Biomarkers for Ectopic Pregnancy. Why is it So Hard?

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The search for biomarkers to identify early cases of ectopic pregnancy (EP) has been sought by many [1-8]. Nevertheless, β-hCG is the only biomarker that has been widely clinically used for the diagnosis of EP [9]. A promising commercially available biomarker [10] was not confirmed in a larger cohort [11].

Many questions are raised about these discrepancies. The answer is not complex, but it is long. We have four phases to develop a biomarker for clinical use: 1) Preclinical exploration, 2) Clinical assay development, 3) Assessment of predictive ability in a retrospective study and 4) Validation in a prospective setting [12]. The fourth phase is the real test and many biomarkers do not pass the test. The reason for this failure is that basic aspects of epidemiology and Bayesian theorem are forgotten.

We need to know the incidence of a condition, signs and symptoms, risk factors, and the performance of ancillary exams. After these procedures, a probability is obtained. This probability may cross an arbitrary threshold of action and no further diagnostic test will be necessary. For instance, a physician decides that after crossing the 85% chance of having EP, no further diagnostic tests are needed and surgery is scheduled; if the probability of ectopic is less than 1%, EP is excluded. A negative biomarker with excellent performance is useless when embryo heartbeat is present outside the uterus. Consider the following parameters: the probability of having EP in an asymptomatic woman, without risk factor, is 2% (patient 1), while in a woman with pelvic pain and vaginal bleeding and a history of tubal ligation is 45% (patient 2). A hypothetical biomarker has a sensitivity and specificity of 84% and 93%, respectively. In the first patient, the probability of having an EP is 19.8%, while in the second, is 90.8% when the same biomarker is positive.

Therefore, the problem with biomarkers is how and when they are used. In medicine, we need to know the incidence of a disease in our setting, which risk factors really matter, the performance of each exam and what sequence they should be applied. The sequence of exams varies by different society guidelines [13]. In a case of pregnancy of unknown location, the use of biomarkers should be used in light of the signs, symptoms and risk factors of the patient.

Medicine is not made solely of biomarkers; they are ancillary tests to confirm or to exclude a diagnostic hypothesis. Thus, the physician should have a hypothesis first, apply the risks of having the disease, perform the physical exam and use the biomarker. They should not do the opposite, ask the biomarker and then check the patient. As we used to say in medical school, if lab exams are inconclusive, perform history and physical examination.

Bibliography


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