an abnormal rise usually is followed by a recommendation to empty the uterus in an attempt to find chorionic villi.<sup>1,2</sup> The most recent versions of several widely used textbooks advocate this practice,<sup>3-5</sup> and a current UpToDate article includes a flow chart suggesting that a “suboptimal rise” is sufficient for diagnosis of an abnormal pregnancy requiring treatment.<sup>6</sup>

Kadar and colleagues originally suggested that 85% of viable intrauterine pregnancies (IUPs) will have a rise in hCG levels of at least 66% every 48 hours, leading to what is commonly called the “doubling rule.”<sup>7</sup> Barnhart and colleagues showed that the slowest recorded hCG rise for a viable pregnancy in 48 hours was 53%, demonstrating that the hCG level does not double in 48 to 72 hours as traditionally expected.<sup>8</sup> In their final model, the authors calculated that 99% percent of normal IUPs should have an increase of at least 53% in 2 days, moving the bar for a “normal” hCG rise even lower. This also implies that 1% of viable IUPs may have a rise of less than 53% over 2 days. I have to wonder how many



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viable, wanted pregnancies have been interrupted by the misguided use of discriminatory zones or abnormal rises resulting in the emptying of the pregnant uterus?

Clinical assessment and ultrasonography should continue to be the mainstay of management of ectopic pregnancy. When surgical diagnosis is needed, laparoscopy should be considered. In this day and age, when we are being more cautious about emptying a uterus based on ultrasound measurements of the fetus or gestational sac, why are we still so eager to base that decision on laboratory values? Are we really willing to accept that 1% of the time we will be terminating a viable pregnancy? We should stop the continued propagation of flow charts and strategies that use hCG discriminatory zones or abnormal rises to determine viability and when to evacuate the uterus. A contemporary update to address the issue is needed.

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**Why not use serum progesterone to determine early pregnancy viability?**

I read with attention Dr. Barbieri’s recent editorial about evaluation of early pregnancy. My question is: Why is serum progesterone not recommended or used to assess the health of an early pregnancy?

In my practice, I always use a serum progesterone test along with hCG measurements to ascertain if an early pregnancy is healthy. I have observed, as biased as this observation can be, as I have not done any study about it, that a serum progesterone level above 12 ng/dL correlates quite well with a healthy pregnancy. I only follow more intensively with serial ultrasonography and hCG measurements in a patient whose progesterone level is below 11 ng/dL.

When a patient’s only symptom is bleeding, if the serum progesterone level is below 11 ng/dL, and her serum quantitative hCG level does not double as appropriate, I consider the pregnancy not normal

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and counsel the patient about continuing observation or terminating the pregnancy.

In the same laboratory scenario but with a patient who has bleeding and pain, and even moreso if the progesterone level is below 8 ng/dL, I strongly consider an ectopic pregnancy until it is proven otherwise. In this case, I offer treatment with methotrexate, as it's my experience that the vast majority of these patients are carrying an abnormal pregnancy—either a spontaneous abortion or an ectopic pregnancy. Methotrexate therapy will prevent further complications without causing the loss of normal pregnancies.

For me, progesterone levels add one more piece to the puzzle. A patient with pain, vaginal bleeding, a quantitative hCG value of 500 mIU/mL, and a serum progesterone level of 20 ng/dL will have a normal pregnancy and is not a candidate for any intervention besides a follow-up hCG measurement to ascertain “doubling” of the analyte as expected in a normal pregnancy.

An asymptomatic patient whose quantitative hCG measurement is 1,000 mIU/mL and progesterone level is 4 ng/dL is carrying an abnormal pregnancy. If this quantitative hCG does not double appropriately in the follow-up, I counsel the patient about the greater chance of a spontaneous abortion or ectopic pregnancy.

Is this approach faulty?

**Tomas Hernandez, MD**  
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### Know the sensitivity of the hCG test

I found Dr. Barbieri's editorial very timely. It brings some clarity to the use of the hCG discriminatory zone in symptomatic pregnant patients.

An additional important point

is that it is the clinician's obligation to know the sensitivity of the test the laboratory uses. Serum tests use the threshold for a negative result of either less than 1 mIU/mL or less than 5 mIU/mL. If possible, serial hCG measurements should be performed in the same laboratory, because the result may not represent a true change in the hCG concentration if the second test is performed at a different laboratory.<sup>1</sup> This is especially important when the clinician is considering the use of methotrexate to treat a suspected ectopic pregnancy.

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### Further thoughts on hCG, ultrasound, and early pregnancy diagnosis

I want to thank Dr. Barbieri for his important, timely message about suspected nonviable pregnancy. I agree with virtually all of his excellent suggestions. In fact, I was part of the consensus panel that developed the findings diagnostic of and suggestive of IUP failure.<sup>1</sup> There are a few points, however, that I believe the readership of OBG MANAGEMENT should know.

The endothelial heart tube, the first organ system to form, folds in on itself and begins to beat at 21 days postconception. Thus, it is present and beating prior to our ability to image it on transvaginal ultrasound. Yet new guidelines<sup>1</sup> now say not to call an IUP failed until there is a crown-rump length of 7 mm or greater with no cardiac activity. In the

past, many clinicians used 4 or 5 mm. In fact, one of the most recent studies utilizing an 8-mHz transducer found all cardiac activity was visualized by 3.1 mm embryonic size!<sup>2</sup>

So why has the number been increased to 7 mm? I've given this a lot of thought. Most clinical trials, from which guidelines were derived in the past, were well-designed, tightly controlled, and performed by better-trained clinicians, often with state-of-the-art equipment. In contrast, well-meaning health-care providers practicing in the field are often without the same level of quality control, equipment, or expertise but are still expected to duplicate the data from the trials used to create the guidelines. The reason this is relevant pertains to the statement that 94% of 291 cases of ectopic pregnancy had an adnexal mass.<sup>3</sup> This is an excellent study, done at one of the nation's most outstanding academic institutions by world-class sonologists. I do not believe that well-meaning clinicians in the field will be able to achieve this level of detection.

Dr. Barbieri also discusses an inability to see an IUP even when hCG levels are greater than 1,500 or 2,000 mIU/mL or above. He mentions obesity, fibroids, and adenomyosis as increasing the risk of an ultrasound failing to detect an early IUP. This point needs to be expanded upon. Twenty-seven years ago, we claimed a discriminatory level of 1,025 mIU/mL of hCG if the gestational sac was normal and the uterus was normal with normal echo patterns. We had three cases with markedly greater hCG levels (one, in fact, as high as 5,544 mIU/mL) with coexisting fibroids.<sup>4</sup>

I would also submit that it is the axial uterus that is a very important source of potential error. The closer the beam of sound coming

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off of the footprint is to a right angle with the endometrium (as it will be in a markedly anteverted or retroverted uterus), the better the resulting image. With an axial uterus, the endometrium is in the same plane as the beam of sound, and this diminishes imaging capability. Furthermore, twin pregnancies are a potential confounder in attempting to correlate hCG levels in transvaginal ultrasound findings.

I wholeheartedly agree with Dr. Barbieri: There is virtually no role to administer methotrexate based on a single hCG determination in a hemodynamically stable patient.

**Steven R. Goldstein, MD**  
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» **Dr. Barbieri responds**

*Dr. Namaky, Dr. Hernandez, Dr. Hull, and Dr. Goldstein provide great clinical advice for readers. I agree with Dr. Namaky that the mainstays of managing a pregnancy of unknown location in a stable patient are clinical assessment and ultrasonography. Dr. Hernandez recommends using the serum progesterone measurement to help guide*

*clinical decisions in a pregnancy of unknown location. I also use serum progesterone in my practice because a very low progesterone level helps the patient to understand that she has a failed pregnancy, and facilitates her acceptance of timely intervention. Many of my colleagues do not use progesterone measurement because they prefer to rely on clinical assessment, serial hCG measurement, and ultrasound results to guide their treatment. I agree with Dr. Hull that serial hCG measurements are most useful when the same laboratory performs all the tests. Dr. Goldstein, a world class expert in the evaluation and management of early pregnancy problems, provides great advice for all readers on how to best integrate ultrasonography in their practices to optimize patient care.*

**Quick Poll results suggest that many birthing units do not offer nitrous oxide analgesia to their patients...yet**

A recent OBG MANAGEMENT Quick Poll took as its subject the December 2014 Editorial, "Nitrous oxide for labor pain." In the Editorial, Robert L. Barbieri, MD; William Camann, MD; and Catherine McGovern, RN, MSN, CNM, discuss the mechanism of action of nitrous oxide (NO) and procedures and cautions for administering NO to the laboring mother, as well as tips for implementing the use of NO in a birthing unit.

Our poll asked if readers' birthing units offer NO analgesia. More than 160 readers responded:

- **99 readers (59.6%)** responded that their birthing unit does not offer NO
- **24 readers (14.5%)** answered that their birthing unit offers NO
- **43 readers (25.9%)** replied that their birthing unit does not offer NO, but they are considering bringing this option to their unit

To participate in the latest poll, see the Quick Poll at [obgmanagement.com](http://obgmanagement.com)

